Traditional Herbal Medicines for Modern Times

Herbal Principles in Cosmetics

Properties and Mechanisms of Action

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Herbal Principles in Cosmetics

Properties and Mechanisms of Action

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Laura Cornara, and Elisa Bottini-Massa

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Series Preface

Global warming and global travel are contributing factors in the spread of infectious diseases such as malaria, tuberculosis, hepatitis B, and HIV. These are not well-controlled by the present drug regimes. Antibiotics, too are failing because of bacterial resistance. Formerly less well-known tropical diseases are reaching new shores. A whole range of illnesses, such as cancer, for example, occurs worldwide. Advances in molecular biology, including methods of *in vitro* testing for a required medical activity, give new opportunities to draw judiciously upon the use and research of traditional herbal remedies from around the world. The re-examining of the herbal medicines must be done in a multidisciplinary manner.

Since 1997, 47 volumes have been published in the book series Medicinal and Aromatic Plants—Industrial Profiles. The series continues and is characterized by a single plant genus per volume. With the same series editor, this new series, Traditional Herbal Medicines for Modern Times, covers multiple genera per volume. It accommodates, for example, the traditional Chinese medicines (TCM), the Japanese Kampo versions of this, and the Ayurvedic formulations of India. Collections of plants are also brought together because they have been re-evaluated for the treatment of specific diseases such as malaria and diabetes. Yet other collections are of the most recent investigations of the endemic medicinal plants of a particular country, e.g., India, South Africa, Mexico, Brazil (with its vast flora), and Malaysia (with its rainforests), and are believed to be the oldest in the world.

Each volume reports on the latest developments and discusses key topics relevant to interdisciplinary health sciences research by ethnobiologists, taxonomists, conservationists, agronomists, chemists, pharmacologists, clinicians, and toxicologists. The series is relevant to all these scientists and will enable them to guide business, government agencies, and commerce in the complexities of these matters. The background to the subject is outlined below.

Over many centuries, the safety and limitations of herbal medicines have been established by their empirical use by the "healers" who also took a holistic approach. The healers are aware of the infrequent adverse effects and know how to correct these when they occur. Consequently and ideally, the pre-clinical and clinical studies of a herbal medicine need to be carried out with the full cooperation of the traditional healer. The plant composition of the medicine, the stage of the development of the plant material, when it is to be collected from the wild or when from its cultivation, its post-harvest treatment, the preparation of the medicine, the dosage and frequency, and much other essential information is required. A consideration of the intellectual property rights and appropriate models of benefit sharing may also be necessary.

Wherever the medicine is being prepared, the first requirement is a well-documented reference collection of dried plant material. Such collections are encouraged by organizations like the World Health Organization and the United Nations Industrial Development Organization. The Royal Botanic Gardens at Kew (UK) is building up

its collection of traditional Chinese dried plant material relevant to its purchase and use by those who sell or prescribe TCM in the United Kingdom.

In any country, the control of the quality of plant raw material, of its efficacy, and of its safety in use are essential. The work requires sophisticated laboratory equipment and highly trained personnel. This kind of "control" cannot be applied to the locally produced herbal medicines in the rural areas of many countries, on which millions of people depend. Local traditional knowledge of the "healers" has to suffice.

Conservation and protection of plant habitats are required and breeding for biological diversity is important. Gene systems are being studied for medicinal exploitation. There can never be too many seed conservation "banks" to conserve genetic diversity. Unfortunately, such banks are usually dominated by agricultural and horticultural crops with little space for medicinal plants. Developments such as random amplified polymorphic DNA enable the genetic variability of a species to be checked. This can be helpful in deciding whether specimens of close genetic similarity warrant storage.

From ancient times, a great deal of information concerning diagnosis and the use of traditional herbal medicines has been documented in the scripts of China, India, and elsewhere. Today, modern formulations of these medicines exist in the form of powders, granules, capsules, and tablets. They are prepared in various institutions such as government hospitals in China and Korea, and by companies such as Tsumura Company of Japan, with good quality control. Similarly, products are produced by many other companies in India, the United States, and elsewhere with a varying degree of quality control. In the United States, the Dietary Supplement and Health Education Act of 1994 recognized the class of physiotherapeutic agents derived from medicinal and aromatic plants. Furthermore, under public pressure, the U.S. Congress set up an Office of Alternative Medicine. In 1994 this office assisted in the filing of several Investigational New Drug (IND) applications required for clinical trials of some Chinese herbal preparations. The significance of these applications was that each Chinese preparation involved several plants and yet was handled as a *single* IND. A demonstration of the contribution to efficacy, of *each* ingredient of *each* plant, was not required. This was a major step forward toward more sensible regulations with regard to phytomedicines.

The subject of Western herbal medicines is now being taught again to medical students in Germany and Canada. Throughout Europe, the United States, Australia, and other countries, pharmacy and health-related schools are increasingly offering training in phytotherapy. TCM clinics are now common outside of China. An Ayurvedic hospital now exists in London with a BSc Honors degree course in Ayurveda available: Professor Shrikala Warrier, Resistrar/Dean, MAYUR, The Ayurvedic University of Europe, 81 Wimpole Street, London, WIG 9RF, Tel +44207 224 6070, e-mail sw@unifiedherbal.com. This is a joint venture with a university in Manipal, India.

The term *integrated medicine* is now being used, which selectively combines traditional herbal medicine with "modern medicine." In Germany there is now a hospital in which TCM is integrated with Western medicine. Such co-medication has become common in China, Japan, India, and North America by those educated in both systems. Benefits claimed include improved efficacy, reduction in toxicity and the period of medication, as well as a reduction in the cost of the treatment. New terms such as *adjunct therapy*, *supportive therapy*, and *supplementary medicine* now

appear as a consequence of such co-medication. Either medicine may be described as an adjunct to the other depending on the communicator's view. Great caution is necessary when traditional herbal medicines are used by doctors not trained in their use, and likewise when modern medicines are used by traditional herbal doctors. Possible dangers from drug interactions need to be stressed.

As well as giving beauty to a person via the skin, the cosmetic industry has now strongly linked its products medicinally to the subject of anti-ageing of the skin. The industry has also coined such terms as *actives*, *cosmeceuticals*, *nutricosmetics*, etc., and the legislation associated with cosmetology and dermatology has become similar.

Within a very challenging range of subject matter, the authors have presented clearly the essential basic scientific information in their Introduction and three concise chapters. Seventy medicinal botanicals are then described in an identically structured monographic way.

For the resultant Cosmetic Volume, I heartily thank the team of four authors—a cosmetics manufacturer, a physiologist, a botanist, and a chemist—and the supporting staff of CRC Press, namely Barbara Norwitz, executive editor and Patricia Roberson, project coordinator.

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Foreword

The past decade has witnessed a growing interest in the molecular and mechanistic aspects of cosmetic research. By borrowing validated technologies of drug discovery to assess bioactivity, the search for new cosmetic active ingredients has gone molecular, bringing to the forefront of innovation targets like sirtuins, NFkB, and peroxisome proliferator-activated receptors (PPARs). At the same time, plants have emerged as the best source of cosmetic ingredients that meet the consumer's growing demand of natural character, efficiency, and safety, and are increasingly replacing synthetic ingredients. While drugs are designed to treat or prevent disease, cosmetics used to be confined to the realm of appearance and decoration, with no functional activity. According to their legal definition, cosmetics should not affect skin physiology and go beyond its simple ornamentation, but nowadays cosmetic ingredients, just like dietary supplements, are designed by producers, used by consumers, and investigated by researchers with an activity goal in mind. In cosmetic lingo, *actifs* has therefore given way to *cosmeceuticals*, a name that merges cosme(tic) and (pharma)ceutical implications, and is amenable to semantic variations like nutricosmetics ("beauty from inside" actives) and neoceuticals (products for the treatment of hypersensitive skin conditions).

It is surprising that plant molecular cosmetology, an art widely practiced, advertised, and talked about, has so far remained an orphan of a reference book where its molecular, cellular, and mechanistic aspects are systematically discussed. Furthermore, the amazing range of novel botanical ingredients developed from exotic tropical plants, often through fair trading practices, requires constant update and critical inventory. This book fills these gaps, critically discussing the botanical, ethnopharmacological, phytochemical, and molecular aspects of plant active ingredients of cosmetic relevance. Along with dermatological and cosmetic uses, toxicological aspects are also treated, maintaining a balanced view and dissecting hype from solid science. This task is particularly difficult in the literature swamp of bioactive natural products, where readers are often overwhelmed by a tsunami of sometimes conflicting data. By capitalizing on their specific expertise, the authors have provided readers with a book that is fat on facts and references and lean on speculations. Beauty might be only skin deep, but its science should not be, and needs a multidisciplinary expertise that this book is well suited to provide.

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Introduction

All living organisms are composed of cells, and the human body does not make an exception. The life of cells depends on a complex of metabolic activities sustained by the uptake of nutrients and by the reception of extracellular signals that are brought by chemical compounds of various nature and origin. In higher organisms, like humans, physiological signal molecules are known as hormones, growth factors, cytokines, and neurotransmitters. These compounds have the ability to sustain or modify the metabolic activities of the cell, and their incessant action is essential for the survival of cells, and hence of the whole organism. The harmonious integration of these mechanisms is at the basis of a healthy organism, while disorders affecting one or more of them are a general feature of ailments and diseases.

Since prehistoric times, humans have started to understand that many natural sources, like minerals, plants, and animals, can provide remedies for various kinds of dysfunctions. However, it has been only in the twentieth century that the development of modern chemistry and biology has allowed us to understand the chemical structure of many natural principles used for therapeutic purposes[1] and, in a fewer number of cases, their mechanisms of actions.

Natural and synthetic drugs exert their actions essentially through the same pathways, which are in most cases also overlapped to the metabolic pathways triggered by physiological signal molecules. Drugs act as a defense against injurious agents, such as infectious organisms and viruses, toxic chemicals, and free radicals, or otherwise modulate the functioning of cells by inducing apoptosis or proliferation, modifying enzymatic activities and gene expression, and interfering with cell signaling. Herbal drugs show an amazing diversity in terms of chemical composition and biological properties, and their rational use significantly contributes to treat some diseases or alleviate the side effects of synthetic drugs.

Apart from medical practices, herbal drugs have been intensively used since very ancient times in skin care,[2] a complex of beautification techniques that should not be confused with medical therapies. A distinction between drugs and cosmetics is generally made not only on technical grounds, but also on legal grounds, owing to the need to protect the consumer from unsafe products. Precise definitions for drugs and cosmetics are published in regulations and guidelines, such as those of the U.S. Food and Drug Administration or the European Community. Put simply, a drug is generally considered to be a product that is able to affect the structure or function of the human body, thereby possibly healing a condition of sickness. Conversely, a cosmetic is a preparation or substance intended to be placed in contact with the external parts of the human body, or the teeth and buccal mucosa, with the aim of cleaning, perfuming, improving the appearance, and keeping them in good condition.[3]

However, it has never been possible to define a clear boundary between dermatology and skin care. Moreover, due to the pressure to fulfill the consumer's needs and expectations, technical progresses in the cosmetic field reveal a clear tendency to develop antiage products able to deeply modify the physiology of the skin. Hence,

many products may fulfill at the same time the definition of a cosmetic product and the definition of a medicinal product, and even in the area of legislation, the borderline between cosmetology and dermatology is frequently blurred.[4,5]

The possibility of classifying any product as either a drug or a cosmetic is an obvious utopia. Moreover, on scientific grounds, such a distinction is needless, since any compound that causes some interaction with the human body is, by definition, able to modify it to some extent. Hence, in order to understand the real meaning and function of cosmetics, we should focus on the purpose of using a specific product, rather than on its effects. While the application of cosmetics to skin is generally different from a therapeutic approach, it is conversely closely related to a correct lifestyle in feeding and nutrition. The use of healthy food does not obviously pertain to medical activities, and yet it can be of great help in the prevention of disease, and lay the basis for an overcoming of pathological syndromes and for contrasting the noxious effects of aging. Similarly, a proper skin care regimen can enormously improve the role of the skin in protecting the body against aggressive environmental factors, such as infections, UV irradiation, dryness, and pollution, thus preventing skin disease and aging.

Cosmetics are an extremely various and diversified set of products, including creams, powders, perfumes, lotions, washing products, and the wide sector of decorative cosmetics or makeup. Natural substances are extensively used in the preparations of cosmetics,[6] and there is an ever-growing interest in the understanding of their mechanisms of action, in order to achieve a more sophisticated targeted design of skin care products.

Plants and other botanical sources, such as fungi, algae, and cyanobacteria, are able to synthesize an amazingly vast set of chemical compounds.[7] Carbohydrates, lipids, and proteins, which are present in large amounts in different tissues of botanical organisms, can play an essential role as nutrients, while they have a relatively lower relevance as drugs. Alkaloids, terpenoids, and flavonoids conversely show a more powerful bioactivity in terms of medical drugs. These compounds are generally produced as secondary metabolites by source organisms, and are mainly involved in protective roles, such as UV radiation screening, free radical scavenging, antimicrobial activity, and repulsive effects. The various chemical structures found in secondary metabolites go along with an extraordinarily wide range of biological activities exerted by these chemicals on the cells of mammals, and of humans, in particular. These activities are linked to a complex of molecular mechanisms, involving almost all sectors of the cell biochemical network. Many of these mechanisms are being exploited, more or less consciously, in the pharmaceutical and cosmetic fields, while many others are going to be discovered by an ever-growing field of research activities.

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1 The Skin
Morphophysiological Traits and Disease

The skin is an outer organ of the body that protects underlying muscles and organs. It is a multilayered sheath of tissue weighting about 10 kg and having a surface of about 2 m^2. The anatomy of the skin consists of three primary layers: the epidermis, providing waterproofing and serving as a barrier to infections; the dermis, a connective tissue hosting hair bulbs and skin glands; and the hypodermis, a subcutaneous adipose tissue covering the underlying muscles, bones, and ligaments.[1]

The skin performs different essential functions. It forms an anatomical barrier for pathogens; contains nerve endings for the sensory perception of heat, cold, mechanical stimuli, and pain; is involved in thermoregulation, either under cold or under

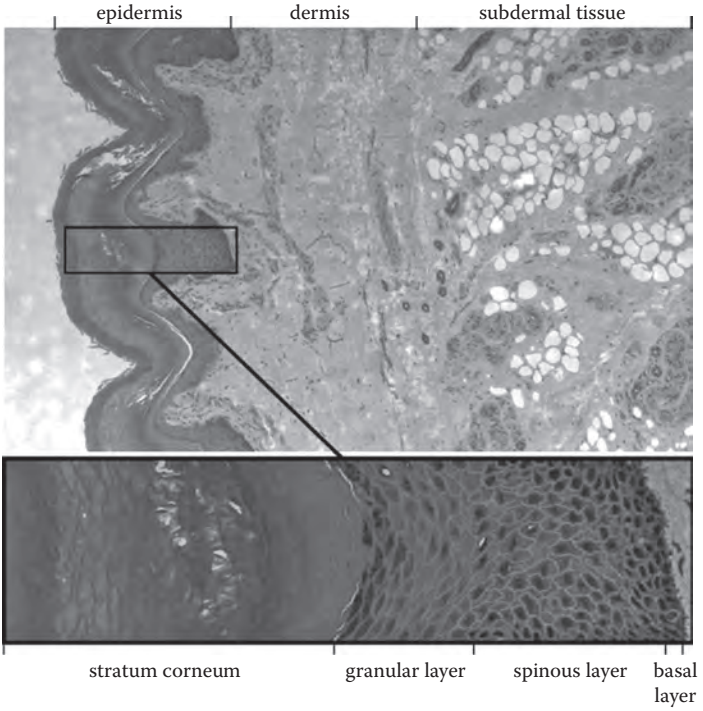

FIGURE 1.1 Histological section of the skin, and inset showing the different layers of the epidermis.

warm conditions; acts as a water-resistant barrier; is a storage for lipids and a crucial site in the synthesis of vitamin D by the intervention of UV radiations; and is also involved in excretory processes.

EPIDERMIS

The epidermis is the outermost layer of the skin. It consists mainly of cells named keratinocytes, arranged to form a pluristratified epithelium of 0.1–3 mm in thickness. The epidermis rests on a basal membrane formed by extracellular matrix proteins that connects the epidermis to the underlying dermis. Keratinocytes undergo a differentiation process, starting from a single layer of stem cells at the basis of the epidermis. During their differentiation, keratinocytes are pushed up toward the top of the epidermal layer. At the end of this process, these cells die and eventually desquamate, thus producing a continuous renewal of the skin surface. The different steps of keratinocyte differentiation produce morphological changes in the epidermis that allow the individuation of a series of layers.

The basal layer, or *stratum germinativum*, is located at the base of the epidermis and consists of a single layer of cuboidal or columnar cells, which proliferate and give origin to keratinocytes. A few cells in this layer are melanocytes producing melanin, a pigment derived from the amino acid tyrosine, which is the primary determinant of skin and hair color. Melanocytes activated by UV rays produce nitric oxide, a chemical mediator of cellular metabolism, which upregulates the gene of tyrosinase, the enzyme providing a key step in the synthesis of melanin. Keratinocytes are also involved in this process through a paracrine mechanism.

The high proliferative activity of basal keratinocytes is related to their response to mitogenic and differentiation stimuli, such as the keratinocyte growth factor (KGF), and the Notch and Rho pathways, respectively. In addition, phosphoinositide 3-kinase signaling to AKT promotes keratinocyte differentiation and concomitantly inhibits apoptotic pathways, while activation of the ERK 1/2 MAPKs is essential for the onset of transglutaminase activity, a marker of keratinocyte differentiation.

Division and differentiation of keratinocytes of the basal layer originate the *stratum spinosum*, consisting of a multilayered array of cuboidal cells interconnected by junctions called desmosomes. In histological preparations these cells may shrink while remaining joined together by desmosomes, thereby assuming a spiny appearance. At this stage of differentiation, keratinocytes actively synthesize various types of keratins that become arranged to form intermediate filaments. These filamentous structures are anchored to desmosomes and strengthen the adhesion among cells and the resistance of the skin to frictional forces.

The *stratum granulosum* is formed by a few layers of squamous cells that have lost most of their organelles due to autophagocytic processes, and contain basophilic keratohyalin granules crossed by keratin filaments. Granules contain highly sulfurated proteins rich in the amino acid cysteine, such as loricrin, filaggrin, and involucrin. They also contain the glycolipid acylglycosylceramide that is released after cell death. At this level, nutrient support to cells becomes insufficient, due to the distance from the blood vessels, which reach the dermis but do not penetrate into the epidermis. Nutrient shortage leads to cell death in the outer keratinized layers of the epidermis.

In the thick skin of palms and soles a *stratum lucidum* is also found, consisting of flattened, dead cells containing a refringent substance, mainly formed by keratin, which confers clearness and waterproof properties to this layer.

The outermost horny layer, or *stratum corneum*, is composed of dead cells and keratin scales that are continuously shed and replaced by the underlying layers. This layer realizes a defense barrier against external intrusions, while the lipid acylglycosylceramide acts as a cementing substance for keratinocyte scales, thereby realizing a waterproof barrier. In case of prolonged immersion, the lipid substance is washed away, thus allowing hydration of keratin and eventually producing the characteristic wrinkling of the skin on fingers and toes. At the tip of fingers and toes, the dorsal surface of the skin gives rise to nails. These hornlike structures are tough plates of keratin formed by the proximal portion of an invagination of the epidermis that extends deeply into the dermis.

The skin surface is crossed by lines and creases that become more abundant and evident during aging. The epidermis also hosts antigen binding Langherans cells, involved in immune defense and inflammatory processes, and Merkel's cells playing a sensory role.

DERMAL AND SUBDERMAL TISSUE

The dermis is a connective tissue developing beneath the epidermis. The most superficial portion, called papillary dermis, gives rise to fingerlike projections, or papillae, which interdigitate with the lowermost layer of the epidermis. The underlying region is called reticular dermis and is of variable thickness in different body regions. In palms and soles the occurrence of conspicuous papillae creates outward projections of the epidermis that form ridges in the skin's surface, thus contributing to the grasping function of the extremities. These friction ridges show patterns that are specific for single individuals and produce fingerprints that can be used as a means of identification. The dermis is characterized by an extensive extracellular matrix containing high levels of collagen and elastin, matrix proteins conferring strength, firmness, and elasticity to the tissue.

Fibroblasts are the main cell type of the dermis. These cells are present in all connective regions of the body, where they do not realize structurally arranged aggregations, but are dispersed across the tissue framework, or stroma. Fibroblasts have an elongated shape, can move across the tissue, and produce precursors of the extracellular matrix that self-assemble to form collagen and elastin fibers. The integrity of the tissue, i.e., matrix homeostasis, depends on a complex equilibrium between the deposition of collagen, elastin, and other matrix components, such as proteoglycans and glycosaminoglycans, and the occurrence of degradative processes operated by metal binding enzymes, known as matrix metalloproteinases, released by fibroblasts and by other cells, like keratinocytes.

The dermal tissue is perfused by a network of blood vessels, whose most superficial portion gives rise to loops that enter into the papillary zone but do not penetrate in the epidermis. Blood vessels provide nourishment and waste removal to the dermis and to the lowermost layers of the epidermis. Dermal elements of the nervous system include the terminations of nerve fibers and sensory organs for pain,

pressure, and temperature. Limited numbers of lymphocytes, macrophages, and mast cells are also present.

The hypodermis is a deep cutaneous layer characterized by fat or adipose tissue, primarily composed of adipocytes, subdivided by strands of connective tissue that are in continuity with the upper dermis. This tissue extends deeply to contact the connective sheaths of muscles and skeletal system, and acts as a thermal insulator, a reserve of fuel for the body's metabolism, and a cushion that smoothes the potentially damaging effects of bumps and other traumatic events. In some body regions, this layer hosts the deeper portions of hair follicles, like in head hairs, or of sweat glands, like in armpits, hand palms, and feet soles.

CUTANEOUS ANNEXES

Hair follicles develop in the epidermal layer and consist of a tubular arrangement of concentric cell layers with a basal expansion, named bulb, engulfing a portion of dermal tissue, named hair papilla, which contains blood capillaries and nerve terminations. The cell layers of the follicle become progressively keratinized and enter to form the hair stalk, which grows toward the exterior, forming a portion external to the follicle. Melanocytes are also present in the follicle and are responsible for hair pigmentation. Sebaceous glands are acinar secretory elements connected to hair follicles, which produce a fatty substance, known as sebum, consisting mainly of wax monoesters, triglycerides, free fatty acids, and squalene. The functions of sebum include skin lubrication, reduction of water loss, and antibacterial activity.

Hairs are present on many regions of the body and normally undergo a growth phase (anagen) and a resting phase (telogen). During the anagen, materials are deposited in the hair shaft by follicle cells, while in the telogen the follicle is resting and the hair may be lost. Head hairs are the longest hairs of the human body, and their health is generally deemed of aesthetic valence. They have a central part named medulla that is surrounded by two layers, a cortex and a superficial cuticle. The medulla is formed by elastic keratin, while the cortex and cuticle contain harder keratin. Different hair color tones are due to structural differences and to a variable concentration of melanin in the cortex. The lipid secretion of sebaceous glands protects hairs through lubrication and inhibition of bacterial growth.

Sudoriparous glands are simple tubular structures that are commonly found in the entire skin and develop deep in the dermal tissue. These glands produce sweat, a body liquid that is transported along the gland duct and is released at the skin surface. Some sudoriparous glands, having a distribution limited to armpit, perianal, and inguinal areas, are connected to hair follicles, similarly to sebaceous glands. Sweat is an odorless substance, but bacterial fermentation can produce smell that is generally considered socially unpleasant.

SKIN DISORDERS

A vast number of skin alterations and syndromes have been classified in the medical field, the most common of which are allergenic and nonallergenic eczema, photo- and

chronoaging, and tumors.[2] Baldness is also generally considered an altered condition, although its causes can be due to pathological or physiological processes.

Skin inflammation, or dermatitis, is an altered state of skin commonly developing in skin disease. Different noxious agents, such as infections, cigarette smoke, ultraviolet radiation, trauma, hormonal imbalance, ethanol ingestion, psychological stress, and anoxia, share the ability of triggering the synthesis of intercellular adhesion molecule 1 (ICAM-1) in endothelial cells. ICAM-1 acts as a signal to circulating monocytes and macrophages that migrate into the dermis and release pro-oxidant compounds, as well as proteases and elastase, thus inducing tissue damage. Damaged cells trigger the arachidonic acid cascade, which releases prostaglandins and leukotrienes that signal skin resident mastocytes to release histamine and tumor necrosis factor (TNF). These chemical mediators provide further sustenance to the inflammatory process.[3] Following these kind of processes, the skin can manifest conditions ranging from simple dryness to severe erythema and scaling, frequently accompanied by edema, pruritis, and various degrees of discomfort.

Eczema is a term referring to a wide range of skin inflammatory conditions, originating from many causes and including atopic eczema and contact dermatitis. Dandruff is a dry or greasy scaling of the scalp caused by a form of eczema known as seborrhoeic dermatitis. In subjects suffering from dandruff there is a marked decrease in skin lipid levels, with a consequent loss of the epidermal water barrier.

Acne is an altered or inflammatory state of hair follicles and associated sebaceous glands, involving the formation of a plug of keratin and sebum (a microcomedo), which can grow to form an open comedo (blackhead) or a closed comedo (whitehead). Such a condition can be worsened by the commensual bacterium *Propionibacterium acnes*, thus producing inflammatory lesions such as papules, pustules, or nodules.

Psoriasis is a disorder characterized by red scaly patches developing to variable extensions on the skin, mainly at the elbows and knees. Patches are due to inflamed tissue and excessive proliferation of keratinocytes in the epidermis. Psoriasis is also viewed as an immune-mediated disorder, since excessive keratinocyte growth would be caused by abnormal activity of T cells that migrate to the dermis and release cytokines like TNF-α, causing inflammation and rapid keratinocyte growth. However, the role of the immune system is not fully understood, since while immunodepressant therapies generally improve psoriasis, HIV-affected individuals are more likely to contract this disorder despite their immunodepressed state.

The skin may become affected by various microbial infections; fungal infections, such as athlete's foot and ringworm; and parasites, like scabies. Two common types of skin cancer are basal and squamous cell carcinoma. Basal cell carcinoma can locally produce severe damage to skin tissue but is unlikely to form metastasis. Malignant melanoma is another kind of skin cancer, which originates from neoplastic transformation of melanocytes and is responsible for the greater number of skin cancer–related deaths. The risk of these tumors is considerably increased by exposure to ultraviolet radiation. More rare types of skin tumors include Kaposi's sarcoma, which is caused by the infection of human herpesvirus 8 and produces papules on the skin and on internal surfaces.

Vitiligo is a chronic disease involving loss of skin pigmentation due to melanocyte dysfunction or death, and resulting in the formation of pale patches. It is thought to depend on genetic, autoimmune, and environmental causes. Urticaria is characterized by the appearance on the skin of wheals of various size and shape. These skin eruptions are caused by allergic reactions, but can also have nonallergic causes. Wheals are due to leakage of fluid from blood capillaries, forming edema, elicited by histamine and other mediators of inflammation. Rosacea is a dermatosis with various subtypes, but is essentially characterized by facial flushing or permanent erythema, which can progress to telangiectasia, or even form papules and pustules. Couperose is a mild condition, consisting of facial redness due to capillary vasodilatation, which in some cases can degenerate into rosacea.

Cellulite is a degenerative skin condition that may occur in both sexes but is much more common in women. The insurgence of cellulite is mainly due to a growth and expansion of cutaneous adipocytes that produce bulgings or deformations of the upper skin layer, thus giving rise to typical unaesthetisms like orange peel skin. This occurs more frequently in women, since the lower limbs, abdomen, and pelvic region tend to accumulate fat after puberty. Conversely, in men there is usually less fat on the thighs, while the outer skin is thicker and hence less prone to bulging. The causes of cellulite are poorly understood. Hormonal changes are clearly involved, mainly concerning estradiol, but also insulin, catecholamines, thyroid hormones, and prolactin. Other factors may include disorders of water metabolism, alterations of the connective tissue, and venous insufficiency.

Baldness is generally related to hair loss, and the head is the body region where this condition is most conspicuous. Different forms of baldness can be observed, ranging from androgenic alopecia and alopecia areata, involving a partial loss of head hair, to alopecia totalis and universalis, involving the loss of all hairs from the head or from the entire body, respectively. Androgenic alopecia occurs more frequently in men and is linked to high levels of the enzyme 5-α-reductase, which converts testosterone to the more powerful androgen dehydrotestosterone (DHT). An increase in DHT levels in the scalp leads to follicle degeneration and hair loss. Sex hormone binding globulin is a protein that binds testosterone and prevents its conversion to DHT. This protein is downregulated by insulin, and therefore, an increase of insulin levels in the metabolic syndrome can also lead to baldness.

Alopecia areata, or spot baldness, is an autoimmune disorder affecting hair follicles, and involves the loss of hair from more or less extended regions of the body, mainly the head. This syndrome starts to appear with small bald patches of rounded shape. Thereafter, hair may grow back or a greater number of patches may form and the syndrome can progress to alopecia totalis, or more rarely to alopecia universalis.

Skin aging is a degenerative process affecting all skin tissues that can be linked to the general senescence of the body (intrinsic or chronoaging), or derive from an accumulation of tissue damage induced by external causes, mainly sun irradiation but also smoking (extrinsic or photoaging). Skin aging is characterized by a loss of skin elasticity, reduction of local vascularization, and the appearance of conspicuous lines and wrinkles on the skin surface. Both intrinsic and extrinsic aging involve a deterioration of the skin matrix, with a lower deposition or faster degradation of

collagen, and a loss of the elastic properties of elastin. A slower renewal of cell layers in the epidermis also occurs. Loss of underlying fat, skin thinning and drying, and hair whitening and loss are other signs of intrinsic skin aging. According to a free radical theory of aging, a significant role in senescence would be played by increased free radical production that would lead to an unbalance between cell oxidative processes and antioxidant defense. This would cause the release of inflammatory cytokines and the upregulation of matrix metalloproteinases, thus leading to an excessive breakdown of collagen. Such a degeneration of the extracellular matrix would be related to the formation of wrinkles.

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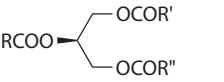
2 Botanical Compounds and Their Dermatologic and Cosmetic Uses

Herbal drugs traditionally used in medicine and skin care consist of herbs and spices from higher plants, thalli from lower botanical organisms, microbial biomasses, and the various extracts that can be obtained from these sources. These products generally contain complex mixtures of chemical compounds, including both organic and inorganic components such as mineral salts. In some cases, the biological properties of herbs are due to one or a few chemical principles, but in other cases these properties are due to the synergistic actions of many compounds of very different chemical nature. The possibility of obtaining specific therapeutic effects starting from a complex mixture of natural compounds is fundamental in very ancient herbalistic and medical practices, such as Chinese traditional medicine and Ayurveda, and is currently considered a key element of modern herbalism and skin care.[28,34] This kind of approach is also sometimes opposed to the one-drug-one-target paradigm that is often applied in the pharmaceutical field.

The complex of principles deriving from the metabolism of herbal source organisms can be divided into major classes according to their chemical composition and structure.[32] In general, all classes of organic compounds find some use in skin care; however, some of them, like polyphenols, flavonoids, saponins or other phytosterols, fatty acids, and waxes, show the highest variety of relevant biological properties in dermatology and skin care.

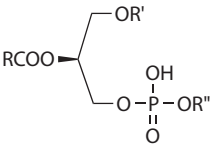
LIPIDS

Lipids are highly hydrogenated, lipophilic organic compounds, with low or null solubility in water. Simple lipids are fatty acids, alcohols, or aldehydes, linked to a medium to long saturated or unsaturated hydrocarbon chain. Complex lipids are esters of glycerol with fatty acids, like triglycerides, or of fatty acids with fatty alcohols, like waxes. Nonfatty moieties, such as phosphates, amino acids, or sugars, can also be present in complex lipids (phospholipids, ceramides, glycolipids). Various plants yield lipid materials in liquid (oils) or solid form (butters), depending on the relative amount of saturated and unsaturated fatty acids. Unsaturated fatty acids decrease the viscosity of lipids and are more abundant in oils.[2] Oils are also named fixed oils, as opposed to volatile essential oils, which are also common in plants and are generally secreted by specialized glands. Fixed oils are prevalently extracted from seeds, where they represent a reserve of energy for the developing embryo.



R = R' = R'" = satured or unsatured fatty acid

triacylglycerol



R' = alkyl or acyl chain
R" = choline, serine, inositol

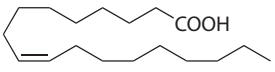
a phospholipid

Fats can be divided into a saponifiable and a nonsaponifiable fraction. The former consists of compounds like triacylglycerols, phospholipids, glycolipids, sphingolipids, and waxes that can be hydrolyzed under basic conditions, such as in the process of soap production. The nonsaponifiable fraction can be a very complex mixture of nonesterified, simple lipids, whose main component is often a sterol. The properties of oils derive from the saponifiable fraction, depending on the abundance of a particular fatty acid or from a well-calibrated mixture of different fatty acids. However, in some cases the properties of nonsaponifiable compounds can be of equal or prevalent importance.

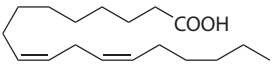
In cosmetics and toiletries, vegetable oils are used in detergents, creams, lotions, ointments, and makeup. They act as simple emulsifiers but also produce a variegate set of biological effects, including skin moisturizing, smoothing and lubrication, antieczema, anti-inflammation and arthritis, soothing of sunburning, and the healing of wounds, ulcers, and burns.[23,39] Fatty acids, tryglicerides, and glycerol are used as emollient and hydrating components. These functions depend primarily on the physical properties of these compounds, which can easily penetrate the lipophilic fraction of the skin and provide sustenance to the waterproof barrier. Such a function is particularly useful, or essential, if the skin is affected by irritative or inflammatory processes. However, the biological actions of fatty acids, particularly of polyunsaturated fatty acids (PUFAs), also depend on a deeper interaction with the physiological mechanisms of skin cells.

PUFAs are divided in ω-3, ω-6, and ω-9 fatty acids, depending on the position of the double bond closest to the noncarboxylic end. Some of them are termed essential fatty acids (EFAs), since they cannot be produced by the human organism starting from non-EFA precursors. The ω-3 α-linolenic, and ω-6 linoleic acid, having 18 carbon atoms, are extremely important since they are precursors of other essential PUFAs, like the ω-3 eicosapentaenoic and docosahexaenoic acids, and the ω-6 γ-linolenic and arachidonic acids. EFAs are abundant, for example, in the oil extracted from borage (*Borago officinalis*) or from Inca Inchi seeds (*Plukenetia volubilis*). Ricinoleic acid, the main component of castor oil (*Ricinus communis*), is a ω-9 used for skin dryness, acne, and baldness.

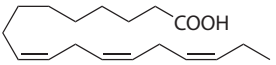
Arachidonic acid, a component of biological membranes, plays a central physiological role as a precursor of signal molecules. Arachidonic acid is released from membrane phospholipids by the enzyme phospholipase A2, and is converted to leukotrienes by 5-lipoxygenase or to prostaglandins by cycloxygenase. Leukotrienes are promoters of



oleic acid (ω-9)



linoleic acid (ω-6)



α-linolenic acid (ω-3)

inflammatory processes and asthma, while prostaglandins are also involved in inflammation, but have many other roles, such as pain neuron sensitization, blood vessel relaxation and constriction, and the control of cell growth. The basic roles played by PUFAs in the cellular metabolism also make these compounds important elements in cosmetics, due to the different regulatory effects that they exert on skin cells, particularly on cell membrane turnover, cell growth, and tissue repair processes. The importance of EFAs is dramatically highlighted by the noxious effects caused by their deficiency. For instance, a shortage of linoleic acid, the main ω-6 in vegetable oils, can produce eczema, hair loss, reduced wound healing, and circulatory defects.

Cocoa butter extracted from the seeds of the cocoa plant (*Theobroma cacao*), and mango kernel oil (*Mangifera indica*), contains high amounts of the monounsaturated oleic acid, and also the saturated palmitic and stearic acids, both present as triglycerides and as free fatty acids. These fats are widely used in cosmetics as emollients, moisturizers, and in the treatment of dry skin. Sunflower oil (*Helianthus annus*) is rich in polyunsaturated linoleic acid and is particularly useful for scaly lesions due to essential fatty acid deficiency, or for psoriasis and burns.

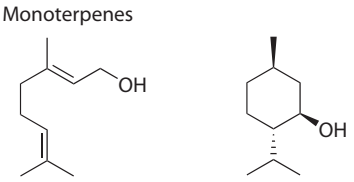
The liquid wax derived from the seeds of jojoba plants (*Simmondsia chinensis*) is widely used in skin treatments due to its sebum affinity, allowing a high penetrability, and deliverability to deep skin layers of nonsaponifiable steroid components acting as anti-inflammatory agents. It exerts various actions on the skin, including hydration, antioxidant and anti-inflammatory effects, and antibacterial and antiparasitic actions. Its clinical uses include extrinsic skin aging and hair strengthening.

Ceramides are a class of sphingolipids having a sphingoid base linked through an amidic group to a fatty acid. These lipids are major and essential components of the waterproof barrier of the epidermis, and a high portion of them contain linoleic acyl esters. Ceramides from botanical sources can therefore be extremely useful in skin rehydration treatments due to their close affinity with the physiological molecules, which accomplish this task.

TERPENOIDS

Terpenoids are present in large abundance in botanical organisms.[20] They are the largest group of natural products, and are also referred to as isoprenoids, since

they derive from the assembly of 2-methylbutane residues, also referred to as isoprene units, $(C_5)_n$. Many of these compounds are multicyclic structures differing from one another in the presence of different basic carbon skeletons and functional groups. In nature, terpenes occur predominantly as hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids, and esters. Depending on the number of 2-methylbutane subunits, terpenes are classified as mono- (2 isoprene units), sesqui- (3), di- (4), ses- (5), tri- (6), tetra- (8), and polyterpenes (>8).



Essential oils, also known as volatile oils, are mixtures of hydrophobic aroma compounds, most of which are terpenoids. The constituents of essential oils are present as monoterpenoids and sesquiterpenoids, including various cyclic and acyclic forms, such as hydrocarbons, alcohols, aldehydes, ketones, esters, ethers, peroxydes, phenols, and epoxides. They are produced by secretory cells of various plant organs, and are stored in plant anatomical cavities or in glandular trichomes. Essential oils are responsible for the characteristic flavors that distinguish different plants or their parts (flowers, fruits, leaves, etc.). They are mainly extracted by steam distillation or supercritical fluid extraction.

These oils are very complex natural mixtures, generally containing about 20–60 volatile components characterized by low molecular weight. They can be divided into a major group, consisting of terpenes and terpenoids, and a minor one, composed of aromatic and aliphatic constituents. Typical plants containing essential oils are citrus fruits, conifers, mint and other Labiatae, and Myrtaceae (*Eucalyptus* sp.).

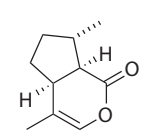
Essential oils show a certain cytotoxicity due to their high lipophilic nature, which can induce damage to the cell membranes of both prokaryotes and eukaryotes. In the sanitary field, the cytotoxicity of essential oils can be used for personal hygiene, or for the preservation of crops and food stocks. Some essential oils also contain photoactive compounds that worsen the damage produced to skin by sun irradiation. Essential oils are also used in the cosmetic industry as preservatives, in the formulation of perfumes and hair care products, or to provide conditioning and a pleasant aroma and shine.[3] These oils can also be used as cooling agents, giving a refreshing feeling to the skin.

A very specific use of essential oils concerns aromatherapy, a kind of complementary medicine used to cure both physical and psychological disturbances.[42] In aromatherapy essential oils can be vaporized or administered through a massage onto the skin. In this latter case, the essential oil must be diluted in a carrier, such as grapeseed or sweet almond oil. A widely used essential oil is the tea tree oil, extracted from *Melaleuca alternifolia*, not to be confused with the tea plant, *Camellia sinensis*. The tea tree oil has long been regarded as a useful topical antiseptic agent, and is extensively used in cosmetics, hair preparations, and skin creams.

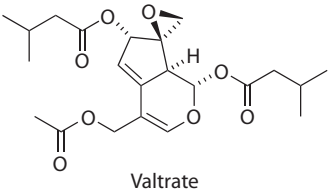
Iridoids are monoterpenoids deriving from the oxidation and cyclization of geraniol, a monoterpenoid alcohol occurring in many essential oils.[11] Their structures typically consist of two condensed rings, a cyclopentane, and a six-membered oxygen heterocycle. Most iridoids are glycosides, and the sugar part is generally a glucose unit linked to the C1 or C11 position of the aglycone, which is the reactive part of the molecule. Iridoids are bitter compounds showing laxative, anti-inflammatory, neuroprotective, and hepatoprotective properties.[46] A few examples include harpagoside, a major component of Devil's claw (*Harpagophytum procumbens*), frequently used for rheumatologic conditions, and aucubin, used in allergic inflammations.

Nonglycosidic iridoids are a heterogeneous group of cyclopentane monoterperpenes. Nepetalactone from the catnip (*Nepeta cataria*) is used as an insect repellent but is also known for its property of rendering cats euphorically giddy. Valepotriates from the valerian (*Valeriana officinalis*) are presumed to play a role in the anxiolytic effects showed by this plant. Secoiridoids derive from the oxidative opening of the cyclopentane ring. Gentiopicroside and amarogentin characterize gentian plants (*Gentiana* ssp.) and are used as bitters and tonics, and as appetite and gastric stimulants.

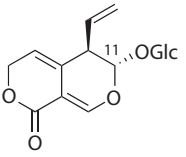
Iridoids, secoiridoids



Nepetalactone



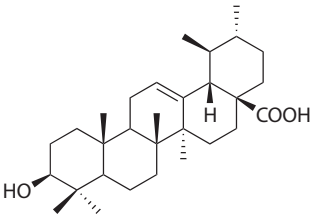
Valtrate



Gentiopicroside

Sesquiterpenes are derivatives of farnesyl pyrophosphate and may have a linear, monocyclic, or bicyclic structure. They constitute a widely differentiated group, chiefly occurring in Labiatae, Myrtaceae, Pinaceae, Rutaceae, Umbelliferae, and Malvaceae. A particular class is represented by sesquiterpene lactones, frequently present in Compositae. The dimeric sesquiterpene lactone absinthin is a component of absinthe, a bitter spirit drink derived from the wormwood plant (*Artemisia absinthium*). This product can be used as an antiseptic for skin diseases such as acne, herpes, and scabies.

Triterpenes are particularly useful compounds for dermatological conditions. Ursolic acid, for example, widely diffused in many plants, is a pentacyclic triterpene used in cosmetic preparations for skin revitalization. This compound inhibits elastase and other enzymes, such as metalloproteinase 9, which are activated by UV rays and are involved in skin aging.

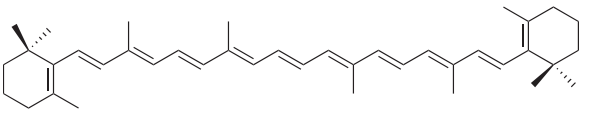


Ursolic acid, a triterpene

Saponins are glycosylated triterpenoids, forming soaplike foam when shaken in aqueous solutions.[7] The lipophilic aglycones of saponins have a triterpene or a steroidal skeleton. Some of these frameworks incorporate nitrogen, thus conferring on saponins the chemical and pharmacological features of alkaloids. Typical sources of saponins are peas and soybeans, but many other plants contain them. Saponins have been traditionally used in the treatments of cancer, cardiovascular and gastric diseases, rheumatism, and arthritis,[17] and these properties have been confirmed by a very wide spectrum of reported biological activities, including cytotoxic, antitumor, antifungal, immunoregulatory, hypoglycemic, and cardiovascular properties.

Saponins are known to exert on the skin antioxidant effects; protection against damage from UV-B; antiaging effects, due to the inhibition of extracellular matrix degradation; and anti-irritation due to their anti-inflammatory action. The antiseptic activity is particularly useful for the treatment of acne. Saponins also strengthen dermal capillaries, thus alleviating the symptoms of couperose and cellulite. The steroid saponins ginsenosides, which are the main active constituent of the root of the medicinal plant ginseng (*Panax ginseng*), are used in dermocosmesis for their skin tonifying and antiaging properties. Other terpenoids of great importance for skin care practices are carotenoids, retinoids, and the tocopherols-tocotrienols family. These compounds are largely used as antioxidants, since they are effective in quenching oxidative reactions and in retarding radical propagation. Their role in skin care is particularly important because, owing to their lipophilic nature, their action is directed to protect cellular membranes from processes of lipid peroxidation. Such a role is of primary importance for the maintenance of the integrity of epithelia, and in particular of the epidermis, which is continuously threatened by external pro-oxidant agents, including ultraviolet radiation, drugs, and air pollutants. Besides external oxidants, the skin has also to contrast endogenous reactive oxygen species and other radicals produced by cellular metabolism.

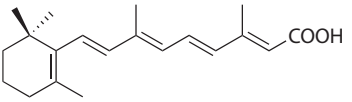
Carotenoids are plant pigments including carotenes and xanthophylls,[14] and β-carotene is the most diffused one. In the wall of the small intestine and in the skin it can be broken down to retinal, a variant of vitamin A, by the enzyme β-carotene dioxygenase.



β-carotene

Natural retinoids include vitamin A (all-*trans* retinol) and its metabolites, such as all-*trans* retinoic acid, also known as tretinoin.[18] These compounds perform many important functions in the human body, including their essential role for vision in the retina, the regulation of cell proliferation and differentiation in the embryo and in various tissues, the development and growth of bone, the activity of the immune system, and the activation of tumor suppressor genes. Retinoids also have the ability to modulate epithelial growth, and their action assumes then a particular importance in the renewal of the epidermal layer. Tretinoin is the most effective drug in the treatment of acne, since it is able to reduce the secretion of sebaceous glands, thereby reducing

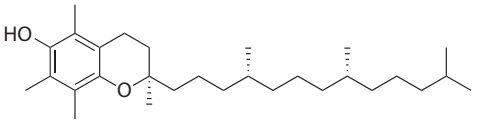
bacterial infection in the gland ducts and at the skin surface. Tretinoin can also be used to reduce inflammation, since it inhibits the chemotatic responses of monocytes and neutrophils, and is particularly indicated for the treatment of photoaging.[21] Clinical studies have also demonstrated beneficial effects of retinoids on skin diseases such as psoriasis, ichthyoses, keratodermas, melanoma, and nonmelanoma skin cancers.



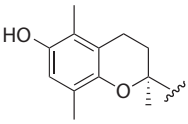
tretinoin

Retinoids can induce gene transcription in target cells through binding to specific nuclear receptors belonging to the steroid/thyroid superfamily of transcription factors. Retinoic acid receptors (RARs) bind tretinoin and its stereoisomer 9-*cis* retinoic acid, while retinoid X receptors (RXRs) bind exclusively 9-*cis* retinoic acid. Both kinds of receptors are present in human skin. A specific marker of retinoid action in the skin is the induction of the mRNA encoding for the retinoic acid binding protein (CRABP).

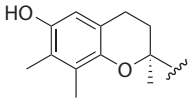
Natural tocopherols and tocotrienols constitute a family of isomers that are collectively referred to as vitamin E.[5,26] Tocopherols are generally present in common vegetable oils, while tocotrienols are main components of cereal grains and palm oil. These compounds belong to the isoprenoid class, like carotenoids, and in particular they are unique examples of linear diterpenes (phytyl derivatives).



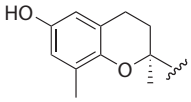
α-tocopherol



β-tocopherol



γ-tocopherol



δ-tocopherol

The levels of cutaneous vitamin E depend on its oral intake or topical delivery. Vitamin E is generally considered an antioxidant acting in the lipid bilayer of cellular membranes and preventing lipid peroxidation. It is largely used in skin care products, but since it is not a pharmaceutical drug, evidence of therapeutic properties is poor due to the scarcity of double-blind, placebo-controlled clinical trials. However, a certain body of evidence, collected *in vitro* or on animal models, suggests that vitamin E could be beneficial to a variety of altered skin conditions, including erythema, wrinkling and sagging, tumor incidence, and photodamage from UV irradiation.[43] Topical administration of vitamin E may not be sufficient to sustain skin's antioxidant defenses, and current clinical research focuses on systemic delivery to the skin. It has been recently shown that sebum contains high amounts

of α-tocopherol and that sebaceous glands provide a relevant physiological delivery pathway in specific regions, such as facial skin.

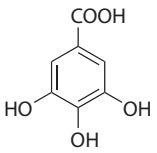
Various data indicate that tocopherols and tocotrienols can also modulate the activity of membrane-dependent enzymes, such as diacylglycerol kinase, PI3-kinase, and NADPH oxidase. This kind of evidence suggests that their action may depend on a direct or indirect interaction with membrane-resident enzymes. Some research suggests that tocotrienols are more potent antioxidants than tocopherols, due to the presence of the unsaturated tail that would allow them to penetrate membrane lipid layers more efficiently, thus making them potentially more useful for skin care products.

Natural polyterpenoids are totally hydrocarbons and are the constituents of rubber and rubberlike substances. Natural rubber is an elastic hydrocarbon polymer, formed by *cis*-1,4-polyisoprene molecules, which is extracted from the rubber tree (*Hevea brasiliensis*). Another largely exploited material is the latex of gutta-percha (*Palaquium gutta*), consisting of *trans*-1,4-polyisoprene. Gutta-percha latex has been used as a vehicle for drug application to the skin, or as a tissue for coating medical dressing.

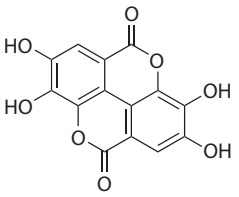
PHENOLS AND RELATED COMPOUNDS

Phenolics are characterized by having at least one aromatic ring bearing one or more hydroxyl groups. These compounds occur very frequently as secondary metabolites of botanical organisms and bacteria. Phenolics range from simple, low-molecular-weight, single aromatic-ringed compounds to large and complex macromolecules.

A main biosynthetic pathway of their formation is through shikimic acid, an intermediate metabolite deriving its name from the Japanese flower shikimi (*Illicium anisatum*), from which it was first isolated. A structural analogue and chief derivative of shikimic acid is gallic acid, consisting of a benzene ring bearing a carboxylic and three hydroxylic functionalities. Gallic acid dimerizes to give ellagic acid, and both compounds polymerize to give hydrolyzable tannins, which also bear glucose esters. Gallotannins and ellagitannins are commonly present in various trees, such as poplars, birches, oaks, and pines.



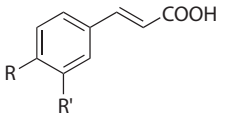
Gallic acid



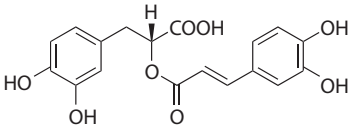
Ellagic acid

Aromatic amino acids derived from shikimic acid, such as phenylalanine, are biosynthetically prone to oxidative deamination to give a class of phenolic compounds known as phenylpropanoids, characterized by a C6 (aromatic)-C3 basic structure. Of mentioning are a few examples of widespread phenylpropanoids. Cinnamic acid is a main phenylpropanoid from the shikimic acid–phenylalanine pathway that, together with its derivatives, is particularly abundant in the Peru balm extracted from legume trees of the genus *Myroxylon*. These compounds are used as main components in

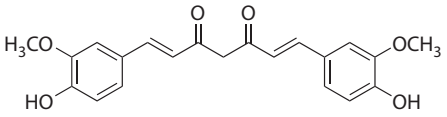
flavors, perfumes, and pharmaceuticals, and are also used as sunscreen agents to reduce skin damage by filtering UV-A and UV-B. Caffeic acid and its dimer, rosmarinic acid, common constituents of rosemary (*Rosmarinum officinalis*), have many dermocosmetic uses, in particular against baldness. The Indian curry spice turmeric is the dried rhizome of the curcuma plant (*Curcuma longa*) containing yellow curcuminoids. Curcumin (diferuloylmethane), the primary of these compounds, derives from phenylpropanoid ferulic acid. It acts as an antibacterial, antiparasitic, anti-HIV, cicatrizing, antitumor, antioxidant, and anti-inflammatory agent. This drug has been used for many skin problems, including eczema, psoriasis, acne, wound and burn healing, and aging.



R = R' = H, Cinnamic acid
R = R' = OH, Caffeic acid
R = OH, R' = OCH_3, Ferulic acid

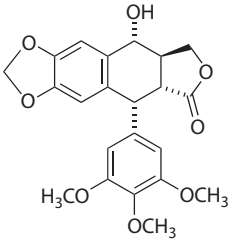


Rosmarinic acid



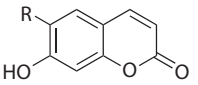
Curcumin

Phenylpropanoid polymerization gives rise to lignin, a main component of wood, while the fusion of two units produces lignans. Lignans are common in the plant kingdom, and generally show antimicrobic or cytostatic properties. Plant lignans can be converted into the mammalian lignans enterodiol and enterolactone through the activity of bacteria present in the colon. These lignans are potent antioxidants and can reduce cardiovascular risk.[41] In addition, they act as pseudoestrogens, thus relieving menopausal symptoms, and inhibit the enzyme 5α-reductase, thus protecting against androgenic alopecia and prostate cancer. Secoisolariciresinol diglucoside (SDG) is a main lignan from flaxseed (*Linum usitatissimum*), which has been claimed to provide benefit to hair loss and acne.[35] Podophyllotoxin is a toxic lactone of the lignan podophyllic acid that is commonly extracted from mayapple (*Podophyllum peltatum*). It is used as a pharmacological base for anticancer drugs, but can also be applied topically as a treatment of anogenital warts.



Podophyllotoxin

Coumarins are phenylpropanoids deriving from the cyclization of *ortho*-hydroxycinnamic acid. The basic coumarin structure gives rise to a wide family of compounds through hydroxylation (hydroxycoumarins), or condensation with a furan (furanocoumarins) or a pyran ring (pyranocoumarins). These compounds occur in plants in either free or glycosylated forms. Umbelliferone (7-hydroxycoumarin), esculetin (6,7-dihydroxycoumarin), and scopoletin (7-hydroxy-6-methoxycoumarin) are widespread coumarins used in cosmetics as fragrances and skin-whitening products.



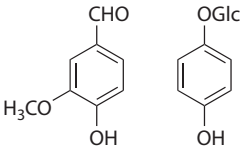
R = H, umbelliferone
R = OH, esculetin
R = OCH_3, scopoletin

Phenolics can also biosynthetically derive from acetyl coenzyme A, whose multiple condensation leads to polyketides and then, through cyclization, to highly oxygenated polycyclic structures, like chromones, depsides, xanthones, quinines, and tetracyclins. Mixed pathways can also occur, resulting in the synthesis of important active compounds, such as flavonoids.

Due to their high antioxidant capabilities, plant phenolic compounds have attracted a significant pharmaceutical interest as chemopreventive agents against the insurgence of tumors, and in particular of skin cancer induced by photocarcinogenesis.[1,22,29] However, the notable chemical diversity of this class of compounds entails a differentiated panel of dermatologic properties.

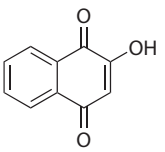
Simple phenolic compounds frequently bear diverse functional groups: hydroxyls, aldehydes, carboxyls, and other substituents. Hydroxyl groups are also frequently glycosylated. These compounds have in general an antiseptic action and can be used for skin infections like acne. However, they also show various other properties that can be exploited in skin care. Salicylic acid, a simple phenolic acid extracted from willow trees (*Salix*), is used as a nonirritative exfoliant in cosmetic treatments of fine lines and wrinkles. Vanillin is extracted from the beans of the vanilla orchid vine (*Vanilla planifolia*), and is one of the most important aromatic flavors used in foods and cosmetics. Arbutin is a hydroquinone glucoside present in bearberry plants in the genus *Arctostaphylos*, which can reduce the formation of melanin via tyrosinase inhibition and is used to contrast skin hyperpigmentations.[49] The naphthoquinone lawsone, an orange dye present in the leaves of the henna plant (*Lawsonia inermis*), has the ability to bind keratin and can therefore be used for skin and hair staining, while it is also known as a hair growth stimulant. Another naphthoquinone used in dermatological products is the lichen compound naphthazarin.

Anthranoids are polyphenolic aromatic compounds formally derived from the tricyclic structure of anthracene.[9] They are widely distributed in nature, and are particularly prominent in higher plants and fungi. Anthraquinones have ketone functionalities in the central ring and are mostly known for their purgative properties, deriving from an irritative action on the gut wall. The main pharmaceutical compounds are emodins from the rhubarb (*Rheum officinale*) and from aloe (*Aloe vera*),

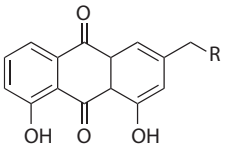


Vanillin

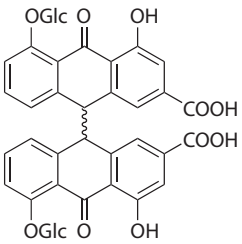
Arbutin



Lawsone



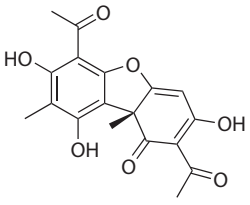
R = H, chrysophanol
R = OH, aloe-emodin



Sennosides

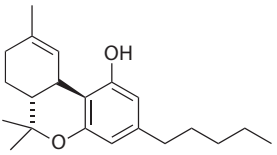
frangulins from the buckthorns (*Rhamnus* ssp.), the glucosides cascarosides from cascara (*Rhamnus purshiana*), and the dianthrone glycosides sennosides from senna (*Cassia acutifolia*).[4] Diverse anthraquinones also show antimicrobial and anticancer activities. An anthranoid of dermatological relevance is the antipsoriatic anthrone chrysarobin, a reduced form of chrysophanol extracted from the drug Araroba, also known as Goa powder, extracted from the aguiar tree (*Andira araroba*).

Depsides are formed by esterification between a phenol structure and a benzoic acid, and in depsidones an ether linkage realizes polycyclic structures. Depsides and depsidones are typical of lichens, organisms consisting of a symbiosis between fungi and algae.[36] A main property of depsides is the inhibition of 5-lipoxygenase, involving a reduction of the synthesis of leukotrienes, the chemical mediators of inflammation in animal tissues. The prototype dibenzofuran usnic acid and its derivatives, present in various lichen species, are well-known antimicrobial, antiproliferative, and potentially also antipsoriatic agents.



Usnic acid

Cannabinoids are a group of terpenophenolic compounds occurring in cannabis plants (*Cannabis indica*) and having psychoactive properties. The major of these compounds is δ-9-tetrahydrocannabinol. Cannabinoids exert their actions by binding to cannabinoid receptors, belonging to the G protein–coupled receptor class, which are expressed in the nervous system and physiologically respond to endocannabinoid neurotransmitters.[10] Besides various pharmaceutical uses, cannabinoids are also the psychoactive ingredients of marijuana and hashish, two drugs commonly leading to abuse and addiction.[15] Cannabinoid agonists are known to attenuate histamine responses in human skin.



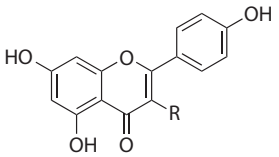
Tetrahydrocannabinol

FLAVONOIDS

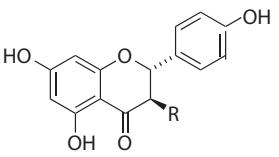
Flavonoids are polyphenolic compounds, typical of higher plants, which for their extreme diversification and biological properties deserve a specific description. Flavonoids are very common in plants, where they can be found in fruits, seeds, stems, and flowers. A total of about 5,000 different structures have been catalogued so far. These compounds are frequently responsible for plant colors and act as a screen against possible damages induced to plant tissue by sunlight. The red color of autumn foliage is mostly due to the glycosylated anthocyanin cyanidin 3-O-glucoside. Flavonoids are also abundant in herbs and spices, as well as in popular plant-derived beverages such as tea and red wine, and are regular components of fruits and vegetables consumed in the human diet.

From a chemical point of view, flavonoids are phenylbenzopyranes (phenylchromanes) comprising 15 carbons, with two aromatic rings connected by a three-carbon bridge. Such a structure is made up from a phenolic moiety, substituted with one or more hydroxy or methoxy groups, linked to a cinnamic acid moiety, which can also be substituted with one or more hydroxy or methoxy groups. Hydroxy groups can be frequently glycosylated. According to the different oxidation patterns of the pyrane ring, flavonoids are divided in flavones, flavanones, flavanols and flavonols, anthocyanidins, and chalcones.[47] Isoflavonoids are another subclass where the phenyl group is present at the 3-position of the pyrane ring, instead of the 2-position of flavonoids.

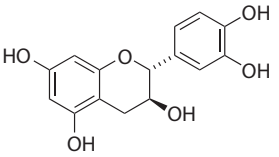
The most frequent and abundant flavonoids and their representative plant sources are the flavones apigenin (apple), kaempferol (broccoli), luteolin (celery), and quercetin (lettuce, olives, onions, and parsley); the flavanones fisetin, hesperetin (citrus), and naringin (grapefruit); the catechins catechin (red wine), epicatechin, and epigallocatechin gallate (green tea); and the anthocyanins cyanidin (berries), delphinidin (cherries), malvidin, peonidin (red grapes), and petunidin (fruit peels with dark pigments). Proanthocyanidins, also known as condensed tannins, are polymeric or oligomeric polyphenols, composed of catechin units, which can be found in many plants and fruits, including apples, cinnamon, grapes, cocoa, bilberry, cranberry, black currant, and tea.



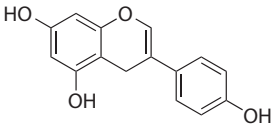
R = H, apigenin (flavone)
R = OH, kaempferol (flavonol)



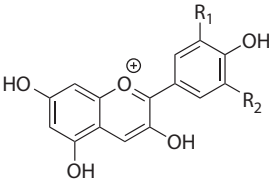
R = H, naringin (flavanone)
R = OH (flavanonol)



(+)-catechin



genistein (isoflavonoid)



$R_1 = R_2 = H$, pelargonidin
$R_1 = OH$, $R_2 = H$, cyanidin
$R_1 = R_2 = OH$, delphinidin

Flavonoids share the chromane ring with tocopherols, and similarly to these latter show strong antioxidant activity. Major mechanisms for such an effect include direct scavenging of oxygen and nitrogen free radicals; iron chelation; inhibition of oxyradical-producing enzymes, such as xanthine oxidase; and reduction of leukocyte adhesion to the blood vessel wall during tissue inflammation and reperfusion. Flavonoids also show a wide panel of clinical effects. Anticancer properties possibly derive from antioxidant, antiproliferative, and antiangiogenic effects.[33,38] Cardiovascular protection might derive from antioxidant and antithrombogenic effects and from the lowering of blood cholesterol levels. Anti-inflammatory, and possibly antiallergic, properties are probably linked to a series of mechanisms, including reduced activation of complement and immobilization of leukocytes, coupled to inhibition of myeloperoxidase, cycloxygenase, and 5-lipoxygenase. Reduction of ischemia/reperfusion injury may also derive from these effects, as well as from the neutralization of nitric oxide.

Another well-known property of flavonoids, also tested in clinical trials, is the relief of symptoms from chronic venous diseases, such as leg heaviness, cramps, pain, and edema. These compounds are therefore indicated in the treatment of fluid retentions, including cellulite. The mechanism of action of this effect has not been completely clarified, but a possible role could be played by the inhibition of metalloproteinases, which degrade extracellular matrix components and may induce alterations of vessel walls under pathological conditions.

Some flavonoids show a remarkable antiviral effect, due to the inhibition of key viral enzymes, such as reverse transcriptase and integrase. For instance, apigenin shows a manifest activity against herpes viruses, while it also acts as an anticancer. Other flavonoid activities that are important in cosmetic practices concern skin aging.[25] Flavonoids like kaempferol can retard skin aging by contrasting enzymes that degrade the extracellular matrix, such as collagenases, elastases, and hyaluronidases. The isoflavones genistein and daidzein, particularly abundant in soybeans

(*Glycine max*), are phenolic phytoestrogens that in the human body mimic the activity of estradiol. Phytoestrogens are used to overcome menopausal disorders such as osteoporosis and hot flashes, but they also improve the quality of the skin and delay the effects of aging. Equol, an active daidzein metabolite, protects the immune system from photosuppression caused by UV, and can also be clinically used for a series of skin altered states, including psoriasis, eczema, acne, and other skin eruptions. Finally, anthocyanosides from the bilberry (*Vaccinium myrtillus*) are famous for their ability to improve night vision, an effect that has been correlated to an increase in rhodopsin, a pigment involved in photoreception in the rods of the retina.

ALKALOIDS

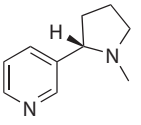
Alkaloids are a very heterogeneous group of natural organic bases, which are biosynthesized starting from amino acids.[16,24] In typical alkaloids a basic nitrogen is inserted in a heterocyclic ring, while nontypical alkaloids can be simple amines, or have exocyclic or nonbasic nitrogen atoms. These compounds are produced by various organisms, including plants, fungi, and bacteria, but also by a few animals.[40] They are generally classified by their common precursors, and can be divided into monocyclic (pyrrolidinic, pyrrolic, imidazolic, pirimidinic), 6-carbon bicyclic (quinolinic, isoquinolinic, quinolizidinic), and bicyclic with one or two 5-carbon rings (indolic, pyrrholizidinic, tropanic). The group of alkaloids is made more complex by the existence of polycyclic structures or of other frameworks deriving from the fusion of an amino acid derivative with other molecules, frequently monoterpenes.

Alkaloids are secondary metabolites playing a role of defense against predators and parasites in their source organisms. However, they also have several biological properties, particularly a dose-dependent toxicity that can occur in some cases at very low doses. Some alkaloids are also known for their effects on the nervous system and for hallucinogen effects, due to a chemical structure that in some cases is very similar to that of brain neurotransmitters. Other alkaloids are also active on other excitable cells, such as cardiomyocytes.

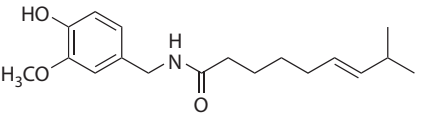
The most famous alkaloids include cocaine from the coca plant (*Erythroxylon coca*), the opioids morphine and codeine from the opium poppy (*Papaver somniferum*), atropine from the deadly nightshade (*Atropa belladonna*), nicotine from tobacco (*Nicotiana tabacum*), strychnine from the nux vomica tree (*Strychnos nux-vomica*), mescaline from the peyote cactus (*Lophophora williamsii*) and related species, and capsaicin from chili pepper plants of the genus *Capsicum*.

Vinca alkaloids from the lesser periwinkle (*Vinca minor*), such as vincristine and vinblastine, and colchicine from the autumn crocus (*Colchicum autumnale*), are potent cytostatic drugs that bind tubulin and inhibit the assembly of microtubules, thus interfering with the mitotic process. Taxol, another cytostatic compound from the Pacific yew, *Taxus brevifolia*, also acts on microtubules and interferes with mitosis, but differs from the former compounds in inhibiting microtubule disassembly. Cytostatic alkaloids can be used in cancer chemotherapy, and their use against psoriasis has also been suggested.[48] The toxicity of alkaloids can also be exploited in the treatment of skin infections.

Other important alkaloids belong to the xanthinic or purinic group. These latter include theophylline, prevalently found in tea (*Camellia sinensis*), theobromine from the cocoa plant (*Theobroma cacao*), and caffeine that is abundant in the coffee plant (*Coffea arabica*). A main property of these methylxanthines is the inhibition of the enzyme phosphodiesterase, leading to an intracellular accumulation of cyclic AMP (cAMP). In the adipose tissue, cAMP activates the enzyme lipase, thereby inducing a lipolytic action that can be exploited for reducing fat accumulation in cellulite. Caffeine can also block the destructive action of dihydrotestosterone on hair follicles, thus being helpful to combat androgenic alopecia.



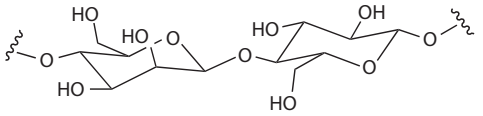
Nicotine



Capsaicin

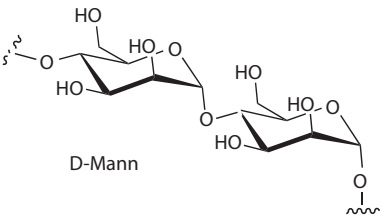
CARBOHYDRATES

Carbohydrates are highly hydroxylated compounds existing as simple units, dimers, and polymeric forms of various lengths, termed polysaccharides.[12] These compounds have long been recognized as nonspecific stimulants of the immune system, in particular activating macrophagic elements. Such an effect can be explained by the presence on the macrophage cell surface of a receptor that has a binding affinity for β-(1–3)-D-glucans, and other polysaccharides bearing α-(1–6), and α-(1–4) linkages. The major carbohydrate fraction isolated from aloe, *Aloe vera*, known as acemannan, is a potent immunoactivator and consists of a polydispersed α-1,4-linked acetylated mannan interspersed with O-acetyl groups. Other immunoactive polysaccharides are present in fungi and algae.



D-Mann D-Glc

β1 → 4-glucan



D-Mann

D-Mann

α1 → 4-mannan

Glucans are also used as film formers, humectants, and skin moisturizers, due to their capability of retaining mineral cations and thereby producing osmotic accumulation of water.[13,31] This property can be efficiently improved by combining polysaccharides and proteins, thus mimicking the properties of tissue matrix proteoglycans. A role in tissue regeneration and wound healing has also been envisaged, e.g., for β-glucan produced by *Saccharomyces* strains, which behaves like hyaluronic acid in stimulating collagen synthesis by fibroblasts.[30] Carragenans from various red algae (Rhodophyta) are used as emulsifiers in the preparation of creams, gels, pastes, and emulsions. Oat β-glucan (*Avena sativa*) is an unbranched polysaccharide that has been claimed to alleviate the signs of aging, protect against UV, activate collagen synthesis, and strengthen the hairs. A combination of β-glucan and hydrolyzed oat protein is also used to moisturize and soothe irritated skin.

Gums and mucilages are complex mixtures of polysaccharides of various viscosity, which are employed as additives in products for topical applications. However, these components also have therapeutic uses. For instance, mucilages from the fenugreek (*Trigonella foenum-graecum*) have antioxidant and emollient properties and have been used for ulcers of the oral cavity.

Among simple carbohydrates, ascorbic acid (vitamin C) is a sugar acid with pronounced antioxidant properties that can be used in antiaging cosmetics. Ascorbic acid exerts a synergistic action with tocopherol, by serving as an electron donor that restores the reduced state of this molecule and then favors its antioxidant defense role in cellular membranes.

GLYCOSIDES

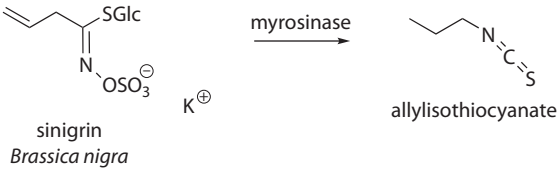
Sugars are frequently present as glycosidic moieties of terpenes, flavonoids, polyketides, and alkaloids, contributing to their overall water solubility and sometimes playing an important or essential role for their biological activities.[8] In a glycoside, a sugar (the glycone) is bound to a nonsugar portion (the aglycone). This latter is usually released from its glycosidic form by hydrolytic enzymes acting in the source organism or in a different organism, which may have assimilated the glycoside from the diet, e.g., by the bacteria of the intestinal flora. The aglycone is in many cases the active substance, but the glycosidic form is frequently essential for the expression of biological properties. Glycosides are natural pro-drugs whose pharmaceutical usefulness is related to their stability and solubility in the liquids of the human body.[6,27] This allows a proper release of the active aglycone to its reactive center. Alternatively, sugars act through binding affinity to cell wall glycoproteins, driving the active portion (the aglycone) to the site of action.

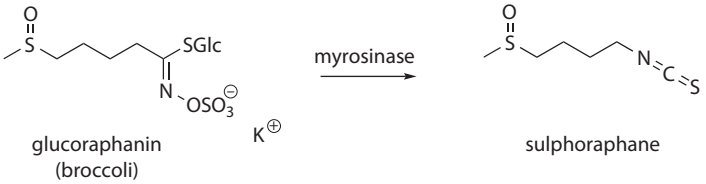
Glycosides can be classified in different ways. According to the glycone portion, it is possible to distinguish glucosides if the sugar is glucose, fructosides if it is fructose, glucuronides if it is glucuronic acid, etc. Glycosides can have one (monoglycosides) or more than one (diglycosides, etc.) sugar unit. They can also differ for the orientation (α-glycosides, β-glycosides) and chemical nature of the glycosidic bond: O-glycosides, C-glycosides, and less frequently S,N-glycosides. However, the

most useful classification for biochemical and pharmacological purposes concerns the type of aglycone.[19]

Hydroquinone glycosides, like arbutin, release hydroquinones or methyl-hydroquinones by hydrolysis. Their most relevant property is an antiseptic action on the urogenital tract due to the *in loco* release of the aglycone moiety.

S-glycosides, also known as thioglycosides or glucosinolates, are typical of Brassicaceae plants (cabbage, cauliflower, rapeseed, radish, etc.) and their allies. These compounds derive from glucose and sulfur-containing amino acids and can release thiocyanates, isothiocyanates, and nitriles, which are the active substances. They are responsible for the sharp taste of common foods and condiments, such as mustards. Extracts of maca (*Lepidium meyenii*) containing benzyl glucosinolates and benzyl isothiocyanates have been found to protect the skin of rats from UV rays.

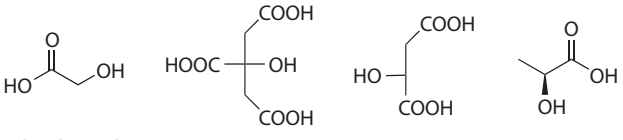




A pharmaceutically prominent group of O-glycosides is cardioactive glycosides, which are widely used for the treatment of heart failures.[37,44] Cyanogenic glycosides are nitrogen-containing O-glycosides that release hydrogen cyanide upon hydrolysis, and therefore are generally considered natural toxicants.[45]

HYDROXY ACIDS

The group of α-hydroxy acids (AHAs), also known as fruit acids, includes glycolic, citric, malic, and lactic acids. AHAs play a main role in skin care and dermatological therapy. They are principally used in the treatment of wrinkles as exfoliating agents. Their action induces a thinning effect on the stratum corneum, involving desquamation, cell renewal, and collagen synthesis with an increase in the thickness of the dermis.



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3 Herbal Cosmetic Formulations
A Fuzzy Line between Actives and Vehicles

FORMULATIONS AND SKIN PENETRATION

The practice of herbal skin treatment has very ancient origins. The earliest news about the use of medicinal plants dates back to 8000–4000 B.C. in Asia, and to 3000–2000 B.C. in the Mediterranean basin. Historical findings testify to the occurrence of cosmetics in Babylonian and Jewish societies of antiquity. The ancient Egyptians were masters of cosmetics, as evidenced by formulations described in the Smith's papyrus (1650 B.C.) and in the Eber's papyrus (ca. 1550 B.C.).[22,24,28] Cosmetics were also commonplace in ancient Greece and in the Roman Empire, both as makeup and skin care products.[12] Moreover, a number of archaeological records show that the technology of cosmetics in ancient civilizations was astonishingly similar to that of our times.

Until the beginning of the 1900s, no clear difference existed between active and inactive components in dermatological and cosmetic preparations. Later, it became possible to assign specific therapeutic effects to certain chemical substances, and the concept of vehicle, i.e., a rather inactive carrier substance, started to be developed.[34] Nowadays, formulations are mixtures of components that basically include one or more vehicles and one or more active principles. The efficacy of dermatological and cosmetic products is influenced by the type of vehicle and active principles. In general, formulations will work if the active ingredients penetrate into the epidermis. Hence, the correct selection of a suitable vehicle plays an important role during the development of a product.

Pharmaceutical preparations are aimed at obtaining a curative effect. In these cases, the role of the vehicle is primarily to allow the delivery of the active principles to the site of application. Cosmetic formulations do not contain strictly curative drugs, but their purpose is rather to help skin homeostasis and prevent degenerative processes. As we have seen, a clear boundary between the medical and cosmetic fields cannot be easily traced, while the marked tendency of cosmetic industries to develop products containing pharmaceutically active principles has led to the introduction of the concept of cosmeceuticals.[16] This term indicates cosmetic-pharmaceutical hybrids aimed at enhancing the beauty of the skin by means of ingredients that modify skin functionality or provide additional health-related function or benefit.

In cosmetics and cosmeceuticals, the vehicle is of great importance since it generally also plays specific skin care functions.[29] Vehicles can be used as cleansers, such as in soaps and detergents; as soothers against skin irritation; as skin hydrating agents, like various oils and sebumlike fatty substances; and for the protection of skin against environmental noxious agents, like anti-UV screens. Despite increasing technological efforts in the field of skin care, with new molecularly complex classes of vehicles being continuously researched, no universal vehicle has been so far identified. Each drug or herbal principle requires a different vehicle for an optimized treatment. In addition, the stability and compatibility of excipients and active moiety are essential elements for pharmaceutical or cosmetic formulations, coupled with the local and systemic safety of their components.[34]

Basically, the vehicle should have the ability to penetrate the stratum corneum of the epidermis, and thereby deliver at proper rates the active principles to lower epidermal, dermal, or subdermal site, where the action of these principles is required. The stratum corneum is made up of corneocytes intertwined with a specialized lipid matrix forming the skin's protective moisture barrier. Corneocytes derive from the apoptosis of keratinocytes, which migrate from inner epidermal layers. The ability of the stratum corneum to retain water is due to several low-molecular-weight compounds, including mineral ions, lactic acid, urea, and amino acids and urocanic acid, deriving prevalently from the breakdown of the keratin-associated protein filaggrin. These compounds are collectively known as the natural moisturizing factor (NMF), which functions as a humectant and reaches the highest levels in the lowest regions of the stratum corneum, where the greatest amount of moisture is retained. The lipid matrix of the stratum corneum consists chiefly of fatty acids, ceramides, and cholesterol. These hydrophobic compounds form bilayers that surround the above hydrophilic phase, allegedly forming a brick-and-mortar arrangement that prevents transepidermal water loss (TEWL).[4,35] Alterations of the lipid component lead to increased TEWL, resulting in dry and aged-looking skin. A well-known consequence of the physiological presence of a lipid barrier in the outer skin is that water-soluble compounds, such as polar electrolytes and ionized salts, penetrate poorly the skin, whereas lipophylic molecules penetrate more easily.

The measurement of the percutaneous absorption of exogenous chemicals is of significant interest with regard to the delivery of molecules of pharmaceutical and cosmetic concern.[25] Assessing the skin permeability of materials by using *in vivo* experiments alone is extremely difficult. *In vitro* methods using excised skin in diffusion cells have therefore been established and validated. Human skin excisions and animal skin have been used for the *in vitro* assessment of percutaneous penetration,[2,5,39] while current tendencies move toward the introduction of reconstituted human epidermis models.

VEHICLES

Vehicles can be classified according to various principles described in the literature (for a comprehensive classification, see Buchmann[3]). However, cosmetic preparations are rather complex systems, and therefore it is very difficult to set up a universal classification system. Depending on the vehicle used, the appearance of dermatologic and cosmetic preparations can be liquid, semisolid, or solid, although

according to the temperature a lipid-based vehicle might be either liquid or semisolid. Aqueous, oil or grease, powder, and emulsified materials can be combined to form a variety of topical formulations.[20] In a monophasic system, only substances with mutual solubility are combined together, while in multiphasic systems, like emulsions and suspensions, the phase-forming components are mutually insoluble. Moreover, the preparation and solubilization of multiphasic systems require the addition of amphiphilic substances, such as emulsifiers and surfactants.

A prevalence of aqueous components is found in soaps and lotions. Suspensions are simple dispersion systems consisting of particles, generally containing active principles, dispersed in a liquid phase. Creams include more or less equivalent portions of aqueous, emulsifier, and lipid components (e.g., oil-in-water or water-in-oil creams). Ointments consist of a mixture of oil and emulsifier, sometimes with a lesser presence of water (water-in-oil ointments), or the exclusive presence of fat substances. Pastes are mixtures of powders and oils, while powders alone are also used. Emulsions are probably the most common formulations, due to comfortable skin feeling, consumer appeal, and ease of application. Emulsions are biphasic products containing both lipophilic and hydrophilic compounds, which are maintained in a metastable mixed state by an emulsifier. They can either be of the water-in-oil (w/o) or oil-in-water (o/w) types.

Biphasic systems may be regarded in analogy to skin cells, since in both cases lipophilic and hydrophilic components are present. However, a delivery system that is much more similar to the structural arrangement of a living cell is represented by liposomes. Liposomes are spherical vesicles consisting of a liquid phase surrounded by a membrane. This latter is formed by one or more bilayers of phosphatidylcholine or other phospholipids, which are the main components of cell membranes. Phosphatidylcholine is mainly obtained from soy, and shows a fatty acid composition dominated by unsaturated fatty acids. Soy phosphatidylcholine can contain up to 70% linoleic acid, and is able to fluidize the lipid component of the horny layer and deliver linoleic acid very effectively into the skin. The observed antiacne properties of soy are thought to derive from this mechanism.[15]

Other technologically advanced dispersion formulations, known as nanoparticles, consist of particles having a size ranging from 10 to a few hundred nanometers, which are used as carriers for active substances. Nanoparticles usually consist of liquid or solid lipid micelles covered by a surfactant and dispersed in an aqueous medium.[40]

Besides the extensive use of herbal compounds as active principles, some of these substances have been used, both in folk and in modern herbal skin care, as vehicles in topical formulations. Botanical sources provide almost any possible kind of vehicles, including emulsifiers, surfactants, oils and butters, waxes, and hydrophilic solutions. These substances combine the properties of drug delivery to the skin, typical of vehicles, with the ability to produce specific actions on the skin, such as occlusive, moisturizing, smoothing, firming, soothing, and conditioning effects.

Moisturization of the skin is essential for skin health. Moisturizing formulations generally include occlusive and humectant compounds. Occlusives, such as various plant oils, are thought to moisturize by forming a hydrophobic shield on the external surface of the stratum corneum, under which water is trapped. Humectants, like glycerine and urea, draw water from the surrounding milieu into the stratum corneum.[33]

α-Hydroxy acids (AHAs), also known as fruit acids, are organic acids that improve skin moisturization, reduce wrinkles, and stimulate cell renewal. The most frequently used in cosmetics are glycolic, malic, lactic, and citric acids.[19] Mucilages, such as those of aloe gel, are mucopolysaccharide-rich substances that have the ability to form a protective coating over the skin, and therefore have high moisturizing properties.[10] Glycosaminoglycans like hyaluronic acid and chondroitin sulfate are highly hydroxylated compounds able to retain large amounts of water. Hyaluronic acid is a linear polysaccharide, formed from disaccharide units containing N-acetyl-D-glucosamine and glucuronic acid, which is widely used in cosmetics for various purposes, including moisturization. High-molecular-weight hyaluronic acid molecules form a superficial film, while low-molecular-weight molecules can penetrate the skin together with bond water and hydrate the deeper layers of the stratum corneum.[36]

Plant-derived oils are rich in essential fatty acids (EFAs), which are known to regulate the TEWL and are valuable moisturizing cofactors in cosmetics. One of the most popular lipid materials in cosmetic formulations is jojoba (*Simmondsia chinensis*) liquid wax, a mixture of fatty acid and fatty alcohol esters that is used pure or in oil-in-water emulsions for lotion and cream moisturizers. The presence of natural lipids in cosmetics renders them particularly suitable for xerotic skins. In addition, EFAs exert a soothing action that protects the skin against environmental stress factors, such as sun, wind, and air pollutants.[31] This action, possibly associated with natural antioxidants like tocopherols, is also effective in slowing down processes that cause premature aging of the skin, such as excessive TEWL and reactive oxygen species.

Emollients are substances added to cosmetics in order to soften and smooth the skin. They function by filling the spaces between desquamating corneocytes, and many of them also act as humectants or occlusives. Common emollients are the above-mentioned jojoba oil; castor oil, obtained from the castor bean (*Ricinus communis*); and various other plant oils.

SURFACTANTS

Surfactants are used in cosmetic technology for creating a variety of dispersed systems, such as suspensions and emulsions. They are usually added to aqueous formulations in order to solubilize lipophilic active ingredients, and so they have the potential to promote lipid absorption into the stratum corneum. Surfactants possess at least one polar and one nonpolar moiety, and therefore also have the ability to produce foam due to a reduction of surface tension. They can be classified as cleansing, emulsifying, and solubilizing agents, or foam boosters.[30]

Both synthetic and natural compounds, either ionic or nonionic, are employed as surfactants in pharmaceutical and cosmetic products. Anionic (e.g., sodium lauryl sulfate (SLS)) and cationic (e.g., cetyltrimethyl ammonium bromide) surfactants can potentially damage the skin. SLS is a strong irritant and increases the transepidermal water loss. Nonionic surfactants are considered safer than ionic surfactants, and generally have low chronic toxicity. Moreover, bioemulsifiers have various advantages over chemical surfactants, such as low toxicity, biodegradability, and biocompatibility.

Naturally occurring alkyl and fatty acid glycosides are generally tasteless, odorless, nontoxic, nonirritating, and biodegradable surfactants. They therefore have broad applications in the food industry, cosmetics, detergents, and medical supplies. A great variety of this kind of compounds are produced by bacteria and fungi, but they are also present in higher plants. Sucrose esters of fatty acids (SEFAs) are nonionic surfactants consisting of a sugar (e.g., glucose or sucrose) as the hydrophilic group and a fatty acid as the lipophilic group. SEFAs are present, e.g., in leaf surface exudates from Solanaceae plants of the genera *Datura*, *Lycopersicon*, *Nicotiana*, and *Solanum*.

A series of simple alkylglycosides, or fatty alcohol glycosides, isolated from different plant species are also arousing interest for several applications. Alkylglycosides have been isolated from the fruit of acerola (*Malphigia glabra*), the essential oil of the dried leaves of oregano (*Origanum vulgare*), the methanolic extract of cumin fruit (*Cuminum cyminum*), the fruit of bupleurum (*Bupleurum falcatum*), and the aerial parts of the sage plant *Phlomis lunariifolia*.[6]

Other natural surfactants of great interest are fatty acid (FA) amides, such as ceramides, anandamide, oleamide, N-arachidonoyldopamine, and N-acylethanolamine. These compounds generally have high biological properties. For example, N-palmitoylethanolamine is an anti-inflammatory contained in soybean and peanut oil. FA amide glycosides, such as gangliosides, aminoglycosides, and their derivatives, also show biological activities.[8]

Other surfactants include carotenoid glycosides, isoprenoid glycolipids, and terpenoids.[7,9] Saponins are glycosides of triterpenes, steroids, or steroid alkaloids with high surfactant properties.[18] These compounds derive their name from the soapwort plant (*Saponaria officinalis*), the roots of which have been traditionally used as a soap. Other well-known botanical sources of saponins include ginseng (*Panax ginseng*), the roots of licorice (*Glycyrrhiza glabra*) and butcher's broom (*Ruscus aculeatus*), and the seeds of horse chestnut (*Aesculus hippocastanum*).

THICKENING AGENTS

Due to the broad performance criteria that cosmetics have to meet, viscosity-increasing, thickening agents are frequently used in topical formulations. These materials serve the purpose of producing solid cosmetics or rendering suspensions, emulsions, or ointments more easily spreadable and appealable, and improving skin moisturizing, emolliency, and absorption characteristics.[14] According to the type of formulation, aqueous or oily thickening agents, or a mixture thereof, have to be used.

Most common natural aqueous thickening agents include polysaccharides such as carrageenan; a sulfated polysaccharide extracted from red seaweeds, glucomannan, which is present in aloe gel and is particularly abundant in the corm of the konjac plant (*Amorphophallus konjac*); xanthan gum, a bacterial product obtained from fermentation processes operated by *Xanthomonas campestris*; guar gum, a galactomannan obtained from guar (*Cyamopsis tetragonoloba*) beans; and carob gum, a galactomannan extracted from the seeds of the carob tree (*Ceratonia siliqua*). In addition, chief components of plant cell walls are also commonly used as viscosity enhancers, such as pectin, a main source of which are citrus fruits, and cellulose, mostly employed in the

form of its derivatives, like methylcellulose and hydroxyethylcellulose, which do not occur naturally but are synthesized starting from plant material. Proteins are also used as aqueous viscosity enhancers, usually gelatin, which is obtained from the collagen contained in by-products of the meat and leather industry.

Examples of natural oily thickening agents include waxes, such as carnauba wax, derived from the leaves of the carnauba palm (*Copernicia prunifera*), and beeswax produced by honey bees (*Apis mellifera*). Nontoxic, nonirritating, lipophilic synthetic materials derived from naturally occurring substances are also widely used, including dextrin fatty acid esters, such as dextrin palmitate, and sucrose fatty acid esters.

Several polysaccharides used in personal care formulations can undergo gelation as a function of ionic strength, pH, and heat treatment. The consistency of gels is caused by the formation of a three-dimensional network. Particularly dense gels or solid mixtures of waxes and greases are commonly used in the preparation of sticks.[32]

PENETRATION ENHANCERS

Although surfactants and emulsifiers play a role in the delivery of active principles to the skin, specific penetration enhancers are also used, especially in medical and cosmeceutical formulations containing low-diffusible drugs such as hydrophilic compounds.[38] Penetration enhancers generally act on the stratum corneum, and their possible mechanisms of action include the reduction of the skin permeability barrier via the disruption of the tightly packed lipid regions, the modification of intracellular keratin, causing swelling and increased hydration, and the alteration of desmosome links that ensure the cohesion between corneocytes. In synthesis, penetration enhancer would affect the lipid-protein partitioning behavior of the vehiculated compounds.[1] Accordingly, they tend to work well with cosolvents such as propylene glycol or ethanol. Penetration enhancers induce modification in the skin texture, especially in the stratum corneum, which can lead to irritation or other injurious effects to the skin, and should always be used after careful testing.

The simplest approach to improve transdermal and topical delivery of cosmetics and medicaments is soaking the skin in water. However, water exerts a very poor penetration-enhancing activity as an external agent, while a more efficient approach consists in the use of occlusive materials or patches, which increase the amount of water in the stratum corneum by preventing transepidermal water loss. Ethanol is commonly used to increase the solubility of a drug in the vehicle and in transdermal formulations, and is often the solvent of choice for use in patches. Urea is also used as a penetration enhancer, probably acting by increasing the water content of the stratum corneum and exerting keratolytic activity.

A number of organic compounds have been evaluated as penetration enhancers in the pharmacological and cosmetic fields. Many of these are synthetic molecules, such as azone (1-dodecylazacycloheptan-2-one or laurocapram), dimethylsulfoxide (DMSO) and its derivatives, and pyrrolidones and related compounds. However, many natural compounds also find wide application as penetration enhancers. Drug absorption has been increased by a wide variety of long-chain fatty acids, such as oleic and lauric acids. It has also been shown that the permeability-enhancing effects of fatty acids are maximum if they are used in combination with propylene

glycol (PG).[26] This system probably acts by disorganizing the multilaminate, alternate hydrophilic and lipophilic layers of the stratum corneum.[28] However, PG has also been used as a penetration enhancer in its own right. Although the mechanism by which fatty acids enhance the permeation of drugs through the skin is not clearly understood, oleic acid is supposed to interact with stratum corneum lipids and disrupt their structures, thus increasing their fluidity and consequently the flux of permeants. Fatty acids have been used to improve transdermal delivery of drugs like estradiol, progesterone, acyclovir, 5-fluorouracil, and salicylic acid, indicating that these enhancers can be used to promote delivery of both lipophilic and hydrophilic permeants. Fatty alcohols may also have penetration-enhancing activity. Phospholipids are prevalently used in liposomes to carry drugs into and through the human skin, but they can also act in a nonvesicular form as penetration enhancers.

The essential oils of eucalyptus (*Eucalyptus globulus*), wormseed (*Chenopodium ambrosioides*), and ylang ylang (*Cananga odorata*) have been tested as penetration enhancers *in vivo*. Such a kind of activity in volatile oils is mainly due to the presence of various terpenes and terpenoids.[37] The enhancing activity of single terpenoids, such as the cyclic ether 1,8-cineole (eucalyptol), has also been evaluated. These compounds operate by modifying the solvent nature of the stratum corneum, improving drug partitioning into the tissue. However, many terpenes also have pharmacological activity, and their use as an enhancer must therefore be carefully evaluated.

PRESERVATIVES

Various methods of preservation are available to the formulators of cosmetic preparations, in order to prevent alteration and degradation of their products. Due to the toxicity properties of many preservatives, their application and selection are strictly defined by legal rules in many countries. Among methods of preservation, botanical materials and natural molecules offer different possibilities of use. Even though these materials may entail higher costs, they are frequently preferred with the aim of enhancing the dermatocosmetic properties of products.[13]

Botanical organisms differ from animals in that they have developed a defense system against spoiling organisms and pathogens based on the production of toxic secondary metabolites, instead of an immune system based on cell-to-cell recognition and antibody production. Plant natural preservatives, also known as phytoalexins, frequently possess other biological effects besides their antimicrobial properties. This is, for instance, the case of resveratrol, for which a wide number of therapeutic properties have been described, including cardiovascular protection and tumor chemoprevention, and of some flavonoids showing antimicrobial and anti-inflammatory properties.[21]

A vast number of phytocompounds show antimicrobial effects that can be exploited for preservation purposes, including terpenoids, organic acids, oxygenated fatty acids, aliphatic alcohols, polyols, and polyphenols. Many of these compounds are not suitable for use in cosmetics, while others are not only suitable as preservatives, but also contribute to the beneficial effects of formulations.

Essential oils are rich in aromatic compounds and fragrances, but their use is problematic due to irritative properties. Glyceryl monoesters, such as glyceryl caprylate,

generally employed as moisturizing ingredients, also play an efficient antibacterial role. Alkyl esters of p-hydroxybenzoic acid (parabens) and related compounds are among the most frequently used preservatives in cosmetics, toiletries, and pharmaceuticals. A number of natural compounds belonging to this group can be found, such as benzoic acid and benzyl alcohol, mostly active against gram-positive bacteria, which can be obtained from balsamic resins. Other systems, such as lactoperoxidase and glucose oxidase, a natural preservative of honey, are based on enzymatic generation of reactive oxygen species like H_2O_2. Various lichen compounds, such as usnic acid, are also known as powerful antimicrobial agents.[13]

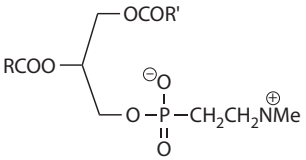
The prevention of oxidative processes in formulations is realized by the addition of proper antioxidant compounds. Vitamins are commonly added to cosmetics, frequently in an esterified form with fatty acids such as palmitic acid, in order to increase their stability. Vitamin A, retinoic acid, and β-carotene have been popular additives in cosmetics for years, and moreover, these compounds have the ability to regulate keratinocyte growth and differentiation and decrease skin wrinkling. Vitamin C has a good antioxidant action, and in addition it functions as a cofactor in collagen synthesis. Vitamin E is a potent quencher of free radicals, especially lipid peroxyl radicals, and also protects the skin from UV damage.

Among natural antioxidants, phenolic compounds are in the forefront since they have the structural requirements of free radical scavengers. Various phenolic classes can be used for this purpose, including phenolic acids, anthocyanins, cathechins, hydroxycinnamic acid derivatives, and flavonoids.[23]

NOXIOUS SIDE EFFECTS OF TOPICAL FORMULATIONS

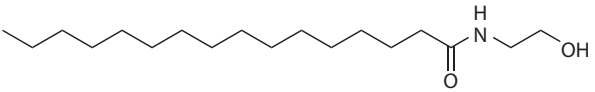
It has long been recognized that topical products can produce skin disorders, including irritation, contact dermatitis, and photosensitization. Various studies have revealed that up to 10% of dermatologic patients manifest allergic reactions to pharmaceutical and cosmetic products.[27] The diagnosis of cosmetic allergy is generally confirmed with patch testing. These problems can indistinctly arise from natural or synthetic products, including deodorants and perfumes, skin and hair care products, UV filters, and nail cosmetics. It has been also found that allergic contact dermatitis mainly results from fragrances and preservatives. Therefore, much concern exists about the potential for irritant or allergenic skin reactions when a topical formulation is developed, and the use of hypoallergenic components is a major goal to be pursued by cosmetic and pharmaceutical manufacturers.

Another major source of concern is the ability of various agents to promote an abnormal differentiation of the hair follicular epithelium, resulting in the formation of microcomedones (comedogenicity) or, in more severe cases, the insurgence of folliculitis (acnegenicity). Comedones are the primary acne lesions, due to hyperkeratinization within the pilosebaceous duct, leading to partial (open comedone or blackhead) or complete (closed comedone or whitehead) obstruction of the duct and accumulation of sebum. These processes can occur naturally, mostly in young people, with increased androgen production (e.g., dehydroepiandrosterone sulfate). Moreover, the commensal bacterium *Propionibacterium acnes* can cause inflammatory lesions (papules, pustules, and nodules) in the dermis around the comedo.

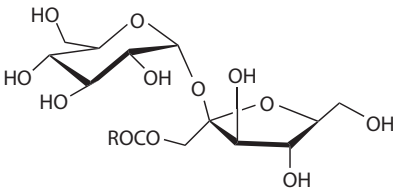


R and R' are fatty acids

phosphatidylcholine

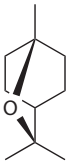


N-palmitoylethanolamine

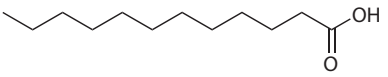


R = fatty acid

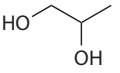
fatty acid sucrose ester



1,8-cineole (eucalyptol)



lauric acid



propylene glycol

It is of crucial importance to evaluate ingredients and finished products for comedogenicity. This was frequently done using animal models, such as the rabbit ear assay (REA), but the banning of animal experiments for cosmetic products has made it urgent to find alternative procedures or clinical methods, such as skin surface biopsy and skin fluorescence imaging.[17] The list of ingredients that have shown varying degrees of comedogenicity is quite extended and includes lanolin and its derivatives, petroleatum and mineral oils, vegetable oils, fatty acid esters like isopropyl myristate and its analogues, isopropyl isostearate, decyl oleate, octyl palmitate or stearate, etc., pigments (xanthenes, monoazoanilines, fluorans, indigoids), and various sunscreens. However, the properties of single ingredients cannot be *a priori* translated

to what might occur in the final product, since the concentrations of ingredients show great variability, the vehicles can alter the comedogenic and acnegenic potentials, and the interactions among ingredients may alter their noxious effects. Hence, besides the separate evaluation of single ingredients, finished products should always be tested.[11]

CONCLUSIVE REMARKS

The skin stratum corneum acts as a barrier that isolates the organism from the environment and avoids water loss from tissues. Such a sealed sheath is essential for the physiological processes of the skin and of the entire body, but poses problems for the topical delivery of substances to the tissues. This kind of hindrance has been known since ancient times and has been empirically approached, e.g., by the use of greasy or oily materials in skin care applications. Technological achievements in the topical administrations of medicaments and in skin care products have led to the development of vehicles and penetration enhancer and to the design of technologically advanced formulations. Although synthetic chemical structures have been abundantly used in this field, traditional practices and scientific studies have shown through the years that botanical sources can provide all kinds of elements for vehiculating drugs and active compounds and for enhancing their permeation through the skin. Natural compounds ensure in most cases desirable features such as biocompatibility, low irritancy, and optimal partitioning of permeants in the skin. Moreover, they form an astounding horizon of chemical diversity for the development of new components to be used in dermatologic and cosmetic formulations.

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4 Monographs of Herbal Principles

A growing trend in cosmetic and pharmaceutical industries is to replace synthetics products and revert to the use of natural ingredients. An important set of activities concerns the development of new products from natural sources. Consequently, a growing interest has been addressed to materials of the American, Euro-Mediterranean, and Eastern traditions, and to exotic plants that in many cases have been introduced to Western countries through fair trading practices. The commercialization of these products on a wide scale can provide major benefits to the local communities of both developed and underdeveloped countries, in terms of reforestation of marginal land, new diversified farming activity, sustainable development of rural conditions, and utilization of renewable natural resources.

The following monographs concern a series of botanicals deriving from traditional practices and currently used in dermatology and cosmetics. Each monograph contains: (1) a brief description of anatomical features, ethnobotanical uses, and commercial value; (2) a list of constituents, with a particular emphasis on active principles; (3) a review of biological and therapeutic properties, dealing in particular with the mechanisms of action at the cellular and molecular levels; (4) a review of dermatologic and skin care applications; and (5) a list of side effects, including toxic properties and allergies.

For scientific names and common names of higher plants we have followed the nomenclature databases available at the International Plant Names Index (IPNI) and U.S. Department of Agriculture (USDA) and Duke's *Handbook of Medicinal Herbs*.[1–3] For algae, lichens, fungi, and cyanobacteria the nomenclature database at the National Center for Biotechnology Information (NCBI) was followed.[4] The authors wish to clarify that animal experimentation is described as part of the reviews, while ethical approval is not implied.

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ABYSSINIAN KALE

Scientific name: *Crambe abyssinica* Hochst. ex R. E. Fr.
Family: Brassicaceae
Parts used: Seeds
Other names: Crambe

Features

Branching annual crucifer of 1–1.5 m in height, with a swollen tap root and pinnately lobed leaves. Flowers are small, white, and arranged to form long racemes. They produce small capsules, each containing a single, spherical seed. Seeds are greenish brown and measure 0.8–2.5 mm in diameter.

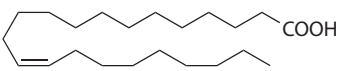
This species probably originated from the Turko-Iranian region of Southwest Asia, but is now largely cultivated in many regions of the world. In Europe it is used as a spring crop. An oil can be obtained from the seeds by mechanical pressing.

Constituents

The seeds have a fat content of about 35% and a protein content of about 30%. The oil is primarily composed of erucic acid (about 50–60%), followed by oleic, linoleic, linolenic, eicosanoic, palmitic, nervonic acid, and other minor components.[5,15] The residual meal obtained after pressing has a content of 50–60% protein and can be used as stock meal.

The high content in erucic acid makes the oil suitable for different industrial processes, such as the synthesis of plastics and the production of lubricants and anti-corrosive materials.[4,7,12,14]

A small protein of 46 amino acids, known as crambin, has been isolated from the seeds,[1] while in the leaves there is an accumulation of derivatives of the flavones apigenin and luteolin.[13]



erucic acid (ω-9)

Properties

Erucic acid has some relevance in the medical field, since it is a chief active principle of Lorenzo's oil, which is used in the treatment of the childhood form of adreno-leukodystrophy, and has been made popular by an acclaimed movie. However, the therapeutic use of erucic acid has raised some concern since it has been found that it involves an alteration of the blood platelet fraction.[3,6]

Attention has been focused on erucic acid also due to its presence in food products like rapeseed oil, also obtained from a plant of the Brassicaceae. Although cases of toxicity on humans have not been confirmed, in laboratory animals it has been

observed that high doses of erucic acid in the diet cause lipid accumulation in the myocardium.[9] Consequently, erucic acid is generally considered a toxic substance and its alimentary use has been restricted. Rapeseed cultivars with low erucic acid, known as canola, have been developed in order to obtain safer rapeseed oil (canola oil) for human consumption.

Other compounds that are present in the seeds of abyssinian kale, but not in the oil, are glucosinolates (70–150 μmol/g).[8] These compounds induce phase II detoxification enzymes like glutathione-S-transferase and quinone reductase, thus favoring the conjugation and excretion of toxic and carcinogenic compounds. Another compound isolated from the plant that is an inducer of detoxification processes is the nitrile 1-cyano-2-hydroxy-3-butene (crambene).[11] This compound is also able to promote apoptosis in pancreatic acinar cells, thereby reducing the severity of acute pancreatitis.[2]

Dermatologic and Cosmetic Use

Thanks to the high content in long-chain fatty acids, crambe oil is used in cosmetics as a thickening compound and for its emollient and soothing properties.[10,16,17] It is also employed in preparations for hair care.

Side Effects and Toxicity

No cases of allergic reactions or toxic effects have been reported following topical applications of crambe oil.

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AÇAI PALM

Scientific name: *Euterpe oleracea* Mart.
Family: Arecaceae
Parts used: Fruit

Features

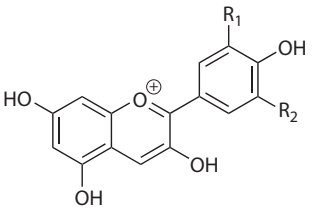
High and slender palm native to the Amazon forest, which can reach a height of 20 m and has pinnated leaves of up to 3 m length. The fruit is a rounded drupe of an intense purple, similar to a grape but with less pulp and a unique big seed. Fruits are grouped in panicles formed by 700–900 elements.

FIGURE 4.1 Açai Palm. Courtesy of Dr. Jean-Christophe Pintaud, IRD, Montpellier, France. (See color insert following page 40.)

Constituents and Properties

The açai fruit has been much appreciated by Amazonian people since long ago, because it represents a feeding resource endowed with excellent nutritional properties.[6] Conversely, the fruit has been introduced in Western markets only around the year 2000. The juice extracted from the fruit is a health-promoting drink containing high amounts of antioxidants.[7–9] The properties of the juice are mainly due to the presence of anthocyanidins and their glycosides, and of other polyphenols.[5] These compounds confer the purple color to the fruit and are present mainly in the skin, in much higher amounts than in grape and berries.[3] They exert antioxidant and anti-inflammatory actions and produce positive effects on the cardiovascular system, eyes, skin, and the immune system. Polyphenol glycosides have been shown to induce apoptosis of HL-60 leukemia cells.[4]

The fruit also contains a perfect balance of essential amino acids, which are of extreme importance for the exercise of muscles and their regeneration. In the lipid fraction there are important antioxidants, such as vitamin E and omega 3, 6, and 9 fatty acids. These latter contribute to regulate blood cholesterol, decrease LDL levels, and help to maintain proper levels of HDL. Similarly to the saw palmetto (*Serenoa repens*), which belongs to the same botanical family, the açai fruit contains phytosterols that can prevent prostate hypertrophy.



$R_1 = R_2 = H$, pelargonidin
$R_1 = OH$, $R_2 = H$, cyanidin
$R_1 = R_2 = OH$, delphinidin

Dermatologic and Cosmetic Use

The pulp of the fruit yields an oil with remarkable dermatologic properties. The oil is rich in essential fatty acids, phytosterols, and vitamins. It has regenerative and anti-aging properties on the skin, and can be used in after-sun products, creams, lotions, shampoo, face masks, and other cosmetics.[1] A formulation containing anthocyanins from açai oil, γ-oryzanol from rice oil, and passion flower seed oil is popularly used in Brazil for the health of head hairs.[2]

Side Effects and Toxicity

No adverse effects or allergic reactions have been reported.

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ACEROLA

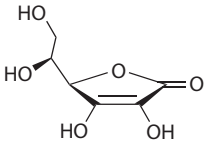
Scientific name: *Malpighia glabra* L. (syn. *Malpighia punicifolia* L., *Malpighia emarginata* D.C.)
Family: Malpighiaceae
Parts used: Fruit
Other names: Barbados cherry, West Indies cherry

Features

This species is native to Central America, but it is also distributed in the southern regions of North America and in parts of South America, where it is present as both wild and cultivated plant. It is a slow-growing, large, spiny bush, reaching a heigth of 3 m. The leaves are evergreen, ovate-lanceolate, and up to 5–10 cm long. Flowers are borne in groups of two to five, possess five pink or red petals, and have a diameter of 1.5 cm. The fruit is a sharp-red drupe, and it is similar to a cherry, although this plant is not a close relative of cherry trees (*Prunus*). As the fruit becomes ripe, it tends to acquire an orange color, while its flavor is slightly acidic and recalls that of apples. The largest cultivations of acerola are located in South America, particularly in Brazil, while the fruit is principally on the market for the production of juices, jelly, cakes, and drinks.[5,7,8,16]

Constituents

The fruit macronutrients are composed of protein (0.2–0.8 g/100 g of wet weight), lipids (0.2–0.8 g/100 g), and sugar (4–8 g/100 g). Most abundant simple sugars are dextrose, fructose, sucrose, and L-malic acid. The fruit is also rich in vitamins, including vitamin A, whose amount is comparable to that of carrots, thiamin, riboflavin, piridoxine, niacin, and above all vitamin C, which is present as both ascorbic and dehydroascorbic acid.[2,17] The content in vitamin C varies from 1.5 to 3.5% of the wet weight, but in some varieties it can even reach 5%. These amounts are from 50- to 100-fold higher than those of citrus fruits, such as lemon and orange.[1] Acerola is then considered one of the richest natural sources of vitamin C.



L-ascorbic acid

The most abundant polyphenols are cathechins (about 1–2 mg/g) and anthocyanins,[3,15] while the main carotenoids are β-carotene, β-cryptoxanthin, luthein, and violaxanthin.[6,9] The total amount in carotenoids is about 1.5 mg/100 g. Volatile components, which confer to the fruit its typical flavor, are more than 100, and include such

compounds as furfural and limonene. The minerals present in relatively high amounts are iron (0.24 mg/100 g), calcium (11 mg/100 g), and phosphorus (17 mg/100 g).

Properties

In the traditional medicine of Brazil and Central America, the fruit is used to combat fever and rheumatisms, dysentery, liver disorders, and as an astringent and a diuretic. It is also used as a food supplement to contrast anemia, diabetes, and hypercholesterolemia.[4,13]

The presence of vitamin C and polyphenols confers to acerola juice a high antioxidant power, which contributes to improve its nutritional value.[14] The antioxidant activity of vitamin C is linked to its ability of acting as an electron donor in the reaction that, starting from ascorbic acid (reduced form), leads to dehydroascorbic acid (oxidized form). Owing to this reaction, this compound plays a determinant role in a number of biological processes, including collagen synthesis (antiscurvy effect), corticosteroid synthesis (stimulatory effect), the synthesis of folic acid (antianemic vitamin) and its conversion to folinic acid, prevention of the formation of carcinogenic nitrosamines in the lung, prevention of osteoporosis, conversion of cholesterol into biliary acids, intestinal uptake of iron and its passage from blood transferrin to tissue ferritin, and finally the stimulation of the immune system.

Different fractions of the fruit extract, separated through high-performance liquid chromatography (HPLC), have shown antitumor properties by *in vitro* tests. Some of these fractions have also reduced oxidative damage caused by pro-inflammatory stimuli, by acting through free radical scavenging and the prevention of NO synthase activation in macrophages.[11,18] *In vitro* studies have also shown that the juice exerts antibacterial and antifungal activities, although specific clinical tests about these properties are not available.

Dermatologic and Cosmetic Use

Vitamin C is essential for the normal synthesis of collagen, since it allows the hydroxylation of proline and lysine in the collagen peptide chain. The collagen is the most abundant protein in the connective tissue, particularly in the dermis, where it contributes to render the skin smooth and resistant. Moreover, vitamin C prevents the action of free radicals, which degrade the collagen and then lead to the formation of wrinkles. Therefore, the extract, due to its high content in vitamin C, is particularly indicated for skin antiage treatments.[10,19] In addition, its mineral salt content acts as a coadjuvant for the remineralization of the skin, particularly after exposure to various kinds of stress, while the presence of mucilage and peptides confers rehydratation properties and promotes blood microcirculation. The antioxidant properties of the extract are also exploited in products used against skin hyperpigmentations, which can also be related to aging. Antioxidant and antiage properties have been detected in the seed extract.[12]

Side Effects and Toxicity

No unwanted effects have been observed following the use of juice or food supplements from acerola, nor has contact dermatitis been reported following topical use

of derivatives of the plant. However, the ingestion of massive doses can produce gastrointestinal ailments, promote the formation of kidney stones, and interfere with the uptake of hydroquinones or other drugs.

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ALMOND

Scientific name: *Prunus dulcis* (Mill.) D. A. Webb var. *dulcis*
P. dulcis (Mill.) D. A. Webb var. *amara* (DC) H. Moore
Family: Rosaceae
Parts used: Seeds

Features

Deciduous tree of medium height or shrub, growing to between 4 and 12 m in height. The branches are red tinged, thorny in the wild form and smooth in the cultivated form. Leaves are dark green, oblong-lanceolated-acuminate or serrate. Flowers are white or pale pink, with five petals, and 3–5 cm in diameter. The fruit is an oblong-ovoid, compressed drupe, 3.5–6 cm long, with a leathery, pubescent, grey-green exocarp, and a reticulated, hard woody endocarp surrounding the seed.

The species is native to a wide area spanning from northern India to Minor Asia. It was spread to the Mediterranean, northern Africa, and southern Europe in ancient times, and more recently to northern America and other regions of the world.

There are two forms of the plant: the wild form, with pink flowers, produces bitter almonds, while the domesticated one, frequently with white flowers, produces sweet almonds. The seeds of wild almonds contain the poisonous cyanogenic glycoside amygdalin, while a genetic mutation causes the absence of amygdalin in the cultivated form. Toxicity can be removed by wild almonds through leaching or roasting.

Sweet almonds are eaten raw or used as ingredients of cakes and desserts. The seed yields an oil that is widely used in cosmetics.[11]

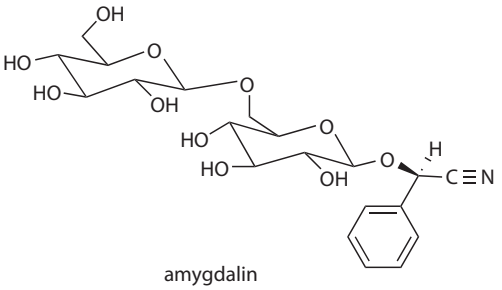
FIGURE 4.2 Almond.

Constituents

The seed is composed of triglycerides (45–50%), proteins (20–25%), mineral salts (2–3%), cellulose fiber (4–5%), mono- and disaccharides (5–6%), and vitamins (A, B1, B2, B3, B6). The seed also contains an enzymatic complex, including emulsin (β-glucosidase), amylase, and oxynitrilase.

The seed of the wild form contains the glycoside amygdalin, which upon the action of β-glucosidase is decomposed into the essential oil benzaldehyde, the extremely toxic cyanide, and two molecules of glucose.[10]

A pale yellow, sweetish oil is obtained from seeds by pressure. Bitter almonds contain the cyanogenic glycoside amigdalin, but the oil does not contain this substance.[4] Therefore, both sweet and bitter almonds are indicated by pharmacopeia for oil production. The oil has a slight odor and a nutty taste. Chief constituents of the lipidic fraction are oleic (75% of total lipids), linoleic (20%), palmitic (3%), stearic (1.5%), and linolenic (0.5%) acids.[9,13]



amygdalin

Properties

In Ayurveda almond is considered a good nutrient for the nervous system and is thought to act as an aphrodisiac.[12]

The oil is one of the most used intestinal regulators and laxatives and has also been reported to prevent gut cancer.[3] It is rich in monounsaturated fats, and has been shown to elevate the blood levels of HDL cholesterol and to lower the levels of LDL cholesterol.[6,15] Anti-inflammatory properties on the respiratory and urinary tracts, and antihepatotoxic effects of the oil have also been reported.[7]

Dermatologic and Cosmetic Use

About 95% of the oil is represented by ω-3 fatty acids (mostly oleic and linoleic). The oil is therefore widely used in cosmetics for its emollient, lenitive, and nourishing properties.[8] Thanks to its good tolerability, it is indicated for the skin of adults and kids, and even for the particularly delicate skin of newborns. It is used as a lubricant, sebum restitutive, and reepithelialization agent, and is recommended for dry skins and to alleviate itching caused by dermatitis, eczema, measles, and chickenpox. The oil can also be used against stretch marks caused by birth or slimming diets,[1] and to soften and moisturize dry or frizzy hair, or hair bleached by sun

and saltiness. It can be mixed with essential oils for massage for joint pain or after physical exercise.

Side Effects and Toxicity

Bitter almonds are toxic due to the presence of amygdalin, and their ingestion can produce serious consequences.[14] Almond oil lacks amygdalin but is counterindicated for people with allergy to almonds. Cases of food allergies and contact dermatitis caused by the oil in newborns have been reported.[2,5]

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ALOE

Scientific name: *Aloe vera* (L.) Burm. f. (syn. *A. barbadensis* Mill., *A. vulgaris* Lam.)
Family: Asphodelaceae
Parts used: Leaves

Features

Succulent plant growing to a height of up to 80–100 cm. It has a very short stem and a rosette of lanceolate leaves. The leaves are thick, fleshy, greyish green with occasional white spots, and have aculeate margins. The flowers form a racemous inflorescence, up to 90 cm long; they are 2–3 cm long and have a tubular yellow corolla.

The species is native to northern Africa, but it grows spontaneously in most temperate and temperate-warm regions.[9,36] It is cultivated as an ornamental and medicinal plant and is also used as food or to manufacture products such as drinks and yogurt.[5,6,15,19]

FIGURE 4.3 Aloe. (See color insert following page 40.)

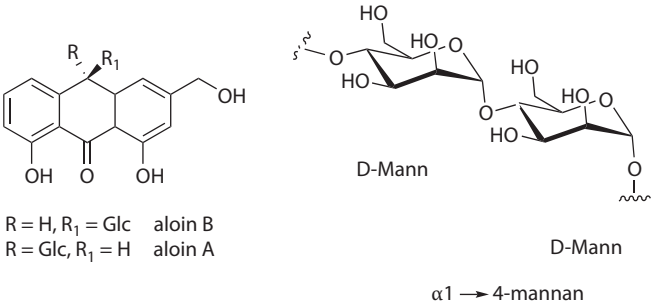
Constituents

The active principles are obtained from an exudate, or latex, produced by a secretory tissue located under the leaf surface, or from a gel derived from the leaf parenchyma after elimination of the more superficial tissues.[46,56] The latex is yellowish in color and contains anthronic and dianthronic glycosides, collectively known as anthranoids,[1,16,49] among which the most abundant are emodins (aloin) A and B and their derivatives (forming up to 30% of the leaf exudate). Derivatives of benzopyrane (chromones) are

also present, of which the main glycosides are aloesin and aloeresin. The leaves also contain phenylpyrone glycosides, cinnamic acid, and 1-methyltetralin.

The gel is composed of pectins and other polysaccharides, including glucomannan, galactan, galacturonan, arabinan, arabinorhamnogalactan, and other compounds containing glucuronic acid.[25,41,62] Mannan is the best-studied compound and is constituted of mannose residues linked by β1–4 bonds. An acetylated mannan extracted by the gel, known as acemannan, is of particular pharmaceutical interest and has been put on the market under patent.

The lipid fraction of the plant contains γ-linolenic and arachidonic acid, phosphatidylcholine, and phosphatidylethanolamine. The leaf also contains phytosterols and related compounds, such as the triterpene lupeol and the steroids cholesterol, campesterol, and β-sitosterol.[35]



R = H, R_1 = Glc aloin B
R = Glc, R_1 = H aloin A

Properties

The plant gel and exudate have been used since ancient times as medicaments.[10] In the procedure for gel extraction, the mechanical separation of the pulp from the leaf skin is not always complete. Hence, the resulting product can be contaminated by the anthraquinonic glycosides of the latex that can alter its properties.[53] The gel is a thixotropic liquid; i.e., it increases its viscosity under resting conditions, while it becomes more liquid upon stirring. It must be conserved in the dark at low temperature, since it tends to easily become rancid.

The gel has multiple therapeutic properties, and it is used for topical application or oral administration.[37,50,60] The topical use is indicated for promoting the healing of abrasions and small wounds,[11,12,27] while it is not suitable for deep wounds, such as those made in surgical operations. The gel is also useful for burns, frostbite, and ulcers of the oral mucosa.[40]

Wound healing is a complex process depending on a number of factors, including the stimulation of the synthesis of essential matrix components, such as collagen, hyaluronic acid, and dermatan sulfate, and the promotion of angiogenesis. Acemannan plays an activatory role in wound healing due to its ability to activate macrophages,[39] which protect tissues against infective agents, and induce fibroblast proliferation. Among the various processes involved in these effects there is also a decrease in the production of thromboxanes A2 and B2, which are pro-inflammatory molecules that tend to exacerbate tissue damage.

Clinical tests and studies on animals about the topical use of the gel have highlighted its anti-inflammatory and antiedematous effects.[58,59] Reduction of inflammation has been ascertained in typical animal models, such as rat paw edema and rabbit ear, and in inflammatory conditions induced by irritating agents that promote prostaglandin synthesis or leukocyte tissue infiltration. The anti-inflammatory effect is significant also in arthritis, which can be treated by injection of leaf extracts. Conversely, topical applications are scarcely effective against allergenic agents. The leaf phytosterols have induced anti-inflammatory effects in the mouse, while they have also been identified as antidiabetic compounds.[57] Proteins have a role in the anti-inflammatory effect of aloe,[61] for the presence of both lectins[2] and bradykinase activity.[23] The gel has also revealed the ability of enzymatically degrading the vasodilatatory peptide bradykinin, and of inhibiting the conversion of histamine into histidine.

Another important activity of mannose and acemannan is immunostimulation.[50] Upon tissue injection, acemannan stimulates antigenic and mitogenic responses in T lymphocytes, as well as the differentiation of various kinds of lymphocytes in the spleen and the bone marrow of mice. Macrophages stimulated *in vitro* with this substance have shown increases of the respiratory burst and phagocytic activity. The substance is also able to stimulate interleukin synthesis and the genes of nitric oxide synthase, thus leading to a rise in the cellular production of nitric oxide. The stronger activity of acemannan with respect to other polysaccharides is possibly due to the presence of acetyl residues on the hydroxy groups, thus increasing the diffusion of the compound across the hydrophobic cell membrane.

The leaf extracts can also be used by oral route. Clinical studies or experiments on animals have converged to show that the phytocomplex of aloe helps the organism face oxidative stress.[33] Such a treatment improves detoxification mechanisms, by decreasing the activity of phase I enzymes, which promote oxidative processes, and inducing phase II enzymes, which are involved in the elimination of pro-oxidant agents. The plant can also prolong the half-life and availability of physiological antioxidants like vitamins C and E.

Oral assumption of aloe reduces blood levels of sugars and triglycerides in diabetic subjects. Both the gel and its phytosterols reduce hematic levels of glucose and improve serum parameters of liver function and oxidative stress in murine models of diabetes.[8] In addition, it has been shown in animal studies that polysaccharides and glycoproteins also play a role in this kind of effect.

Lectins and acemannan have shown inhibitory properties on the growth of tumor cells. Acemannan has been reported to reduce tumor growth in laboratory animals through an activation of macrophages. The main lectin of the gel, aloctin 1, is able to prevent tumor development in the mouse, possibly also in this case by the activation of the immune system.[3]

Anthranoid compounds of the latex have marked laxative properties.[4,29–32] Upon ingestion, these compounds reach the colon mainly in their glycosylated form, and thereafter the aglycone portion is released by the activity of gut bacteria and can exert its action. This mechanism involves an increase of colon peristalsis and of the hydric content of the gut lumen. The rise in the water content seems due to an inhibition of the sodium/potassium pump, entailing a reduction of intracellular water reabsorption and an increase of its paracellular secretion. Anthranoids can

also reduce the synthesis of prostaglandin E, involved in the transport of mineral ions and water, and increase the sensitivity of smooth muscle fibrocells to serotonin and histamine, resulting in an increase of contractility.

Various studies have pointed out antibacterial and antifungal activities in leaf extracts,[21] which can be partially ascribed to the anthraquinones of the exudates.[52] These activities could also contribute to wound and burn healing. Barbaloin shows antifungal activity, while acetylated mannan has shown an ability to limit the growth of the yeast *Candida albicans* by activating macrophages. Acemannan is also used on patients affected by AIDS,[42] and it has shown *in vitro* antiviral activity on cells infected by the viruses of measles, herpes, and HIV-1.[34] Similar effects have been obtained with gel fractions containing lectins.

Anthraquinones also exert cytotoxic effects.[55] Emodins have shown mutagenic activity on the bacterium *Salmonella typhimurium*, and *in vitro* clastogenicity on mammalian cells, but they have not induced genotoxic effects on rats *in vivo*. These compounds also inhibit the growth of neurectodermal and other tumors, both *in vitro* and *in vivo*.[26,47] The latex also exhibits antileishmanial activity,[18] while diethylhexyl phtalate, another compound isolated from the plant, has been able to induce apoptosis on various leukemic cell lines cultivated *in vitro*.[38]

Dermatologic and Cosmetic Use

The plant has been used to heal skin disorders for more than 2,000 years. The gel is present in a great variety of cosmetic and dermatologic products.[22,24,43] Its main application is for skin hydration in the treatment of dry skin.[13,14] Skin hydration properties have been proved by transepidermal water loss (TEWL) measurements performed on volunteers.

Even though the gel does not act as a UV screen, it can prevent the arising of sun erithema. The gel also reduces the production of interleukins that induce immunosuppression in keratinocytes.[7,48,51] Besides protection from sun rays, the anti-inflammatory action of the gel makes it useful for eczematous conditions, while a clinical test has also shown beneficial effects on psoriasis.

Thanks to the presence of glutathione peroxidase and superoxide dismutase, the gel is also able to promote collagen synthesis and restrict the damage induced by free radicals.

Side Effects and Toxicity

Laxative anthranoid compounds present in the latex can irritate the colon and induce renal inflammation when used in massive doses or for prolonged periods. The use of these compounds must be avoided in case of colitis, Crohn's disease, irritable bladder, and intestinal obstruction. Moreover, the loss of potassium induced by laxatives can interfere with heart drugs such as antiarrhythmics.

Aloe compounds must be avoided during pregnancy, lactation, and in newborns.

The plant or the gel can cause allergy or contact and photodermatitis in sensitive subjects.[17,20,28,44,45,54]

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ARGAN TREE

Scientific name: *Argania spinosa* (L.) Skeels
Family: Sapotaceae
Parts used: Seeds

Features

The plant is native to southwestern Morocco; it is a very long-lived tree that on the average reaches an age of 120–150 years. The tree grows to 8–10 m high, and is thorny, with a gnarled trunk. The leaves are oval, 2–4 cm long, the flowers are small, with five petals of a pale yellow-green color, and the fruit is a drupe of 1.5–4 cm having a thick peel surrounding a pulpy pericarp and a very hard nut containing one, or more rarely two or three, oil-rich seeds.

The plant is very resistant and tolerates very poor soils, thus being able to survive under severe environmental conditions characterized by high temperatures and scarce rain. The species plays an ecological role that is important for humans too, since it can maintain soil humidity and fertility, thereby hindering processes of desertification and allowing the development of more remunerative agricultural activities.[3,5]

The tree is an essential resource for African rural populations, like Berber people, who use it as a source of fuel, as food for cattle, and above all for its precious oil.

(A)

FIGURE 4.4 (A) Argan Tree.

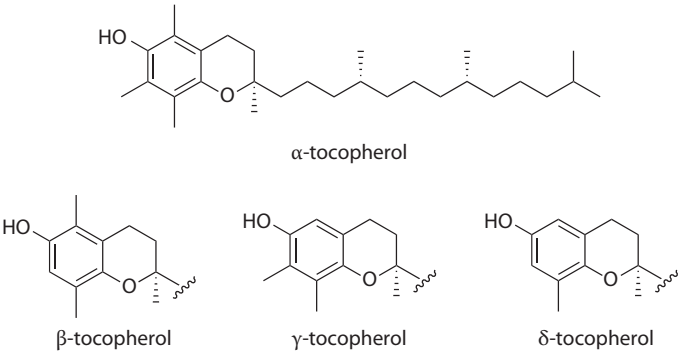
(B)

FIGURE 4.4 (B) Seeds of the Argan Tree.

In Morocco the extraction of oil from seeds is traditionally done by women organized in cooperatives. The extraction is an intense labor comprising the removal of peel and pulp from the fruit, the cracking of nuts, and the collection and gentle roasting of seeds. Roasted seeds are then grinded to form a brown paste known as amlu, and the paste is mixed with warm water and squeezed to obtain an emulsion from which the oil is collected as supernatant by decantation.[16] Much of this work is done by hands or using very simple tools. An amount of about 100 kg of seeds and a total time of about 10 h are needed to manufacture 1–2 L of oil.

Constituents

The seeds contain a large amount of oil, which can reach a value of more than 50%.[11] The oil is composed of triglycerides (95%), mostly consisting of unsaturated



fatty acids (30% linoleic). The unsaponifiable fraction consists of carotenes (37%), vitamin E (8%), triterpenic alcohols (20%), sterols (20%), and xanthophylls (5%). The phenolic component contains benzoic, hydroxybenzoic, phenylacetic, and caffeic acids, while oleuropein, flavonoids, and their glycosides are also present.[4,6,12,14]

Properties

The oil has a characteristic flavor, similar to that of walnut oil, and possesses a high nutritional value. If it is present in the diet, it seems able to induce changes in the content of polyunsaturated fatty acids of cell membranes. It can also improve the cellular antioxidant defense, probably due to its high content in vitamin E, and helps to contrast oxidative processes associated to aging.[7]

The oil is known for its choleretic and hepatoprotective properties, and acts as a remedy against hypercholesterolemia and atherosclerosis.[2] Experimental studies have shown its antihypertensive and hypolipidemic effects.[1] The residual paste of oil extraction contains triterpenoid saponins whose aglycones are protobassic and 16α-hydroxyprotobassic acid. These saponins are effective in activating lipolysis in human adipocytes. *In vitro* studies have shown that tocopherols and saponins extracted from the seed exert an antiproliferative effect on prostate cancer cells.[8]

Dermatologic and Cosmetic Use

Argan oil has been used for centuries in the traditional medicine of Morocco to heal skin disease and as a vehicle for massage.[10] Its properties make it a useful remedy for psoriasis, dermatitis, eczema, furuncles, acne, and chickenpox blisters.[9,15] It is also recommended as an unguent for rheumatic diseases.

A number of cosmetics and skin detergents based on argan oil are on the market.[13,15] These products are generally manufactured by using enriched oil, containing threefold higher levels of unsaponifiable compounds. The oil is indicated to contrast skin dehydration and for the treatment of wrinkles. It can also protect the skin against UV-B radiations.

Side Effects and Toxicity

No cases of allergies or dermatitis caused by argan oil have been reported.

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BAOBAB TREE

Scientific name: *Adansonia digitata* L.
Family: Malvaceae
Parts used: Fruit, seeds, leaves

Features

The name *baobab* is used for different tree species belonging to the genus *Adansonia*, among which the most common one is the African baobab tree, *A. digitata*.[30] This latter tree is of large size, reaching over 20 m in diameter and 20 m in height, and can live to an age of much more than 500 years. The trunk is quite thick and massive, with a conic-cylindric shape, and contains a parenchymatous tissue that can accumulate large amounts of water. Both animals and humans use parts of the trunk and the roots to quench thirst. The bark is about 2.5 cm thick and smooth, is of a grey, green, or brown color, and contains a mucilaginous material. Young leaves, or the leaves of young individuals, are simple, whereas older ones are palmate-compound. Flowers are large, up to 20 cm in diameter, white, pendant, born single or in pairs, and bloom during the rainy season, concomitantly with the appearance of young leaves. Similarly to the bark, the flowers also contain mucilage. Fruits, known as "monkey bread," are ovoidal, up to 40 cm long, with a tough, woody epicarp and an endocarp consisting of a mucilaginous pulp. The pulp is divided into segments by fibrous filaments. In ripe fruits it turns into a white powdery substance containing numerous black seeds.[14]

The word *baobab* derives from the arab *bu hobab*, meaning "fruit with many seeds." The species lives in the wild in all tropical regions of Africa, but has been introduced to other continents by chance or for park ornamentation. In its native countries it has great economic importance.[20] The fruit was known to ancient Egyptians, probably as foodstuff imported from southern regions, while it was also present on the markets of Cairo in the sixteenth century. The wooden parts of the plant are still used as building material, fibers, and fuel. The leaves, seeds, and bark can be used as foods or herbs.[10,16,25] The fruit pulp is mixed with water to obtain a whitish liquid that is used as a substitute of milk. It is also used as a leavening agent for making bread, thanks to its high content in tartaric acid.

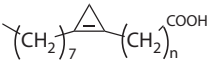
Constituents

The fruit pulp is composed of carbohydrates (75%), proteins (2.5%), and a limited amount of lipids.[18] The pulp material is partially (50%) in the form of fibers, both soluble and insoluble, which are mainly composed of pectin. Organic acids include citric, tartaric, malic, succinic, and ascorbic acids.[7] This latter (vitamin C) is present in an amount of about 300 mg/100 g of pulp, i.e., sixfold higher than the content of an orange.[6,26] Other components include terpenoids, such as α- and β-amirin palmitate, β-sitosterol, ursolic acid, group B vitamins, and minerals, among which calcium, potassium, magnesium, and iron are abundant.[17,22,27]

FIGURE 4.5 Baobab Tree.

Leaves are rich in vitamin C, carotenoids, rhamnose, uronic and tartaric acids, tannins and catechins, calcium, and iron.[23,31]

The seeds yield an oil containing oleic, linoleic, and linolenic acids, and cyclopropenic fatty acids.[9,11] The unsaponifiable fraction is mainly constituted of cholesterol derivatives, tocopherols, and hydrocarbons, of which the most abundant is squalene.[5] The seeds also contain O-acetylethanolamine.



n = 6 malvalic acid
n = 7 sterculic acid

Properties

The baobab has been used in African traditional medicines for a number of therapeutic applications.[8,13,19] The pulp of the fruit contains astringent compounds, such as tannins, mucilage, and cellulose, which exert an antidysenteric action due to an osmotic effect and an inhibitory interaction with acetylcholine, the neurotransmitter that is responsible for gut spasms. The fruit has anti-inflammatory, febrifuge, and analgesic properties, due to the presence of saponins and sterols, while experimental data have also shown hepatoprotective effects.[21]

The bark is used as febrifuge, antimalaric, and diaphoretic, while its mucilages are a remedy for gastrointestinal inflammations and diarrhea.[1,28] The bark is also

popularly considered a cardiotonic, and such a belief has been experimentally confirmed by demonstrating the positive inotropic effect of an ethanolic bark extract on the isolated atrial muscle of rat. A white, viscous gum, bleeding from cuts made in the bark, can be used to disinfect skin ulcers and wounds.

The leaves are used as an anti-inflammatory, expectorant, astringent, febrifuge, hypotensive, antiasthmatic, antidiarrhoic, for urinary tract infections, as a vermifuge or an antidote to snake bites, and against *Tripanosoma* infections.[3,12,28] Boiled leaves are applied topically to cure the Guinea worm disease, caused by the nematode *Dracunculus medinensis*. Such a preparation promotes the emergence of the parasite from its subcutaneous locations, and promotes the healing of the blisters formed on skin by the extraction procedure.

Leaves and bark also contain a typical alkaloid, named adansonin, which is used as an antidote to the alkaloid strophanthin that is present in vines of the genus *Strophanthus*. In past years, adansonin was on the market as a substitute of quinine for its febrifuge properties. *In vitro* studies have shown that the bark, leaves, and roots have antiviral and antimicrobic properties, while an ethanolic extract from flowers has shown antifungal effects. The root decoction is used as an aphrodisiac, and the infusion can be used for the bath of babies to maintain their smooth and soft skin.

Dermatologic and Cosmetic Use

Various products derived from baobab are useful for skin care.[29] The complex of the vitamins of the fruit pulp exerts a positive synergistic action that includes the emollient and levigating effect of vitamin A, the induction of melanin synthesis by the complex B1/B2, the regulation of sebaceous gland excretion by vitamin B6, the improvement of cutaneous circulation by vitamin B4, the antioxidant defense and collagen synthesis stimulation by vitamin C, the contrasting action against lipid peroxidation by vitamin E, and the protection from tissue matrix degradation by triterpenic compounds.

The fiber contained in the pulp exerts antiaging and antioxidant effects on the skin. Leaf extracts have antioxidant, emollient, and soothing properties on the skin, render it soft and elastic, and also exert an antibacterial action.

The seed oil improves the hydration, firmness, and lightness of the skin. It also has lenitive and anti-inflammatory effects due to its content in essential oils, sterols, and hydrocarbons. The oil is then an ideal treatment for dry skin and to prevent wrinkles. It can moreover heal skin abrasion, sunburns, and hematomas, while it also promotes tissue regeneration.

Side Effects and Toxicity

The fruit pulp does not cause toxic or allergenic effects due to alimentary use. Also, allergenic or irritating effects due to topical use have not been observed.[15] Cyclopropenic fatty acids contained in the seed oil can interfere with cellular processes of lipid desaturation, thereby altering cell membranes, the synthesis of prostaglandin and sterols, and other metabolic processes.[2,4,24] However, these properties do not generally produce noxious effects on humans due to dietary use of the oil, since it is generally cooked, and this process drastically decreases the levels of cyclopropenic acids.

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BEARBERRY

Scientific name: *Arctostaphylos uva-ursi* (L.) Spreng.
Family: Ericaceae
Parts used: Leaves

Features

Small procumbent woody shrub with elastic branches. The leaves are evergreen, alternate, glossy and coriaceous, obovate, entire-marginate, and slightly revolute. The flowers are ovoid to jug shaped, 5–6 mm long, white reddish, with a red border and five short tips rolled backward. They are grouped in terminal clusters. The fruit is a pea-sized, scarlet drupe with an acid taste.

The plant grows commonly on acid soils in stony places and open woodlands. Its distribution is circumpolar, widespread in northern latitudes, and confined to high altitudes farther south.

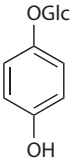
The Latin name *uva ursi* derives from the belief of the seventeenth-century French botanist Michel Adanson, who first described the species, which was eaten by bears. The English common name of *bearberry* is accounted for by this belief. The leaves are gathered in the wild and dried before being marketed.

FIGURE 4.6 Bearberry. Courtesy of Remo Bernardello. (See color insert following page 40.)

Constituents

The chief active principles are phenolic heterosides, up to a total content of approximately 6%, of which the most important ones are arbutin (hydroquinone-O-β-D-glucopyranoside, about 5%), methyl-arbutin, and piceoside.[3] Other constituents are

gallotannins (15–20%); flavonoids, such as quercetin and myricetin; triterpenes, such as ursolic acid, uvaol, and amirin derivatives; the iridoid monotropein; organic acids like malic and quinic acids; allantoin; resins, such as ursone; essential oil; and wax.[4,9,11]



Arbutin

Properties

The plant has been used in the European traditional medicine since the Middle Ages and in the 1700s it was included in the British Pharmacopeia. It is a diuretic, antiseptic, and astringent, and is generally used for infections, inflammations, calculi, and other ailments of the urinary tract.[16,17]

The extract has antimicrobial effects, which are generally ascribed to arbutin.[8] However, these properties seem to depend on the activity of hydroquinone, which is produced in the organism from arbutin hydrolysis after oral intake of bearberry leaf extract. Hydroquinone undergoes a process of glucurono- and sulfo-conjugation in the liver, and is then excreted by the kidney, where it exerts antibacterial action. Hydroquinone is also formed in the urine, and this process is favored by an alkaline pH.[6] Hence, sodium bicarbonate is an adjuvant in the therapeutic use of arbutin.

The adhesion of gram-negative bacteria to host cells is an important step in the pathogenesis of bacterial infections and depends on the surface hydrophobicity of these microorganisms. It has been shown that the plant aqueous extract can reduce the hydrophobicity of *Escherichia coli*, *Helicobacter pylori*, and other bacterial strains, and such antibacterial activity is generally ascribed to arbutin.[19] It seems that the mechanism of this action should depend on the β-glucosidase activity of the infective agents, which would convert arbutin to hydroquinone. Aqueous and methanolic extracts have also shown molluscicidal activity, probably due to the presence of tannins.

Quercetin and ursolic acids are powerful diuretics. It has been observed in animal studies that the exposure of rats to the dry extract enhances the renal excretion of water, mineral salts, and uric acid.

The alcoholic extract has a high antioxidant power and is used as an additive for food preservation.[5] Arbutin enhances the anti-inflammatory activity of indomethacin, as shown by the carrageenan-induced rat paw edema test.[15] A similar effect has been obtained by the combination of arbutin with prednisolone or dexamethazone.[10,13,14]

Plant extracts have induced *in vitro* the inhibition of various isoforms of the P450 cytochrome. The extracts have inhibited the P glycoprotein transporter in human monocytes and CaCo2 enterocytes after 1 h exposure, while in contrast they have induced a stimulatory effect after 18 h.[1]

A study on the gene expression profile of melanoma cells has shown that arbutin can inhibit the expression of genes potentially involved in tumor progression.[2] Moreover,

the *in vitro* treatment with hydroquinone of hepatoma cells has induced higher cytotoxic effects with respect to antitumor drugs like azauridine and colchicine.

Dermatologic and Cosmetic Use

The plant is used in skin care products mostly for its depigmenting action.[7,12] Hydroquinones are well-known inhibitors of tyrosinase, the enzyme responsible for L-tyrosine oxidation in the biosynthetic pathway of melanin. An *in vitro* experimental study has shown that arbutin inhibits the synthesis of melanin in human melanoma cells and in a three-dimensional human skin model.[18]

Ursolic acid exerts an anti-inflammatory action on the skin, and moreover, it inhibits elastase, hence being an interesting compound for antiaging products. Allantoin is used as an active principle in creams against herpes and vaginal infections.

Side Effects and Toxicity

The plant is contraindicated during pregnancy, especially in the first trimester, since it can induce uterine contractions. It should also be avoided during lactation. The ingestion of high amounts of hydroquinone (1 g = 6–20 g of leaves) produces severe systemic toxicity.

Because of the high amounts of tannins, the prolonged use of the plant, even at proper doses, can induce liver malfunction. One case of retinal macular degeneration due to prolonged use has also been reported.[20]

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BILBERRY

Scientific name: *Vaccinium myrtillus* L.
Family: Ericaceae
Parts used: Fruits, leaves

Features

Deciduous dwarf shrub with branched stems, up to 50 cm high. Leaves are 6–18 cm long, alternate, ovate to elliptic, acuminate, with a serrate margin. Flowers are axillary, white–pale pink, with a globular, jug-shaped corolla having five tips and a five-lobed calyx fused to the ovary. The fruit is a globular, blue–dark berry, with a purple pulp and many oval, reddish seeds.[17,34]

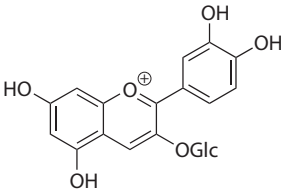
The species grows in alpine woods with humus-siliceous soil. It is diffused in temperate cold areas of Europe, Asia, and North America.[41] The leaves are collected in June-July, dried, and stored in paper or cloth bags. The fruits are collected in August, when they reach ripeness, and have a high nutritional value. They can be eaten fresh or used to make jam, juices, or to flavor drinks.

FIGURE 4.7 Bilberry. (See color insert following page 40.)

Constituents

The main constituents of leaves are catechol-derived tannins, chlorogenic acid, iridoids, hydroquinone, and its β-D-glucoside arbutin.[46] Chromium and manganese are relatively abundant among minerals. The fruits contain anthocyanic flavonoids

(about 0.5% dry weight) in the form of galactoside, glucoside, rhamnoside, and arabinoside glycosides, while the aglycone moieties are delphinidin, cyanidin, petunidin, peonidin, and malvidin.[16,19,20,36] Other components are catechin tannins; pectins; citric, malic, lactic, oxalic, and ascorbic acids; provitamin A; group B vitamins; carotenoids; and quinolizidine alkaloids such as myrtine and epimyrtine. The seeds yield an oil containing unsaturated fatty acids.



cyanidin 3-O-glucoside

Properties

Anthocyanic pigments (anthocyanosides) have different pharmacological properties. Similarly to vitamin P, they protect blood vessels and improve blood circulation, thus preventing tissue edema and in particular lower limb swelling and fatigue.[26] These compounds seem to act on the basal membrane of the endothelium, the epithelial layer that surrounds blood vessels. The basal membrane is composed of different elements of the extracellular matrix, whose degradative processes are prevented by the active principles of bilberry. Anthocyans inhibit jaluronidase, the enzyme that degrades jaluronic acid, and stimulate the enzyme prolyne oxidase, which promotes the formation of cross-links between collagen fibers. Anthocyans also bind to the phospholipids of cellular membranes, as shown by buccal mucosa staining after the ingestion of berries. These bonds contribute to strengthen the endothelial layer and reduce its permeability.

Anthocyanic pigments also have a relaxation effect on vessel smooth muscles, probably through the stimulation of prostacyclin and nitric oxide production.[11] It has been shown that cyanidin-3-glucoside increases the activity of the endothelial nitric oxide synthase (eNOS).[48] This occurs through the activation of a phosphorylation cascade involving the Src tyrosine kinase, the ERK1/2 MAP kinase, and the Sp1 transcription factor.[47] eNOS produces nitric oxide, which induces a relaxation of smooth muscles, thereby causing vasodilation.

Another well-known property of bilberry anthocyans concerns the improvement of night vision.[6,24] Such an effect is due to a faster turnover of rhodopsin, a protein contained in rods, the photoreceptors of retina that can function in less intense light. Rhodopsin contains 11-*cis*-retinal, a pigment derived from *trans*-retinoic acid, which upon absorption of one photon is converted into the all-*trans* form. This induces a conformational variation of rhodopsin, which triggers the conversion of the light stimulus into a nerve impulse. Rhodopsin is then decomposed into opsin and all-*trans* retinal, and is eventually regenerated through recombination with a molecule of 11-*cis*-retinal. Various studies indicate that the anthocyanins cyanidin and delphinidin

and their glycosylated forms promote the turnover of rhodopsin, and therefore ensure an enhancement of the cone sensitivity to light.[2,22,30,43] The phytotherapeutic use of bilberry for vision disorders dates back to World War II, when bilberry jam was fed to the English RAF pilots in order to improve their night vision.[35]

The reinforcement of blood circulation also has positive effects on vision, since it ensures a better blood supply to the retina. The use of bilberry is therefore indicated for diabetic or hypertensive retinopathy, pigmentary retinitis, and short-sightedness.

Anthocyanosides can prevent diseases linked to hyperglycemic conditions. These compounds inhibit the enzyme aldose reductase, which converts glucose to sorbitol and in diabetic or obese subjects produces an accumulation of sorbitol in various tissues like the lens, the nervous system, and the kidneys, leading to various diseases such as diabetic retinopathy. In diabetic mice, anthocyanosides in combination with proanthocyanidins and chromium have induced a decrease of glycemia by 13%. Trivalent chromium, Cr(III), contained in high amounts in the leaves, about 9 ppm, is essential for the regulation of glycemia. Chromium insufficiency is associated with the development of type 2 diabetes mellitus.

Clinical studies have indicated that the plant extract would increase the ratio HDL/LDL, thus reducing the risk of cardiovascular disease. It has also been shown that cyanidin and quercetin inhibit the oxidation of LDL lipoproteins.[25,32] A leaf alcoholic extract has reduced the glycemia of diabetic rats and decreased the blood levels of triglycerides in rats treated with a hyperlipidic diet.[9]

Bilberry is one of the plants with the highest antioxidant power.[13,29,45] Anthocyanosides act in synergy with other polyphenols like tannins in free radical scavenging.[3] It has been shown that an extract rich in anthocyanins is able to protect blood cells and the cells of the hematopoietic tissue from oxidative damage induced by the wide-spectrum chemotherapy drug 5-fluorouracil.[8] Another extract containing various polyphenols stimulates human retina cells *in vitro* to synthesize antioxidant enzymes, such as glutathione-S-transferase and heme oxygenase 1.[33] A similar extract has protected rat hepatocytes from oxidative damage induced by tert-butyl-hydroperoxide and allyl alcohol.[44] Cyanidin-3-glucoside has protected hepatoma and colon adenocarcinoma cells from oxidative injuries induced by aflatoxin B1 and ochratoxin A.[18] The same compound, administered orally to rats, has reduced the oxidative damage induced by hepatic hyschemia/reperfusion, and has limited the infiltration of neutrophils, a process that induces inflammation.[42]

The antitumor properties of anthocyanosides have also been deeply investigated.[5,23,28] In murine hepatoma cells, delphinidin increases the activity of different antioxidant enzymes, including glutathione-S-transferase and heme oxygenase, and reduces cell growth rates.[21] Various tumor cells exposed to peonidin-3-glucoside or cyanidin-3-glucoside have shown the inhibition of proteins that regulate the cell cycle, like the cyclin-dependent kinases CDK-1 and CDK-2, and the cyclins B1 and E, thereby producing an arrest of cell cycle at G2/M, caspase 3 activation, chromatin condensation, and apoptosis.[7]

An ethanolic extract and the anthocyanins delphinidin and malvidin isolated from it have inhibited the growth of leukemia HL-60 and of colon carcinoma HCT-116 cells. Cyanidin-3-glucoside induces the differentiation of leukemia

HL-60 cells in macrophage-like cells, blocking their proliferative activity and inducing apoptosis.[14,15] This compound can also induce a differentiation of human melanoma cells from a proliferative to a nonproliferative condition.[39] Cyanidin and delphinidin block the activity of the epidermal growth factor receptor (EGFR) in vulvar carcinoma cells A431, thus inhibiting the activation cascade that stimulates the cell growth.[31]

Anthocyanosides exert anti-inflammatory and antiulcer action.[27] It has been observed, in particular, that cyanidin-3-glucosylrutinoside and cyanidin-3-rutinoside inhibit cycloxigenases 1 and 2.[38] Bilberry extracts also inhibit the platelet aggregation induced by collagen, ADP, and arachidonic acid. It has been experimentally shown that the fruits and the leaves prevent the growth of coli bacilli in the intestinal and urinary tract. The plant can also protect the gut from pinworms, frequently occurring in children.

Dermatologic and Cosmetic Use

The extract can be used for skin diseases and unaesthetisms like ulcers, eczema, folliculitis, and varicose veins.[12,37,41] The improvement of microcirculation prevents the development of periocular edema (eyelid laxity), cellulite, leg fatigue, and skin vasodilations like telangiectasia. The anti-inflammatory and lenitive properties of anthocyans are useful to soothe particularly sensitive skin areas such as eyelids. The infuse is used as a colluttory for inflammations of the mouth and upper airways. Anthocyanosides and anthocyanidins are also interesting as skin photoprotecting agents.

Experimental studies have shown that cyanidin-3-glucoside protects HaCaT human keratinocytes *in vitro* against UV-A-induced damage, by reducing DNA fragmentation, oxidative stress, and apoptosis.[40] This compound also protects kertatinocytes from UV-B, through the inhibition of the NFkB transcription factor, interleukin 8 production, and caspase 8 activation.[10] Delphinidin also protects HaCaT cells from injury induced by UV-B rays, such as lipid peroxidation, poly-ADP-ribose polymerase (PARP) degradation, and the activation of caspase and other proapoptotic agents.[1] The topical application of this latter compound to nude mice irradiated with UV-B has inhibited the induction of DNA damage and apoptosis in the skin tissue.

Side Effects and Toxicity

Fresh fruits consumed in high amounts can cause diarrhea.[41] Conversely, dry fruits have astringent properties due to the presence of concentrated amounts of tannins and pectins. The ingestion of fruits can also interfere with the intestinal adsorption of iron. Leaves can be toxic if taken in high doses or for a long time.[4]

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BLADDERWRACK

Scientific name: *Fucus vesiculosus* L.
Class: Phaeophyceae (brown algae)
Family: Fucaceae
Parts used: Fronds

Features

Perennial brown alga distributed along the coasts of the British islands, Baltic Sea, and North Atlantic and Pacific oceans. It forms wide seagrass meadows that appear at the surface during low tides. The alga attaches to rocky sea bottoms by means of rhizoids shaped like a sucker, and can grow to a length of 100 cm or more. The fronds are straplike with dichotomous branchings and a central midrib on either side of which regularly spaced pairs of vesicles (aerocysts) are present. Vesicles are filled with nitrogen gas and allow for buoyancy.

In the Far East the alga is used as food, while in Europe it is on the market as a feeding integrator and is moreover used as livestock crop.

FIGURE 4.8 Bladderwrack.

Constituents

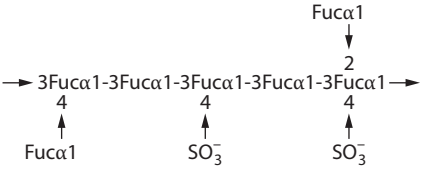
The alga contains large amounts of polysaccharides (about 65% dry weight), mainly components of the cell wall, such as alginate (up to 25% dry weight) and fucoidan, a sulfated polysaccharide containing L-fucose.[19,27] Another main polysaccharide is laminarin, a storage glucan consisting essentially of D-glucose and similar to amylopectin.[26]

Bladderwrack has a low protein content, less than 10% dry weight, which is a common feature of brown algae. Conversely, it is rich in fatty acids, mainly eicosapentanoic

and arachidonic acids.[1] Other lipids include fucosterol, phytol, C18–30 aliphatic alcohols, C10–35 paraffins, pristane, squalene, and essential oil.

The alga also contains polyphenols belonging to the group of phlorotannins (5–15% dry weight); bromophenols; vitamins, chiefly C and E (200–600 mg of tochopherols/kg of dry weight); and carotenoids like fucoxanthin, violaxanthin, and β-carotene.[12,14,16,24,25]

Iodine is the mineral present in the highest amounts (300–1,000 ppm of dry weight). However, the levels of iodine show some variability in different algal populations, according to their site of origin (North Sea: about 0.1%; Baltic Sea: about 0.03%; etc.). The highest quantity of iodine is present as inorganic iodide, while the rest is bound to amino acids and proteins. Relatively high amounts of potassium and arsenic are also present.



Pankter model for the average structure of fucoidan (from Li et al. 2008)

Properties

In traditional medicines the alga is mainly used as a source of iodine and for various thyroid disorders.[5] Goiter is a swelling of the thyroid due to iodine deficiency, and the therapeutic use of the alga to treat this disease has been known since at least the middle of the nineteenth century. The stimulation of the thyroid gland can also increase the metabolic rate, thereby contrasting hyperglycemia and obesity.[17] For the same reason, the alga can be used to diminish lipid degenerations in various organs, such as heart steatosis.

The presence of other active principles makes this alga interesting also for other therapeutic purposes. Alginic acid swells upon contact with water, and such a behavior can be used to contrast gastric acid reflux, while in the intestine it can generate a laxative effect.

Fucoidans have been studied for their anticoagulant, antihumoral, antiviral, and anti-inflammatory properties.[2,3,6,7,9,20,21,29,30] These compounds make the alga suitable for rheumatisms by topical application, and to decrease kidney irritation and congestion or chronic bladder inflammation. Arabinogalattan and fucoidan have shown immunostimulatory properties *in vitro*, by promoting the proliferation of spleen lymphocytes and peripheral macrophages.[4,15]

Dermatologic and Cosmetic Use

The use of algae in body care practices has a long tradition and has become a well-established area of natural medicine, which is known as algotherapy and is strictly related to thalassotherapy.

The high content in mucilaginous polysaccharides of the bladderwrack is exploited as an emollient and protective remedy for the epidermis, while the good levels of iodine confer the alga-slimming and anticellulite properties.[13,31]

In vitro studies have shown that the extract promotes the contraction of a collagen gel containing fibroblasts, due to an increased expression of integrins by these cells. It has also been shown that the active principle responsible for this effect is fucoidan.[10] In agreement with such a result, it has been assessed that repeated application of a preparation containing 1% of the extract on the cheek of volunteers causes a reduction of skin thickness and an increase in skin elasticity, thus contributing to reduce the traits of aging.[11]

Side Effects and Toxicity

The alga contains organic iodine and must therefore be administered carefully to individuals with cardiovascular diseases, hyperthyroidism, diabetes, or during pregnancy and lactation.[22] Moreover, excessive or prolonged doses can induce hyperthyroidism associated with tremor and increased heart rate and blood pressure.[8,28]

The accumulations of heavy metals and arsenic in sea algae suggest caution for their use as food, drugs, and cosmetics.[23] *In vitro* studies have pointed out both genotoxic and antigenotoxic effects of the extract on human lymphocytes.[18]

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BOSWELLIA

Scientific name: *Boswellia serrata* Roxb. ex Colebr.
Family: Burseraceae
Parts used: Gum resin from the bark

Features

The genus *Boswellia* comprises different species, some of which produce aromatic resins commonly known as incense. One of these species is *Boswellia serrata*, a medium-size tree indigenous to India. The leaves are pinnate, hairy, and borne near the branch tips. The flowers are small, white, and scented. The fruit is a drupe containing three small seeds. The bark is ash grey in color and has many resin channels. When the bark is cut, a gum resin oozes out from it. The dried resin is known as *salai guggul* in India and as Indian frankincense in Western countries.[52] In India the resin has been collected in such large quantities that the Indian government has put restrictions on these activities in order to avoid overexploitation. Indian frankincense was used in the religious ceremonies and embalming practices of ancient Egyptians, as well as having been used for many centuries in the Greek and Roman churches.[13,14,26,33] The resin smoke seems to have psychotropic properties that would induce the mind to get into meditation.[30] The resin combustion releases transhydrocannabinol, a compound similar to tetrahydrocannabinol, the main active principle of *Cannabis*.[23]

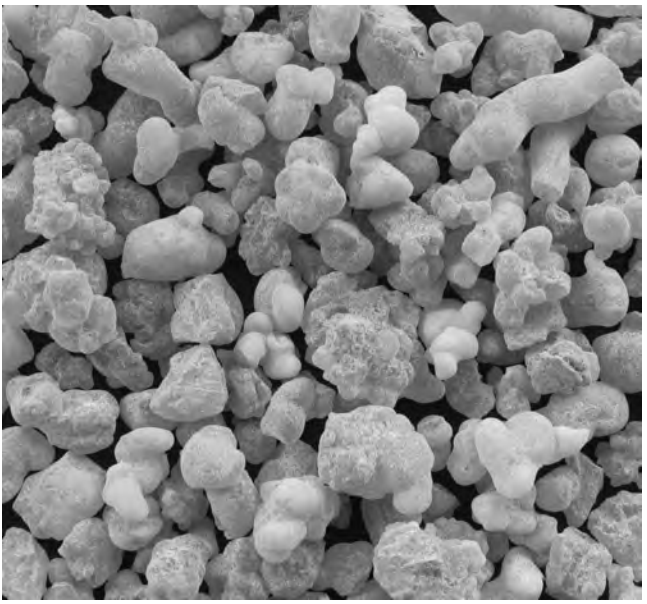
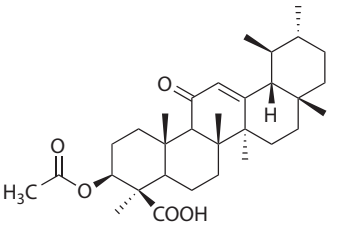


FIGURE 4.9 Indian Frankincense.

Constituents

The gum resin consists of an ethanolic fraction (65–85%), composed of resins (diterpenes, triterpenes), and of a hydrosoluble fraction, composed of gums.[7,20,21,37,44] The chief active principles are the pentacyclic triterpenes boswellic acids, the most powerful of which are 3-O-acetyl-11-keto-β-boswellic acid (AKBA) and acetyl-β-boswellic acid (ABA). An essential oil (5–9%), including mono- and sesquiterpenes, is also present in the resin and in other plant portions.[11,35,46]



3-O-acetyl-11-keto-β-boswellic acid

Properties

The use of the plant is common in the African, Chinese, and Ayurvedic traditional medicines.[40,54] Its anti-inflammatory properties can be exploited to treat rheumatic pains, respiratory syndromes, enteric inflammations, and various skin diseases.[6,19,24]

The plant was also used empirically in Western countries, but the advent of synthetic drugs obscured its pharmaceutical use. Later on, however, it was reported that an ethanolic extract exerts anti-inflammatory and antiarthritic effects, and it was shown that these effects are primarily due to the action of boswellic acids.[4,8,9,15,47,48] These compounds are specific inhibitors of 5-lipoxygenase, and therefore they hinder the formation of leukotrienes, which are main mediators of inflammatory processes.[3,5,36,39] It has also been found that AKBA can partially inhibit cycloxygenase 1, another enzyme playing a main role in inflammation.[45] In addition, the gum resin seems not to induce the typical side effects of conventional anti-inflammatory drugs, such as gastric irritation and ulcer, even after prolonged oral therapy.

Another relevant action of boswellic acids is the inhibition of enzymes such as leukocyte elastase and hyaluronidase, which degrade the extracellular matrix and contribute to the tissue degeneration processes typical of inflammation.[38]

AKBA and ABA can also inhibit the activities of topoisomerase and IkB kinase (IKK), thereby inducing apoptosis in tumor cells.[22,50,51,55] Direct inhibitory effects of boswellic acids on cancer cell growth and on cancer-induced angiogenesis have also been shown.[27–29,43,49] At the cellular level, acetyl-β-boswellic acids mobilize intracellular calcium and induce the activation of the p38 and ERK1/2 MAP kinases.[2,17]

Due to their multiple properties, boswellic acids are used as analgesic, antirheumatic, antiallergic, antiarthritic, antiasthmatic, antiedemic, antileukemic, and antitumor agents.

Another resin constituent, the diterpenoid incensole acetate, has shown inhibitory effects on the gene activation factor NFkB, which is involved in immune and

inflammatory responses.[34] This finding suggests that the anti-inflammatory properties of the plant should not be ascribed only to boswellic acids.

Dermatologic and Cosmetic Use

The gum resin is used in a number of cosmetic and dermatologic products, and is particularly effective in the treatment of seborrhea and acne.[12,16,41] Its anti-inflammatory properties make it extremely useful in the soothing of skin irritations. In these treatments, the inhibitory action of boswellic acids on metalloproteinases plays a substantial role, since some of these enzymes become activated in case of skin irritation. This kind of inhibition can prevent or retard photo- or chronoaging, wrinkle formation, and other processes linked to the degeneration of cutaneous and subcutaneous connective tissue.[18,31,32]

By using a murine model of psoriasis, it has been found that AKBA diminishes NFkB activation in macrophages, thus ameliorating skin inflammation.[53]

Side Effects and Toxicity

In vitro studies have shown that the gum resin and AKBA induce moderate to low toxicity on different skin cell types.[10] In line with these results, the therapeutic uses of *Boswellia* extracts are generally devoid of side effects.[25,42] Allergic skin reactions have been observed only in rare cases.[1]

However, *in vitro* studies on human keratinocytes have shown that AKBA can increase interleukin 1α–induced activation of metalloproteinase 9 (MMP-9). In similar experiments, using the gum resin combined with interleukin 1α, MMP-9 activation has been increased at higher resin doses, while it has been inhibited at lower doses. These data suggest that in skin treatments the gum resin should be carefully dosed, in order to avoid noxious side effects under specific conditions.

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BREWER'S YEAST

Scientific name: *Saccharomyces cerevisiae* Meyen ex E. C. Hansen
Phylum: Ascomycota (ascomycetes fungi)
Family: Saccharomycetaceae
Parts used: Cells
Other names: Baker's yeast

Features

Unicellular fungus with ovoid-elliptical cells measuring about 5–10 μm in diameter, which proliferate by budding. Under stress conditions, the cells produce quiescent spores, which at the return of favorable conditions germinate and reconstitute the vegetative form.

The fungus is the major source of baking powder used in domestic activities and food industries. It is mainly used in the bakery, in the brewery, in the biological production of ethanol, and as a food integrator.[24]

Brewer's yeast is one of the most studied organisms, since it can be easily cultured in laboratory. Moreover, knowledge achieved on its cellular and molecular mechanisms can be applied to humans. It was the first eukaryotic organism for which a complete sequencing of the genome was achieved, and various human proteins have been described after the discovery of their homologues in the yeast.[2,8,13]

Brewer's yeast is massively produced in industrial processes making use of fermentation reactors where cells are grown on malted barley. In this process, the temperature can be set between 0 and 5°C, yielding bottom-fermenting yeast that is

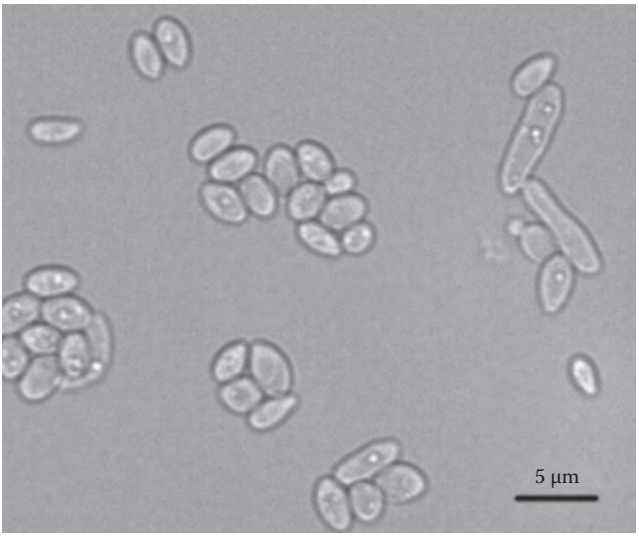
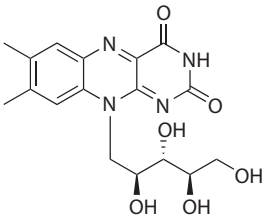


FIGURE 4.10 Brewer's Yeast. Courtesy of Dr. Lorena Avidano, Prof. Simonetta Sampò, University of Piemonte Orientale, Alessandria, Italy.

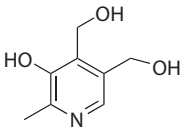
collected at the bottom of tanks, or between 15 and 20°C, yielding top-fermenting yeast that forms a foam floating on the surface. Yeast cells are then separated by the substrate, simply dried or freeze dried, and put on the market. The two kinds of yeast are used in the fermentation of different brews of beer, e.g., top-fermenting for ale and bottom-fermenting for lager.

Constituents

Brewer's yeast is rich in protein and sugars, while it contains limited amounts of lipid. It is also a complete source of vitamins of the B complex, including niacin (B3), pyridoxine (B6), thiamine (B1), folic acid (B9), riboflavin (B2), pantothenic acid (B5), biotin (B7), and cobalamin (B12). Other relevant constituents are monoterpenoids and mineral salts, such as potassium, calcium, phosphorous, zinc, iron, chromium, and selenium.[21]



riboflavin (vitamin B_2)



pyridoxine (vitamin B_6)

Properties

Brewer's yeast is mainly used for its nutritional properties.[7,20] For instance, the supply of vitamin B3 prevents the onset of pellagra. However, it is also a useful remedy against neural inflammations, due to the presence of neurotropic vitamins like B1 and B6; against anemia, due to vitamins B9 and B12; and against malnutrition and emaciation, due to the presence of anabolizing vitamins like B2 and B5.

The body districts that benefit from group B vitamins include the immune system (B2, B5, B6), digestive system (B1, B2, B3), adrenal glands (B5), hematopoietic tissue (B2, B5, B9), skin and mucosae (B1, B2, B3, B6, B9), and liver (B1, B2, B6, B9). Vitamins B3 and B6 are essential for the production of the neurotransmitter serotonin, ensuring mental health and preventing sleep disorders.

The nutritional importance of brewer's yeast is also linked to the presence of organic trivalent chromium, known as glucose tolerance factor (GTF).[23] This factor improves the action of insulin, contributes to normalizing glycemia, and reduces glucose and free fatty acid blood levels in diabetics.[4,18]

Various other therapeutic properties of yeast are known. It is a tonic of the nervous and cardiovascular systems, stomachic, digestive, antianemic, antimicrobial, antiatherosclerotic, detoxifier, and antidiabetic. In addition, a polysaccharide extracted from the cell wall, β-(1,3)/(1,6)-glucan, is a strong immunostimulant, while the presence of selenium and β-glucan is responsible for antitumor properties.[3,9,12]

Dermatologic and Cosmetic Use

Yeast extracts are indicated for fatty skin and acne. Extracts also exert a trophic action on the deep skin layers and skin annexes, and have been shown to accelerate wound healing.[5,10,22]

An alcohol extract used for topical application, known as skin respiratory factor (SRF), enhances the oxygen consumption and metabolism of the skin tissue and is used in products against wrinkles, infections, and inflammations, or as a cicatrizant. Yeast derivatives have also been patented as pigmenting agents and collagen synthesis promoters.[6,14,16,17]

Side Effects and Toxicity

Oral ingestion of vital *S. cerevisiae* cells can give rise to rare fungemic episodes, particularly in subjects treated with the yeast *S. boulardii* as a probiotic.[11,19] Hence, the oral use of *S. cerevisiae* should be avoided by subjects with infections, immunodepression, or under any other kind of stressful condition. The brewer's yeast can also induce food allergy, and due to the presence of the amino acid tyramine, can interfere with antidepressant and narcotic drugs.[1,15]

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BURDOCK

Scientific name: *Arctium lappa* L.
Family: Asteraceae
Parts used: Roots, leaves, fruits

Features

Biennial grass of medium size with a fleshy taproot, forming a basal rosette of large leaves in the first year, and a flowering stem in the second year. The plant can grow up to 1.5 m in height. The stem leaves are cordiform, green on the upper side and whitish-greyish on the lower side. The plant flowers from July to September, forming spherical head inflorescences of a purple color, frequently arranged into corymbs. The heads are surrounded by an involucre of spiny bracts that can attach to the fur of animals or the clothing of people. The bracts inspired the invention of Velcro. The fruits are achenes with pappus. The species is native to temperate regions of Europe and Asia, and is naturalized in North America. It is a nitrophilous plant growing spontaneously in natural meadows or cultivated in urbanized areas, up to an altitude of 1,500 m a.s.l. Stems, roots, and seeds can be used as food, mainly in Asian countries. Roots are mostly used for therapeutic purposes. They have to be collected during the first year, i.e., before the flowering period.

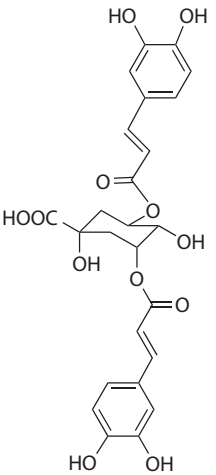
FIGURE 4.11 Burdock. (See color insert following page 40.)

Constituents

The plant's active principles include polyacetylenes; terpenoids like the sesquiterpenes arctiol, β-eudesmol, and fukinone; bitter principles like costusic acid and derivates; thiophenes like arctinone, arctic acid, and derivates; and lignans like arctiin, arctigenin, and lappaols.[17,28,32] The main polysaccharides are inulin and other fructose-oligosaccharides (up to 70% in the root), mucilages (up to 40%), pectin, and simple sugars.[12] There are also organic acids, among which are acetic, butyric, caffeic, chlorogenic, and γ-guanidine butyric acids, aldehydes, and amino acids.

The lipid fraction contains linoleic, linolenic, myristic, and oleic acids. The plant is moreover rich in fibers and contains such compounds as the bitter principle lappatin, phytosterols (sytosterol and stigmasterol), resins, and tannins.[34] Among minerals, the relatively more abundant ones are calcium, potassium, and iron.

The root also contains an essential oil in which tens of compounds have been identified. The lignans neoarctin B, daucosterol, matairesinol, and lappaol F have been isolated from achenes.[35]



3,5 dicaffeoylquinic acid

Properties

The medicinal importance of the plant dates back to ancient times. In the Middle Ages it was used for scurvy, diabetes, syphilis, and leprosy. In traditional Chinese medicine it has been used in combination with other herbs to heal colds, measles, pharyngitis, and tonsillitis. It has also been traditionally used as a detoxificant, diuretic, laxative, anti-inflammatory, or for skin diseases and chronic disorders like gout, arthritis, and rheumatism. The plant is also considered a good remedy for kidney stones.[1,33] However, many of the properties claimed by traditional medicines have not yet been supported by clinical evidence.

The presence of bitter principles is probably at the basis of the stimulatory properties on the gastrointestinal tract, liver, and pancreas. The plant has an antiseptic

action that can be ascribed to polyacetylenes and arctiopicrin, a bitter principle acting against gram-positive bacteria and fungi.[8]

Arctic acid has a draining and detoxifying action on the liver, while γ-guanidine butyric acid has an insulin-like effect, inducing a suppression of gluconeogenesis, a stimulation of anaerobic glycolysis, and an inhibition of glycogenolysis. This latter compound also inhibits glucose uptake in the gut. These actions are responsible for the hypoglycemizing effect, which is further accentuated by sesquiterpenes and inulin.[13] Plant extracts can reduce the intestinal absorption of cholesterol and lipids, and inhibit the formation of lithocholic acid, a derivative of biliary acids that is considered a marker of risk for colorectal cancer.[29] The plant is also a mild laxative, most likely due to its high content in inulin. In addition, it has been shown that a fiber-rich diet can reduce the intestinal uptake of environmental contaminants, such as polychlorinated biphenyls (PCBs).[20,30]

The plant is a diuretic, and it helps the renal function of blood toxin excretion. It is also a diaphoretic, hence favoring the excretion of toxins through sweat. The mechanisms of the antiflogistic action can be explained by the results of *in vitro* studies. The lignan isolappaol C and other derivatives of lappaol, which have been isolated from the methanolic fruit extract, inhibit the production of NO induced in macrophages by lipopolysaccharides.[23] Moreover, studies carried out in the mouse have shown that the crude extract reduces carrageenan-induced paw inflammation, and protects the liver from injury caused by CCl_4 combined with ethanol or acetaminophen.[15,16] These latter properties have been attributed to the free radical scavenging activity.[5,14] Protective effects on the liver have also been exerted by derivatives of dicaffeoylquinic acid.[2]

The extract has also shown antimutagenic properties,[21] e.g., by preventing the formation of chromosome aberrations in rat bone marrow cells exposed to methyl-benzo(a)anthracene.[11] A fructofuranan similar to inulin, isolated from the root, has shown immunostimulatory properties on laboratory animals.

The extract has also been studied for its antitumor activity.[4] *In vitro* studies have reported that the lignan arctigenin 1 and its derivates induce apoptosis in leukemia cells, or their differentiation into phagocytic cells.[18,19,31]

Dermatologic and Cosmetic Use

The plant is indicated for various skin disturbances. In traditional Chinese medicine it is used for acne, seborrhoeic dermatitis, and eczemas. These properties derive from a wide range of actions of the extract, which is an antiseptic, cicatrizing and detoxifying. The plant is used in creams for the treatment of greasy skin, which is prone to develop acne and seborrhea,[22] and is also used in shampoos and lotions for head skin affected by an excessive production of sebum.[10] Plant extracts are also used against dandruff and psoriasis. As for the action of active principles, caffeoylquinic acid protects collagen from alterations induced by UV-A, while caffeoyl conjugates like cichoric and caftaric acid inhibit the enzyme hyaluronidase,[6,7] which is the main enzyme responsible for skin damage induced by acne and seborrhoeic dermatitis.

Side Effects and Toxicity

The plant is inadvisable during pregnancy or lactation since it can induce uterine contractions. It should also be used carefully on patients treated with antidiabetics and diuretics, due to its possible interaction with these drugs. The high presence of fibers can interfere with the intestinal absorption of iron and other minerals.[9]

A case of atropine intoxication has been reported, caused by a product containing a root extract. It was later shown that the poisoning was actually due to contamination by deadly nightshade's root, which can be easily confused with great burdock's root.[3]

The plant can induce contact dermatitis and anaphylaxis,[26,27] while the pappus of the fruit has been reported to induce conjunctival foreign body keratitis in horses.[24,25]

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BURITI PALM

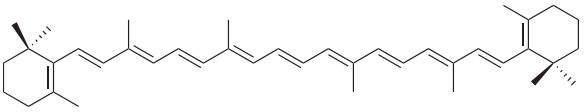
Scientific name: *Mauritia flexuosa* L. f.
Family: Arecaceae
Parts used: Fruit
Other names: Moriche palm

Features

The buriti is a palm growing in tropical wet areas of South America. The Brazilian vernacular name *buriti* means "tree of life" and is due to the extraordinary nutritional properties of the palm fruit.[3] The plant is also known by other names, such as aguaje palm, since it grows in aguajal, i.e., forest swamps that are periodically flooded by river water.

FIGURE 4.12 Buriti Palm. Courtesy of Dr. Jean-Christophe Pintaud, IRD, Montpellier, France. (See color insert following page 40.)

The palm can reach 35 m in height and has wide palmated leaves forming a rounded crown. Flowers are yellowish and blossom from December to April. The fruits are borne in clusters. They have a reddish-brownish color, are covered with scales, and have a fleshy yellow pulp with large seeds.[9] Buriti fruits are a pleasant food for various animals of the Amazon forest, like parrots and other birds, tapirs, deer, and jaguars. The fruits are also an important resource for people. They are used to manufacture juice, jam, and a fermented drink.



β-carotene

Constituents and Properties

The fruit has a very high content in vitamin C and carotenoids.[4,8] A reddish oil is extracted from the fruit pulp. The oil is rich in tocopherols and carotenoids, and is a remarkable source of essential fatty acids like oleic, palmitic, and linoleic acid. The oil also has significant medicinal properties. It is known, for instance, as an anti-inflammatory,[6] and due to its richness in provitamin A, it is used in the treatment and prevention of xerophthalmia.[7] It is also used for promoting wound cicatrization.

Dermatologic and Cosmetic Use

Buriti oil is the natural source with the highest content in carotenoids.[5] It also contains good levels of tocopherols, or vitamin E, and it is then able to exert excellent protection against oxidant agents.[2] The high content in essential fatty acids ensures an improvement of skin hydration. Essential fatty acids also protect the skin matrix, thus maintaining the skin's firmness, softness, and smoothness, and preventing aging.

An experimental study has shown that buriti oil can shade and absorb UV rays, thereby reducing skin damage and the development of tumors caused by sun irradiation.[1]

The oil is used in a number of cosmetic preparations, like regenerating creams and lotions, hydrating after sun, and oils for bath and massage.

Side Effects and Toxicity

In vitro studies have shown low cytotoxicity for creams and lotions formulated with buriti oil.[10]

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BUTCHER'S BROOM

Scientific name: *Ruscus aculeatus* L.
Family: Liliaceae
Parts used: Roots and rhizome

Features

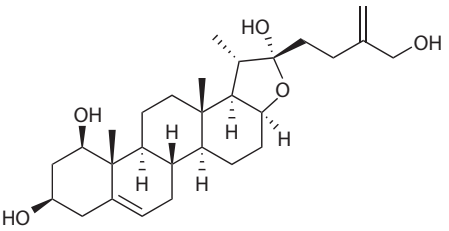
Periennial evergreen subshrub, growing 20–80 cm high, with a heavily branched, erect stem. The leaves are small, scalelike, and brown-membranous, while short shoots, known as phylloclades, are spread in the form of acuminate, leathery leaves. The flowers are small, greenish white, dioecious, and borne at the middle of the phylloclades. The fruit is a scarlet berry.

The plant is distributed across the Mediterranean region. It grows as a ground cover in shady positions, forming small colonies. It has been known since ancient times for its vasoprotective and diuretic properties.[2,11,19]

FIGURE 4.13 Butcher's Broom. (See color insert following page 40.)

Constituents

The root and rhizome contain steroid saponins, such as ruscogenin, ruscoside, and ruscin.[5–7,15,16,18] Other active compounds are flavonoids like anthocyanins (pelargonidin 3-O-rutinoside, pelargonidin 3-O-glucoside, pelargonidin 3-O-*trans*-p-coumarylglucoside) and trace amounts of essential oils.[14,17]



ruscogenin

Properties

The plant is used as a coadjuvant treatment for discomforts associated to chronic venous insufficiency, such as leg pain, heaviness, swelling, and nocturnal calf cramps.[1,20,21] It is a powerful vein tonic and is included in the composition of many antihemorroid and antivaricose pharmaceuticals.[3,10,12]

The main active principles exerting these effects are the steroid glycosides ruscin and ruscoside, and their hydrolysis products. These compounds have a capillaroprotective effect similar to that of vitamin P. It has been proposed that such a vasoprotective activity could be at least in part due to the inhibition of elastase, an enzyme that degrades elastin, a component of the extracellular matrix, and hence weakens the walls of blood vessels.[4,9] The vasoprotective properties of the plant ensure a regulation of the vascular tone, resulting in an improvement of peripheral circulation.

The plant is also used in the treatment of diseases of the urinary tract. It promotes kidney function and reduces edema caused by nephritis. It is also known as a depurative and antigout herb, and for its anti-inflammatory effect on the genitourinary system.

Dermatologic and Cosmetic Use

Because of its beneficial properties on the subepidermal microcirculation, the root extract is used in skin care products for the treatment of capillary weakness and couperose. It is also used for topic preparations against cellulite and venous insufficiency of lower limbs.[3]

Mixtures of the plant with horse chestnut (*Aesculus hippocastanum*) and witch hazel (*Hamamelis virginiana*) can be used to obtain a clearing and astringent effect, while mixtures with marigold (*Calendula officinalis*) and German chamomile (*Matricaria recutita*) serve to have a lenitive and refreshing effect.

The extract also protects the skin against external agents, such as sun, wind, sharp temperature variations, and shaving, and is recommended for genital and foot hygiene.

Side Effects and Toxicity

Because of their vasoconstriction properties, the plant's active principles must be used with great attention by persons suffering from high blood pressure. Topic preparations can cause contact allergies.[8,13]

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CHAMOMILE

Scientific name: *Matricaria recutita* L.
Family: Compositae
Parts used: Heads

Features

Annual herb growing to a height of 20–50 cm. The stem is thin and branched above, with pinnatisect, laciniate leaves. The inflorescences are pedicled heads having a diameter of 10–17 mm and surrounded by involucral bracts arranged into two or more series. The receptacle is conical or hemispherical. The heads consist of margin and central florets. Margin or ray florets are white, linguiform, female, and form a peripheral crown. Central florets are yellow, tubular, and hermaphrodite. Fruits are mucilaginous achenes, obliquely truncated above. The pappus is lacking or consists of a small border with protruding lobes.

The plant grows wild in orchards and open fields, and is cultivated in different regions of Europe. After harvesting, heads are dried and the spice has a characteristic scent, typical also of the whole plant. The plant has been one of the best-known medicinal herbs since ancient times. Egyptians held it sacred to the sun, owing to the yellow disc at the center of the inflorescence, but also for its property of healing colds, flus, and fevers, similarly to the warm rays of the sun.

The name *chamomile* derives from ancient Greek and means "soil apple," due to the typical apple scent emitted by the plant. In England, during the Middle Ages, the

FIGURE 4.14 Chamomile. (See color insert following page 40.)

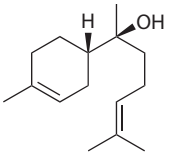
plant was cultivated in orchards and monasteries, while it was also used to refresh houses, to prepare infusions for meat preservation, and for flavoring beer.

The alcoholic extract of the dried heads yields an essential oil that is used for the manufacture of perfumes and drinks.[6]

Constituents

The essential oil contains lipophilic compounds, including terpenes, coumarins, and azulenes.[16] These latter confer to the oil a typical blue color. Chief components of the volatile oil are α-bisabolol and derivatives, β-*trans*-farnesene, and chamazulene.[10,14]

Other principles of the plant include flavonoid and coumarin glycosides, like apigenin-7-O-glucoside, and hydroxycoumarins like umbelliferone. Mucilages are also present, of which a main component is rhamnogalacturonan.



(–)-α-bisabolol

Properties

The aqueous extract has spasmolytic action, while the alcoholic extract has antibacterical and anti-inflammatory actions.[4,9,12,19] The chief active compounds include chamazulene and bisabolol.[2] The first one has a notable hormonelike gonadotropic action.[7] The infusion is used as a mild sedative and anxiolytic, probably due to the action of apigenin on benzodiazepine receptors.

Therapeutic uses are mainly linked to the anti-inflammatory properties of chamazulene and bisabolol, also including the treatment of skin diseases. Azulenes show different properties, including the improvement of wound healing, suppression of histamine release, inhibition of leukocyte migration, and antiulcer effect. Bisabolol glycosides can reduce lipid accumulation in adipocytes.[22] The external use of concentrated infusions or decocts can soothe burns, irritations, and skin rushes.

Despite a large body of information on the active principles of the plant and the inclusion of this latter in main pharmacopeia, studies carried out on humans and clinical trials are very limited.[17] Hence, the reliability of specific therapeutic uses of the plant's extracts and principles has still to be confirmed.

Dermatologic and Cosmetic Use

The chamomile herb is listed among the main botanical products used in skin care.[5,21] The antiseptic and anti-inflammatory properties allow neutralization of skin irritations, and therefore, the plant is particularly indicated for sensitive skin.[11] The soothing and antiflogistic action on the epidermis is mainly due to mucilages.

The plant is moreover used for lightening treatments on head hairs.[3] The antiobesity action of bisabolol glycosides can also be exploited in the treatment of cellulite.

It has been experimentally shown that the use of supercritical extraction of chamomile allows the production of cosmetics that ensure a better preservation of the water skin barrier, most likely due to a higher recovery of waxy compounds.[18]

Side Effects and Toxicity

Chamomile is generally considered a safe herbal remedy. The moderate use of infusions has no contraindications, whereas excessive consumption can induce vomit and vertigo. Moreover, the plant can increase the risk of hemorrhagia in case of a concomitant anticoagulant therapy, due to the presence of coumarins.[8] It can also amplify the effect of antiepileptics and sedatives.[1]

The use of dried heads can induce allergic reactions in individuals sensitive to the plant's pollen.[15,20] Cases of contact dermatitis have also been reported.[13]

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CHASTEBERRY

Scientific name: *Vitex agnus-castus* L.
Family: Lamiaceae
Parts used: Dried fruit, flowering apices

Features

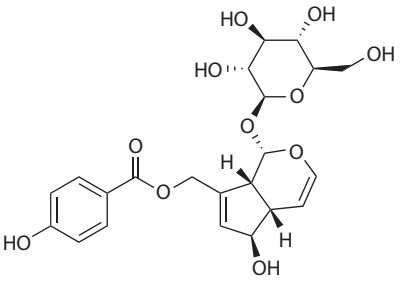
Small shrublike tree reaching a height of 5–6 m. The name *Vitex* refers to grape, and derives from the long, flexuous branches of the plant. The leaves are palmately compound, with five to seven lanceolate segments, the inflorecences are purple-pink, and the fruits small and brownish. The plant grows wild in temperate warm and subtropical areas of Europe, North America, and Asia, while it is also cultivated as an ornamental plant.

The plant portions used for herbal purposes are the flowering apex and the dried ripe fruits.[15] These latter are small, dark drupes similar to black pepper. Chasteberry is also known as monk's pepper, since in the Middle Ages it was considered an anaphrodisiac, and by this reason it was used in the kitchen of monasteries instead of pepper. Also, the Latin name of this species (*Agnus castus* = "chaste calf") as well as the English one are inspired by this legend. The twigs have been traditionally used to manufacture baskets.

FIGURE 4.15 Chasteberry. (See color insert following page 40.)

Constituents

The fruit contains glycosylated iridoids, viz., agnuside and aucubin, diterpenes (rotundifuran, vitexilactone, vitexifolin), flavonoids, such as vitexin, penduletin, casticin, luteolin-7-glucoside, and orientin, and the alkaloid viticin.[5,8,26] Other components include steroids, sesquiterpenes, triterpenes, and phenols.[27] The leaves and fruits contain an essential oil whose principal constituents are α-pinene, 1,8-cineol, limonene, sabinene, β-phellandrene, terpinyl acetate, *trans*-β-farnesene, and bicyclogermacrene.[4,12] However, the oil composition can vary sensibly in different portions of the plant or among different chemotypes.[22]



agnuside

Properties

Chasteberry has been used since ancient times as an emmenagogue and sedative. Its main effects consist of antiestrogenic, progestinic, and antispasmodic actions.[34,35] The plant is mainly useful for woman syndromes linked to the function of gonad hormones and lactation.[23,25,28] Premenstrual syndrome is due to an unbalance of gonadal hormones, and includes symptoms such as irritability, tension, and anxiety. The ethanol extract, particularly its lipophilic fraction, can bind opioid receptors, thereby acting similarly to β-endorphin, and thus alleviating the annoying symptoms of this syndrome.[2,14]

Many premenstrual problems derive from a deficiency of progesterone during the luteinic phase of the cycle, which precedes the onset of menstruation. This can possibly lead to the formation of ovary cysts. The plant extract seems to exert a beneficial stimulation of the anterior lobe of the pituitary gland, inducing a higher production of the gonadotropic luteinizing hormone (LH) and a decrease of the follicle-stimulating hormone (FSH). This is followed by an increase in the activity of the luteal body that shifts the estroprogestinic balance toward progesterone.[21] The plant is then indicated for amenorrhea caused by luteal body insufficiency, for premenstrual syndrome due to hyperfolliculism, for conditions characterized by elevated serum prolactin (hyperprolactinemia), in premenstrual water retention, and in youth acne.

Thanks to its antispasmodic activity, the plant can be used for disorders of the digestive system and abdominal organs. In the ethanolic extract of the dried seed clerodanic diterpenes with dopaminergic activity are present, which have been shown to decrease the production of prolactin in cells of the anterior pituitary. Such

a pharmacological activity can explain the effects of the plant on cyclical mastodynia and premenstrual mastalgia,[6,9] which derives from mammal gland hyperstimulation produced by excessive production of prolactin. The usefulness of the fruit extract in the treatment of the premenstrual syndrome is also supported by its ability of binding to μ-opioid receptors.[32] In addition, this kind of activity can stimulate melanin production by melanocytes through a β-endorphin-like mechanism.

The effect of the extract on male subjects is apparently paradoxal. Despite the popular belief that the plant induces anaphrodisiac effects, men consuming plant extracts generally show increases in testosterone levels. This latter effect is so evident that the plant is frequently used as a supplement by bodybuilding practitioners. Such a contradiction has been explained by a clinic study where it has been shown that at low doses the extract induces a rise in prolactin, which is followed by a reduction in sex hormones, and hence a decrease of testosterone in men. Conversely, higher doses induce the opposite effect, i.e., a decrease in prolactin, which can explain the observed increase in testosterone.[20]

Phytoestrogens have also been isolated in the plant extract.[10] These compounds, such as the flavonoids penduletin and apigenin, can bind the β-estradiol receptor,[19] but this kind of activity does not seem linked to the plant effects on the pituitary-gonadal axis.[11,13] A clinical study has shown that the extract causes an increase in the blood levels of melatonin,[3] a hormone that regulates the circadian rhythm and mood, suggesting a possible use of the plant for insomnia and jet lag. The extract is also used in food supplements for slimming treatments, aimed at modulating the stimuli of hunger.[17] *In vitro* studies have shown that the extract is able to produce toxic effects and induce apoptosis in human tumor cells.[7,24,33] Finally, in the leaves and seeds compounds acting as noxious insect repellents are present.[18]

Dermatologic and Cosmetic Use

The extract of chasteberry is used in combination with acetyl-tyrosine, a substrate in the synthesis of melanin, for the production of cosmetics that stimulate tanning by inducing physiological mechanisms, even in the absence of sun exposure.[29] The extract acts synergistically with acetyl-tyrosine thanks to its β-endorphin-like activity, i.e., by acting on the α-MSH hormone receptor that induces the activation of skin melanocytes.[30] Moreover, the presence of phytoestrogens in the extract can improve the synthesis of collagen and hyaluronic acid, thus ameliorating skin hydration, smoothness, and firmness. The essential oil is a powerful antiacne product,[1,16] and according to traditional Chinese medicine, it is also used for an estrogen-progestinic balancing massage.[31]

Side Effects and Toxicity

The plant does not generally produce toxic effects, while cases of erythema have been reported only occasionally. However, because of its effect on gonadotropic hormones, the extract is contraindicated for pregnant women or other people making use of anticonceptive or estrogenic drugs.

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CHLORELLA

Scientific name: *Chlorella vulgaris* Beijerinck
Phylum: Chlorophyta (green algae)
Family: Chlorellaceae
Parts used: Biomass

Features

Marine unicellular alga belonging to green algae, which are also known as Chlorophyta. The cells are spherical, 2–10 μm in diameter, and lack flagella. They contain chloroplast with photosynthetic pigments, including chlorophyll-*a* and -*b*. The alga needs for its growth carbon dioxide, light, and small amounts of mineral salts.[12]

It grows wild in brackish water of Equatorial Africa, but it can also be easily cultivated *in vitro*, and various applications of its artificial cultures have been proposed, e.g., as a source of oxygen through photosynthesis in spacecrafts.[13] It is also used as a food integrator in Japan and other countries.[4]

The alga has had an important role as an experimental system in scientific research. It was used by the German scientist Otto Heinrich Warburg, who in 1931 won the Nobel Prize in Physiology and Medicine for his studies on photosynthesis. In 1961 the U.S. scientist Melvin Calvin won the Nobel in Chemistry for his research on the path of carbon in photosynthesis carried out using this alga.

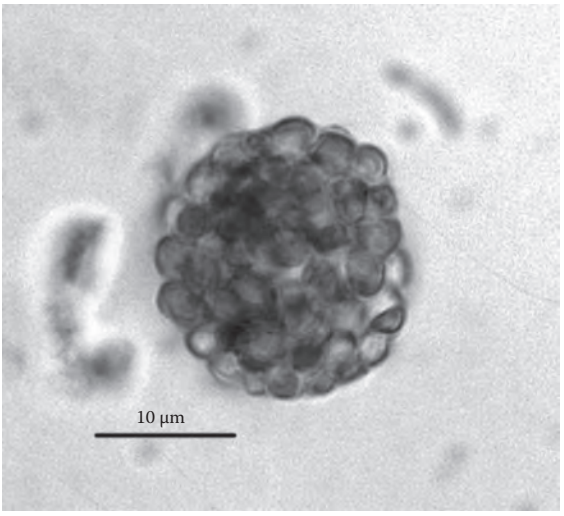
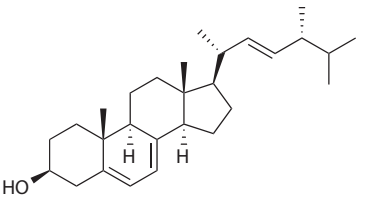


FIGURE 4.16 Chlorella.

Constituents

The alga has a high content in protein and essential nutrients (dry residual: 45% protein, 20% fat, 20% carbohydrates, 15% mineral salts and vitamins). It is

particularly rich in calcium, magnesium, and iron, and has a very high content in chlorophyll, from 10- to 100-fold higher than that of leafy vegetables. It also contains carotenoids, different vitamins (B1, B2, B6, B12, C, E), and an unusual sterol mixture, the main components being ergosterol, poriferasterol, and their derivatives.[8]



ergosterol

Properties

Chlorella is mainly used as a food supplement acting as an energizer, tonic, detoxifier, digestive, and hypocholesterolemic. Studies carried out on laboratory animals have also shown a powerful effect of the algal extracts on the immune system, due to the presence of polysaccharides with high molecular weight.[7,14]

The algal polysaccharides are composed of glucose, galactose, rhamnose, mannose, arabinose, N-acetylglucosamine, and N-acetylgalactosamine. When injected into animals they cause a proliferation of splenocytes and an increase of interleukin production (IL-6, IL-10, INF-γ, and TNF-α).[2] It has been reported that a glycoprotein, known as ARS2, can inhibit tumor growth through its immunostimulatory effect.[3,7] The immunostimulation seems also able to prevent gastric ulcer by acting through the brain-gastric axis.[15]

Besides the effects on the immune system, oral administration of extracts to the mouse has shown the ability to protect against ionizing radiations,[10] while in the rabbit antilipidemic and antiatherosclerotic effects have been observed.[9]

Among other therapeutically relevant data, sterols isolated from the alga have shown anti-inflammatory effects,[18] while the topical application of extracts has prevented the occurrence of skin tumors in experimental animals.[11]

Dermatologic and Cosmetic Use

The extracts of chlorella protect collagen and elastin from the degrading action of matrix metalloproteinases, and these properties preserve the texture and elasticity of the skin.[1,2] Sterols could play a role in such an effect. Collagen synthesis is also stimulated, thus preventing the effects of aging and facilitating the reconstitution of damaged dermal tissue.[16] The reinforcement of the dermal matrix can also protect against the noxious effects of cellulite, such as the formation of stretch marks.

Side Effects and Toxicity

Preclinical studies on subacute and acute toxicity, carried out in the rat, have shown no significant effects induced by orally administered algal extracts.[6] However, cases of allergy in humans have been reported.[17]

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CINNAMON

Scientific name: *Cinnamomum verum* J. Presl (syn. *Cinnamomum zeylanicum* Bl.)
Family: Lauraceae
Parts used: Bark and leaves

Features

Highly branched, evergreen tree with a thick, wrinkled bark. Leaves are oval, with entire margin and apex acuminate. Flowers are small, whitish-yellowish, arranged in branched panicles. The fruit is an oblong-ovoid berry.

The species is native to Sri Lanka, but is also cultivated in India, Indonesia, various islands of the Indian Ocean, Madagascar, and Brazil.

Herodote reports the use of cinnamon in the mummification technique of ancient Egyptians. In the Roman age, scented wines like claret were prepared using honey and various spices like cinnamon. This latter is also cited in the Bible, such as in the tale of Moses receiving the Tablets (Exodus 30:23).[15,25] In the Middle Ages cinnamon was a very appreciated spice and was used as a condiment for meat.

The spice is prepared from the bark of young branches and is on the market in the form of dried sticks, or quills. The word *cinnamon* is inspired by the shape of the sticks and derives from the Greek *kinnamon*, meaning "tube." Cinnamon is also marketed as a powder.

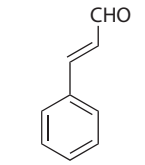
The main countries of production are Sri Lanka and China. It is used in the kitchen to scent cakes, creams, jellies, fruit salads, and in the distillation of liquors

FIGURE 4.17 Cinnamon Sticks.

and bitters. The bark also yields an essential oil having a delicate aroma and a stinging flavor. The oil is used in food, cosmetic, and pharmaceutical industries.

Constituents

The essential oil obtained from the bark and leaves (0.5–1.0% and 1.6–1.8%, respectively) is very aromatic and spicy.[23] Its composition is highly variable, depending on the geographic area and the different portions of the plant. In general, the main constituents are aldehydes, like (*E*)- and (*Z*)-cinnamaldehyde (about 60–80%), benzaldehyde, and cuminaldehyde; esters like (*E*)- and (*Z*)-cinnamyl acetate and benzyl benzoate; phenols like eugenol, methyl eugenol, and pinene; and alcohols like linalool.[36,38] A chief active compound of the leaves is eugenol.[31] The bark extract also contains tannins and anthocyanidins.[16]



cinnamaldehyde

Properties

Cinnamon is a well-known remedy in Ayurveda and in traditional Chinese medicine. It is used for menstrual disturbances, fever, and intestinal disorders.[13,32,43,45] The active principles present in the bark induce a digestive, astringent, and antiseptic effect at therapeutic doses.[10,12,17] The antiseptic and antimycotic action, principally due to the essential oil,[24,41,42] is also exerted on the respiratory system and on the skin and cutaneous annexes, particularly for infections with *Onyxis*, *Candida*, and *Staphilococcus*.[2,30,39] An antispasmodic action on the intestinal and uterine traits has also been reported.

The oil can be used for infections of the respiratory ways and to soothe phlogosis and pain associated with flu, arthritis, and rheumatism. Experimental studies have also highlighted such properties as protection against oxidant agents,[35,48] and antiproliferative effects on tumor cell lines. Cinnamaldehyde induces apoptosis in various cancer cell types, and the activation of proapoptotic proteins of the Bcl-2 family has also been detected.[49]

Cinnamon has also gained importance in studies on obesity and diabetes.[9] It has been shown to reduce hematic levels of glucose, triglycerides, and cholesterol.[3,18,44] Derivates of hydroxycinnamic acid can stimulate glucose uptake in adipocytes, by acting similarly to insulin through an increase of the expression of the GLUT4 transporter on the plasmamembrane.[7,20,34] The extract can reduce insulin resistance by activating the pathway of phosphatidyl-inositole-3-kinase. However, the extract has also been shown to inhibit the production of the hormone adiponectin,[37] and therefore, its role in the treatment of diabetes has been questionable. A pilot study on

women has demonstrated that the extract reduces insulin resistance in the polycystic ovary syndrome.[47]

Cinnamaldehyde is also anti-inflammatory, since it inhibits cytokine production in macrophages and monocytes.[8] The compound inhibits the activation of toll-like receptors in macrophages,[51] and this could explain the quenching of the signaling pathway that involves NFkB activation and induces the transcription of genes like COX and IFN-β.[14,19] In addition, cinnamaldehyde has shown a vasorelaxing effect on rat-isolated aorta, occurring through endothelium-dependent and -independent mechanisms.[11,50]

Data concerning eugenol and its derivates are contrasting, probably due to the fact that at low concentrations these compounds exert an anti-inflammatory action, while at higher concentrations their prevalent effect is cytotoxic.[28]

Insecticide compounds like the diterpenes cinnzeylanin and cinnzeylanol have also been isolated from the plant.

Dermatologic and Cosmetic Use

The essential oil is used in perfume and cosmetic industries,[29] but the dosage must be carefully controlled due to the oil's capability of inducing irritation and sensitization on the skin and mucosae. Noxious effects are mainly due to the presence of cinnamaldehyde. In aromatherapy it is preferable to use the oil extracted from leaves, owing to a lower content in cinnamaldehyde. Cinnamon oil is used for tonifying massage, since it exerts a vasodilatatory effect caused by cinnamaldehyde. Such a property is responsible for the emmenagogue effect of the plant, while it can also be exploited for aesthetic purposes, such as lip volumizers, or in the treatment of cellulite.

Side Effects and Toxicity

The essential oil, if used in pure form, can produce skin irritation.[5,6] Different cases of allergic dermatitis caused by the oil have been reported.[1,21,40] Also, cinnamaldehyde contained in perfumes and toothpastes can induce contact sensitization on the skin and oral mucosa.[4,22,26,27,33] The oil should not be used on susceptible skins, and neither should it be used during pregnancy, owing to its emmenagogue properties.[46] Prolonged assumption of cinnamon in food and drinks can worsen gastric ulcer. The use at high dosages can interfere with antidiabetics and should therefore be avoided in patients treated with these drugs.

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COCONUT PALM

Scientific name: *Cocos nucifera* L.
Family: Arecaceae
Parts used: Fruit, seeds

Features

Large palm tree growing to a height of 20–40 m. The stem is slender and the bark is shaggy, with remains of the bases of fallen leaves. The stem bears a crown of large paripennate fronds, 4–5 m long and 1–1.7 m wide. Adventitious roots arise from the base of the trunk. Flowers are small, yellowish, grouped in long, spindle-shaped, branching axillary inflorescences, bearing five female flowers at the base and a number of male flowers above. Fruits are big drupes with a thin, smooth exocarp and a

FIGURE 4.18 Coconut Palm. Courtesy of Dr. Jean-Christophe Pintaud, IRD, Montpellier, France.

fibrous mesocarp that is closely attached to a woody and hard endocarp fused with the seed tegument. The endocarp is the outermost portion of the coconut seed, which is incorrectly called a nut. Three germination pores are clearly visible on its surface. The seed is the greater portion of the coconut and consists of a thin, brown tegument that surrounds a white, soft, and fat endosperm, containing the embryo. The matured endosperm, broken into pieces and well dried, is commonly known as copra.

The endosperm forms a juice contained in an inner cavity, known as coconut water. A sweet, white liquid, known as coconut milk, is derived from the meat of the mature coconut. The color and taste of the milk are due to the high oil and sugar contents. Coconuts are on the market worldwide. In nontropical countries they are freed from the outer green husk before being marketed.

The species grows in tropical coastal areas. It is native to the Indonesian archipelago but is currently diffused throughout the Pacific Ocean with a number of varieties. In the sixteenth century it was discovered by Portuguese and Spanish sailors, and it was then introduced to Central and South America.[27] Today the plant is widely cultivated in its native countries, where it is a main source of raw materials and food products.

The coconut can be used as fresh food, to extract an oil with culinary and cosmetic uses, and to make glue, soap, flour, and food for livestock.[24] The mesocarp can be used to make a fiber for rope and carpets, known as coir. The flowers yield a sap that can be used to make wine and coconut sugar. The apical bud, whose removal causes the death of the entire plant, is a delicious and expensive ingredient for salads, known as coconut heart. The trunk provides wood used to make furniture and other objects, or to build huts. The leaves are used to weave mats or hut roof shingles.[11]

Constituents

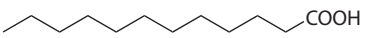
Coconut water contains sugars (4%), mainly glucose, fructose, and sucrose,[5] while other components include malic and citric acids; proteins (0.1%); fats (0.1%); amino acids; vitamins, particularly vitamin E; and mineral salts (0.4%), of which the most abundant is potassium, followed by calcium and phosphorus, while iron is also relatively abundant.[10]

The liquid portion and other parts of the plant contain cytokinins like zeatin and its derivatives.[19] These molecules stimulate the growth and differentiation of the plant tissues.

The fresh pulp of the seed is composed of lipids (about 35%) and sugars (about 10%), while in the dried copra the content of lipids is higher (about 70%).[20]

From the seed pulp is extracted an oil with a low level of unsaturated fatty acids, forming an ivory white, aromatic solid mass below a temperature of 25°C.[7] The chief component is a substance known as cocoin, a mixture of various glycerides, of which the most abundant contains lauric acid (about 50%). Other fatty acids include myristic, palmitic, caprylic, caproic, stearic, oleic, and linoleic acids.

The woody shell of the coconut is maximally composed of cellulose (53%) and lignin (33%).



lauric acid

Properties

Coconut has a long tradition in Eastern medicine,[6,15] although its properties have also been studied in depth by Western medicine. Coconut water is an isotonic liquid with refreshing, rehydrating, and antioxidant properties, which can also be administered intravenously.[2,3,13]

The composition of saturated fatty acids of coconut oil, which is unique in the plant kingdom, helps to prevent heart diseases and the hardening of arteries.[21] The high content in lauric acid, a compound that is also abundant in maternal milk, makes the oil easily digestible. In addition, this fatty acid strengthens the immune system and protects against viral, bacterial, and fungal infections.

The action of coconut lipids on the liver results in a higher metabolic rate and an increased production of lipoproteins, thus improving triglyceride secretion from the liver and preventing liver steatosis.[14,25] Coconut lipids also induce a higher production of biliary salts, involved in the digestion of fat.

The oil exerts beneficial effects on various organs, and reduces the risk of diseases like cancer, osteoporosis, and diabetes. Medium-length chain fatty acids, which are a typical component of the oil, promote the consumption of the body's energy reserves and are therefore useful in the treatment of obesity or hypothyroidism.

A husk fiber aqueous extract has antinociceptive and radical scavenging activities.[1] Fibers also yield a polyphenol-rich extract that has been shown to possess antiproliferative, antioxidant, antiseptic, and anticholesterolemic properties.[4,8,12] In the palm's area of origin, the roots are used to heal gastric ailments and dysentery.

Dermatologic and Cosmetic Use

The coconut oil is widely used in cosmetics and soaps due to its high content in lauric acid. It is also used in dermatologic products, e.g., in the treatment of psoriasis.[23] The oil has a strengthening effect on hairs, mainly due to the presence of lauric acid glyceride.[16,17] This compound can easily penetrate the cheratin structure of the hair stem, thanks to the short, linear chain of lauric acid, and helps in preserving the hair from degenerative processes.

The oil has emollient, rehydrating, and elasticizing properties, thus preventing wrinkle formation and other skin aging processes. Polynesian women, who habitually use the oil, are known for the beauty of their skin and hairs, despite the fact that they are continuously exposed to the action of sun and wind.

Products obtained from coconut water through a freeze-drying process stimulate tissue growth and are employed in rejuvenation treatments on the skin and scalp.

The lignified mechanical tissue of coconuts is used to obtain particles that find application as skin exfoliants.

Side Effects and Toxicity

No toxicity has been detected for coconut water, pulp, and oil. The pollen is known to contain allergens,[9] while occupational allergies to the fiber and rare food allergies have also been observed.[18,22,26]

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COLA

Scientific name: *Cola acuminata* (P. Beauv.) Schott & Endl.
C. nitida (Vent.) Schott & Endl.
Family: Malvaceae
Parts used: Seeds

Features

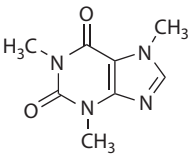
Cola nuts are produced by plants of the species *Cola nitida* and *C. acuminata*. Less frequently, marketed cola nuts derive also from *C. vera* and *C. verticillata*. The cola nut tree is native to western Africa, but it is also cultivated in many tropical areas, including Central and South America, West Indies, Sri Lanka, and Malaysia.

The plant can reach 10–15 m in height. The leaves are oval and with an acuminate apex. Flowers are grouped in small clusters. They lack a corolla, and the calyx is formed by five white sepals with reddish stripes. Fruits are formed by woody follicles in groups of two to six. Each follicle contains five to ten seeds of variable color, from white to red-purple.

Cola nuts are not fruits but seeds freed from their seminal teguments. They are traditionally chewed raw or taken in the form of powder or liquid extract. Preparations obtained from the seeds are widely used to manufacture cola drinks that are very popular worldwide.[7] The seed extract is also used as a source of caffeine for pharmaceutical preparations, in the production of essential oils, and in the chocolate industry.[9]

Constituents

The seeds are characterized by a discrete content in protein and by a limited content in lipids. The main carbohydrates are starch and cellulose. The chief active principles are xanthine alkaloids, of which the major one is caffeine, followed by theobromine. Polyphenols are also present, particularly catechin, epicatechin, procyanidins B1 and B2, quinic acid, and chlorogenic acid.[1,2,14]



caffeine

Properties

Many of the properties of the cola nut are due to caffeine and related compounds, acting as stimulants.[13] African people have had the habit of chewing the seeds since ancient times, in order to increase mental acuity and combat fatigue. Centuries ago the Arabs traded gold powder for cola nuts before leaving for long, restless travels

across the desert. European travelers have reported news about the cola nut since the sixteenth century. The Italian explorer Filippo Pigafetta, in 1593, described some exotic fruits, which he called red chestnuts, that could be chewed or used to flavor water and alleviate thirst, and had beneficial effects on liver ailments.

In traditional medicines, cola nuts are used as an aphrodisiac, hunger suppressor, and to treat morning sickness, migraine, and indigestion.[3] They can also be applied directly to the skin to treat ulcers and irritation, while the twigs of the tree are used to brush the teeth.

The presence of caffeine in cola nut is responsible for an increase in blood pressure and diuresis. Caffeine also stimulates the heart and the lungs, and reinforces the effect of analgesics like aspirin. It exerts a tonic effect on the stomach by increasing gastric secretion and stimulating the motility of gastric musculature.[6] Caffeine can also stimulate the activity of cerebrospinal and simpathetic nerves, increase mental keenness, and reduce depression and sleepiness. It also acts on the skeletal muscles by increasing their strength and resistance. Caffeine promotes the degradation of lipid reserves, thus being useful as a complementary factor in diet programs for body weight loss.

Although the presence of caffeine is fundamental for the biological properties of cola nut, the administration of its active principles is not equivalent to that of pharmacological treatments with caffeine. It has been shown that cola nut has a more gradual effect, probably due to the binding of xanthines to polyphenols, which makes their delivery slow and their action progressive.[11]

Dermatologic and Cosmetic Use

Plant extracts based on cola nut induce an increase of lipolysis (similar to those of *Coffea arabica*, the coffee plant, and of *Camellia sinensis*, the tea plant), also involving a reduction of adipocytes in peripheral body areas. These preparations are therefore helpful in treatments against cellulite.[5]

It has been shown that caffeine reduces the occurrence of skin tumors in hairless mice exposed to intense UV irradiation through a prevention of p53 gene mutation.[8,10] Similar studies indicate that the topical application of extracts containing xanthines suppresses a series of UV-induced dermal alterations, including wrinkle formation and collagen accumulation.[12] It has also been suggested that xanthines play a role in reducing neutrophil infiltration in the dermis caused by UV rays.

Other studies have shown that a cola nut extract devoid of caffeine can reduce the release of elastase from polymorphonuclear neutrophils, thereby protecting the extracellular matrix and also exerting an anti-inflammatory effect.[4]

Side Effects and Toxicity

It has been reported that the consumption of cola drinks poses a risk of bone mineral density reduction in the woman. This seems linked to the high content in phosphate of the cola nut, leading to a change in the calcium-phosphorus ratio in the diet and ultimately to a negative effect on bone mineralization.[15,16]

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COTTON

Scientific name: *Gossypium hirsutum* L.
Family: Malvaceae
Parts used: Seeds

Features

The cotton plant is widely cultivated for the production of textile fiber. It is a small shrub, up to 1.5 m in height, developing vegetative and fructiferous branches. Leaves are lobed, and each fertile branch bears six to eight yellow or white flowers. The fruit is a spherical, dehiscent capsule, 4–6 cm long, containing about 35 seeds.

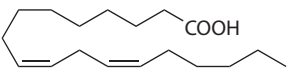
The seeds are covered by hairs of two types: longer fibers called staples and shorter fibers called linters. The longer fibers are used for the manufacturing of high-quality textiles, while the shorter ones yield lower-quality textiles.

An oil can be extracted from the seed after the removal of hairs. Cottonseed oil is used to manufacture candles, soaps, foods, and condiments.

FIGURE 4.19 Cotton. Courtesy of Dr. E. Parisi.

Constituents

The oil has a saponifiable fraction rich in ω-6 fatty acids (50%, mostly linoleic), whereas omega ω-3 fatty acids are present in traces.[3] In the unsaponifiable fraction there are phytosterols (β-sytosterol), tocopherols, and minor components, such as cyclopropenic fatty acids and gossypol.[15] This latter is a red, toxic polyphenol pigment that protects the plant from parasites and herbivores. Gossypol and cyclopropenic fatty acids are removed during oil processing.



linoleic acid (ω-6)

Properties

Cotton was mentioned early by the ancient Greek scholar Herodotous (450 B.C.) for its curative properties, and it has long since been used in various popular medicines. Tisanes prepared with the seeds are useful remedies for bronchitis, diarrhea, and dysenteria.

Gossypol is known as an antimalarial, and has been used to heal endometriosis in women. It acts as a dehydrogenase, protein kinase C (PKC), and calcineurin inhibitor;[2,12] is proapoptotic, probably due to the regulation of Bax and Bcl-2;[4] and has shown antitumoral properties on prostate cancer cells[6,7] and colon carcinoma cells.[14] It also inhibits the replication of HIV type 1.

Gossypol has also been used as an oral male contraceptive in China, but serious side effects have been reported.[5] Cottonseed oil is used as a vaginal contraceptive.[13]

Dermatologic and Cosmetic Use

Cottonseed oil is commonly used in soaps and cosmetic products,[10,11] while cotton fiber can also be used in the cosmetic field.[8] The importance of the oil is linked to the high content in linoleic acid. This fatty acid is essential for the structure of cellular membranes and ensures the integrity of the skin water barrier. Linoleic acid reduces skin dehydration, but it also has protective effects against external irritating agents.

Side Effects and Toxicity

Cottonseed oil is generally considered a safe natural product.[9] However, proteins of the seed, which are absent in the oil, can induce allergic reactions in sensitive individuals.[1]

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CUPUAÇU

Scientific name: *Theobroma grandiflorum* (Willd. ex Sprengel) Schumann
Family: Sterculiaceae
Parts used: Fruit, seeds
Other names: Copoasu, Theobroma, wild cacao

Features

Small to medium tree of the Cacao family, reaching up to 15–20 m in height. The bark is brown and the leaves are simple, alternate, coriaceous, 25–35 cm long, pink when young and green when mature. The flowers are dark red and are born gathered in groups of three to five, forming cymose inflorescences. The fruit is an oblong drupe, 12–25 cm long, and consists of a husk or pulp encasing 20–50 seeds.

The species is distributed in the rain forest of the Amazonian region. It is considered a pre-Colombian crop and is locally domesticated.[1,2]

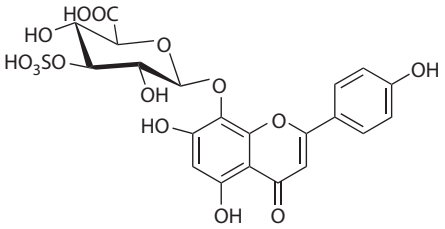
The fruit is one of the most popular in the Amazon market. The pulp is processed to produce juice, ice cream, jam, and liquor. A soft and creamy butter is pressed from the seeds. The wood is commonly used for timber.[11]

Constituents

The fruit pulp consists of protein (approximately 9% dry weight); lipids (12%), with palmitic and oleic acids being the dominant fatty acids; sugars (50%), mainly sucrose, fructose, and glucose; fiber (14%); and ash (5%). The most abundant minerals are potassium, phosphorous, magnesium, calcium, and sodium. Trace elements include zinc, iron, copper, and manganese.[7]

The pulp contains a considerable amount of starch as well as pectin polysaccharides. A pectic fraction has been found to be composed mainly of a homogalacturonan, with rhamnogalacturonan insertions carrying side chains containing galactose and arabinose.[12,13] The pulp also contains theacrine (1,3,7,9-tetramethyluric acid) instead of the xanthines found in cacao.[9] Many volatile compounds have been identified in the fruit, including ethyl butanoate, ethyl hexanoate, and linalool.[6]

The sulfated flavonoid glycosides theograndins I and II have been isolated from the seed. Other flavonoids have also been identified, including (+)-catechin, (–)-epicatechin, isoscutellarein 8-O-β-D-glucuronide, hypoletin 8-O-β-D-glucuronide, quercetin 3-O-β-D-glucuronide, quercetin 3-O-β-D-glucuronide 6″-methyl ester, quercetin, kaempferol, and isoscutellarein 8-O-β-D-glucuronide 6″-methyl ester.[14] The butter extracted from the seeds contains oleic acid (approximately 44%), stearic acid (30%), arachidic acid (10), palmitic acid (7%), linoleic acid (4%), and lower amounts of palmitoleic, heptadecanoic, linolenic, and myristic acids. The butter is also rich in sterols, chiefly β-sitosterol, followed by stigmasterol, campesterol, and Δ5-avenasterol.[4,11]



theograndin I

Properties

The fruit has been traditionally used as food by Amazonian natives. It is also locally used for abdominal pain, diarrhea, and difficult birth.[5,8]

Theograndin II has displayed antioxidant activity in a free radical assay, and weak cytotoxicity to HCT-116 and SW-480 human colon cancer cell lines.[14]

Dermatologic and Cosmetic Use

The butter from seeds has remarkable water absorption properties and higher moisturizing capabilities than lanolin. It contains high levels of essential fatty acids and phytosterols, which are responsible for its ability to restore skin elasticity and treat eczema and dermatitis. The butter offers broad-spectrum protection from UV-A and UV-B rays. It possesses a softer and creamier consistency than cocoa butter and is a good stabilizer for emulsions.[3]

Because of its numerous properties, the butter is used in moisturizing, emollient, soothing, regenerating, and antiaging skin care products, and can also be used in sunscreens and hair cosmetics.

Side Effects and Toxicity

Hazards or noxious effects are not known for proper dosages.

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DULSE

Scientific name: *Palmaria palmata* (L.) Kuntze
Phylum: Rhodophyta (red algae)
Family: Palmariaceae
Parts used: Fronds

Features

Red alga with simple or deeply lobed blades, which can reach a length of 30–50 cm. The thallus is slender at the base and is attached to the substratum by means of a disclike holdfast. The alga forms dense tufts on rocks and laminarian stipes, growing in intertidal and shallow waters along the shores of the North Atlantic. The alga is collected during low tide, from May to October, dried in open air, and then processed and put on the market.[6] Once dried, it acquires a pleasant taste and is very popular as food among people living on the coasts of the North Atlantic.

In the seventeenth century sailors chewed it like tobacco to prevent scurvy, and in the eighteenth century Scottish and Irish migrant workers brought the alga to the coasts of Canada and New England. In the first half of the twentieth century the alga lost its popularity in Western countries, but today it is gaining a new interest, like many other natural products.

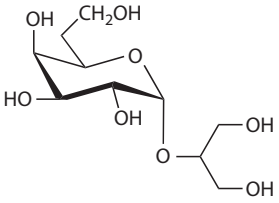
FIGURE 4.20 Dulse.

Constituents

The alga is mainly composed of carbohydrates belonging to the group of xylans (about 30% dry weight).[9] These compounds are the chief component of the cell wall and of the algal thallus.[4] Cellulose is also present, but to a lesser extent. Xylans are composed of xylose, glucose, and galactose and form complexes with proteins, sulfates, and phosphates. Another important constituent is floridoside [α-D-galactopiranosyl-(1–2)-glycerol], a typical heteroside of red algae.[2,7,15,16] This compound is considered the main energy storage compound of photostynthesis in these algae, and is also known as the Floridean starch.

Proteins amount to about 20% of dry weight, a particularly high content for an alga, similar to that of Nori (*Porphyra tenera*) and comparable to vegetables with high protein content, like pods.[10] Main lipids are myristic and palmitic acid and the highly abundant eicosapentaenoic acid (EPA), an ω-3 polyunsaturated.[12] Oil can be obtained from the alga by supercritical CO_2 extraction.[11] Other constituents include polyphenols, phenolic acids, and desmosterol, a direct precursor of cholesterol.[8,13]

Like many marine algae, it is rich in mineral salts, and has a relatively high content in potassium and a relatively low level of sodium. Iron is particularly abundant among trace elements (about 80 mg/100 g), followed by iodine, zinc, and manganese. The most abundant vitamins are those of the B group, and vitamins C, A, and E.



floridoside

Properties

The alga exerts positive effects on a series of pathological conditions, including digestive, urogenital, and nervous disorders, anemia, asthenia, and mineral salt insufficiency. In addition, the high content in protein, vitamin, and mineral salts renders the alga a good nutritional supplement.[5]

The mixture of vitamins and amino acids is particularly effective against various kinds of stress. Vitamin C promotes redox processes, which prevent free radical damage, and protects against infectious diseases. This vitamin also promotes collagen synthesis, and therefore it acts favorably in tissue repair processes, such as wound healing and bone regeneration. The high presence of lysine, an amino acid that is generally rare in botanical organisms, promotes the gastrointestinal function, and in association with vitamin C prevents infections by *Herpes simplex* virus.

The high content in iron, associated with vitamin B12, makes this alga suitable to treat anemia, e.g., during pregnancy, while the high levels of iodine can be helpful for thyroid disorders.

The abundant presence of mucilage protects against contaminations from heavy metals or radioactive elements, by forming nonabsorbable complexes with contaminants in the gut, and thereby promoting their fecal elimination.

A buthanolic extract has been shown to possess *in vitro* antiproliferative activity on HeLa cells, probably due to the presence of polyphenols.[18] These latter compounds and phenolic acids also confer antioxidant properties to the extract.[17,19]

Dermatologic and Cosmetic Use

Dulse is a common constituent of skin care products.[1,14] The algal extracts are generally used as soothing agents against skin irritation, and in addition have been shown

to act specifically against herpes. They are also used in anticellulite preparations aimed at improving microcirculations and tissue draining. Xylans are used in hydrating and regenerating cosmetic compositions.[3] The high content in B group vitamins contributes to the regeneration of hairs and nails.

Side Effects and Toxicity

The high content in mineral salts, particularly iodine and potassium, is not suitable for people affected by hyperthyroidism or renal dysfunction.

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ENGLISH IVY

Scientific name: *Hedera helix* L.
Family: Araliaceae
Parts used: Leaves, berries

Features

Evergreen vine with creeping or climbing stems, which can reach up to 20–30 m in height in the presence of adequate support. The Latin name of the plant derives from the word *haerere*, meaning grasping to something. The plant sticks on to the barks of trees or to rock crevices by using short, adventitious roots. Leaves are alternate and palmately lobed on sterile stems, while they are unlobed and cordate on fertile branches stemming from the higher portions of the plant. Flowers are small and grouped to form dense umbels of 3–5 cm in diameter; they are yellowish-greenish, rich in nectar, and are in bloom since late summer until mid-autumn. Fruits are black or dark blue berries ripening in winter. They are consumed by various birds but are toxic to humans.

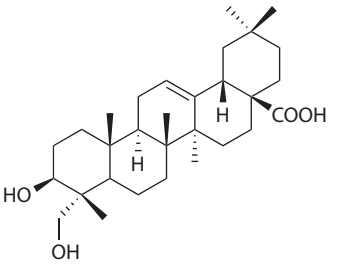
The species is native to Europe and southwestern Asia and is naturalized in North America, where it has become invasive. Ornamental varieties have been obtained in cultivation practices.

FIGURE 4.21 English Ivy. (See color insert following page 40.)

Constituents

The leaves and fruits contain about 5–8% of saponins, of which the most important are glycosides of hederagenin, such as hederacoside-C and α-hederin, and glycosides

of oleanolic acid, such as hederacoside-B and β-hederin.[1,6,13] Other constituents are polyphenols, including caffeic and chlorogenic acid, flavonol glycosides like rutin and rhamnoglucosyl-3-kaempferol, sterols like sitosterol and stigmasterol, sesquiterpenes, and polyacetylenes like falcarinone and falcarinol.[2,5,29] Leaves also contain antioxidants like β-carotene and vitamin E, sugars, calcium oxalate, and mineral salts.



hederagenin

Properties

In European traditional medicine the plant has been used for ailments of the grastrointestinal tract and calculosis. It is also used by external applications as an antalgic for neuralgia and rheumatism, and as a revulsive for ulcers and burns. It has expectorant and spasmolytic properties and is also used in inflammatory bronchial diseases and bronchial asthma.[9,16,28] Saponins are the main bioactive components, owing to their higher abundance, but polyphenols and flavonoids also participate in these therapeutic effects.

The plant has vasoprotective properties, deriving from the inhibition of elastase and hyaluronidase.[8] These enzymes degrade elastin and hyaluronic acid, respectively, and are involved in the turnover of the perivascular extracellular matrix, of which elastin and hyaluronic acid are main components together with collagen. It has been shown that the inhibitions of elastase and hyaluronidase are mainly due to the triterpenic moieties of saponins, i.e., sapogenins like hederagenin and oleanoic acid. Vasoprotective properties make the plant useful for the treatment of venous insufficiency.

α-Hederin has been shown to protect liver from hepatotoxic compounds like acetaminophen and carbon tetrachloride.[4] The mechanism of this protective effect could depend on the inhibition of P450 cytochromes, a cellular enzyme that can produce oxidative stress through the metabolization of xenobiotic compounds and is partially responsible for their hepatotoxic effects.[20] In a study on cadmium hepatotoxicity, it has been shown that α-hederin protects the liver by inducing the synthesis of metallothioneins, which can bind heavy metals and reduce their toxicity.[19]

Other studies have shown that α-hederin has an antibiotic action against bacteria, yeasts, and other fungi.[3] Anthelminthic and molluscicidal activities have also been detected.[17,18,23] α-Hederin, hederasaponin-C, hederacolchiside-E, and hederacolchiside-F have shown strong anti-inflammatory activity in carrageenan-induced rat paw edema.[12,27]

N-phenylpropenoyl-L-amino acid amides have been isolated from the leaves. These compounds can stimulate the P450 cytochrome CYP1A2 and inhibit glutathione-S-transferase in hepatocytes, promote cell proliferation in keratinocytes, and inhibit adhesion of *Helicobacter pylori* to the stomach wall.[15]

Dermatologic and Cosmetic Use

The plant is indicated as an emollient against skin irritation and itching. The extract has tensioactive and decongestive properties, and can be used on skins showing a seborrhoeic tendency.[21,26] Flavonoids exert a protective action on head hairs.

Vasoconstrictive and astringent properties due to saponins, and the lenitive properties of flavonoids, improve microcirculation and produce an antalgic effect. The plant is therefore useful in promoting the drainage of dermal tissue, which is essential in the treatment of cellulite and lower limb swelling, and in the decongestion of saggy eyes.[7,22]

Side Effects and Toxicity

The contact with leaves and extracts can induce dermatitis due to the presence of falcarinol and its derivatives.[10,24] These reactions can arise either as simple irritations, i.e., without an involvement of the immune system, or in the form of contact allergies, entailing an activation of the immune system.[11,14,25,30] However, these problems normally do not arise at the doses used in products for skin care.

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EUROPEAN ELDER

Scientific name: *Sambucus nigra* L.
Family: Caprifogliaceae
Parts used: Flowers, fruits, leaves, bark

Features

Tall bush growing to a height of 3–7 m. The trunk has a light brown-grey, fissured bark, while young branches have a green bark covered with lenticles. Leaves are pennatoseptate, with three to seven ovate, oblong acuminate and densely serrate leaflets. They are light green above and blue-green beneath. The flowers are yellowish white, have a strong scent, and are arranged in flat, umbelliform corymbs. The fruit is a black-violet, berrylike drupe containing a blood red juice.

The species is indigenous to Europe, Asia, and North Africa, and is naturalized in North America. It grows in shady, wet places, frequently in the undergrowth of forests.

It is a highly versatile plant, since almost all its portions have been used by man.[28] It has been used as food, medicine, and to make tools or ornaments. It was known of by ancient Greeks and Romans, and according to Pliny, the Greeks used the branches to build wind instruments. The fruits are traditionally used to prepare wines, syrups, and cakes. The flowers are ingredients of fritters, cordials, and refreshing beverages, and can be used to aromatize jams.

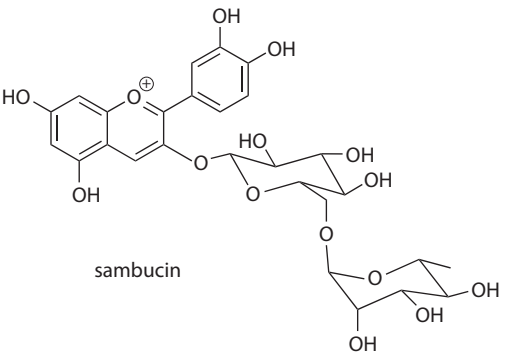
FIGURE 4.22 European Elder. (See color insert following page 40.)

Constituents

The flowers contain an essential oil, flavonoids, mainly rutin and quercetin, phenols (chlorogenic, p-coumaric, caffeic and ferulic acids), triterpenes (α- and β-amirin, ursolic acid, oleanolic acid, sterols), mucilage, and tannins.[19]

The fruits contain tannins, anthocyanins (sambucin, sambucyanin, chrysanthemin), cyanogenic glycosides, sugars, organic acids (citric and malic), vitamins A and C, and factors of the B complex.[15–17,23] Constituents of the bark include potassium salts, tannins, flavonoids, sugars, cyanogenic glycosides, and anthocyanins.[29]

The plant also contains lectins like nigrin, sieboldin, and ebulin, also known as ribosome-inactivating proteins (RIPs).[12,18] These lectins are similar to those of castor (*Ricinus communis*), but are less toxic.[4]



sambucin

Properties

Different parts of the plant, viz., leaves, bark, flowers, and fruits, have been used since remote times in traditional medicine.[2] The flowers are used as a sudorific tea to treat fever, flu, sinusitis, colds, and other diseases of the upper respiratory tract. Flowers and fruits are used as a diuretic, diaphoretic, and laxative.[24] The main active principles responsible for these properties are the flavonoid rutin and the triterpene β-amirin. The bark is used as an anti-inflammatory for arthritis and rheumatism.

The plant also exerts analgesic activity, possibly due to the cyanogenic glycoside sambunigrin. Experimental studies and clinical tests have shown that the fruit extract reduces the infectivity of influenza virus strains.[25,31,32] By using *in vitro* cultures of human fibroblasts, it has been shown that the extract inhibits the replication of various *Herpes* virus strains.[21] Similar results have been found with HIV. Ribosome-inactivating proteins inhibit the protein synthesis activity of ribosomes, and are known for their antiviral effects. It is therefore conceivable that the plant's antiviral properties may depend on the presence of this kind of protein.

The plant has also immunomodulatory activity. It stimulates the production of TNF-α and interleukins, which are known to activate blood phagocytes and promote their migration into inflammation sites.[3,14]

Many diseases entail oxidative stress conditions, including cancer, cardiovascular and neurodegenerative syndromes, and autoimmune diseases. The plant has strong antioxidant properties, and its anthocyanins are particularly suitable as a food supplement.[5,6,8,11,20,27] It has been shown that these latter constituents protect endothelial cells against oxidative stress.[30] The treatment of healthy individuals with a fruit extract containing 10% anthocyanins, in the presence of a hyperlipidic diet, has prevented the alteration of blood triglycerides, total blood cholesterol, and the HDL/LDL ratio.[1,22]

In traditional medicine, flowers have been used as a remedy against diabetes. Experimental studies have provided a scientific basis to these therapeutic practices, showing that the flower extract increases the insulin secretion of pancreatic cells and the glucose uptake and metabolism of muscle cells.[13] However, clinical trials concerning antidiabetic properties are still lacking.

Dermatologic and Cosmetic Use

The plant has various dermatologic and cosmetic uses.[9] The leaves can be used to treat mild burns. The flowers are a remedy for reddened eyes, irritated and inflamed skin, and for the healing of small wounds and ulcers.

The plant extract has an emollient effect on the skin, due to the presence of mucilage. It also reduces the feeling of heaviness and fatigue of lower limbs, because of the anti-inflammatory effect of flavonoids and their stimulatory effect on circulation. This latter property can also be exploited in anticellulite preparations.

Side Effects and Toxicity

Plant extracts do not generally induce side effects at the recommended doses. However, these products stimulate insulin release, and therefore they must be used with care by diabetic patients treated with insulin.

The ingestion of raw fruits can induce nausea and vomit because of the presence of cyanogenic glycosides. The leaves and the bark have some toxicity; too.[7]

The contact with flowers and plant derivatives can induce allergies, mostly due to the presence of ribosome-inactivating proteins.[10,26]

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GINKGO

Scientific name: *Ginkgo biloba* L.
Family: Ginkgoaceae
Parts used: Leaves

Features

Deciduous tree growing to a height of more than 30 m. The individuals are long-lived and with aging produce aerial roots. These latter grow very slowly and their function is unclear. The leaves have a typical fanlike shape with radiate veins, and in autumn turn from dark green to golden yellow. Yellowish leaves are rapidly shed, frequently within one or two days. The species is dioecious, i.e., having separate male and female individuals. Male plants bear small polliniferous cones, while female plants produce pairs of ovules at the apex of fertile branches, which develop into 2-cm-long seeds. The shell of the mature seed (sarcotesta) is soft, yellow brownish, and looks like an apricot. It is also improperly known as ginkgo's fruit. When the seeds fall to the ground, their scent resembles that of rancid butter, due to the presence of butanoic acid.

The species is native to China and Japan and is a living fossil whose appearance on earth can be dated back more than 250 millions years ago. To date, it is almost extinct in the wild, with the main exception of some residual natural populations in the Zhejiang province of eastern China. A contribution to the conservation of this species in historic times came from cultivations carried out by Chinese monks in religious places. Nowadays, the species is cultivated in various countries and is also frequently used in urban environments for its good capacity of adaptation.[14]

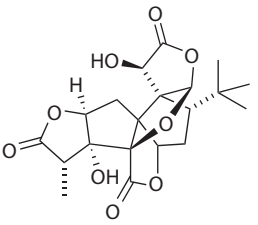
FIGURE 4.23 Ginkgo. (See color insert following page 40.)

The name *ginkgo* was actually due to a transcription mistake. The first report of the species in Europe was by the German naturalist Engelbert Kaempfer, at the end of the sixteenth century, who adopted the name *ginkyo*, based on a phonetic interpretation of Japanese writing. Later on, the *y* was confused with a *g*, and such a misspelling eventually led to the diffusion of the current name.

The curative properties of the plant were already known in China in 2800 B.C., as evidenced by a treatise of the physician Pen T'Sao Ching. Leave extracts are currently used in different Eastern and Western countries for the treatment of vascular and mental diseases.[26] In different Asian countries the pulp of the seed is considered a delicacy possessing aphrodisiac properties.

Constituents

Chief bioactive compounds are flavonoids, including flavonol glycosides (isorhamnetin, kaempferol, myricetin, quercetin), dimeric flavones, and amentoflavone[13,35], sesquiterpene lactones (ginkgolides, bilobalides)[5,24], polyphenols (ginkgolic acids, cathechins, gallocatechins); and anthocyanosides.



ginkgolide A

Properties

In traditional Chinese medicine the plant is primarily used to contrast neural syndromes and circulatory disorders and to reinforce the heart and lungs. In Western countries, main uses include the treatment of microcirculation dysfunctions and inadequate blood flow to the body extremities, frequently occurring in aged people.[1,8,34] The active principles protect the walls of arteries, veins, and capillaries, maintaining their tone and elasticity. Flavonoids are particularly responsible for the manifestation of these properties, since they exert an action similar to that of vitamin P, consisting in a reduction of capillary permeability and an increase of their resistance.

The plant extracts can also act against neural disorders such as memory loss, senile dementia, Alzheimer's syndrome, insomnia, and tinnitus.[7,9,12,22,27,28] Positive effects on the nervous system can be ascribed on one hand to an improvement of blood flow to the brain, and on the other hand to an antioxidant effect of flavonoids, which would protect nervous cells from injury due to amyloid protein accumulation in Alzheimer's, and more in general from processes of aging.[10,15,21] In addition, there would also be a protective action on the blood-brain barrier that regulates the exchanges between blood and brain. More specific mechanisms have also been

highlighted, including the ability of bilobalide to bind GABA receptors, the maintenance of good levels of cholinergic receptors, favoring cholinergic mechanisms, and the improvement of choline uptake by the brain.[17,25,32]

In a study on ginkgo's neuroprotective properties, the standard extract EGb761 has been tested on the nematode worm *Caenorhabditis elegans*, proving its ability to contrast toxic effects due to β-amyloid protein accumulation, and showing that such a protective action is to be ascribed to the terpenoid ginkgolide A.[33]

Another main effect, due to ginkgolide B, is the inhibition of the platelet-activating factor (PAF), a chemical mediator involved in various processes, including platelet aggregation, blood coagulation, capillary permeability, inflammation, and asthmatic spasms due to allergic reactions.[6,19]

The properties of the EGb761 extract and of ginkgolide B have also been investigated by the technique of DNA microarray, which allows one to point out genes that are upregulated or downregulated by a certain treatment or under specific pathologic conditions. By this method, it has been possible to detect genes involved in neuroprotective effects and in the inhibition of the growth of tumor cell lines mediated by plant compounds.[4]

Cellular studies have also shown an inhibitory action on the induction of the MMP-2 and MMP-9 metalloproteinases operated by the pro-inflammatory cytokine TNF-α in vascular smooth muscle cells.[30] Due to the role of metalloproteinases in inflammatory processes, this latter result can explain, at least in part, the plant anti-inflammatory properties.[36]

Dermatologic and Cosmetic Use

Cosmetic formulations based on extracts of the plant exert stimulating, tonifying, antibacterial, and antioxidant effects, and can be used to prevent or amend skin aging and cellulite.[3]

Ginkgo's dimeric flavonoids, administered to human subjects as a phytosome preparation in combination with phosphatidylcholine, have shown marked vasodilatory, microvasculokinetic, and antierythema properties. Such a treatment has improved microvascular perfusion, with a consequent amelioration of the supply of nutrients to the skin.

The reinforcement of the vascular function produces an improvement of the drainage of interstitial fluids, thus favoring the removal of edema caused by the adipose deposits of cellulite.

The plant is also used in products that stimulate hair growth. Also in this case, the promotion of microcirculation seems to play a determinant role, by acting favorably on piliferous bulbs, and moreover inducing anti-inflammatory, antioxidant, and antibacteric effects.[18]

Finally, thanks to its antioxidant properties, the plant can also be used to protect the skin from damage due to sun irradiation.[11]

Side Effects and Toxicity

Allergic and contact dermatitis can be induced by the seed pulp due to the presence of ginkgolic acid, which has been identified as the allergenic compound.[20,23,29]

Cases of intoxication caused by the ingestion of the fruit, which is commonly used in Asian cuisines, have also been reported. The compound responsible for this kind of toxicity seems to be ginkgotossin (4-O-methylpiridoxin), which has a structure similar to that of vitamin B6 (pirydoxin).[16] The ingestion of high doses of this compound can produce disorders similar to vitamin B6 deficiency.

Caution should also be used in patients treated with anticoagulant drugs, due to the plant property of reducing platelet aggregation, which can produce additive effects increasing the risk of hemorrhages.[2,31]

The use of the plant should also be avoided by subjects treated with monoamino oxidase inhibitors or during pregnancy.

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GOTU KOLA

Scientific name: *Centella asiatica* (L.) Urb.
Family: Araliaceae
Parts used: Leaves
Other names: Indian Pennywort

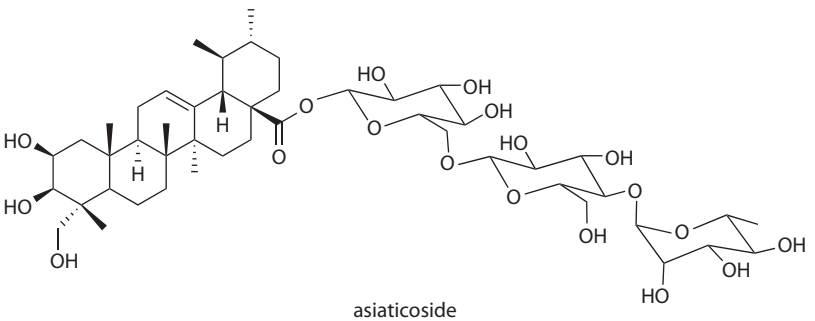
Features

Small perennial herbal plant, common in tropical and subtropical regions, such as Madagascar, eastern Africa, India, Pakistan, Sri Lanka, Brazil, and Venezuela. It grows from plains up to a height of more than 600 m above sea level, colonizing shaded wet places, swamps, and riverbanks. The stems are creeping and have roots at the nodes. The leaves are circular-reniform and form rosettes at the nodes. Flowers are sessile, reddish or purplish.

The natives of the eastern Indies call this plant Brahmi in honor of God Brahma, to celebrate its remarkable medicinal properties. It has been recommended in Ayurveda for thousands of years and is present in other Asian and African traditional pharmacopeias, such as the traditional medicine of Madagascar. A legend tells that the Bengal tiger rubs his body on the plant to heal wounds, so that the plant is also called the tiger plant. Another legend has it that the plant would be a kind of life elixir, since an ancient Chinese herbalist would have lived for more than 200 years by using it.

Constituents

The most important active principles are triterpenoid glycosides, of which the most abundant are asiaticoside and madecassoside.[3,17] The hydrolysis of these compounds releases the sugars glucose and rhamnose, and the aglycones asiatic and madecassic acids, respectively. Oligosaccharides, like *meso*-inositol and centellose, and polysaccharides, like arabinogalactans, are also present.[32] Other bioactive compounds are sterols (stigmasterol), flavonoids (kaempferol, quercetin), and polyphenols.[36] The plant also furnishes an essential oil containing various terpenic compounds, mainly α-humulene (about 20%) and β-caryophyllene (about 20%).[27,34]



asiaticoside

Properties

In popular medicines the plant is mostly used as a cicatrizing remedy against leprosy blisters, ulcers, eczemas, dermatosis, and psoriasis. In Ayurveda the plant is also used to keep the nervous system and the mind alive. The plant also finds application in decubitus ulcers and in disorders of the collagen matrix.

Thanks to its action on blood vessel walls, it can slow the progression of venous insufficiency, and prevent the dystrophic degeneration of blood vessels, and the leg ulcers caused by an altered venous flow. It is also a remedy against the loss of blood vessel elasticity, and therefore it can prevent limb swelling and varicose veins.

The plant can alleviate mind stress and anxiety, reinforce the memory, and improve other nervous functions.[1,4,8,10,28,33] It also stimulates hematopoiesis and the immune response.

These beneficial effects are mainly due to triterpenoids and their glycosylated derivatives. These compounds stimulate collagen synthesis and deposition, thus reinforcing mechanical tissues such as tendons, bones, cartilage, and connective. They also exert a positive action on blood vessels, leading to a functional improvement of the circulatory system. Terpenoids also stimulate the reticuloendothelial system, thus ameliorating blood cell turnover, iron metabolism, and immune responses.

It has been shown that the plant extract promotes the activation of genes involved in the synthesis of growth factors, in angiogenesis, and in the remodeling of the extracellular matrix. These data offer a basis for the understanding of therapeutic properties concerning disorders of the connective tissue, microangiopathies, and the healing of wounds.[15,30,35]

Various studies have shown that the main active compound is the terpenoid asiatic acid, which is able to act in both glycosylated and free forms.[5] Its action involves the induction of collagen I synthesis in fibroblasts, the main cellular component of connective tissue.[6,22,23] It has been reported that the induction occurs through the activation of the SMAD transcription factors. These latter regulates gene transcription in response to growth factors like transforming growth factor β, which is involved in tissue remodeling during development.[20]

Experimental data have also shown anxiolytic properties of the extract and its ability to protect the liver from oxidative stress.[14] In addition, asiatic acid can induce apoptosis in various tumor cell lines, viz., melanoma, hepatoma, and breast cancer cells,[13,21,26] suggesting a possible use of the plant extract in antitumor therapies, although clinical trials are lacking.

The presence of arabinogalactans, which are known for their ability to stimulate lymphocytes, has been put in relation with the plant's action on the immune system. The essential oil has been mainly investigated for its antibacterial properties.[25]

Dermatologic and Cosmetic Use

Skin aging seems mainly linked to a scarcity of collagen I, the main component of the dermal tissue. Gotu kola's effects on the connective tissue are most useful for skin firming and hydration, and therefore the plant acts as a remedy against skin wrinkles, creases, and sagging.[9,24,29,31]

The cause of cellulite is generally ascribed to an alteration of the trophic support to dermal connective tissue, due to insufficient vascularization. The trophic action of the plant on blood vessel wall tissue favors skin drainage, thus contributing to improve cellulite conditions. A clinical study has been conducted to explore the possible use of the plant in the treatment of atopic dermatitis.[19]

Side Effects and Toxicity

The plant can induce sedative effects through an interaction with anticonvulsivants, antidepressants, anticholinergics, and antihistaminics. Moreover, it seems to increase the blood levels of cholesterol and glucose, thus interfering with statins and drugs for glycemic control.

Cases of hepatotoxicity associated with prolonged oral use of plant extracts,[18] and various cases of allergic contact dermatitis have been reported.[2,7,11,16] However, the plant is generally considered a mild allergen or sensitizer.[12]

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GRAPE

Scientific name: *Vitis vinifera* L.
Family: Vitaceae
Parts used: Fruits, seeds, leaves

Features

Climber vine with woody trunk, striped bark, and deep, branched roots. The branches are very long, glabrous, and finely grooved. The leaves are 5–20 cm long, orbicular, and palmately lobed. The flowers are small and arranged in compound panicles. The fruit is an oblong to globular berry, blue-violet, green, or yellow in color. It consists of an esocarp, or skin, a mesocarp, or pulp, which is juicy and sweet, and an endocarp, or grapeseed. The seed is pear shaped and consists of a woody tegument, a fat-rich endosperm (16–21% fat), and the embryo.

The plant is indigenous of southern Europe and western Asia, while today it is cultivated in all temperate regions of the world. It is one of the most well-known plants in the world, and numerous varieties have been grown from the wild form along centuries. It has enormous commercial importance, mainly due to the production of table grape, and to wine and liquor making. Grape is also used to make juice, jam, and other food products, such as raisins and grapeseed oil.[4]

FIGURE 4.24 Grape. (See color insert following page 40.)

Constituents

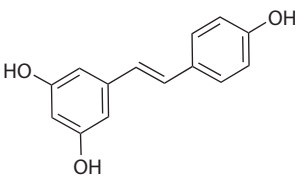
Because of the economical interest of the plant, its chemical composition has been accurately determined. The twigs contain prevalently tannins (2–3%), carbohydrates (1%), tartaric acid (1%), and other organic acids, minerals (1%), and nitrogen compounds. The fruit skin is covered by a waxy substance and contains tartaric acid (0.2–0.3%) and other organic acids (1%), mineral salts (1.5–2%) with a particular abundance of iron, and in addition, flavonoids, terpenic alcohols, and other volatile compounds. Grapeseeds contain high amounts of lipids (10–12%) and tannins (5%). The fruit pulp is particularly rich in carbohydrates (more than 20%), mainly glucose and fructose, and organic acids, principally malic, tartaric, and citric acid. It also contains fats (0.6%), proteins (0.7%), and minerals like K, P, Ca Mg, Na, Fe, and Zn, and vitamins like B6, B1, B2, C, A, E, folate, and niacin.

The main bioactive compounds, besides tannins, are flavonoids like anthocyanidins (e.g., peonidin, delphinidin, petunidin, and malvidin) and their glycosides anthocyanins (up to 0.3% dry weight), which are responsible for the red color of the leaves in autumn and of the fruits of the red varieties.[29] White grapes are derived from red grapes through gene mutations that turn off the production of anthocyanidins. Other flavonoids include flavonol glycosides and catechin oligomers known as proanthocyanidins.[7] Flavonoids are particularly abundant in seeds and fruit skin. Anthocyanidins and other polyphenol pigments are also responsible for the varying shades of purple in red wines.

The stem, roots, and fruit peel contain the stilbene derivative resveratrol (*trans*-3,4′,5-trihydroxystilbene), stilbene dimers (viniferins), and glycosides (astringin and piceid).[9,60,74] The seeds also contain polyphenols (5–8%) such as flavonoids, gallic acid, flavan-3-ols (catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin-3-O-gallate), and proanthocyanidin oligomers.[59]

During wine maturation, polymeric pigments are formed from the reaction of anthocyanins with other flavonoids and low-molecular-weight compounds, such as piruvic acid. These anthocyanin derivatives include pyranoanthocyanins, vitisins, and anthocyanin vinylflavanols.[30,63]

The leftovers of wine pressing are used to extract grapeseed oil. The oil has a fine texture and is almost odorless. It contains antioxidants like vitamins E, C, and β-carotene, and fair amounts of the essential fatty acid linoleic acid. Other fatty acids are palmitic, palmitoleic, stearic, oleic, α-linolenic, icosanoic, icosenoic, and docosanoic acids.



resveratrol

Properties

A great number of therapeutic properties of grape have been recognized. Anthocyanins and proanthocyanidins exert capillaroprotective and anti-inflammatory actions, which are useful for the treatment of circulatory insufficiency, varicose veins, and hemorrhoids.[19,31] Clinical studies indicate that the administration of proanthocyanidins improves lower limb edema, feeling of heaviness, cramps, and itching. In addition, the strong presence of polyphenols confers astringent effects.[51]

The phlebotropic, venotropic, and capillarotropic actions seem due to the inhibition of elastase, an enzyme that is released by polymorphonucleate leukocytes at sites of inflammation.[44] Elastase degrades elastin and collagen fibers, thus weakening the wall of blood vessels. The action on elastase is accompanied by the inhibition of hyaluronidase, which degrades the polysaccharides of the extracellular matrix. In addition, grape's principles promote the hydroxylation of proline in neosynthesized collagen molecules, an essential process for the maturation of collagen fibrils.

Proanthocyanidins exert anticoagulant properties by preventing platelet aggregation through the inhibition of cycloxygenase, which is responsible for the conversion of arachidonic acid to prostanoids.[22,41,76] These compounds inhibit the angiotensin converting enzyme, and therefore contrast the formation of the vasoconstrictor hormone angiotensin II. It has been observed that the prolonged therapeutic use of these compounds reduces the incidence of stroke in the rat and produces an antiarrhythmic effect on the rabbit ischemic heart.[64] Similar effects could also depend on the scavenging of the superoxide anion free radical, a reactive oxygen species that is formed abundantly in ischemia-reperfusion events. In addition, there is an increased release of vasoactive prostacyclins, which reduce cytotoxic processes occurring in cardiac cells during ischemia, such as sustained intracellular calcium rise and lysosomal enzyme release. Proanthocyanidins are also able to inhibit matrix metalloproteinases (MMPs), the main effectors of extracellular matrix degradation, which play a role in inflammation and tumor invasiveness.[49]

Clinical data surveys have shown that proanthocyanidins, and in general polyphenols, cause a lower incidence of cardiovascular diseases. The French paradox is the observation that in some regions of France there is a relatively low risk of death for cardiovascular diseases, despite a diet relatively rich in saturated fats.[62] This body of evidence led to the theory that the consumption of red wine decreases the incidence of cardiac diseases, although the dietary intakes of fruit, vegetables, and other plant foods should also be taken into account. It has also been shown that a moderate intake of wine is associated with a rise in blood HDL cholesterol and apolipoproteins A1 and A2, lower oxidation of α-tocopherol, and reduction of fibrinogen concentration.[54] Moreover, grape polyphenols increase the antioxidant power of plasma, reduce LDL oxidation, which is considered a primary cause of atherosclerotic injury, increase the activity of LDL receptors, and reduce the levels of LDL cholesterol.[17,21,23,27,32,70,73,75]

The grapeseed extract has a stronger antioxidant power than vitamins C, E, and β-carotene, is cytotoxic to breast, lung, and stomach adenocarcinoma cells, and protects mouth keratinocytes from *in vitro* apoptosis induced by tobacco.[6,13,14,28,37,45,66,68] It also protects hepatic cells from cytotoxicity induced by chemotherapeutic drugs, through a modulation of genes that regulate cell cycle and apoptosis, such as Bcl2, p53, and c-myc, and inhibit the cytochrome P450 2E1, thus limiting the hepatotoxic effects of various drugs. Grapeseeds protect the human organism from age-related diseases, like degradation of joint collagen and tissue damage caused by sun exposure.[78]

A lot of studies on grape compounds have been focused on resveratrol.[34] This compound is a phytoalexin, i.e., an antibiotic produced by various plants, which plays a defensive role against the aggressions of parasites and pathogens. Resveratrol can be present in simple or glycosylated form, which protects the molecule from oxidative degradation and improves its intestinal absorption. This compound has been shown to prevent cardiovascular diseases by modulating the function of cardiac cells, inhibiting LDL oxidation, suppressing platelet aggregation, and reducing myocardial damage during ischemia-reperfusion.[12,33,57] It also modulates the metabolism and peroxidation of lipids and reduces the expression and activity of cycloxygenases. Its molecule is structurally similar to diethylstilbestrol, a synthetic estrogen, and therefore it also exerts a weak estrogenic activity.

Resveratrol has also been widely investigated for its chemopreventive effects, because it contrasts the pathogenesis of tumors and the processes of angiogenesis and metastasis.[2,3] The *in vitro* effects of resveratrol have been observed on various tumor cells, and generally involve an arrest of cell cycle and the induction of apoptosis. In squamous carcinoma cells, it provokes cell cycle arrest at G1, with induction of p21WAF1/CIP1, decrease of cyclins D1/D2/E and cyclin kinase, and activation of MEK1, ERK1/2, and AP-1. In prostate carcinoma cells, it induces apoptosis through the loss of mitochondrial membrane potential, inhibition of the antiapoptotic protein Bcl-2, and increase of the proapoptotic Bax, Bak, Bid, and Bad. In breast cancer cells, it regulates gene transcription by binding to estrogen receptor-α and -β, and inhibits the growth of prostate tumor cells by altering the expression of androgen-responsive genes. It can prevent stomach cancer by inhibiting the growth of *Helicobacter pylori*, an infective agent that is involved in the pathogenesis of this tumor. It prevents lung carcinoma by inhibiting the expression of cytochorome P450 1A1 and 1B1, which metabolize polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene, and are responsible for the formation of carcinogen metabolites. In pancreatic tumor cells and leukemic cells, resveratrol induces apoptosis through mitochondrial depolarization, cytochrome c release, and caspase 3 activation.[11]

Despite a great number of *in vitro* data, studies *in vivo* on mice have produced contrasting results about the real efficacy of resveratrol as a chemotherapeutic drug. Doubts remain that the dietary intake of resveratrol could result in tissue concentrations able to produce antitumor effects. The relatively low resveratrol tissue concentrations derived from grape consumption suggest that the dietary intake of the compound could play a preventive role rather than a therapeutic one, possibly through a synergistic interaction with other substances. *In vitro* studies have shown a synergistic induction of apoptosis by the combination of resveratrol with quercetin and ellagic acid.

Resveratrol protects the genome from DNA damage by acting as a free radical scavenger or by activating repair mechanisms. Double-strand DNA breaks are recognized by such cellular systems as ataxia telangiectasia mutated protein (ATM), Rad3-related protein (ATR), and DNA-dependent protein kinase (DNA-PK). Resveratrol activates these systems and thereby inhibits the error-prone recombination process that can lead to the duplication of damaged DNA and consequently to genomic instability.[38,39] The maintenance of genome stability by resveratrol could also in part explain its chemopreventive action.

It has been shown that, depending on the concentration level, resveratrol can induce either cell survival signals or cell death mechanisms, by possibly acting on different cell sites.[36,40] In leukemic and breast cancer cells, the induction of apoptosis by high doses of resveratrol occurs through cell death receptors like CD95 (Apo1/Fas). It has been supposed that the compound could act by means of a redistribution of CD95 and other receptors of the TNF family, such as TRAIL-R, to sphingolipid-rich lipid rafts, thus producing an amplification of the cell death signals induced by the agonists of these receptors. Conversely, at low concentration the compound inhibits cell death by contrasting the drop of mithocondrial membrane potential and cytosolic pH, the cellular production of H_2O_2, the mitochondrial translocation of Bax, and the activation of caspases 3 and 9. Hence, depending on the dose, resveratrol could be alternatively used as a chemotherapeutic agent, or as a protective agent against cell death processes.[1,42]

Resveratrol reduces tissue inflammation through the inhibition of lipoxygenases (LOXs) and cycloxygenases (COXs), which are responsible for the synthesis of leukotrienes and prostanoids, respectively, and also via the activation of NFkB and AP-1 nuclear factors and the reduction of superoxide production by NADPH oxidase.[20,53] Resveratrol has been shown to contrast obesity and insulin resistance induced by a hypercaloric diet in the mouse, due to a rise in the aerobic capacity induced by AMP kinase and PPAR1-α activation and an increase in the number of mitochondria. Caloric restriction can prevent the pathogenesis of Alzheimer's through the activation of the SIRT1 histone deacetylase. In murine models of Huntington's disease and Wallerian degeneration, resveratrol has induced protective effects on neurons via SIRT1 activation, suggesting its possible use as an antineurodegenerative.

Resveratrol derivatives like viniferins have antifungal and anti-inflammatory properties.[18,69] The resveratrol dimer ε-viniferin inhibits the uptake of norepinefrine and 5-hydroxytryptamine and the enzymes monoaminoxydase A and B (MAO-A, MAO-B) in rat brain.[79] Hence, this compound offers an interesting molecular structure for the development of antidepressive drugs. The compound also inhibits phosphodiesterase 4, and inhibits more strongly than resveratrol various P450 cytochromes: CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2E1, CYP3A4, and CYP4A, as shown *in vitro* by making use of such substrates as ethoxyresorufin, coumarin, benzoxyresorufin, chlorozoxasone, testosterone, and lauric acid.[61]

Vitisins present in wine have been shown to exert anti-inflammatory and vasorelaxant effects. Vitisin A reduces the activation of Akt and STAT-1 induced by influenza virus A in alveolar epithelial cells, thus reducing the release of chemokines that promote the inflammation of the respiratory tract.[43] Vitisin C potentiates the vasodilation induced by nitric oxide produced in endothelial cells.[67]

Dermatologic and Cosmetic Use

Red grape extracts and active principles are widely used in cosmetic products, as also shown by the number of related patent publications.[8] The importance of grape in skin care is evidenced by wine therapy, which originally developed in the region of Bordeaux, France, and then diffused to other countries. Wine therapy basically consists of baths or applications of wine and grape extracts rich in polyphenols in order to stimulate microcirculation and strengthen blood vessels. The stabilizing action of proanthocyanidins on capillary vessels gives a contribution to the maintenance of skin elasticity and improves disorders linked to skin circulation, such as couperose, or to an insufficient draining of subdermal tissue, like cellulite.[55]

The antioxidant power of flavonoids and polyphenols contrasts aging processes induced by UV radiations and free radicals. In dermatologic and cosmetic products, grape polyphenols can be stabilized by the combination with fatty acids in order to ensure a full antioxidant power when they are applied to the skin. A main change involved in skin aging is the degradation of glycosaminoglycans and collagen, with a consequent reduction in skin thickness. The transdermic administration of the antioxidant lipoic acid and proanthocyanidins has induced in the rat an increase of collagen synthesis and deposition. Proanthocyanidins have also induced a rise in collagen synthesis in fibroblast cell cultures.

Resveratrol has a tightening and firming action on the skin and favors tissue renewal, thus acting similarly to retinol.[35] The topical application of resveratrol to nude mice has protected the skin from phototoxicity and tumorigenesis induced by UV-B radiations. In melanoma cells, the compound has inhibited cell growth and induced apoptosis, but *in vivo* tests have not confirmed its efficacy as a therapeutic agent for melanoma.[5] Proanthocyanidins and resveratrol seem able to improve wound healing, while topical application of resveratrol to mice has been found useful against herpes.[24–26,50] Resveratrol has also shown antimicrobial effects against bacteria and dermatophytes that infect the skin.[15]

Resveratrol and α-viniferin inhibit the enzyme tyrosinase, a limiting factor in the synthesis of melanin, thus suggesting their use in the treatment of hyperpigmentations.[48,52] Another possible mechanism related to the depigmenting action of resveratrol concerns the inactivation of the microphtalmia-associated transcription factor (MITF), since the hyperactivation of this factor has been associated with cAMP-induced melanization of melanocytes.[56]

A grapeseed extract has promoted the expression of vascular endothelial growth factor (VEGF) in keratinocytes, thus favoring skin angiogenesis and wound healing. A similar extract, administered orally to guinea pigs, has reduced the pigmentation caused by direct exposure to ultraviolet irradiation, probably acting via the inhibition of melanin synthesis and melanocyte proliferation.[77]

Grapeseed oil is easily absorbed by the skin, on which it exerts emollient, mildly astringent, and hydrating effects. It is particularly suitable for stress-induced skin damage, particularly in the periocular region, because of its high regenerative properties. The oil forms a thin film on the skin and is therefore used as a vehicle of essential oils in aromatherapy. It is also useful in the treatment of acne.

Side Effects and Toxicity

The plant is well tolerated by humans. No cases of toxicity have been reported, although its therapeutic use during pregnancy should be avoided.[46] Sporadic cases of food and respiratory allergies and contact dermatitis caused by the plant and by its products have been reported.[47,65,72,80] Allergenic properties have been ascribed to endochitinase 4A, a lipid-transfer protein (LTP) showing some homology and cross-reactivity with an LTP from peach (*Prunus persica*), and a 24 kDa protein that is a homologue of the taumatin-like allergen of cherry (*Prunus avium*).[58]

Occupational allergies have been reported in wine growers, including dermatitis, asthma, alveolitis, acute bronchial irritation, and fibrosis.[10,16] However, it is not clear if these conditions have been caused by the plant, by its associated microorganisms, or by pesticides used in grape cultivations.

The prolonged use of grape extracts can occasionally induce mild epigastric pain with digestive disorders or astringent effects, or potentiate the action of anticoagulants. In patients treated with cyclosporine, dietary uptake of red wine has reduced by 50% the plasma levels of the drug without altering its half-life, suggesting that the wine active principles limit the intestinal absorption of cyclosporine but not its degradation rates.[71] Grape compounds can also affect the intestinal absorption of milk.

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GREEN TEA

Scientific name: *Camellia sinensis* (L.) Kuntze
Family: Theaceae
Parts used: Leaves

Features

Evergreen tree, native to southeastern Asia, reaching a height of up to 20 m. In cultivation the plant is kept pruned to a low, highly branched shrub in order to facilitate the collection of the leaves. The leaves are glossy dark green, short-petiolate, alternate, lanceolate or elongate-ovate, serrate, and coriaceous. The young leaves, appearing silver from the presence of hairs, are the medicinal parts from which tea is prepared. The flowers are white or pale pink, short pedicled, borne singly or in small clusters in the leaf axils. They have five to seven sepals and petals, numerous yellow stamens, and an ovary with three chambers. The fruit is a woody capsule containing one to three brown, smooth seeds.

The Assam variety (*C. sinensis* var. *assamica*), predominantly grown in the Assam region of India, is a small tree with large leaves. In the wild it reaches a height of 6 to 20 m and is native to northeast India, Myanmar, Vietnam, and southern China. The Chinese variety (*C. sinensis* var. *sinensis*) was the first tea plant to be discovered and used to produce tea, about 3,000 years ago. It is a small-leaved bush with multiple stems that reaches a height of 3 m and is native to southeast China.[30]

The leaves of the plant are used to prepare tea, a very popular beverage that is consumed by more than two-thirds of the world population. Different types of tea are regularly traded on the market, of which the most widely diffused are green and black teas. Green tea is most popular in Asian countries and is obtained from a simple process of heating, which inactivates the enzyme polyphenol oxydase and preserves leaf polyphenols from oxidation. Black tea is more popular in Western countries, and is obtained from a fermentation process that induces the oxidation of catechins to theaflavins and thearubigins. Another type, more widely diffused in China, is wulong or oolong tea, obtained through a partial fermentation of leaves. White tea is a Chinese specialty obtained from the very young, unfolded leaves, thickly covered by a whitish wool, which are simply dried in order to avoid oxidation processes.

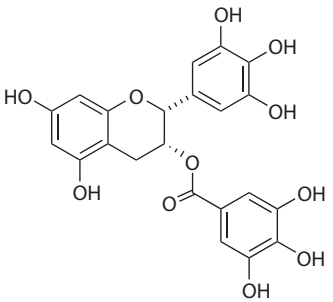
In China, there are various legends about the origins of tea drinking. Most sources attribute the discovery of tea to Emperor Shen Nung, who lived in the third millennium B.C. The greatest Chinese authority on tea was Lu Yu, who lived between the eighth and ninth centuries A.D. His book *The Classic of Tea* is considered the very first milestone in the literature on the properties of tea. This book became a popular manual for tea drinkers in Tang China (618–907), and exerted a great influence on later Taoist and Zen writings.[39]

Besides the importance of leaves, the plant is also used to obtain oil from seeds, which is used for cooking and dressing.

FIGURE 4.25 Green Tea. Courtesy of Dr. R. Albericci. (See color insert following page 40.)

Constituents

The main bioactive compounds occurring in the leaves are flavonoids such as catechins, of which the most abundant is epigallocatechin-3-gallate (EGCG). Other catechins include (–)-epicatechin, epigallocatechin, (–)-epicatechin-3-gallate, and their oligomeric derivatives, the proanthocyanidins.[18] Green tea contains a higher amount of catechins with respect to black tea. Its phenolic content can vary from 20 to 40% of dry weight, according to plant variety and geographical region. Other important constituents are the amino acid L-theanine (N-ethyl-L-glutamine), and methylxanthines like caffeine, the most abundant one, theophylline, and theobromine.[5] The main fatty acids are palmitic, linoleic, and α-linolenic acids. The plant also contains tea saponins, oleanane-type triterpene glycosides, and volatile compounds.[48,50]



(–)-epigallocatechin-3-gallate

Properties

In traditional Chinese medicine the leaves have been used for centuries to treat asthma, bronchial spasms, and coronaric and periferic vascular diseases. Although China has the highest percentage of smokers, the Chinese population shows a low occurrence of some tumors, like prostate cancer, possibly due to the high consumption of green tea. Because of its millenary use as a beverage and medicine, and the empirical evidence about its beneficial effects, many studies have been carried out to explore the therapeutic and pharmacological properties of tea.[9,38] These studies suggest that green tea reduces the risk of cardiovascular diseases and cancer; has antihypertensive, antibacterial, antiviral, and anti-inflammatory effects; improves the regulation of body weight; increases the mineral density of bones; and exerts anti-UV and neuroprotective actions.[7,8]

It has been shown that the therapeutic properties of the plant are mainly due to catechins, and are primarily attributable to EGCG.[36] However, it has also been assessed that the therapeutic effects of catechins occur at higher concentrations with respect to the physiological levels obtained by the dietary ingestion of tea. This suggests that tea drinking has mainly a preventive role, while to obtain therapeutic effects the use of concentrated tea extracts or of chemically synthesized tea compounds is needed.

One of the best-studied properties of EGCG is the inhibitory action on various kinds of tumors.[10] Antitumor activities occur through a series of mechanisms, including the inhibition of tumor promoter TNF-α release, the antiproliferative effect on tumor cells, the induction of apoptosis, and the increased expression of progesterone and estrogen receptors in postmenopause women.[2,16,17,19,28,51]

EGCG is able to inhibit the degradation of proteoglycans and type II collagen, a mechanism that can explain its antiarthritic effect and the protection of cartilage.[1] It is also an antidiabetic able to induce in the liver the phosphorylation of the insulin receptor and of different insulin-dependent kinases, thus repressing the release of glucose.[3,47] Green tea extracts have shown an inhibitory activity on the enzyme fatty acid synthase (FAS), which plays a key role in the development of obesity.[35,45,54] Caffeine also contributes to the regulation of body weight through the induction of thermogenesis and lipolysis.[49]

Proanthocyanidins exert an *in vitro* anti-inflammatory effect on macrophages through a decrease of the expression of cycloxygenase 2, the enzyme that releases prostaglandin E-2 and plays a key role in the pathogenesis of inflammation.[4,20,32] Floratheasaponins present in the flowers show antiallergic and antihyperlipidemic activities, while similar saponins from the seeds exert a gastroprotective effect.[34,52] Thanks to its antioxidant properties, the leaf extract protects the liver from oxidative damage produced by hepatotoxic agents like tamoxifen, a drug used in the treatment of breast cancer, ethanol, or a combination of ethanol and high-lipid diet.[11,13,27,32]

Theanine is able to cross the blood-brain barrier and reduce mental and physical stress.[26] This compound induces an increase of GABA, serotonine, and dopamine levels in the central nervous system, and has an affinity for AMPA, kainate, and NMDA receptors.[37] Green tea extract, theanine in particular, has also shown the ability to stimulate the immune response.[41]

Dermatologic and Cosmetic Use

Skin tumors, like melanoma and squamous and basal cells carcinomas, are very frequent in human populations, mainly due to skin damage caused by UV rays. Gallocatechins prevent UV ray injury on the skin and are therefore potentially useful against the development of skin tumors.[21,24,55] Catechin protection against UV rays occurs essentially through the activity of free radical scavenging.[14] EGCG has been shown to protect keratinocytes from UV-B rays, preventing the activation of the AP-1 transcription factor. Moreover, EGCG also protects these cells from UV-A rays, by inhibiting the activation of cycloxygenase and thereby preventing the release of interleukins like IL-1, IL-10, and IL-12.[25]

Another important mechanism induced by EGCG is the promotion of keratinocyte differentiation associated to the activation of caspase 14, which is involved in the formation of the keratin layer.[21,22,24,29] Gallocatechins also inhibit stress-induced apoptosis through the inactivation of caspase 3.[15] These mechanisms accelerate the formation of the keratinized skin barrier. The activation of caspase 14 is also important in skin disorders linked to a lack of keratinocyte differentiation, such as psoriasis. Catechins can also be used as an adjuvant in the UV-B phototherapy of psoriasis, in order to prevent possible negative effects caused by UV radiations. The ability of catechins to induce keratinocyte proliferation and differentiation suggests their possible use in wound healing.[21]

EGCG inhibits the enzyme 5-α-reductase type 1, particularly in sebaceous glands. This action prevents the release of dehydrotestosterone (DHT), which stimulates sebum production and leads to the development of dandruff and to the pathogenesis of androgenic alopecia in men. EGCG is also used in the prevention of seborrheic dermatitis.[46]

Because of its various properties on the skin, green tea has gained remarkable importance in skin care.[24] Its active principles are used in a vast number of cosmetic products, including anticellulite agents, antiaging and sun creams, perfumes, shampoos, and soaps. However, the topical use of tea compounds requires the solution of technical problems linked to the instability of catechins and their scarce penetration across the keratinized layer.[12] These drawbacks must be circumvented through combinations of tea principles with compounds able to prevent their oxidation and vehiculate them across the epidermis.

Side Effects and Toxicity

The prolonged use of food supplements based on green tea extracts can induce hepatotoxicity.[6,23,33,40] The excessive oral ingestion of green tea can also produce negative effects due to the presence of caffeine.

Caffeine and tannins can induce food allergy, while people employed in the collection of tea can develop nasal allergy and asthma induced by EGCG.[31,42–44] Green tea and gallocatechins do not generally induce contact dermatitis, but in contrast, they are used in the treatment of skin irritation.[53]

Numerous cases of contact dermatitis are known to be caused by green tea oil. However, this product is an essential oil extracted from the tea tree (*Melaleuca alternifolia*), a plant that is completely unrelated from the green tea plant.

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GUARANA

Scientific name: *Paullinia cupana* Kunth
Family: Sapindaceae
Parts used: Seeds

Features

Climbing plant indigenous to the Amazon forest. The leaves are big, compound, and imparipinnate, and the flowers are white and form racemes of 15–20 units. The fruit is a dehiscent, tripartite pyriform capsule of fire red color, containing from one to three dark seeds partially wrapped by white arils. When the fruit split opens, the seed at the interior can be likened to an eye, and such a feature has given rise to various tales.

The seed has a caffeine content equal to about threefold that of a coffee bean. Amazon populations obtain from roasted seeds a hardened dough that is known as Brazilian cocoa or guarana bread.

The plant was discovered by Westerners in the seventeenth century and was put on the market at the end of the 1950s. In Brazil it is widely cultivated and constitutes an important economic resource for the Guarani people. It is a chief ingredient of a drink that is very popular in Brazil, and is also used as a stimulant in various foods and food supplements.[33]

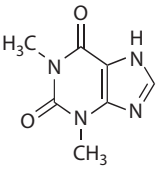
Constituents

The plant is a main source of caffeine (about 2–5% dry weight), and of other xanthines, such as theophylline, theobromine, adenine, guanine, xanthine, and hypoxanthine.[6,27,34,37,49] In the seeds, these compounds are largely bound to sugars, phenols, and tannins, from which they are released by the process of roasting.

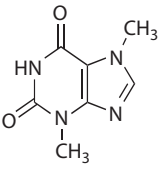
Other compounds include polyphenols, such as catechins and proanthocyanidin dimers, saponins, and a little amount of essential oil.

The seeds yield an oil containing cyanolipids (1-cyano-2-hydroxymethylprop-2-en-1-ol), i.e., fatty acids esterified to a nitrile moiety. The main fatty acids components are *cis*-11-octadecenoic (*cis*-vaccenic) and *cis*-11-eicosenoic acids.[3] Acylglycerols containing oleic and paulinic acids as main constituents are also present.

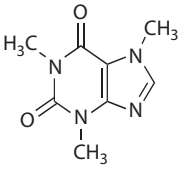
The essential oil contains methylbenzene, monoterpenes, and cyclic sesquiterpenes, methoxyphenilpropene, and alkylphenolic derivatives.[7]



theophylline



theobromine



caffeine

Properties

The seed extract, known as guarana, has been used by Guarani people since the pre-Colombian era, mainly as a stimulant and astringent.[45,48] The extract is considered a natural adaptogen, i.e., able to help the organism to overcome physical and mental fatigue and to heal various ailments, including intestinal disorders, obesity and cellulite, dyspepsy, and atherosclerosis.[36] In Western medicine the plant is principally used as a neurotonic, specifically against memory loss, and in addition to treat overweight and obesity.

The suitability of these therapeutic uses has been verified by experimental investigations.[16] Prolonged administrations of the extract to the rat have resulted in antidepressive effects,[40] while acute treatments on the mouse have produced an increase of physical endurance and of memory strength.[11,38] A study on humans has found that the extract, administered alone or in combination with ginseng, causes psychoactive effects, inducing an improvement of attention and memory.[20–22,24] The essential oil seems to be psychoactive too, probably due to the presence of the aromatic ether estragol and of its isomer anetol. In addition, the plant acts as an analgesic and gives relief to headache, neuralgia, lumbago, and rheumatism.

The extract can induce weight loss and decrease the number of adipose cells in the liver tissue.[1,8,26,43] It has also been shown that the methylxanthines of the extract modify the lipidic metabolism of the rat.[30]

The ethanolic extract has antibacterial properties against *Pseudomonas aeruginosa*, *Proteus mirabilis*, *P. vulgaris*, and *Escherichia coli*.[5,13,32] It can also prevent the growth of *Streptococcus mutans*, and can therefore be used in the treatment of the dental plaque.[47,50]

The extract has antioxidant properties,[35] as also shown by a study on the protection against lipid peroxidation in 3T3-L1 fibroblasts. Such an activity is correlated to the content in catechols. Experimental studies have shown that tannins can protect the liver of the mouse from DNA damage and hepatocarcinogenesis,[18,19] and the stomach of the rat from injury induced by ethanol and indomethacin.[12] Moreover, the extract decreases *in vitro* platelet aggregation through a mechanism that is due, at least in part, to a reduction of platelet thromboxanes.[9,10]

Much of the extract properties depend on the presence of caffeine, which acts mainly on the central nervous system and on the cardiovascular system.[41] This compound stimulates cortical neurons, thereby producing an increase of attention and a reduction of the sensation of fatigue, while it also acts on the bulbar respiratory center.[25,28,29] Caffeine induces positive inotropic and chronotropic effects on the heart, and increases the heart's oxygen consumption. Moreover, it acts as a peripheral vasodilatatory and as a diuretic.[31,42] At the cellular level, caffeine inhibits the enzyme phosphodiesterase, thus inducing an increase in the level of cyclic AMP, which in turn induces the activity of lipase and increases the rate of lipolysis. However, experimental and clinical studies have failed to reveal significant variations of the lipid outline following prolonged exposure to caffeine.

Dermatologic and Cosmetic Use

Guarana is primarily used in the treatment of cellulite, since the high level of caffeine causes an increase of lipolysis and a consequent reduction of subcutaneous adipose

deposits.[15,17,39] This acts synergistically with the vasodilatatory effect of xanthines, which improves the drainage of dermal and subdermal tissues. Thanks to its high antioxidant power and to antibacterial and antifungal properties, the extract also finds various other uses in the dermatologic and cosmetic fields. More specifically, it is used in shampoos contrasting greasy hairs and baldness.

Side Effects and Toxicity

If administered at excessive doses or for prolonged periods, guarana can induce the typical effects of caffeine overdose, viz., tremor, insomnia, irritability, tachycardia, nausea, and vomit. Guarana extract is therefore counterindicated for people suffering from insomnia, anxiety, depression, tachycardia, and allergy to caffeine.[14] Also, it should not be used together with antidepressants, or during pregnancy and lactation.[2,4,23]

Caffeine can increase the pH of the stomach and alter food absorption, while an association between the intake of methylxanthine-containing beverages and colon cancer has been claimed.[46]

In vitro studies on mammalian cells have shown that the extract can induce cytotoxicity, but only at high doses.[44]

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HOPS

Scientific name: *Humulus lupulus* L.
Family: Cannabaceae
Parts used: Female flowers

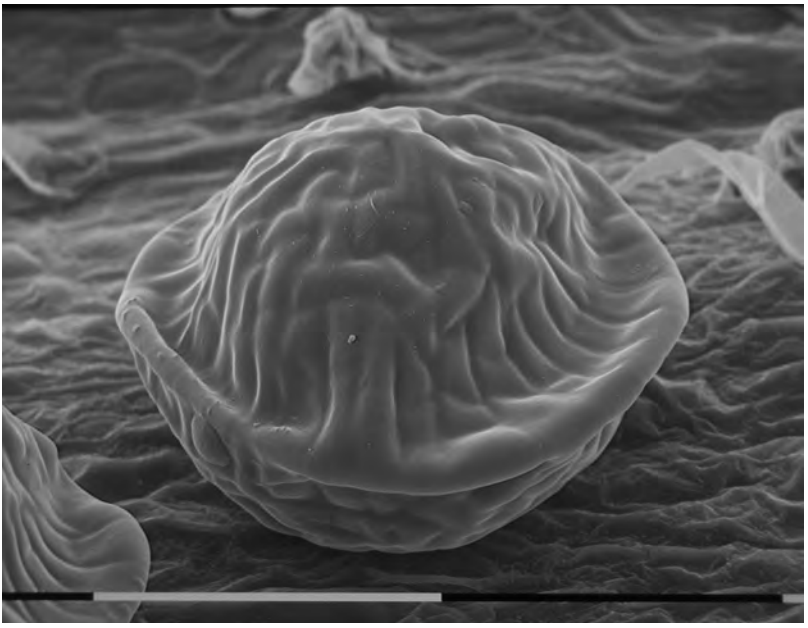
Features

Climbing, perennial, herbaceous plant having a stem covered with tough, hooked hairs. Leaves are opposite, chordate, and divided by three to five lobes with serrated edges. The species is dioecious, with unisexual flowers developing on male or female individuals. Female flowers form inflorescences of 2.5–5 cm in length, named strobili or cones, provided with bracts and bracteoles covered with yellow glands that secrete an aromatic resin. Male flowers are white yellowish and form loose racemes.

(A)

FIGURE 4.26 (A) Hops. (See color insert following page 40.)

(B)



(C)

FIGURE 4.26 (B) Bracts of cones covered with glands. (C) Scanning electron micrograph of a gland. Bar = 100 μm.

This species is native to Southwest Asia, but occurs naturalized in Europe and is cultivated in many temperate regions of the globe.[10,56] The plant has been exploited by man since very early times, and it may have been used as an ingredient in drinks by ancient Babylonians. In the age of the Romans it was already diffuse in Europe, where its cultivation spread farther when the plant was adopted as a preservative and flavor in the making of beer.[6,27] In the Middle Ages, brewery residuals were used in "youth baths" as a remedy against skin aging.

The spice is a yellowish powder, known as lupulin, obtained from the resiniferous glands of female flowers.

Constituents

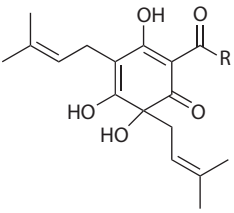
The flowers contain a hexan-soluble oleoresin, about 15–30%, composed of bitter monoacyl-phloroglucinols (hop acids), humulones (α-acids) characterized by two dimethylallyl chains, and lupulones (β-acids) characterized by three dimethylallyl chains, and also including oxidation products, such as 2-methyl-3-buten-2-ol. Non-hexan-soluble, hard resin is also present, containing δ-resin and χ-resin. Derivatives of bitter acids are responsible for the typical taste of beer, and they also act as foam stabilizers and antibacterial compounds.[78]

Other active principles include flavonoids, such as astragalin, kaempferol, quercetin, quercitrin, and rutin, and prenylflavonoids, among which the most important is the chalcone xanthohumol and its derivatives.[24,41,53,82,84,85] The prenylflavonoid 8-prenylnaringenin is one of the most potent phytoestrogens known so far. A fraction of polyphenols is also present (ranging between 2 and 14%), including tannins (catechin gallate, epicatechin gallate), phenolic acids (ferulic, gallic, caffeic, etc.), and proanthocyanidins (leucocyanidin, leucodelphinidin).[34,65,83] The flowers yield a volatile oil composed of more than 100 terpenoids, of which about 90% consist of the sesquiterpenes β-caryophyllene, farnesene, and humulene, and of the monoterpene myrcene.[23,48]

Properties

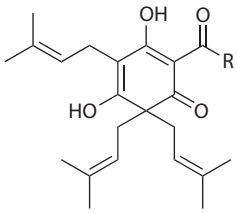
The plant has been used for centuries in different traditional medicines, including Ayurveda and Chinese medicine. It can be used as a remedy for a wide variety of ailments and diseases, such as excitement, nervous tension, and disturbed sleep, due to sedative properties, and difficult digestion, thanks to the stomachic properties of its bitter principles.[45,89,96] It is also employed to stimulate appetite and in nervous dyspepsia, since it can relieve reflux gastric irritation and concomitantly increase the tone of smooth muscles and stimulate digestive gland secretion.[43] Other therapeutic properties include analgesic, diuretic, antispasmodic, and anaphrodisiac, and in topical applications, the healing of ulcers and wounds, and the relief of skeletal muscle spasms.[12,30] It can be also employed in aromatherapy for the treatment of skin and difficult respiration. The German E Commission has approved the use of the plant in the cure of disturbed mood and sleep.[7]

The effects of the plant on the central nervous system have been investigated in a number of studies carried out on animal models,[1,47,74] whereas only a few studies



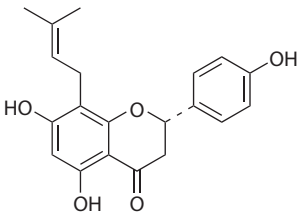
R = $CH(CH_3)_2$ cohumulone
R = $CH_2CH(CH_3)_2$ humulone
R = $CH(CH_3)CH_2CH_3$ adhumulone

α-acids



R = $CH(CH_3)_2$ colupulone
R = $CH_2CH(CH_3)_2$ lupulone
R = $CH(CH_3)CH_2CH_3$ adlupulone

β-acids



8-prenylnaringenin

on humans are available, and its real therapeutic efficacy has yet to be clarified.[91] A lipophilic extract injected intraperitoneally (ip) has produced narcotic effects in mice and has depressed motor activity in mice and rats through a mechanism independent from myorelaxation. In experiment animals, the extract has also induced an improvement of sleep accompanied by antinociceptive effects.

The sedative properties of the plant seem to be primarily due to the compound 2-methyl-3-buten-2-ol, which is present in small amounts in the plant but is likely to be generated in the body of treated organisms by the conversion of bitter α-acids.[37,92,93] Ip injections of the compound have reduced the motility of rats without causing myorelaxation, while higher doses have induced narcosis in mice. Other studies on animals, using fractions containing α- or β-acids, have shown that the former act as antidepressants and accentuate the side effects of pentobarbital, while the latter act as antidepressants too, but reducing the hypnotic effect of pentobarbital.

Electrophysiological studies have shown that the β-acid fraction is able to depress ion currents induced by GABA. The compound myrcenol that derives from myrcene during boiling is able to prolong sleep induced by pentobarbital in the mouse, while *in vitro* it strengthens the response of GABA-A receptors.[72] Such a compound, which is present in small amounts in the plant but is much more abundant in beer, could produce a stimulation of GABA-A receptor following beer consumption.[3]

Other studies have demonstrated the ability of a dry extract, containing flavonoids but not bitter principles, to bind 5-HT6 serotonin receptors, involved in depression and hynsomnia, as well as ML1 melatonin receptors, involved in the regulation of the circadian cycle.[11] Luzindol, a drug acting as an antagonist of melatonin receptors, can contrast the hypothermic effect of a hop extract in the mouse, thus confirming the involvement of the melatoninergic system in the sedative effect of the plant.

In clinical studies hops is generally used in combination with valerian.[58,59] Such a mixture shows properties similar to those of benzodiazepines in the treatment of sleep disturbances, but with the advantage of causing fewer side effects on diurnal vigilance.[42,75] It has been assessed that the hop-valerian complex can alleviate disturbed sleep, while in combination with other principles it can ameliorate chronic cholecystitis, irritated bladder, and urinary incontinence. However, the presence of valerian or other herbs in these preparations is a hindrance for an accurate evaluation of the pharmacologic properties of hops.

The estrogenic activity of the plant started to emerge in the 1950s, when women workers involved in the collection of flowers became affected by disturbances of the menstrual cycle.[5] Moreover, hop baths have long been used in Germany to treat various gynecologic disturbances. Different studies have shown the ability of hop extracts to bind both alpha and beta estrogen receptors (ERs), to induce alkalin phosphatase in Ishikawa endometrial adenocarcinoma cells, a classical test of estrogenic activity, and to activate the progesterone receptor gene in these cells, and of presenelin 2, normally induced by estrogens, in breast cancer cells transfected with an ER gene.[13,14,22] 8-Prenylnaringenin, a derivative of xanthohumol, is considered the main, or exclusive, plant compound endowed with estrogenic activity.[19,51,100] This compound can interact with ERα, although its affinity is about 70-fold lower with respect to 17β-estradiol, and its effects are about 10,000-fold lower than those of the physiological hormone.[73,99] Xanthohumol and other derivatives, like 6-prenylnaringenin, have instead scarce or null estrogenic effects.

The properties of 8-prenylnaringenin have been confirmed by *in vivo* studies on animals, in which subcutaneous administration of the drug has suppressed bone demineralization and the reduction of uterus weight induced by ovariectomy, reduced serum levels of luteinizing and follicle-stimulating hormones, increased prolactin levels, and induced hyperplasia in the vaginal epithelium.[9,16,40,54] In women at menopause, this drug has reduced the incidence of rushes and other disturbances and has also induced a reduction of the levels of luteinizing hormone.[8,33,38,70] The compound has also shown antagonistic effects against the androgen receptor.[101] Thanks to these antiandrogenic effects, hop flowers can also be used for man dysfunctions, such as premature ejaculation and nocturnal pollution, or as an anaphrodisiac.

Although 8-prenylnaringenin is not present at effective doses in the plant, it can be generated in the human organism by intestinal flora or liver P450 cytochromes, starting from isoxanthohumol.[35,69,77] Xanthohumol is also present at low doses in hop-flavored beer, the consumption of which has been indicated for patients requiring long-term treatments with low estrogen doses, such as in premenstrual syndrome and male hypersexuality. However, an accurate evaluation of possible side effects deriving from phytoestrogen therapeutic uses is still lacking, concerning in particular the possibility of breast or uterus cancer insurgence as a consequence of prolonged administration.[68]

Prenylcalcones, particularly xanthohumol, have also shown antitumor activity.[28,31,39,44,52,66,87,90,95] These compounds can inhibit the *in vitro* proliferation of breast cells through a mechanism involving the inhibition of the aromatase enzyme.[57] Xanthohumol has been shown to induce apoptosis and inhibition of NFkB activation

in prostate epithelial cells, while *in vivo* it has been able to inhibit angiogenesis and tumor cell proliferation in the mouse.[2,15,17,20,21,67,76]

The plant also possesses antibacterial activity, mainly against gram-positive bacteria, due to lupulones and humulones, which could inflict damage to the bacterial wall.[79,86] The higher resistance of gram-negative bacteria could be due to the presence of a phospholipid membrane external to the wall, which would inactivate the action of α-acids.[49] The essential oil has also shown antibacterial activity against gram-positive germs, while bitter acids, especially humulones, display a moderate antifungal activity (e.g., against *Trichophyton*, *Candida*, *Fusarium*, and *Mucor*), which is also exerted by flavonoids.[55] Xanthohumol has shown a moderate, wide-spectrum antimicrobial activity against gram-positive bacteria, viruses, fungi, and the agent of malaria *Plasmodium falciparum*.[29]

As for stomachic properties, a dry hop extract has shown the ability of increasing gastric secretion in the rat, most likely acting through a cephalic stimulation induced by the bitter principles. The stomachic effect would seem to depend on cholinergic innervation since it is abolished by atropin. A stimulation of gastric secretion has also been observed in patients suffering from hyposecretion.[88]

The plant is known to also possess anti-inflammatory properties.[36,94,98] A mixture of ρ-iso-α-acids has prevented the production of prostaglandin E2 induced by lipopolysaccharides in murine macrophages, through the inhibition of the inducible COX-2 enzyme. Further studies have showed that ρ-iso-α-acids do not directly inhibit COX activity, but instead interfere with the expression of the enzyme via NFkB inhibition.[46] These compounds are also able to inhibit Syk and PI3K kinases, thus being potentially effective in the treatment of autoimmune syndromes.[4] ρ-Iso-α-acids have also reduced the symptoms of patients affected by ankle osteoarthritis, producing lower side effects with respect to conventional anti-inflammatory drugs.

Dermatologic and Cosmetic Use

The active principles of hops can stimulate the cells of the connective tissue. Herbal preparations of the plant are used in wound healing and in the manufacturing of creams and lotions having emollient, hydrating, and regenerative effects.[64] Hop extracts are also useful in the prevention of skin aging and in the treatment of loose skin, stretch marks, and sagging.[26,61,97] They are also used in breast tightening, for the presence of the phytoestrogen 8-prenylnaringenin, even though clinical trials do not allow a reliable evaluation of this treatment and cannot exclude the insurgence of noxious effects.[25] A hexan extract containing humulones and lupulones, mixed to an oily or creamy vehicle, has been patented as a solar screen due to its ability to absorb UV light.[62,63] This product has also been claimed to prevent erythema and sunburning by the stimulation of cutaneous melanization.

Side Effects and Toxicity

The use of the plant is contraindicated during pregnancy, due to the possible induction of spasmodic activity on the uterine musculature. The plant also induces allergic

reactions in sensitive individuals, including bronchial irritation with cough and dyspnea, and occupational contact dermatitis.[18,32,50,60,71,80,81] However, cases of sensitization due to therapeutic use of the plant are not known. Contact dermatitis seems to be caused by pollen, while humulone and lupulone in the resin, and myrcene in the essential oil are considered the main sensitizing agents with a systemic action.

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HORSE CHESTNUT

Scientific name: *Aesculus hippocastanum* L.
Family: Sapindaceae
Parts used: Seeds, leaves

Features

Large-size tree, up to 35 m high, with rounded crown and brown, scaled, fissured bark. Leaves are palmate-composite, with seven cuneate-obovate segments. Flowers are white-pink, strongly scented, and arranged in stiffly upright panicles. The fruit is a spiny, globular capsule, containing two to four shiny, smooth, red-brown seeds resembling a chestnut.

The species is native to Asia Minor and derives its name from the habit of feeding sick horses with the seeds. It is also commonly grown in temperate Europe as an ornamental plant.

FIGURE 4.27 Horse Chestnut. (See color insert following page 40.)

The physician and botanist Andrea Mattioli (1501–1577) imported the plant from Constantinople to Italy and discovered its astringent properties and its benefits for the circulatory system. However, the plant was used in the past mainly as a febrifuge, while it was initially used for hemorrhoidal problems in France during the 1800s. The importance of its active principles as vasoprotectors was fully acknowledged only in the 1900s, and it is currently one of the most used pharmaceutical remedies for venous diseases.[3]

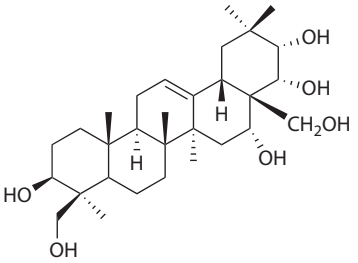
Constituents

The seeds, sometimes improperly called fruits, contain saponins (13% in the fresh seeds, 24% in the dry ones), which upon hydrolysis release triterpenic sapogenins derived from oleanolic acid.[14,15,39] The most abundant product is escin, a complex mixture of saponins bearing the polyhydroxylated triterpenes protoescigenin and barringtogenol as the aglycone moiety.[38,46,47]

The seeds also contain tannins, coumarin glycosides, flavonols like quercetin and kaempferol, vitamins C, D, and of the B group, starch (45%), cellulose (3%), proteins (10%), sucrose (12%), glucose (5–6%), and mineral salts (Mg, Ca, Cu, P, Na, Mn, Cl, S).[12,13,29,30]

The seeds yield an oil (4%) that contains the fatty acids oleic (about 65%), linoleic, and linolenic, and an unsaponifiable fraction.

The bark and the buds contain resins, catechic tannins, allantoin, coumarin glycosides, and their genins. The main coumarin glycoside is esculin (6,7-dihydroxycoumarin-β-D-glucoside), which is present in the bark (2–3%) and in the seeds, and upon heating in acid solution releases the dioxycoumarin esculetin.



protoescigenin

Properties

Horse chestnut seed extracts have been traditionally used to treat people with chronic venous insufficiency.[6,16,20,35,41] These properties have been confirmed by clinical studies based on oral administration.[40] The therapeutic use of seed extracts can relieve various symptoms of venous disorders, such as lower limb swelling and leg pain, itch, and fatigue.[32,33] These results are comparable to those obtained with compression socks and stockings.[5,10]

Escin reduces the permeability of blood capillaries and has vasoconstrictive, antiedema, antiexudative, and capillaritonic effects.[42] It is therefore indicated for edema,

varicose veins, phlebitis, and hemorrhoids, and moreover it exerts anti-inflammatory and antiulcerogenic activities.[1]

The effects of escin are supported by those of flavonoids and tannins, which exert similar effects but have different pharmacodynamics. Esculin and esculetin improve the lymphatic drainage, reduce edema, and act as anti-inflammatory agents.

The protective action on venous vessels is due to an increase of the capillary tone produced by a contraction of the vessels' smooth muscles, an increase of the resistance and elasticity of capillaries, and a decrease of their permeability. An improvement of the function of vein valves and of the lymphatic flux in the thoracic duct has also been shown.

The mechanisms of these effects could primarily depend on the ability of escin to induce calcium entry in vein smooth muscle cells. This would lead to muscle contraction, and hence to vasoconstriction.[4] A role is also played by the release of the prostanoid prostaglandin-F2α and by the inhibition of proteoglycan degradation in the blood capillary wall.[2] With regard to this latter mechanism, escin has been shown to inhibit the hyaluronic acid-degrading enzyme hyaluronidase.[7]

β-Escin has also been studied for its possible antitumor properties, due to its ability to induce the release of prostaglandin-F2α. This latter has been found to inhibit the growth of rat colon adenocarcinoma cells, by acting through cell cycle arrest at the G1-S phase linked to the induction of the cyclin-dependent kinase inhibitor $p21^{WAF1/CIP1}$.[31]

Various experimental studies have shown modulatory effects of escin at the gastrointestinal level.[21] It has been assessed that this compound increases the intestinal absorption of magnesium in the mouse,[18,19] while in different studies the inhibition of gastric emptying[22] and an increase of gastrointestinal transit[23] have also been observed. The effect on gastric emptying would depend on different mechanisms, including the activity of capsaicin-sensitive sensory nerves, the release of dopamine in the central nervous system, and the release of endogenous prostaglandins.[25] The increase of gastrointestinal transit could depend on the production of nitric oxide and the inhibition of prostaglandin release, with a possible involvement of 5-hydroxytryptamine and its receptors.[24,26] It has also been shown that escin inhibits the uptake of glucose in duodenal enterocytes.[27,44,45]

In cellular studies, β-escin has also been used as a tool for cell permeabilization.[28]

Dermatologic and Cosmetic Use

The antiedema and tonifying effects of the plant and its stimulation of peripheral circulation can also be obtained through topical application of creams or gels based on escin.[43] These products can be used in the treatment of acne, couperose, and reddened or irritated skin.

The reduction of capillary permeability and the improvement of vein tone and lymphatic drainage can also be very useful in anticellulite treatments.

Escin has also been used in products for the hygiene of the oral cavity, where it exerts a useful action on gingival bleeding.

In products for the scalp, the plant has refreshing, anti-inflammatory, and soothing effects, while in suntan and after-sun products it acts as a soothing remedy and a sunscreen, mainly due to the presence of proanthocyanidins.

It has been shown in an *in vitro* study that escin can generate contraction forces in fibroblasts due to the formation of actin stress fibers, through the activation of the Rho/Rho kinase system.[8] Also, in a clinical study carried out on a group of volunteer women, the above mechanism has been put in relationship with a reduction of wrinkles obtained by the application of a plant extract on the periocular area.[9]

Another study has shown that a cream based on escin complexed with phospholipids can protect the skin from the formation of free radicals, which reach particularly high levels in individuals affected by severe venous insufficiency.[36,37]

Side Effects and Toxicity

Intravenous escin administration induces hemolytic activity.[17] Hence, even though escin is safe by oral ingestion, it should be avoided in case of hemolytic anemia. Escin is also counterindicated during pregnancy, since it can induce uterine contractions, as well as during lactation and at pediatric age.

High escin doses can cause inflammation and anoxia in various tissues, mainly in the kidney. These effects cannot be detected at therapeutic doses, but patients with kidney or liver diseases should avoid the use of escin.

Esculin, even by oral uptake, delays the formation of the platelet aggregate. Even though the compound is not a true anticoagulant, since it does not alter prothrombin time, it should be used carefully, particularly in individuals with coagulation disorders.[11]

Finally, horse chestnut pollen can cause allergy in sensitive people.[34]

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ICELAND MOSS

Scientific name: *Cetraria islandica* (L.) Ach.
Phylum: Ascomycota (ascomycetes fungi)
Family: Parmeliaceae
Parts used: Thallus

Features

Lichens are mutualistic associations between fungi and algae. Iceland moss is a fruticose lichen with an ascending foliaceous habit giving it the appearance of a moss. It can grow to a height of about 10 cm. The color is brown, green, or pale grey. The branches are rolled into tubes and show flattened lobes with a fringed edge at their tips.

The lichen grows abundantly in arctic or mountainous regions of the northern hemisphere, particularly on volcanic rock beds of Iceland, as indicated by its name.

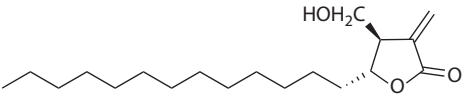
It is on the market in the form of an almost colorless harsh cartilaginous body. It can be used as food or as a medicinal product, and is frequently marketed finely minced or reduced to flour.[18] Lichen products can be treated in order to eliminate the bitter taste.

Thanks to the presence of lichenin, a substance similar to starch, lichen has been used in the preparation of cocoa. Its feeding properties have been exploited by Nordic people during periods of starvation.

FIGURE 4.28 Iceland Moss.

Constituents

The lichen contains about 70% of lichenin, a polysaccharide also known as lichen starch. It also contains the fructosan inulin, and a particular form of chlorophyll called thallochlor. The lichen polysaccharides can be divided into a fraction soluble in warm water, containing lichenans (e.g., lichenin, β-1,3- and β-1,4-D-glucosides) and isolichenans (having α-1,3- and α-1,4-bonds),[1] and an alkali-soluble fraction containing heteropolysaccharides formed by residues of D-mannose, D-galactose, D-glucose, and hexuronic acid.[4] Secondary metabolites are also present, including lichesterinic, protolichesterinic, cetraric (conferring a bitter taste), and fumarprotocetraric acid.[5,14,15,19] It is also rich in calcium, iodine, potassium, phosphorus, and contains vitamin A and vitamins of the B group.



protolichesterinic acid

Properties

The lichen has been used in traditional medicine to heal chest ailments, such as tuberculosis and pneumonia; disorders of the kidney and bladder; ulcers; diarrhea; and gastritis. It has antibiotic and demulcent properties on irritated mucosae, due to the abundant presence of mucilage, and is therefore used for the treatment of inflammations of the mouth, pharynx, and digestive tract. It also acts as an expectorant, and is then suitable for cold and flu symptoms, including fever, cough, and catarrh.

The presence of bitter principles makes it useful for digestive disorders and the loss of appetite. It is used externally for the treatment of skin blisters, vaginal loss, and impetigo.

Protolichesterinic acid has antimicrobial effects against various pathogenic strains.[8,22] It is moreover able to partially inhibit 5-lipoxygenase and platelet's 12(S)-lipoxygenase,[2,7,12] which catalyze the conversion of arachidonic acid into eicosanoids during the inflammatory process. The compound has in particular an antibacterial action against *Helicobacter pylori*,[9] which could explain the traditional use of this lichen for gastric ulcer.

Protolichesterinic acid also shows antiproliferative effects on tumor cells, probably related to the inhibition of lypoxygenases and DNA polymerases and ligases.[6,16,21] Derivatives of the naphtoquinone naphtazarin, isolated from the lichen, show cytotoxic activity against epidermal carcinoma cells,[17] and inhibit the *in vitro* growth of normal keratinocytes used as a model of psoriasis.[13]

The polysaccharide lichenan has immunomodulatory effects and can induce the maturation and activation of monocyte-derived dendritic cells.[3,11] Other polysaccharides can increase the phagocytic activity of cells from the reticuloendothelial system.[10]

An extract containing lichenan, isolichenan, and protolichesterinic and fumarprotocetraric acids has shown anti-inflammatory effects on a murine model of rheumatoid arthritis.

Dermatologic and Cosmetic Use

Lichen extracts are used in creams, lotions, and detergents, sometimes in the form of copper, sodium, or triethanolamine salts. They exert refreshing, emollient, and hydrating properties on the skin. The extracts can also be used as a detergent and disinfectant on furuncles, acne, seborrhea, impetigo, and other alterations of the skin bacterial flora.

Side Effects and Toxicity

The lichen is contraindicated in case of duodenal ulcer. Its prolonged use can induce gastric irritation and problems to the liver.

The lichen's ability to accumulate heavy metals present in the environment as contaminants can be at the origin of cases of intoxication. Lead poisoning can be caused, for instance, by extracts subjected to inadequate quality controls.

Fumarprotocetraric acid can occasionally induce allergic reactions.[20]

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INDIAN COLEUS

Scientific name: *Plectranthus barbatus* Andrews
(syn. *Coleus barbatus* Benth.; *Coleus forskohlii* (Willd.) Briq.)
Family: Lamiaceae
Parts used: Root

Features

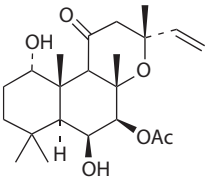
Herbaceous perennial aromatic plant growing spontaneously in subtropical arid and semiarid areas of East Africa, India, Nepal, Ceylon, and Thailand. Roots have a tuberous or fasciculate shape, and the aerial part has a creeping or erect morphology, up to a height of about 1–1.5 m. Leaves are opposite, oval, lanceolate (1.5 × 15 cm), sometimes reddish with a dark green toothed margin. Flowers are grouped in apical spikes. They are small, blue or pink, with an upper lip divided into two lobes and a tripartite lower one.

The plant has been used for centuries in the popular medicines of different countries, and in more recent times it has acquired pharmaceutical importance due to the discovery of forskolin, a compound abundant in the root that is responsible for many of the biological and healing properties of the plant.[36] In India the plant is cultivated and its root is traditionally eaten as pickles.

FIGURE 4.29 Indian Coleus. (See color insert following page 40.)

Constituents

Indian coleus is the only known natural source of forskolin, also known as coleonol, a diterpenoid present in the root at variable amounts, depending on the geographic region and the strain, ranging between 0.05 and 0.60% of dry weight.[37] The root also yields a dark brown essential oil containing about 40 compounds, including sesquiterpenes, monoterpenoids, sesquiterpenoids, and diterpenoids.[10] The main components are bornyl acetate (15%), γ-eudesmol (12.5%), and 3-decanone (about 7%). The aerial parts contain various diterpenoids akin to forskolin (deacetylforskolin; 9-deoxy- and 1,9-dideoxy forskolin; 1,9-dideoxy-7-deacetyl-forskolin).



forskolin

Properties

In Ayurveda the plant is used to cure different syndromes, including insomnia, heart disease and hypertension, lung disease, gut spasms, and convulsions.[9] Following the discovery of forskolin, the plant has been included in the official medicine of Western countries.[6,30,41] The biological properties of forskolin derive from the activation of the enzyme adenylate cyclase, which produces cyclic adenosin monophosphate (cAMP).[39] This latter compound is a main intracellular regulator that mediates the effects of different hormones. Forskolin activates adenylate cyclase through a direct action on the enzyme catalytic subunit, while the presence of a guanine nucleotide binding protein (G protein) is also required.[40] G protein provides a functional link between the activation of a hormone receptor (G protein–coupled receptor) on the cell surface, and the cAMP-producing adenylate cyclase. The discovery of this mechanism has opened the way to a vast number of cell biology investigations, where forskolin is often used as an experimental tool to study the role of cAMP in different cellular processes.[11]

Forskolin effects that do not involve an intracellular increase of cAMP have also been described.[22] Forskolin inhibits ion fluxes through the nicotinic acetilcholine receptor, the activity of specific K channels, and glucose uptake by erythrocytes. However, the action of forskolin via intracellular cAMP rise is the main action mechanism and produces a number of effects in different body areas.

Forskolin acts on the cardiovascular system by inducing inotropic, chronotropic, and hypotensive effects,[14,25,29,31] with an improvement in blood circulation, while an antithrombic effect derives from the inhibition of platelet aggregation.[1] In the endocrine system there is an increased production of the hypophysis hormone ACTH, involving increased steroidogenesis by adrenal glands and testosterone synthesis by gonadal Leydig cells. *In vitro* studies indicate a potential influence on the thyroid gland. There is also a higher production of insulin,[2,5,16] which activates

glucose uptake in various tissues and induces the synthesis of thyroid hormones, thus involving metabolism rise, lipolysis, and thermogenesis.[18,26,32,38,43] The effect of forskolin is directed to induce an increased consumption of energetic reserves, with body weight loss, activation of anabolic processes, and increase of the lean mass.[3,4,7,8,19,24,27,42] Forskolin seems to have a synergistic antiobesity effect in combination with ephedrine (ma huang extract) and caffeine.[15] Antispasmic and antiasthmatic effects are exerted on the respiratory system, while antiglaucoma effect derives from a reduction of the intraocular pressure.[34] Forskolin can also act as an antidepressant, since cAMP rise in the nervous system would maintain high presynaptic monoamine levels. Finally, it also modulates biliary secretion in hepatocytes and pepsinogen secretion by gastric cells.[17,20]

Dermatologic and Cosmetic Use

Coleus root extract is used in preparations for cellulite, usually mixed together with other active principles.[12] The anticellulite action is mainly due to the stimulation of lipolysis by forskolin, leading to a considerable decrease of dermal fat. Forskolin is also indicated as a remedy for eczema and psoriasis, since these diseases involve a reduction of cAMP levels that can be prevented by the compound.

A study about psoriasis has shown decreased responsiveness of β-adrenergic receptors on keratinocytes, which has been overcome after forskolin treatment through cAMP rise.[13] The compound is also able to improve skin resistance to UV irradiation, by stimulating melanin synthesis in the epidermis.[44]

Coleus essential oil is used in aromatherapy and as an antimicrobial for topical applications, particularly against acne (*Propionibacterium acnes*). It is also used in products for oral hygiene to prevent the growth of *Streptococcus mutans*, the etiological agent of dental caries.[35]

Side Effects and Toxicity

Oral administration to rats of a 10% forskolin extract has shown an LD50 greater than 2,000 mg/kg, while no mortality has been observed. Moreover, the same extract did not show bacterial mutagenicity based on the AMES test. These results indicate that coleus extract is safe at the recommended dosages. However, the use of forskolin should be under medical control in case of concomitant administration of drugs such as anticoagulants, beta-blocker antihypertensives, or in the presence of gastric ulcer. Forskolin has an antiasthma effect due to bronchodilation, and is also considered antiallergic because of its inhibition on histamine release from leucocytes and mast cells.[21,23,28] No cases of allergic reactions to the plant are known, and there is only one report of perianal dermatitis caused by the leaves.[33]

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IRISH MOSS

Scientific name: *Chondrus crispus* (L.) J. Stackhouse
Phylum: Rhodophyta (red algae)
Family: Gigartinaceae
Parts used: Thallus
Other names: Carrageen

Features

Small, bushlike red alga growing in the northern hemisphere on the rocky coasts of the Atlantic Ocean. It can grow to a height of up to 20–30 cm, having a discoid holdfast and dichotomous branchings. In its fresh condition it has a cartilaginous consistency, and the color can vary from yellow greenish to red and brown. The alga forms wide meadows covering rocky bottoms of shallow waters and emerging at low tides.

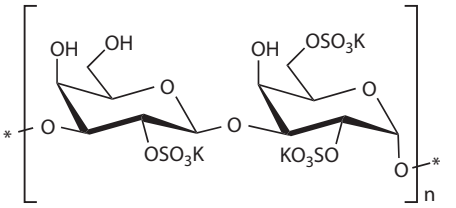
One of the alga's names, viz., carrageen, derives from the Irish village Carragheen, which in turn is derived from the Gaelic word *carraigín*, meaning "rock moss." The alga has been widely used in Ireland since the Middle Ages for feeding and medicinal purposes. The fronds are collected at the end of summer and left to dry in the sun, after which they assume a whitish silver color.

Constituents

The thallus of the alga is mainly composed of carbohydrates (about 70% dry weight), proteins (about 8%), and mineral salts (about 20%).[13] Chief carbohydrates are carrageenans, belonging to the group of galactosaminoglycans.[7] These latter are a particular form of glycosaminoglycans or mucopolysaccharides, a group including chondroitin sulfate, typical of cartilage. Carrageenans are nonramified polysaccharides formed by galactose derivative units linked by alternate 1,3- and 1,4- saccharidic bonds, and containing between 20 and 35% of sulfate groups.[12] Olygosaccharides include sorbitol and dulcitol, two isomers of mannitol.[2]

Fatty acids and sterols account for approximately 0.6 and 0.1 g/kg of dry weight, respectively.[11] Unsaturated fatty acids are prevalent on saturated ones, and include palmitic, palmitoleic, oleic, arachidonic, and eicosapentaenoic acids. The main sterol is cholesterol (more than 94% of total sterols).[10]

It is rich in minerals, of which the most relatively abundant are iodine and bromine. It is also particularly rich in vitamin B1 and carotenoids.



λ-carrageenan

Properties

The alga has been used for centuries for its emollient, lenitive, and antimicrobial properties. It is a main source of carrageenans, forming a thick mucilaginous mass that acts as a cement for the cells that compose the algal thallus. These substances are used as emulsifiers by food industries, while in the pharmaceutical field they are employed for the treatment of dysenteria and for urinary and lung infections.

Carrageenans are known to defend the human body against microbial attacks.[4] During the Second World War, people who lived on the coasts of the English Channel used to eat the alga as a dietary supplement in order to survive scarce food conditions. It has been reported that in those years there was a reduction of colds and bronchitis among these populations. The protection conferred by carrageenans against viral infections seems due to the sulfated polyanions, which would act by hindering the entry of viral particles into human cells.[1]

In the stomach carrageenans exert a protective effect against ulcer, since they form a barrier between the gastric juice and the stomach wall, thus avoiding the proteolytic action of pepsin on the gastric mucosa. Moreover, these compounds have anticoagulant properties similar to those of heparin.[5,6]

The alga can also have a role in reducing the risk of atherosclerosis and cardiovascular diseases, since carrageenans reduce blood lipids and polyunsaturated fatty acids reduce blood cholesterol levels. The monosaccharide sorbitol has a sweetening power that is stronger than that of saccharose, and it is therefore used by diabetics or in slimming diets.

Iodine and bromine are partially bound to polyphenols, forming halogenated phenols with antiseptic and disinfectant properties. The alga has, in addition, high depurative properties, and can protect the human body from contaminant heavy metals, radioactive isotopes, free radicals, and other toxicants. It can therefore be used in therapeutic treatments of intoxications and radiation injuries.

Dermatologic and Cosmetic Use

Carrageenans are used in the cosmetic industry as additives due to their emulsifying and thickening properties.[9] However, these compounds can also exert specific actions on the skin. They are extremely hydrophylic and emollient, and therefore they can contrast the irritation of the keratinized epidermal layer caused by drying or aging processes. Carrageenans also exert an emollient action on nails and hairs, through their specific binding to keratin fibers.

The extract is also used as a coadjuvant in anticellulite treatments. In addition, it contains the dipeptide N-acetyl-L-citrullyl-L-arginine, which has attracted some interest in the skin care area.[8] Arginine and its derivatives act as antioxidants, promote wound healing, and are also used as ingredients in products for lipolysis and sun protection.

Side Effects and Toxicity

This alga is included in the U.S. FDA list of natural products used for topical application or food that does not represent a risk for human health. However, carrageenans

can induce inflammation and edema through subcutaneous injection.[3] Such a property is employed for inducing rat paw inflammation, an experimental model that is used in studies about the inflammatory response and the pharmacological action of anti-inflammatory drugs.

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LEMONBALM

Scientific name: *Melissa officinalis* L.
Family: Lamiaceae
Parts used: Leaves, flowering apices

Features

Perennial herbaceous plant with an articulated rhizome that gives way to erect, quadrangular, branched stems growing up to 100 cm high. Leaves are petiolate, ovate to rhomboid, crenate, and bear many glandular hairs. These latter secrete an essential oil that confers to the plant a lemon scent. Flowers are white, pink shaded, bilabiate, with an upper convex lobe and three lower lobes, and are arranged in false whorls in the axils of upper leaves. The fruit is a brown, oblong-ovate nut.

The latin name *Melissa* (Greek for "honey bee") accounts for the predilection of bees for the plant. The plant is diffused in Europe and western Asia. It grows wild in hedges and shady places, and is also cultivated.[47,48]

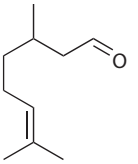
It has been known for its medicinal properties since ancient Greece, where it was considered sacred to the goddess Artemis. In ancient times it was considered a life elixir and was used in the Arab and Western traditional medicines. It was also used as an ingredient of Carmelitan's water, dating back to the seventeenth century, a remedy against hysterics.

The plant is used in food industry and as a culinary scent. It is an essential ingredient of various digestive liquors, such as the Grande Chartreuse created by Benedictine friars.

FIGURE 4.30 Lemonbalm. (See color insert following page 40.)

Constituents

The plant contains polyphenols such as rosmarinic, protocatechic, caffeic, and chlorogenic acids, and derivatives of hydroxycinnamic acid.[6,8,9,51] Flavonoids include luteolin glycosides (luteolin 3'-glucuronide), quercetin, apigenin, and kaempferol.[22] Flowers and leaves yield an essential oil (0.1–0.2%) containing about 50 volatiles, chiefly monoterpenic aldehydes like citronellal (30–40%), citral (20–30%), a mixture of the stereoisomers geranial and neral, and sesquiterpenes like β-caryophyllene and germacrene D.[3,4,25,40]



citronellal

Properties

The plant is used as an antibacterial and antiviral agent, and for its sedative and spasmolytic effects.[16,19,24,30,41] Its use has been approved by the German E Commission. The plant's antimicrobial properties have been tested on different bacterial and yeast strains, also including pathogen agents.[2,15,31,34,35,37,45] *In vitro* studies have proved the inhibitory effects of an aqueous extract on HIV.[50]

The plant exerts an antagonistic action on the thyroid hormone and is therefore useful against hyperthyroidism. The terpenic compounds of the essential oil are responsible for antispastic, sedative, digestive, and antiseptic properties.[42] The essential oil is also used in aromatherapy as a relaxing agent, or for the treatment of hypertension, depression, and Alzheimer's.[17] A study conducted on mice has shown sedative and analgesic properties of a hydroalcoholic extract, while the essential oil obtained through distillation has failed to induce these effects.[43,46]

Clinical trials have shown that good sedative properties can be obtained by using lemon balm in combination with valerian.[32] Oral administration of the dry extract to a group of volunteers for a period of some days has induced an improvement of cognitive performance and memory, together with a reduction of nervous tension.[10,27] Pharmacological studies have shown the ability of the extract to bind nicotinic and muscarinic receptors in the central nervous system.[1,26,28] It has also been assessed that the extract's affinity for cholinergic receptors is linked to memory improvements.

The plant's flavonoids could induce anticonvulsivant, anxiolytic, and mild hypnotic effects by binding to benzodiazepine receptors. Rosmarinic acid has shown antidepressive activity in the mouse and anxiolytic activity in the rat.[44]

A study on the spasmolytic properties of the essential oil has shown that citral can inhibit the contractility of rat isolated ileum, suggesting a possible use of the plant against irritable colon syndrome, gastritis, and gastroduodenitis.[11,20,39] Such a spasmolytic action would not be due to a cholinergic mechanism, but instead to a reduction of intracellular calcium levels in smooth muscle cells.

In vitro studies have shown that the hydroalcoholic and methanolic extracts have strong antioxidant properties,[5,7,13,23,33] while the aqueous extract has been reported to inhibit the protein synthesis by preventing the binding of the EF2 elongation factor to ribosomes.[12,21]

Citral can induce apoptosis in hematopoietic tumor cells, and such an activity seems due to the α,β-unsaturated aldehydic moiety.[14,18]

Dermatologic and Cosmetic Use

The essential oil is used in potpourris and perfumes, and in cosmetic products such as creams and lotions.[36] It has antimicrobial, anti-inflammatory, decongestant, and soothing effects on the skin. The vapors of the essential oil are a useful remedy against acne.

The antiviral properties have attracted some interest in the topic treatment of herpes simplex labialis, which has been verified in clinical tests.[29,49]

A study in the rat has verified that the oral ingestion of the extract can reduce skin oxidative stress and cholesterol rise induced by a hyperlipidic diet.[38] These results suggest that the plant is able to protect the skin from metabolic injury through systemic administration.

Side Effects and Toxicity

The plant should not be used by people affected by hypothyroidism or treated with antithyroid drugs. The extracts can induce mild sleepiness and rare allergic reactions. It is preferable to avoid the use of the plant during pregnancy and lactation.

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LICORICE

Scientific name: *Glycyrrhiza glabra* L.
Family: Leguminosae
Parts used: Roots, stolons

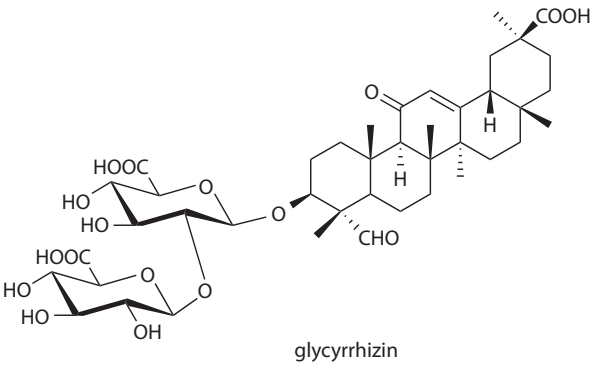
Features

Perennial stoloniferous herb, with creeping stems up to several meters in length and an erect portion up to 1 m in height. Leaves are alternate, odd pinnate, 10 to 20 cm long, with three to eight pairs of leaflets. Flowers are blue and grouped in axillary spikelike inflorescences. The fruit is an elongated and slightly curved pod, containing brown reniform seeds.

The species is native to central-western Asia. It was probably introduced in the Mediterranean region by Benedictine friars around the tenth century, and is currently cultivated in all of the European continent. The related species *G. echinata* is also important as an agricultural plant.

Constituents

Roots and stolons contain starch (25–30%), glucose (3–10%), and sucrose. The main bioactive principles are glycosylated triterpene saponins (about 10%), such as glycyrrhizin and 24-hydroxyglycyrrhizin, having a sweetening power from 50- to 100-fold stronger than sugarcane. Upon hydrolysis, glycyrrhizin releases two molecules of D-glucuronic acid and one of 18-β-glycyrrhetic acid (18-β-glycyrrhetinic). Other relevant compounds are liquiritin and its aglycone liquiritigenin, while constituents also include coumarins, sterols, lactones, and flavonoids, such as flavanones, chalcones, isoflavones, and isoflavonols.[12,13,30]



glycyrrhizin

Properties

The medicinal uses of the plant date back to the prehistoric age. Therapeutic uses have been reported in written documents since ancient Greece. Licorice roots have

been found in pharaoh tombs, proving that the plant was kept in high esteem in ancient times. Hippocrates recommended it in the treatment of gastric ulcer, while Dioscorides found that it could be used to promote wound healing and skin diseases.[17] A Buddhist ritual prescribed that in the eighth day of the eighth month of the year the statue of Buddha had to be sprinkled with licorice root juice. In China the plant is also known as the great harmonizer, since it is assumed that it combines the properties of all medicinal herbs. About two-thirds of all traditional Chinese formulations include licorice.[41]

The plant has been traditionally used to treat different body organs, including respiratory, gastrointestinal, cardiovascular, and urogenital systems, and the eyes. It has long been known to act as an expectorant, laxative, spasmolytic, and antiulcer.

Antigastritis and antiulcer actions are due to the presence of glycyrrhizin, glycyrrhetic acid, and flavonoids.[48] The plant protects the stomach from the damaging effects of drugs like aspirin and is also able to reduce stomach acidity through the inhibition of gastrin production.[11,22] The mechanism of action of these effects involves an increase of the levels of prostaglandins in the gastric mucosa, due to the inhibition of the enzyme 15-OH-prostaglandin dehydrogenase, which transforms prostaglandins into the inactive 5-ketoprostaglandins. Another mechanism concerns the inhibition of δ-13-prostaglandin reductase, which further metabolizes inactive prostaglandins, thereby favoring their renal excretion.

In different studies, glycyrrhizin has been shown to protect the mouse liver from inflammatory processes induced by lipopolysaccharides, and in particular from the action of interleukin 18.[50] A protective effect is also exerted against liver damage induced by hepatectomy in the rat.[47] It has been shown that the anti-inflammatory effects of glycyrrhizin occur through the inhibition of NFkB-dependent gene transcription, a mechanism that does not involve the glucocorticoid receptor.[34] In addition, the anti-inflammatory action can also be partially explained by the binding of glycyrrhizin to the nuclear high-mobility group box 1 (HMGB1) protein, which upon proper stimulation is released by cells and acts as a pro-inflammatory cytokine.[27] Moreover, a derivative of glycyrrhetic acid, known as gliderinin, also shows antiflogistic activity.[5] However, it has also been shown that glycyrrhizin increases the activity of cytochrome P450 in the rat liver, and this could induce oxidative stress in the liver tissue.

Besides anti-inflammatory properties, the plant's active saponins show steroid-like effects. Glycyrrhetic acid inhibits the *in vitro* activity of δ-4,5-β-reductase, which inactivates steroids having a 3-oxo-4 chain. Therefore, glycyrrhetic acid could potentiate *in vivo* the action of glucocorticoids. It has been shown in humans that glycyrrhetic acid and, to a higher extent, 3-monoglucuronyl glycyrrhetic acid inhibit 11-β-hydroxysteroid dehydrogenase, an enzyme that converts cortisol to cortisone.[43,46] These compounds also inhibit β-glucuronidase, thus interfering with the kidney and liver excretion of glucuronated compounds, including steroids.[28] In addition, glycyrrhetic acid is an agonist of aldosterone, causing water and sodium retention, potassium excretion, lower diuresis, and higher blood pressure.[6,16,25,40,45,49] These effects could depend on a direct binding of glycyrrhetic acid to the aldosterone receptor, or on the accumulation of cortisol due to the inhibition of its degradation.

A secondary effect induced by the plant, probably depending on the increase of blood volume, is a release of atrial natriuretic peptide (ANP), a hormone that stimulates diuresis and lowers blood volume and arterial tension.

Another steroidlike effect is an estrogenic action exerted by the plant extract on MCF-7 breast cancer cells.[15,33] A confirmation of the steroidomimetic action of the plant derives from a study in which oral administration to rats of the extract has induced a suppression of the hypophysis-adrenal axis together with a rise in renin blood levels.[1,2]

Different compounds present in the extract have antioxidant and radical scavenging functions, including isoflavans, chalcones, and isoflavones.[9,29] Isoflavans prevent LDL oxidation, an essential step of atherosclerosis. A confirmation of the preventive action of these compounds against atherosclerosis has been provided by a clinical study, in which a plant extract administered to volunteers by oral ingestion has induced a decrease of blood cholesterol and triglycerides and an increase of the blood antioxidant capacity and LDL resistance to oxidation.[18] Glycyrrhizin seems able to inhibit the production of free radicals in neutrophil leukocytes, thus being able to hinder inflammatory processes. Similarly, this compound can also decrease lipid peroxidation in tissues affected by ischemia-reperfusion.

Other compounds with antioxidant properties are the isoflavan glabridin, which has shown a neuroprotective action against ischemic damage due to artery occlusion in the rat, and the phenolic compound isoliquiritigenin, which in the mouse has reduced the formation of colon and lung tumors induced by 1,2-dimethylhydrazine.[7,51]

The plant is also an antagonist of allergic responses, by inhibiting the release of chemical mediators like histamine, leukotrienes, prostaglandins, and bradikinin.[42] Such a property is mainly due to glycyrrhizin, glycyrrhetic acid, and liquiritigenin. Glycyrrhizin can alleviate the symptoms of experimentally induced asthma in the mouse, causing a lowering of interleukins 4 and 5 and a reduction of eosinophil activity.[35] 18-β-glycyrrhetic acid antagonizes the classical complement pathway by inhibiting the C2 component, while glycyrrhizin has shown antithrombin activity.[26]

Root extracts have antibacterial activity, chiefly due to β-glycyrrhetic acid, and antiviral activity due to glycyrrhizin.[10,24,31,44]

The plant has been traditionally used as an anxiolytic, and its effects on the central nervous system have been confirmed by experimental studies. It has been shown that the extract induces an improvement of memory and learning in the mouse, most likely through a strengthening of cholinergic transmission.[14]

Dermatologic and Cosmetic Use

The anti-inflammatory and antiseptic properties of the plant can find application in the treatment of skin diseases and mouth infections.[20,36] The cortisol-like action is useful against contact dermatitis, eczema, and psoriasis.[37] Plant extracts have also a preventive effect against burn infections, and are used in cosmetics as antioxidants, refreshing agents, and to soothe irritations.[38,39]

Plant extracts are also included in antibaldness and depigmenting preparations.[19,21,23] As for the actions of specific compounds, 18β-glycyrrhetic acid is useful

against acne, while glycyrrhizin prevents follicular damage caused by free radicals released by leukocytes in acne and rosacea.[4]

Side Effects and Toxicity

The nutritional or medicinal uses of the plant do not generally involve side effects.[3] However, excessive doses can induce an increase of blood pressure. The plant is not recommended for patients affected by hypertension, diabetes, or nephropathy, and in people prone to develop hypopotassemia and excessive hydrosaline retention. Moreover, the therapeutic association of the plant with steroids and oral contraceptives is contraindicated because these drugs enhance the plant's hypertensive properties. The plant should not be used in prepuberal age, or during pregnancy and lactation.

The cosmetic use of glycyrrhizin and 18β-glycyrrhetic acid is generally considered safe. However, a few cases of occupational asthma and contact allergy have been reported.[8,32]

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LINDEN

Scientific name: *Tilia cordata* Mill.
Family: Tiliaceae
Parts used: Inflorescences

Features

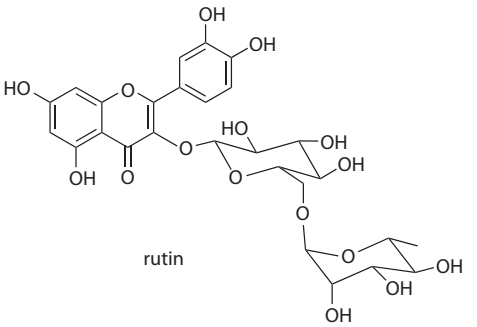
Tree widely diffused in northern temperate regions, having a large crown, growing to a height of up to 30 m, and reaching an age of 500 years. Hybrid individuals are frequently grown in parks and gardens. Leaves are long-petiolate, broadly cordate, with a dark green upper surface and a bluish green lower side. Flowers are yellowish white and arranged in clusters of 5 to 11. At the base of the inflorescences there is a tongue-shaped, greenish or yellowish white bract.[2]

The plant blooms in June and July, and its flowers have a strong, sweet fragrance that attracts pollinator insects like bees. These latter produce a delicious linden honey. The fruits consist of small ovoid achenes, and the bracts are functional for their wind dispersal. The wood is used to make sculptures and musical instruments. In the Middle Ages it was regularly carved to make the statue of the Virgin Mary, and for this reason it was named *lignum sacrum*.

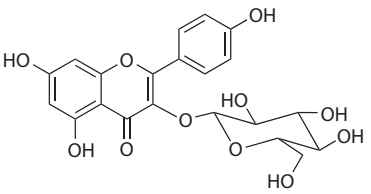
FIGURE 4.31 Linden. (See color insert following page 40.)

Constituents

The flowers develop narcotic properties if they are left to dry on the plant. Therefore, they should be collected just after blooming. Flowers contain 3–10% of mucilaginous polysaccharides, chiefly arabinogalactans and uronic acids; 2% of tannins (procyanidins); 1% of flavonoids, mostly quercetin glycosides (rutin, hyperoside, quercitrin, isoquercitrin) and kaempferol glycosides (astragalin); and phenolic acids (caffeic, p-coumaric, chlorogenic acid). An essential oil extracted from flowers contains prevalently the terpene tricosan and the oxygenated monoterpenes isocyclocitral and hotrienol.



rutin



astragalin

Properties

The flowers have antispasmodic, expectorant, and emollient properties, and are mildly hypotensive, laxative, and sedative.[10] These latter properties should be attributable to the presence of farnesol in the essential oil.

The flower tisane is used against cold-related diseases like cold, cough, and catarrh, and moreover for indigestion, hypertension, anxiety, hysteria, and nervous vomiting.[3,5] Linden charcoal can be used in the treatment of gastric and dispeptic disorders. It can be also applied on burns and painful body areas.

Flower extracts have induced apoptosis in lymphoma cells (BW 5147), have inhibited the mitogen-induced proliferation of normal lymphocytes, and have shown hepatoprotective properties.[6] The coumarin scopoletin, the chief component of the dichlorometane extract, has shown antiproliferative activity on lymphoma cells.[1] Volatile compounds have antimicrobial activity.[4,11]

Dermatologic and Cosmetic Use

The cosmetic relevance of the flowers is mostly due to the presence of mucilage, which exerts hydrating and anti-inflammatory actions on the skin. Mucilage consists of heteropolysaccharides that absorb large amounts of water due to the high presence of hydroxyl groups. These hydrocolloids can be applied as a film to the skin, thereby releasing water to the keratinized layer and protecting the skin tissue from dehydration.

Linden extracts are used in skin care as components of creams, detergent milk, and hydrating, emollient, and antiredness masks suitable for dry and delicate skins.[9] They can also be combined with detergents in order to prevent the irritating effect of foam.

Side Effects and Toxicity

No side effects are known for proper therapeutic dosages. Various cases of pollen allergy and contact dermatitis have been reported.[7,8]

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MACADAMIA NUT

Scientific name: *Macadamia integrifolia* Maiden & Betche
Family: Proteaceae
Parts used: Seeds
Other names: Queensland nut

Features

Tree growing up to 20 m in height, with entire, lanceolate leaves grouped in whorls of three. Flowers are small, white, with four tepals and arranged in thin elongate racemes borne at the axils of leaves. The fruit is a drupe with a fleshy, greenish mesocarp, containing a kernel formed by a woody, hard, smooth, and globose endocarp that surrounds a white seed. The whole fruit or the kernel is known as the macadamia nut.[20]

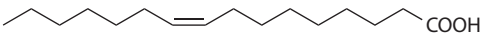
The plant has been used for centuries by native Australians, while its discovery by European colonizers dates back to the mid-1800s. The plant is indigenous from Australia and grows from temperate-warm areas to tropical rain forests. Today it is cultivated in Australia and in other countries, such as the United States, Guatemala, South Africa, Sri Lanka, and Israel. The seed is edible and has important commercial value.[14,19] A clear, amber-colored oil, with a slightly nutty odor, comes from the pressed nuts. The oil is used for cooking and as a dressing.

FIGURE 4.32 Macadamia Nut.

Constituents

The seed is rich in fat (about 70%) and contains 8% proteins and 15% carbohydrates.[21,24] It also contains mineral salts, like phosphorous, potassium, magnesium, calcium, and iron; vitamins like tocopherol and B group vitamins, including niacin (B3), pantothenic acid (B5), thiamine (B1), pyridoxine (B6), riboflavin (B2), and folic acid (B9); phytosterols; and polyphenols, such as cathecol.[15,18,23]

The lipidic fraction and the oil are rich in triglycerides and monounsaturated fatty acids, and are relatively poor in ω-6 fatty acids. This fraction consists of about 60% oleic acid, 20% palmitoleic acid, 3% linoleic acid, and 1% linolenic acid. It also contains saturated fatty acids like palmitic, stearic, and arachidic acids.



palmitoleic acid

Properties

The macadamia nut is an important source of monounsaturated fatty acids (oleic and palmitoleic).[2] The potential benefits deriving from oil consumption have been assessed in different studies. It has been shown that in hypercholesterolemic people the ingestion of nuts leads to a lowering of blood inflammation markers (leukotriene LTB4) and oxidative stress (8-isoprostane), and induces a decrease of blood total cholesterol and LDL cholesterol.[3,6,16] Studies also suggest that these effects are mainly due to oleic acid and to a lesser extent to palmitoleic acid. It has also been shown that a high amount of palmitoleic acid in the adipose tissue is correlated with a lesser incidence of arrhythmia and heart attack.[1] The complex of these data suggests that a regular consumption of macadamia nuts can prevent cardiovascular syndromes.[4]

A group of proteins, known as MiAMP, have been isolated from the seeds.[10,11,13] These proteins inhibit the *in vitro* growth of various plant pathogenic fungi and bacteria, while they show no toxicity to plant and mammalian cells. These proteins have been proposed as antifungal agents, and attempts have also been made at producing bioengineered plants expressing MiAMP genes.[9]

Dermatologic and Cosmetic Use

Macadamia oil is one of the few plant oils having a high content in palmitoleic acid. This fatty acid is also present in the sebum, and therefore it provides a particular affinity of the oil for human skin. Palmitoleic acid is the most effective sebum component in the growth inhibition of gram-positive bacteria.[25] Hence, macadamia oil is potentially useful as a preservative for dermatologic and cosmetic products, or as a defense against skin bacterial infections.

The oil has high penetration properties, can be used as an emollient, and is particularly indicated for dry skins. It is also suitable for massage, as an oxidation stabilizer, and as a component of sun creams.

Side Effects and Toxicity

The ingestion of nuts can induce sporadic allergic reactions with bronchial obstruction or skin reactions.[5,8,17,22] Cases of occupational contact dermatitis and food toxicity in dogs have also been reported.[7,12]

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MAËRL

Scientific name: *Lithothamnion corallioides* (P. & H. Crouan) P. & H. Crouan
Phymatolithon calcareum (Pallas) W. H. Adey & D. L. McKibbin
Phylum: Rhodophyta (red algae)
Family: Corallinaceae
Parts used: Thallus

Features

Calcareous red algae forming large colonies on muddy or sandy sea bottoms at depths of 0 to 25–30 m. These algae live preferably in areas with subtidal currents, particularly on the coasts of western Great Britain, southwestern Ireland, Brittany, and the northern Iberian peninsula. The colonies, known as maërl, consist of living individuals growing on a mat of dead remains. In some areas of western Ireland the dead algae grinded by waves form sandy beaches that extend over long stretches of the coast.

The maërl is mainly composed of two algal species, *Lithothamnion corallioides* and *Phymatolithon calcareum*, which show similar morphological features and can be hardly distinguished by a superficial examination.[4,11] The thallus is composed of cells with walls embedded by layers of calcium and magnesium carbonate. The growth forms vary from encrusting individuals reaching 20 cm in diameter, to highly branched tufts, up to 7 cm in diameter, not adhering to the substrate, with branches 6 mm in diameter having a smooth or flaky surface. The color is variable, deep pink to purple in living individuals and whitish in dead ones.[1]

FIGURE 4.33 Maërl.

Several hundreds of tons of maërl are dredged each year from the sea bottoms of Brittany, the United Kingdom, and Ireland. This material is dried, finely grinded, and put on the market.[2] The overexploitation of maërl banks in the northern seas of Europe can pose a risk to the environment, whereas on a planetary scale such a resource is minimally exploited. For instance, along the coasts of Brazil there are maërl beds, formed by algae of the genera *Lithothamnion* and *Lithophyllum*, which extend for thousands of kilometers and have not yet been significantly exploited.

Constituents

The mineral portion is composed of calcium (25–33% dry weight) and magnesium (1.7–3.3% dry weight). The main carbonate mineral is calcite, the most stable polymorph of calcium carbonate, while magnesium carbonate is less abundant and forms infiltrations in the calcite structure. Aragonite is also present, at about 10–15% of dry weight.[3]

The mineral composition of maërl is similar to that of limestone, a rock formed from the deposition of the calcareous skeletons of sea organisms. However, maërl has higher levels of magnesium, strontium, boron, and iron, with respect to limestone, while the level of manganese is lower. Moreover, in maërl there are higher amounts of trace elements in organic form.

Properties

These algae give an interesting biotrasformation by oxidating fatty acids. A well-studied process in *L. corallioides* is the conversion of arachidonic acid to (13R)-hydroxyarachidonic acid.[7] The pharmaceutical interest of these compounds resides in their affinity to eicosanoids, such as prostaglandins and leukotrienes, which are derivatives of arachidonic acid and play various regulatory roles in the human organism.[8,9] However, these algae do not seem suitable for a large-scale exploitation of these biochemical processes.[10]

Despite its chemical affinity to the more economically convenient limestone, maërl has a finer texture and porosity, thus being more suitable than limestone for uses that require superior mechanical properties. The ultramicroscopic analysis of the algal material reveals that the mineral deposition follows the dense texture of cellular walls.[13]

Maërl is mainly used in agriculture as a fertilizer, to correct the acidity of soils and for its richness in trace elements that are important plant nutrients. However, it is also used in various other activities, including the production of livestock food products, the treatment of water bodies, the potabilization of water, in the cosmetic and pharmaceutical industries, in orthopedic surgery, and in chemical processes of nuclear plants.[5]

Maërl is contained in nutraceuticals for weight loss, since it has been reported that calcium would induce the breakdown of body fat reserves, although these findings are considered controversial.[6,14] However, food integrators based on calcium are useful to prevent osteoporosis in aged people, particularly in postmenopausal women.[12]

Dermatologic and Cosmetic Use

The gravel of *Lithothamnion* and *Phymatolithon* is used for hydrating and refreshing baths and as an exfoliant in products for skin peeling and rejuvenation. It is also used in thalassotherapy, as a component of slimming and anticellulite preparations containing algal mixtures (*Fucus*, *Laminaria*, etc.).

Side Effects and Toxicity

No allergic or adverse reactions to the use of maërl have been reported.

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MAFURA

Scientific name: *Trichilia emetica* Vahl
Family: Meliaceae
Parts used: Seeds, bark, leaves

Features

Medium-sized, dioecious, evergreen tree, growing up to a height of 25 m, with a wide crown, and a dark grey or dark brown bark. The leaves are compound, imparipinnate, with dark green leaflets. The flowers are pale green or yellow. They are borne in cymes at the leaf axils. The fruit is an obovoid-globose capsule that splits into three segments revealing a bunch of seeds covered by a scarlet aril.

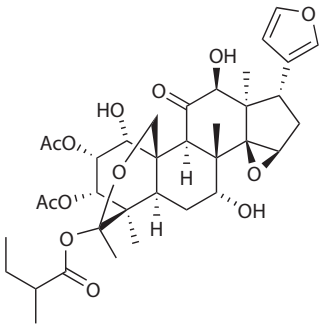
The species grows in riparian forests and woodlands, more rarely away from water. It is distributed in tropical and southern African regions and in the Arabian Peninsula. It is very similar to its congener *T. dregeana*, from which it can be distinguished by subtle anatomical details. It is also grown in urban areas as a shade and avenue tree.[3]

The seeds are edible, and are an important source of oil. The seed testa is bitter and poisonous, and it has to be removed by soaking. The oil can be used for cooking, soap making, and skin care. The seed pulp left after oil extraction is made into candles or used as a fertilizer. The seed arils are also edible.[8,18]

Constituents

The plant contains several limonoids, collectively known as trichilins.[13] Different compounds connected to limonoids have been isolated from the stem bark, including nymania 1, trichilin B, drageana 4, trichilin A, and rohituka 3.[9] The bark is particularly rich in tannins (about 7%) and contains a bitter alkaloid principle similar to that of cailcedrin from the mahogany tree *Khaya senegalensis*.

A chemical analysis of the crude polysaccharides of the leaves has identified arabinogalactan (approximately 54%) and rhamnogalacturonan (approximately 30%) pectins.[15] The root contains phenolic acids, including caffeic, ferulic, p-coumaric, syringic, vanillic, protocatechuic. and gallic acids, showing high antioxidant activity.[6]



trichilin A

The pressed seeds yield an oil that forms a solid butter at room temperature. The oil is rich in monounsaturated oleic acid (about 50%), while other fatty acids include palmitic (35%), linoleic (10%), stearic (3%), and linolenic (1%) acids.[5]

Properties

The plant has different uses in the traditional medicine of various African countries.[16] The most frequent uses are against malaria, abdominal pain, dermatitis, hemorrhoids, jaundice, and chest pain.[14] The grounded roots are used against cirrhosis, parasites like onchocerca and ascaris, stomach aches, and dysmenorrhea. The powder can be mixed with milk and used as a purgative and poison antidote, or mixed with honey against asthma. The root bark decoction promotes woman fecundity, and is a remedy against hepatitis, gastric ailments, fever, and epilepsy.[11] Leaf decoctions and infusions are used against scabies, malaria, hypertension, intestinal parasites, infections, and rheumatism.[2] The fruit is also used as a diuretic.

Pharmacological investigations have shown that the ethanol extract and, to a lower extent, the aqueous extract inhibit prostaglandin synthesis.[12] The plant is used against chronic wounds. Such a property is likely to depend on the presence of polysaccharides that act as immunomodulators via their effect on the complement system. It has been shown that the most active immunomodulatory fraction is a rhamnogalacturonan with arabinogalactan side chains.[4] The immunomodulatory effect could also explain, at least in part, the anti-inflammatory properties of the plant. In addition, the water-ethanol extract is recommended for cough therapy in the form of syrup, and an experimental study has proved that leaf polysaccharides possess a significant cough-suppressive effect.[15]

Kurubasch aldehyde, a sesquiterpenoid with a hydroxylated humulene skeleton, inhibits the growth of *Plasmodium falciparum* and MCF7 cancer cells, and to a higher extent S180 cancer cells.[17] The dichloromethane extract of the leaves has antiplasmodial activity and a good binding activity to the GABA-A-benzodiazepine receptor.[1] The crude ethanolic extract has shown *in vitro* good antitrypanosomal activity.[10] Limonoids present in the ethyl ether fraction of the root extract could be responsible for the antibacterial activity, while either polyphenols or limonoids could confer to the extract hepatoprotective effects.[7]

Dermatologic and Cosmetic Use

The butter from pressed seeds has approximately 35% saturated fatty acids, which are responsible for its semisolid state. It also contains approximately 50% monounsaturated fatty acids, and therefore it is very stable against oxidation. Moreover, the butter has antimicrobial and anti-inflammatory activities, due to the presence of limonoids, such as trichilin A. It can be applied topically to treat rheumatism or fractured limbs, and is also used for leprosy and to heal wounds and burns. It has nourishing and restructuring properties for the skin, mostly due to the presence of essential fatty acids, and is used in moisturizing, soothing, and antiaging cosmetic products.

Side Effects and Toxicity

A leaf extract has been reported to cause lethal edema of the lung in laboratory guinea pigs.[2] The roots are toxic at high concentrations. The residue of oil extraction is toxic, but is also traditionally used as an emetic against poison ingestion.[11]

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MALABAR TAMARIND

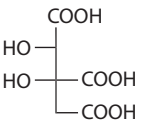
Scientific name: *Garcinia cambogia* (Gaertn.) Desr. (syn. *Garcinia gummi-gutta* (L.) N. Robson)
Family: Guttiferae
Parts used: Fruit

Features

Medium-size tree, growing spontaneously in southern India, Indochina, and the Philippines. Leaves are shiny, dark green, and of variable shape, from lanceolate to elliptic or obovate. The fruit is oval, wide, covered by a big, fleshy pericarp, orange or yellow in color. The bark has an acid taste and, once dried, can be used to flavor the curry. People living in the south of India, particularly on the coast of Malabar, use the plant as an alternative to tamarind and lime.

Constituents

The main active principle present in the fruit and leaves is (–)-hydroxycitric acid.[3,12] Other constituents include polyisoprenylated benzophenones, particularly xanthochymol and isoxanthochymol.[2] The fruit skin contains vitamins, carotenoids, flavonoids, organic acids, and polysaccharides.



(–)-hydroxycitric acid

Properties

The fruit can be used as food or as a natural medicine. It has been exploited by people of Southeast Asia since ancient times. The skin is used externally as an anaesthetic and astringent, while a decoct of the dry fruit is used internally to heal rheumatisms and gastrointestinal ailments. In Ayurvedic medicine, a powder extracted from the plant is recommended for gargling after teeth brushing.

Hydroxycitric acid contained in the dried fruit and in other Malabar tamarind preparations seems able to inhibit the enzyme ATP citrate lyase, which plays an important role in fat metabolism.[7] The compound acts on the liver and on other body districts, e.g., the adipose tissue and the small intestine, by reducing the conversion of sugars into triglycerides (up to a decrease of 27%). Such an activity involves a scaling down of fat accumulation, and in addition an increase of the energetic supply to the organism, due to a complete degradation of sugars through the citric acid cycle.[4] This ultimately leads to a reduced need for food ingestion and to a decrease in appetite.[5]

Plant extracts can therefore be used as diet supplements, particularly in the treatment of metabolism disorders.[11] A hydroxycitric acid-based dietary supplement has been found to induce modifications of gene transcription in primary adipocytes from obese women.[9] Treatments with hydroxycitric acid extract have produced an effect on body weight and selected organ weights.[10]

Hydroxycitric acid also inhibits pancreatic α-amylase and intestinal α-glucosidase, thereby producing a reduction in the rate of carbohydrate metabolism. A study carried out on the rat has shown that an ethanolic extract of the seed causes the induction of erythropoiesis and an antiobesity effect.[6]

Dermatologic and Cosmetic Use

The fruit extract, rich in citric and hydroxycitric acids, is used in the preparation of cosmetics for skin hydration.

Side Effects and Toxicity

No acute or chronic toxicity has been reported with regular consumption of Malabar tamarind or its constituents.[1,8] However, hydroxycitric acid increases cell sensitivity to insulin, so its use should be avoided by diabetic subjects treated with insulin. Another cause of concern may be the formation of ketone bodies due to fatty acid degradation. Hydroxycitric acid should moreover be avoided by people affected by cardiovascular disease or hypertension and by pregnant women. It has been experimentally shown that the administration of the extract to obese rats can produce toxicity to the testicles.

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MANGO

Scientific name: *Mangifera indica* L.
Family: Anacardiaceae
Parts used: Fruit, seeds, leaves, bark

Features

Medium to large evergreen tree (10–40 m in height) with rounded canopy. The bark is usually dark grey-brown to black, smooth, superficially fissured, and peeling off in irregular pieces. The leaves are simple, alternate, and variable in shapes: lanceolate, oval, oblong, or roundish. As the leaves grow, their color changes from reddish to green. The flowers are grouped in large pseudoterminal panicles, measuring up to 45 cm in length and bearing 500–6,000 small flowers, of which 1–70% are bisexual and the remainder are male. The fruit is a fleshy drupe with a variable shape, typically oval or kidney shaped. It has a fragrant and juicy pulp, and contains a seed formed by shell and kernel. The skin is gland dotted, and at maturity it displays green, yellow, and red shades.[21,47]

The species is cultivated all over the tropical regions, while its native home has been suggested as eastern India or the Malay region, where wild populations can still be found. It has been cultivated in India for over 4,000 years, and was probably introduced into Africa in the tenth century and into America by Portuguese colonizers in the seventeenth century. It is one of the most productive plants of the tropical region and contains numerous varieties, of which only a few are of commercial importance. The fruit is used fresh or processed for various purposes. The seed kernel contains 9–13% oil and yields a valuable emollient butter that is used in cosmetics. The fat

FIGURE 4.34 Mango. Courtesy of Dr. Nilamani Dikshit, NBPGR, Akola, Maharashtra, India. (See color insert following page 40.)

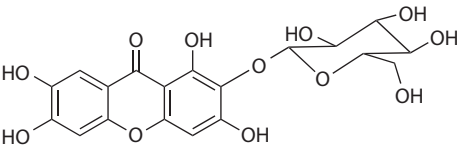
has a high content in stearic acid and is desirable for soap making. The seed residue after fat extraction is fed to cattle or used for soil enrichment.[36,63]

Constituents

The fruit contains protein, fat, carbohydrate, and minerals. Chief simple sugars are saccharose, fructose, and glucose. Pectins are composed essentially by arabinogalactan, containing galactose and arabinose, and rhamnogalacturonans, containing galacturonic acid, arabinose, galactose, and rhamnose. The fruit is also a good source of flavonol O-glycosides and xanthone C-glycosides, gallotannins, and anthocyanins. Dominant volatile compounds are terpene hydrocarbons like δ-3-carene, α-pinene, α-phellandrene, and terpinolene. Other compounds include organic acids like citric, tartaric, ascorbic, and malic acids; benzophenones; vitamin A; carotene; and B group vitamins. Major phenolic compounds include mangiferin (2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one), a biologically active xanthenone C-glycoside, penta-O-galloyl-glucoside, gallic acid, and methyl gallate.[14,19,48,50]

The leaves contain a good amount of mangiferin, and in addition they contain saponins, unsaturated sterols, glycosylated flavonoids, hippuric acid, and benzoic acid. A dark yellowish brown, drying resin, mixed with a gum, oozes out from the bark. The bark contains various pentacyclic triterpenes, β-sitosterol glycoside, mangiferin, and isomangiferin. All parts of the tree are rich in tannins. The resinous sap that exudes from the fruit stalk contains 5-heptadecenylresorcinol, mangiferin, resinous acid, mangiferic acid, and the resinol mangiferol.[8,13,30,49]

The kernel is a good source of gallotannins. The fat is solid at room temperature, and its main components include hydrocarbons, wax esters, triterpene alcohol esters, sterol esters, tri-, di-, and monoglycerides, free fatty acids, phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol. Fatty acids include oleic (41–48%), stearic (22–40%), linoleic (7–17%), and palmitic (7–12%) acids. Main sterols are β-sitosterol, stigmasterol, and campesterol.[6,29,56]



mangiferin

Properties

The plant has a variety of traditional therapeutic uses. The bark is astringent due to mangiferin and is useful for toothaches, internal hemorrhages, bronchitis, and catarrh. Throat disorders and asthma have been cured by the smoke from the burning leaves. Dried flowers contain high levels of tannin (approximately 15%) and are used as an anticholeric, antidysmenorrheic, antiscorbutic, astringent, and diaphoretic, while ripe fruits are used as a diuretic and laxative. The resinous gum from the trunk

is applied on wounds and is used to treat scabies and other parasitic diseases of the skin. The resin is also used for ringworm and other fungi, for syphilis, and to induce sweating. The seeds are anthelmintic, antimenorrhagic, and antidysenteric.[20]

The aqueous stem bark extract Vimang®, which has been used in pharmaceutical formulations in Cuba, has antioxidant and anti-inflammatory activities, as confirmed by several studies. Luminol-enhanced chemiluminescence has shown that the extract inhibits the generation of reactive oxygen species in phorbol myristate acetate (PMA)- or zymosan-stimulated human polymorphonuclear leukocytes, and the production of superoxide radicals generated in the hypoxanthine-xanthine oxidase reaction. Oxidative stress induced by H_2O_2 in red blood cells has been contrasted with Vimang and its main polyphenol mangiferin, possibly due to the antioxidants properties of polyphenolic compounds. Similar results have been found using a peel extract. Vimang has inhibited the decrease of GSH levels and lipid peroxidation induced by t-butyl-hydroperoxide in rat hepatocytes, while the extract or its mangiferin component has decreased the accumulation of iron in the liver of iron-exposed rats, thus reducing oxidative damage to rat serum and liver. The extract has also shown protective effects against injury to liver and brain tissue associated with ischemia reperfusion. Besides *in vitro* and animal studies, in clinical trials it has been found that Vimang tablets prevent age-associated oxidative stress in elderly humans.[5,28,37,42,44,54,55,58,59]

In vitro experiments on the anti-inflammatory properties of Vimang, using the macrophage cell line RAW264.7 exposed to pro-inflammatory stimuli, have shown that the extract is able to inhibit the induction of PGE(2) and LTB4. The extract has also inhibited human synovial secretory phospholipase PLA2 and inhibited the expression of iNOS and cyclooxygenase 2. Cyclooxygenase inhibitory properties have been reported for the alkenylresorcinols 5-(11′Z-heptadecenyl)-resorcinol and 5(8′Z-, 11′Z-heptadecadienyl)-resorcinol, isolated from the fruit peels. Structure-activity studies have indicated that the degree of unsaturation in the alkyl chain plays a key role for the cyclooxygenase inhibitory activity.[12,27,33,35,41]

According to the properties of its components, Vimang has shown anti-inflammatory and analgesic effects on carrageenan- and formalin-induced edema in rats, guinea pigs, and mice.[26] The results of these animal studies lend pharmacological credence to the folkloric uses of the plant in the management and control of painful, arthritic, and other inflammatory conditions. Also, *in vitro* experiments have indicated that the extract blocks the histaminic and muscarinic receptors of rat trachea, and that it inhibits eosinophil generation in bone marrow and blood eosinophilia in infected mice, thus corroborating the traditional use of stem bark in the treatment of asthma.[4,57,60]

A leaf decoction containing mangiferin and C-glucosylbenzophenone as main phenolic compounds has exerted gastroprotective effects on different experimental models in rodents. The gastroprotective effect of mangiferin against gastric injury induced by ethanol and indomethacin in rodents has also been shown, most possibly occurring through antisecretory and antioxidant mechanisms of action.[17,18,62]

The plant has shown an antihyperglycemic effect in hyperglycemic and streptozotocin-induced diabetic rats. Oral supplementation with the Vimang extract or mangiferin shifted the sensitivity of the liver mitochondria membrane permeability transition to control levels in atherosclerosis-prone hypercholesterolemic LDL receptor knockout (LDLr–/–) mice.[2,3,43,61] Mangiferin can restore the balance of serum and heart tissue

lipids in rats subjected to isoproterenol-induced cardiotoxicity, and induce an antihyperglycemic effect in streptozotocin-induced diabetic rats.[38] These results corroborate the empirical use of the plant in the management of type 2 diabetes mellitus.

Various studies indicate that the plant has the ability to modulate the immune system in different ways. Both the extract and mangiferin have depressor effects on mouse antibody responses and on the phagocytic and reactive oxygen species (ROS) release activities of rat macrophages. The extract has also been found to inhibit T cell proliferation and TNF-induced activation of nuclear transcription factor NFkB, and could be of value in the treatment of immunopathological diseases.[22,24,25] In addition, while AIDS is characterized by upregulation of CD95 ligand expression and enhancement of activation-induced cell death (AICD), the extract Vimang has enhanced T cell survival by inhibiting AICD.[31,32] Vimang or mangiferin, administered orally to mice, has inhibited mast cell degranulation as evaluated by the passive cutaneous anaphylaxis test, and induced a dose-dependent inhibition of IgE production, thus indicating an antiallergic activity.[23,53] In another study, however, the administration of an ethanolic, instead of an aqueous, bark extract has produced an increase in humoral antibody titer and delayed type hypersensitivity in mice, showing that the plant can also have immunostimulant properties.[37]

Neoplastic transformation of BALB/3T3 cells and the cell cycle of HL-60 cells is inhibited by the mango juice and juice extracts. Mangiferin has shown chemopreventive, cytoprotective, and antigenotoxic potentials on experimental animals and cultured cells.[46,51,52] Various leaf extracts have shown antibacterial activity on *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and the tetanus-causing agent *Clostridium tetani*,[9,10] while Vimang or mangiferin, administered orally to mice, has shown anthelmintic activity.[53]

Dermatologic and Cosmetic Use

The butter from seed kernel has soothing properties and heals a wide variety of skin eruptions, sores, and boils. The high percentage of tocopherol, phytosterols, and triterpenes suggests its supplemental use in cosmetics as a source for skin active ingredients. The butter is used in emollient creams, sunscreens, shampoos, and hair products, while it also has antibacterial activity. It is excellent as an ointment base, and has been observed to release salicylic acid at a remarkably greater rate than a standard paraffin-based ointment formulation.[1,15,20,39,40]

Side Effects and Toxicity

Young flowers and leaves are edible but could be dangerous to sensitive individuals. The sap oozing out of the trunk and the fruit stalk as well as the skin of the unripe fruit are irritants and may cause skin blistering known as mango dermatitis. Circumoral dermatitis is also frequent if the fruit is eaten without removal of the skin. Hypersensitive persons may react with diffuse swellings and may not even be able to handle the mango or any food containing it. Alkylresorcinols are regarded as the main responsible allergens, particularly 5-heptadecenylresorcinol present in the sap of the fruit stalk and peel. Epicutaneous tests with fruit peel pointed out that the

allergenicity of these compounds, which were found to be IgE mediated, depends on the degree of unsaturation in the alkyl chain.[7,11,16,34,45]

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MARULA

Scientific name: *Sclerocarya birrea* (A. Rich.) Hochst.
Family: Anacardiaceae
Parts used: Seeds, fruits, bark

Features

Medium-sized dioecious tree, growing up to 18 m in height, with a wide spreading crown and grey mottled bark. The leaves are compound with opposite leaflets. The flowers are arranged in bunches, 5 to 8 cm long, and blossom from August to September. The fruits ripen from January to April, and have a light yellow skin, white flesh, and a thick-walled nut containing the seeds. The species is distributed in the savannas of northern tropical Africa and in drier areas of southern Africa.[8,14]

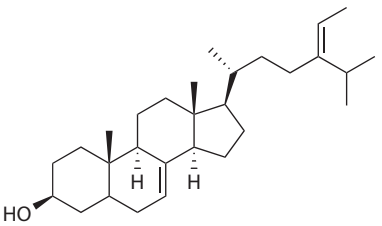
The tree has long since been an important component of the diet of African populations. The fruits are eaten fresh or used to prepare jelly, juice, and alcoholic beverages. An oil is extracted from the seeds using a cold pressing procedure that is traditionally carried out by women. The oil is a valuable ingredient for cooking and skin care products. It is also used traditionally to preserve dried meat.[12,15]

Constituents

The fruit is 85% water and 14% carbohydrate, mostly sucrose. It has a content in ascorbic acid that is more than fourfold the amount of an orange, and has smaller amounts of other vitamins, such as thiamine, riboflavin, and nicotinic acid. Other organic acids include citric, malic, and tartaric acids. The mineral composition shows high levels of potassium, calcium, and magnesium.

A new flavonol glycoside, quercetin 3-O-α-(5″-galloyl)-arabinofuranoside, and other phenolic compounds, among which are two epicatechin derivatives, have been isolated from the leaf methanol extract.[3]

The seeds are rich in protein, with a particularly high content in glutammic acid, and fat. The seed oil contains more than 20% protein and is rich in saponins (about 1%). The most abundant fatty acid is oleic acid (about 70%), followed by palmitic, linoleic, and stearic acids.[9] Nonsaponifiables include γ-tocopherol and sterols like P-sitosterol and 5-avenasterol.[10]



5-avenasterol

Properties

Local African communities have used the fruit for generations to cure hypertension, dysentery, diarrhea, gastrointestinal diseases, scurvy, and diabetes. Blisters caused by irritating caterpillar worms can be soothed by placing fresh inner bark on them. An infusion of the inner bark may be applied to scorpion stings and snakebites.

The bark is also used as a treatment and prophylaxis for malaria. Plant extracts, used both alone and in combination with other medicinal plants, have shown *in vitro* toxicity to different *Plasmodium* strains and *in vivo* antimalarial activity on mice.[6]

Scientific support to the folkloric uses of the plant's bark in the control of pain, inflammatory conditions, and type 2 diabetes has been given by pharmacological studies. Stem bark aqueous extract was tested for its analgesic effect in mice, and for anti-inflammatory and antidiabetic effects in rats.[7,13] Procyanidins isolated from the plant have shown antidiarrheal activity on isolated guinea pig ileum.[5] Different extracts have produced a significant antagonistic effect on caffeine-induced calcium release from sarcoplasmic reticulum of cultured rat skeletal muscle cells.[1]

The bark is widely used in Africa for bacteria-related diseases. Bark and leaf extracts have been found to possess antibacterial activities against various strains.[4] The antifungal activity of bark extracts has been evaluated on different yeast species.[11] The fruit is regarded to possess insecticide properties.

Dermatologic and Cosmetic Use

The oil from seeds is rich in antioxidants and oleic acid, which are essential components for the maintenance of healthy skin.[9,10] It has an extraordinary oxidative stability, which is due to the high content in antioxidants and monounsaturated and saturated fatty acids and to the lower presence of polyunsaturated fatty acids. The oil is easily absorbed by the skin and is incorporated into antiaging and soothing products. It can be used as a vehicle in aromatherapy or in moisturizing lotions and ointments. Because of its reputed antibacterial action the oil is also used to treat wounds and burns.

Side Effects and Toxicity

Toxicological tests made on mice showed that the leaf extracts are moderately toxic.[2]

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METHYLXANTHINES

Features

Methylxanthines are alkaloids occurring in more than 70 different plant species. The most known are caffeine, present prevalently in the coffee plant (*Coffea arabica* L.); theophylline, typical of the tea plant (*Camellia sinensis* (L.) Kuntze); and theobromine, present in the cacao plant (*Theobroma cacao* L.).

FIGURE 4.35 Coffee. (See color insert following page 40.)

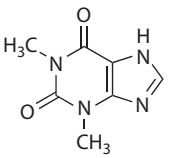
Caffeine is present in the coffee seed (about 2.5% dry weight) and in lower amounts in other plants like tea, mate (*Ilex paraguariensis* St.-Hil.), cacao, guarana (*Paullinia cupana* Kunth), and cola (*Cola* spp.).[26] In these plants caffeine generally acts as a defense against insects by exerting paralyzing effects.[16] In humans it chiefly acts as a stimulant of the central nervous system. It is the most widely used psychoactive compound in the world, and in contrast to other drugs with similar properties, its use is generally not subject to regulation. The use of this drug dates back to very ancient times, and was originally based on the empirical notion that some plants had the property of alleviating fatigue and stimulating mental concentration.

A legend tells that an Ethiopian shepherd ate the drupes of the coffee plant after having observed that they had stimulatory properties on his herd. The first reports about the use of coffee as a beverage can be found in Arab texts of the fifteenth century, while the introduction of coffee in Europe dates from the seventeenth century. Coffee was introduced on the American continent by Europeans, but before their invasion caffeine was already consumed by native people due to the use of cola and cacao plants.

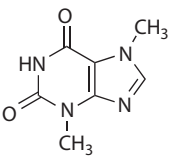
According to a legend, the origin of tea as a beverage goes back to the mythical Chinese emperor Shen Nong, who lived in the third millennium B.C. Thereafter, under the rule of the Tang Dynasty (600–900 A.D.), the use of tea was diffused across all of China by itinerant Buddhist monks who appreciated the stimulatory properties of this beverage and used to drink it during meditation time. The famous *Chajing* book, or *Tea Canon*, written by the poet Lu Yu around 758 A.D., reports the rituals of tea but also news about its medicinal properties, like the effects against headache and joint pain; its actions as a diuretic, febrifuge, expectorant, and cough suppressant; and its ability to promote abscess maturation. The commerce of tea in Europe was started at the beginning of 1600 by the Western Indies Company, and the popularity of the beverage grew rapidly. Theophylline, also known as dimethylxanthine, has various medicinal properties, but its concentration in tea (about 1 mg/kg) is largely below therapeutic doses.

Theobromine is contained in high amounts in the seeds of the cacao plant (10–40 mg/g), as well as in its derivatives like cacao and chocolate.[21] The drug is also present in small quantities in tea, but is absent in coffee. The stimulatory properties of theobromine are about 10-fold lower than those of caffeine. The concentration of the drug in chocolate cannot induce any toxic effect on human. Conversely, pets have less ability than humans to metabolize the compound, and can therefore suffer intoxication from the ingestion of chocolate.

The cacao plant is native to the American continent and was already used by pre-Colombian American people before the arrival of Europeans. The plant was originally appreciated for its aphrodisiac properties. A legend tells that the Aztec emperor Montezuma used to drink a beverage called chocolatl before entering his harem. The cacao was introduced in Europe by the Spanish conquerors.



theophylline



theobromine

Properties

Caffeine is absorbed in the stomach and in the small intestine, from which it can diffuse across the entire organism. In the liver it is metabolized by the P450 cytochrome system, leading to the production of dimethylxanthines, paraxanthine, theobromine, and theophylline. These compounds are eventually processed and excreted by the kidney.

The mechanism of action of caffeine depends on its purinic structure acting on various purinergic receptors that are present at the cell surface or intracellularly, such as ryanodine receptors involved in intracellular calcium release. Caffeine binds adenosine receptors in the central nervous system, whereas any *in vivo* intracellular action seems to be excluded since it would require lethal blood levels.[8,17] The drug exerts an inhibitory action leading to a rise in the neurotransmitter dopamine, which is the physiological mediator of the effects of the drug.[5] At high doses, caffeine can also increase the levels of serotonine, thus acting positively on the mood. The stimulatory effect of caffeine could also be due to an increase of adrenaline release and to the inhibition of the phosphodiesterase enzyme, which degrades cyclic AMP within cells.

Caffeine increases the possibility of doing mental or physical work, but it also influences the cardiovascular system.[2,7] It does not generally exert toxic effects, and the lethal dose is estimated at 150–200 mg/kg, corresponding to 80–100 cups of coffee. However, habitual coffee consumers develop tolerance to caffeine, deriving from an increase of adenosine receptors. This involves the occurrence of undesired effects when caffeine consumption is abruptly stopped, including a lowering of blood pressure, a reduction of epinephrine levels, disorders of the sleep mechanism, and variations of mood that in serious cases can give rise to depression.[20]

In contrast to caffeine, which induces a rapid and strong stimulation of the central nervous system, theobromine exerts milder and more enduring effects on the nervous system and mood. This drug is mainly used as a diuretic, vasodilatator, myorelaxant, and cardiotonic. Theobromine is also a more powerful cough suppressant than codeine, by acting through an inhibition of the vagus nerve.[25]

Theophylline induces a relaxation of bronchial smooth muscles, and is mainly used in the therapy of respiratory disorders like chronic bronchitis, emphysema, and asthma. It also exerts inotropic and chronotropic effects on the heart, leading to increases of blood pressure and renal flux.

The mechanism of action of theophylline consists of the inhibition of phosphodiesterase, causing an intracellular rise in cyclic AMP. The drug also activates the histone deacetylase HDAC2, which operates the deacetylation of histones. Such a mechanism is similar to the anti-inflammatory action of corticosteroids, which by activating HDAC2 promote the winding of DNA on histones and prevent the transcription of genes involved in inflammation.[12]

Theophylline is metabolized in the liver by cytochromes P450, 1A2, and 2E1, a process that leads to the production of 1-methylxanthine, 3-methylxanthine, and 1,3-dimethyluric acid.[24] The therapeutic use of this drug must be carried out carefully due to its low therapeutic index, i.e., the ratio between toxic dose and effective dose. Excessive doses can induce nausea, diarrhea, increased heart rate, and nervous excitation.

Dermatologic and Cosmetic Use

Triglycerides stored in adipocytes undergo a continuous turnover due to their synthesis and degradation occurring through esterification and hydrolysis processes, respectively. The process of hydrolysis depends on the activity of a lipase activated

by cyclic AMP.[6] Hence, agents that tend to increase the cellular levels of cyclic AMP, like methylxanthine, are potentially able to stimulate lipolysis.[3,22]

Anticellulite creams frequently contain caffeine, theophylline, theobromine, or their derivatives.[9,19] The lipolytic activity of caffeine has been assessed in both experimental and clinical studies based on topical treatments.[1,14] However, more in-depth research is needed to evaluate the real anticellulitic potentialities of this compound, as well as its optimal doses in cosmetics. Similar considerations can be applied to the other methylxanthines. This field of investigation has also addressed the development of synthetic derivatives able to induce stronger lipolytic effects. Examples of these compounds are aminophylline, also known as theophylline-ethylenediamine, and the complex methylsilanol carboxymethyl theophylline alginate. It has been shown that caffeine blocks the destructive action of dehydrotestosterone on hair follicles, and therefore it is used in lotions for the scalp.[4]

Theophylline also seems to be effective against psoriasis,[18] probably due to its inhibitory action on phosphodiesterase, while caffeine seems to act as a remedy against atopic dermatitis.[13]

Side Effects and Toxicity

Caffeine can induce reactions of food intolerance.[10,15] Aminophylline has been associated with cases of dermatitis, which, however, seems due to the ethylenediaminic moiety of the molecule.[11,23]

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MORINGA

Scientific name: *Moringa oleifera* Lam.
Family: Moringaceae
Parts used: Leaves, fruits, seeds
Other names: Horseradish tree, Drumstick tree

Features

Small- to medium-size tree or shrub reaching an average height of 5–7 m and a maximum height of approximately 10 m. The trunk is erect or ramified near the base, the wood is tender and spongy, and the branches are drooping. The leaves are light green on the upper surface and glaucous inferiorly, incompletely tripinnate, with oval leaflets. The flowers are cream, pink, or purplish, and borne in axillary panicles. The fruits are pendulous pods, also known as drumsticks, between 30 and 50 cm long, and triangular or nearly cylindrical in cross section. Ripe fruits open along three valves, revealing 20 to 25 rounded seeds bearing papery wings.

FIGURE 4.36 Moringa.

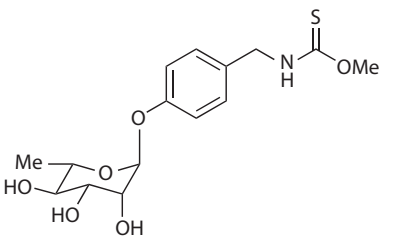
The plant is indigenous to northwest India, but is now widely cultivated and naturalized in many areas of the tropics. It has been used for centuries in traditional medicines and for industrial purposes. The seeds are consumed fresh or cooked, and can be pressed into an oil that is used for cooking, for lubrication, and in the manufacture of skin care products. Powdered seeds are also used to flocculate contaminants and to purify drinking water.[11,23,28]

Constituents

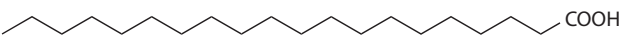
The leaves contain approximately 7% (w/w) protein, 1.5% fat, 15% sugars, and 2.5% minerals. The relatively most abundant minerals are potassium, calcium, phosphorus, iodine, iron, and copper. The leaves are also rich in oxalic acid, vitamins A, C, and E, and vitamins of the B group. They have a high content in essential amino acids, particularly sulfur-containing ones, similar to those of soybean seeds. The leaves also contain good levels of tannins, saponins, and alkaloids. The fruits contain approximately the same components but with different relative amounts.[10] A gum exudate has been found to be composed of L-arabinose, D-galactose, D-glucuronic acid, L-rhamnose, D-mannose, and D-xylose.[4]

The seeds contain approximately 35% protein and 30–50% fat. The most abundant fatty acid is oleic acid (approximately 65%), while other fatty acid constituents include approximately 10% stearic acid, 6% behenic (docosanoic) acid, 4% linoleic acid, 3.5% palmitic acid, and 1.5% myristic acid. The presence of high amounts of behenic acid accounts for the names of ben or behen oil, by which the oil extracted from the seeds is known. The oil has a sterol composition consisting chiefly of campesterol, stigmasterol, β-sitosterol, Δ5-avenasterol, and clerosterol. Other components of the seeds include acidic proteins with hemagglutinating activity, and good amounts of glucosinolates and phytates.[17,36]

The main active principles accounting for the therapeutic properties of the plant are thiocarbamates, isothiocyanates, and glucosinolates. Main representatives include niazinin, niazimicin, pterygospermin, niaziminin, niaziridin, and niazirin.[7,35]



niazinin A



behenic acid

Properties

All parts of the plant are edible, and the tree has been advocated as a source of nutrients suitable for regions of the world plagued by undernourishment. A vast number of reports on its nutritional value are currently available.[12] The plant also has various medicinal uses, which have long been recognized in the Ayurvedic and Unani medicines. A number of therapeutic properties have been ascribed to various parts of the plant, including the treatment of inflammation and infectious diseases, and of cardiovascular, gastrointestinal, hematological, hepatic, and renal disorders.[2]

The plant leaves are a good source of natural antioxidants, due to the presence of fair amounts of ascorbic acid, flavonoids, phenolic compounds, and carotenoids.[21] They also have antinociceptive and anti-inflammatory effects. The results of an animal study indicate that the antinociceptive activity of a leaf aqueous extract is modulated via opioid receptors at the central, but not at the peripheral level. In addition, the bioactive compounds aurantiamide acetate and 1,3-dibenzyl urea, isolated from the root, have been reported to inhibit the production of TNF-α and IL-2, thus helping to clarify the mechanism of action against inflammatory conditions such as arthritis, for which the crude extract is traditionally used.[31,33]

A combination of diuretic properties and serum lipids and blood pressure–lowering effects render the plant useful in cardiovascular disorders. Nitrile and thiocarbamate glycosides are responsible for blood pressure lowering. More specifically, niazinin A, niazinin B, and niazimicin have been shown to exert blood pressure–lowering effect in rats, possibly through a calcium antagonist effect.[8,15,25] Moreover, the fruit has been found to lower serum cholesterol, triglycerides, and LDL, in hypercholesteremic rabbits, while the plant's cholesterol-lowering effects in the rat have been ascribed to bioactive constituents like β-sitosterol.[13,22]

Antispasmodic activities of the leaf ethanolic extract have been attributed to 4-[α-(L-rhamnosyloxy)benzyl]-O-methylthiocarbamate, possibly through a calcium channel block mechanism, which forms a molecular basis for the traditional use of the plant in gastrointestinal motility disorders. Antiulcer and hepatoprotective activities have also been pointed out, especially in the flower, due to the presence of the well-known hepatoprotector flavonoid quercetin.[14,29,32]

The aqueous leaf extracts can regulate the production of the thyroid hormone in rats, suggesting the use of the plant in the treatment of hyperthyroidism.[34]

Antitumor activity has also been detected in plant extracts. Niazimicin has been proposed as a chemopreventive agent in chemical carcinogenesis. Moreover, niaziminin and 4-[(4′-O-acetyl-α-L-rhamnosyloxy)benzyl] isothiocyanate have been found to inhibit tumor-promoter-induced Epstein-Barr virus activation, suggesting that the thiocarbamate or the isothiocyano groups are critical for this kind of activity.[24]

Different portions of the plant have been found to possess antibacterial and antifungal activities. Many of these properties have been detected in root extracts, but it has also been demonstrated that extracts from the leaves and seeds inhibit the growth of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Major antimicrobial principles include pterygospermin, 4-α-L-rhamnosyloxybenzyl isothiocyanate, and the aglycone of deoxy-niazimicin.[5]

The seed extract has coagulation and flocculation properties, due to high levels of cationic proteins with molecular masses between 6 and 16 kDa. Some of these proteins also have antibacterial properties and allow almost complete removal of the bacteria suspended in a sample of water. These properties have promoted the application of the seeds as an alternative method for water treatment in developing countries.[1,20] Different peptides with hemagglutinating and coagulating properties have been isolated from the seeds, and their structure has started to be determined.[18,30]

Dermatologic and Cosmetic Use

The seed oil has been used for beauty care since ancient times. It is highly resistant to oxidative degradation, and this renders it particularly suitable in the production of cosmetics. Also, the crushed seeds are known to have purifying and cleansing effects on hairs. They protect the hair against environmental pollutants and UV, and moreover act by strengthening and conditioning the hair and scalp.[27]

The seed-flocculating proteins extracted from the seed cake that remains after removal of the oil have been claimed to be most suitable for skin and hair care. They seem able to exert emollient, conditioning, and hydrating effects, and can also neutralize harmful pollution and detoxify the skin. These peptides have been found to protect the human skin from environmental agents and to contrast premature skin aging. They have also been tested *in vitro* for cytoprotection of skin cells against such heavy metals as mercury and cadmium. The protein fraction from the seeds was also found to protect and repair hair against damage caused by exposure to air pollution. Hence, moringa seed proteins are recommended for both skin and hair care products.[3,16]

Side Effects and Toxicity

Toxicological evaluations of plant extracts on rats and mice have pointed out low toxicity. No side effects are known on humans for proper therapeutic doses. However, the root bark is abortive and should be avoided during pregnancy.[6,9,19,26]

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MURUMURU

Scientific name: *Astrocaryum murumuru* Mart.
Family: Arecaceae
Parts used: Seeds

Features

Caespitose palm widespread in the Amazon basin. It can be short and stemless or grow up to 2–6 m in height, with one or more trunks. The stem is covered by sharp, black spines that can reach 12 cm. The crown is formed by large, flat leaves with very closely spaced leaflets and silvery undersides. The fruits are born in large clusters, often pendulous. They are up to 9 cm long, reddish, and contain a yellowish pulp and a hard seed with an almond rich in fat.[4,6]

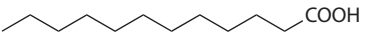
FIGURE 4.37 Murumuru. Courtesy of Dr. Jean-Christophe Pintaud, IRD, Montpellier, France. (See color insert following page 40.)

The palm grows in shaded places, preferably on clayey soils. It is native to the Amazon rain forest and has great economic importance because of its seeds and its leaves, yielding a fiber used to manufacture baskets and cordage.[7,11]

The yellowish, fibrous pulp of the fruit is eaten by the natives, while a creamy butter is extracted by cold pressing from the seeds. The fat is edible and suitable for the manufacturing of margarine or cosmetics.[3,9]

Constituents

The dried seeds contain approximately 40% of fatty material. The chief components of the butter extracted from the seed include lauric acid (approximately 45%), myristic acid (25%), oleic acid (15%), palmitic acid (5%), stearic acid (2%), linoleic acid (2%), glycerol (5%), and unsaponifiables.[2,8,12,13]



lauric acid

Properties and Cosmetic Use

The seed butter is known for its anti-inflammatory, bactericide, and emollient properties, and is mostly used in hair and skin care preparations. It is a powerful skin barrier repair agent, promotes the hydration of the skin, and helps restore moisture balance. It is also able to restore softness, elasticity, and gloss to dry and damaged hair. The butter can be added to moisturizing, protective, and nourishing skin products; to hair treatments, shampoos, and conditioners; or can be applied alone to the skin and hair.[1,5,10]

Side Effects and Toxicity

No contraindications have been reported for the use of the butter.

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NEEM

Scientific name: *Azadirachta indica* A. Juss.
Family: Meliaceae
Parts used: Seeds, leaves, flowers, bark

Features

Tree growing in tropical and subtropical areas. It is native to Bangladesh, India, and Myanmar, but is distributed in the entire tropical Asia and in African regions. The tree can reach a height of more than 15–20 m; it is an evergreen, but generally loses large numbers of leaves during the dry season. The canopy is rounded, and in the oldest individuals can reach a diameter of 20 m. The trunk is rather short and straight, and the bark is greyish or reddish brown. Leaves are imparipinnate pinnately compound and alternate, 20–40 cm long, purple-red when young and dark green at maturity. Flowers are small, white, and scented; they form axillary branched panicles of about 25 cm in length. The fruit is a rounded or ovate naked drupe, similar to an olive, measuring about 1 cm in diameter. The fruit endocarp is white and tough; it encloses one or, more rarely, two or three seeds covered by a brown cuticle.

This plant has been used for centuries for medicinal purposes, as also outlined by some of its popular names.[31] The sanskrit name *Arishtha* means "remedy for any ailment," while in eastern Africa the plant is known as *the tree of the 40*, meaning that it is a remedy for as many as 40 different diseases. In India the sprouts and the flowers are consumed as food, while the young branches are used for dental care. The plant also finds agricultural applications in antidesertification projects.

FIGURE 4.38 Neem. (See color insert following page 40.)

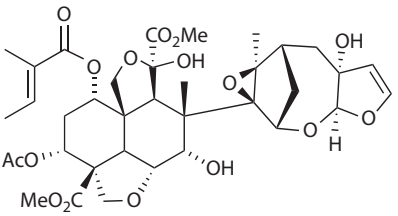
Constituents

The plant components can usually be divided into isoprenoids and nonisoprenoids.[1] The former ones include diterpenoids and triterpenoids belonging to the group of limonoids (protomeliacin, azadirone and derivatives, gedunin and derivatives, vilasinin, and C-secomeliacins, such as nimbin, salannin, and azadirachtin).[48] Azadirachtin is a highly oxygenated tetranortriterpenoid and represents the main active principle.[38,39]

Nonisoprenoids include proteins and amino acids, carbohydrates, sulfurated compounds, polyphenols, among which are flavonoids and their glucosides, dihydrochalcones, coumarins, and tannins.

The seeds furnish an oil containing 0.2–0.4% of azadirachtin, melantriol, salannin, and a mixture of limonoids, known as nimbidin.[15] Various tetranortriterpenoids can be isolated from nimbidin, including nimbin, nimbinin, nimbidinin, nimbolide, nimbocinol, and nimbidic acid.[35]

The mineral composition of the plant shows a relative abundance of macronutrient elements, while the most abundant trace elements are Zn, Fe, Cu, and Al.[44]



azadirachtin

Properties

The plant has been known in India for more than 2,000 years for the flexibility of its therapeutic properties, and it is a main element of Ayurvedic medicine.[10,59] It has various pharmaceutical uses, and is also an important source of natural pesticides.[13,27,32,46,51,53,58]

The oil extracted from seeds and the leaf extract are used to cure leprosy, gut helminths, respiratory disorders and constipations, rheumatism, and chronic ulcers. The oil, leaves, and bark also show anti-inflammatory activities.[6]

Nimbidin has induced anti-inflammatory, antipyretic, and antihistaminic effects on animal models. The antihistaminic effect is specifically due to a block of H_2 receptors, thus conferring to this substance an antiulcer property.[21] This kind of therapeutic property is also shown by the aqueous extract of leaves, but because of a different mechanism, involving maintenance of the mucous coating of the stomach and a reduction of mast cell degranulation. Antiacid and antiulcer actions have also been reported for the bark extract.[4] Bark tannins, containing gallic acid, catechins, and gallocatechins, can inhibit the oxidative burst of neutrophils.

The plant exerts analgesic effects mediated by opioid receptors. The aqueous leaf extract and the oil produce immunostimulatory effects,[5] reduce glycemic values, and prevent hyperglycemy induced by glucose and adrenalin or by diabetes.[24] A study

on a leaf extract containing the flavonoids quercetin, myricetin, and kaempferol has indicated that the hypoglycemizing action could depend on a stimulation of insulin secretion due to a removal of serotonin control on insulin release.[12] Nimbidin has also shown a hypoglycemizing effect.[54] The oil can regulate the adipose tissue and the body weight, due to a prevention of adipocyte differentiation, an increase of adiponectin and leptin secretion, and the inhibition of grelin release.

The leaf extract protects the liver of rats from injurious effects of paracetamol, as shown by a decrease in the hematic levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamil transpeptidase (GGT). In experimental animals, leaf extracts have also shown relaxing and anxiolytic activities on the central nervous system, while the bark ethanol extract exerts hypotensive, spasmolytic, and diuretic actions.

In different studies, plant extracts have shown various anticancer effects.[3,9,16,25,43] The leaf extract has protected the oral mucosa of experimental animals from the insurgence of cancer induced by the tumorigenic compound dimethylbenzo[a] anthracene, possibly due to a modulation of the activity of the enzyme glutathione-S-transferase. The induction of cell detoxification systems also seems to be at the basis of the protective effect against gastric tumors induced by N-methyl-nitro-N-nitrosoguanidine.[2,50] Two polysaccharides isolated from the bark, known as GIa and GIb, can induce via oral administration a complete regression of tumor cells growing in experimental mice.

Various antimicrobic, antiparasitic, and pesticide effects have been reported.[17,19,22,30,33,34,41,45,60] The oil is used as vaginal contraceptive due to the spermicide activity of nimbidin.[29] The oil and the leaf extract have antimalarial activities against various strains of *Plasmodium falciparum*.[40,55,56,62] They are also able to contrast the growth of different fungi and bacteria, such as *Vibrio cholerae*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Streptococcus mutans*, and *S. faecalis*. Leaf extracts show antiviral activity,[57] particularly against *Vaccinia virus* and the agent of measles. The compounds involved in these antimicrobial effects are nimbidin, with bactericidal and fungicidal activities; nimbolide and azadirachtin, with antibacterial and antimalaric effects; and gedunin, present in the oil, with antifungal and antimalaric effects. Tricyclic diterpenoids isolated from the bark, such as margolone, margolonone, and isomargolonone, are also active against various bacterial species.

The plant is widely used, particularly in Asia, against field crop pests.[36,61] Limonoids such as azadirachtin and nimbin inhibit ecdysone 20-monooxygenase, an enzyme of the P450 family, which converts the steroid hormone ecdysone to 20-hydroxyecdysone in insects.[37] This latter compound promotes molting and metamorphosis in insect juvenile phases, thus allowing the insect to reach the adult stage. The effects of these pesticide compounds are suffered only by leaf-eating insects, thus producing no harmful consequences to pollinators that feed on the flower nectar. The insect-repellent properties of the plant can also be exploited to protect humans and domesticated animals from noxious insects.[18,20,23,47] The plant is a popular remedy against scabies and lice, while azadirachtin, in particular, is on the market as a repellent against hematophagous insects.[8] The oil is used on pets as a treatment against fleas, while in its native countries the plant is used for decontamination of drinking

water from parasite worm. Plant extracts are also used in the treatment of crops like corn, wheat, rice, and beans.

Dermatologic and Cosmetic Use

The bark and leaves, as well as the refined oil, are employed in a wide range of herbal cosmetics, including creams, lotions, soaps, and shampoo.[14] The oil has hydrating and antimicrobial properties and, as said above, can also act as an insect repellent.[26] The oil is also used in dermatologic products for acne and other skin infections. The leaf extract is active against skin mycoses, eczema, and scabies. Nimbidin is used in skin-lightening products.[52]

Side Effects and Toxicity

Plant derivatives used to treat crops, particularly the seed oil, can leave residuals representing a potential hazard to consumers.[7] The oil is a mitochondrial uncoupler and decreases the mitochondrial levels of acetyl-CoA and its esters. Moreover, the oil can be frequently contaminated with aflatoxin.[49]

Cases of acute renal insufficiency have been reported after oral or intravaginal use of the plant extracts or their derivatives. The topical use of the oil can cause contact dermatitis,[42] while the pollen can trigger allergic reactions in sensitive people.[11,28]

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OARWEED

Scientific name: *Laminaria digitata* (Hudson) J. V. Lamouroux
Class: Phaeophyceae (brown algae)
Family: Laminariaceae
Parts used: Dried fronds

Features

Brown alga of large size, up to 2 m in length, consisting of a holdfast and a frond. The holdfast is formed by masses of haptera, which are branched cylindrical processes firmly adhering to the substratum. The frond consists of a thick, rounded, flexible stipe, broadening out into a blade that is divided to form straplike segments.

The alga is common in the North Sea, along the coasts of the Baltic Sea, British Islands, and Brittany, and is also distributed on part of the Atlantic coasts of North America.

FIGURE 4.39 Oarweed.

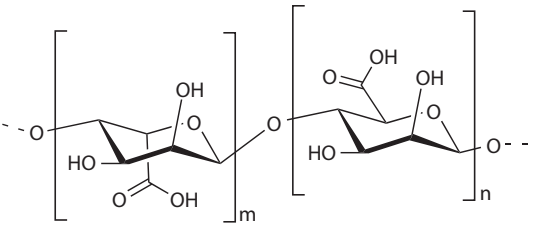
It lives in intertidal zones, forming dense forests that can dry out during low tide. In Brittany and in Ireland it is harvested for the production of alginate fibers, and for human and livestock nutrition.[10] It is particularly appreciated in Asian cuisines.

Constituents

The alga contains a large amount of carbohydrates (65%), of which the main one is alginic acid. This latter is a polysaccharide composed of D-mannuronic acid units, having a structure similar to that of pectin, and is a fundamental component of the algal cell wall. Alginic acid and its derivative salts, known as alginates, form up to 40% of the algal dry weight. Other chief carbohydrates are laminarin, consisting of sulfated polysaccharides (more than 14% dry weight), mannitol, and fucoidin, which contains mainly L-fucose.[1]

The protein fraction (total nitrogen, 1–3% dry weight) consists of proteins, peptides, amino acids, and volatile nitrogen compounds. Other constituents include carotenoids (neoxanthin, fucoxanthinol, β-carotene), vitamins (E, C, B12, B6, B3, A), and mineral salts.[11]

The amounts of macronutrients (Na, K, Ca, Mg, P) and micronutrients (Fe, Zn, Mn, Cu) are higher than in terrestrial plants. In particular, there is a high amount of arsenic (about 70 mg/kg dry weight), which is mainly present in a nontoxic form complexed with polysaccharides, and high levels of organic and inorganic iodine (about 2 g/kg dry weight).[7,12,13]



alginic acid

Properties

The alga is indicated as a remedy for various disorders, including obesity, cellulite, water retention, hypothyroidism, goiter, lymphatic syndromes, hypertension, arteriosclerosis, bad circulation, heavy metal contamination, arthritis, menopause and andropause, demineralization, and constipation. The algal positive action on obesity and goiter is due to its high content in iodine, which would stimulate the function of thyroid.[8]

Algal mucilage can be used for internal and external applications as an emollient for protecting the epidermis and mucosae. Alginic acid forms a dense colloidal gel in the stomach, due to the high acidity of the gastric juice, thereby protecting the stomach wall from injury caused by gastric ulcer. In the gut, alginic acid behaves like vegetal fiber since it is not degraded by digestive enzymes, thus favoring the intestinal transit of food.[2,3]

Laminarin seems to lower lipid and cholesterol blood levels, although these properties have not been confirmed by a study on the rat.[4] Laminarin is also able to stimulate the immune response, by inducing the production of TNF-α in peripheral blood monocytes.[9,14] Similarly, the glucan ficarin, also isolated from the alga, stimulates the activity of the immune system through the increase of IL-1 and IL-6 production.

Fucoidans show a marked *in vitro* antithrombin activity, and in addition inhibit umbilical vein tubulogenesis, suggesting an antiangiogenic action. These compounds can also inhibit the adhesion of breast carcinoma cells to platelets, which entails a restraining of metastasis.[5]

Mannitol has a strong sweetening power, equal to about 70% that of sucrose, and a low caloric content (2 kcal/g). This compound also has hydrating, diuretic, and antibacterial properties.

Iodine has antiseptic properties and is essential for the synthesis of thyroid hormones. It increases the cellular oxygen consumption and metabolism of fat and carbohydrates. The alga also contains factors performing the iodination of amino groups, which exert a positive action on patients affected by obesity and goiter.

Dermatologic and Cosmetic Use

Alginic acid is used in cosmetics as a thickening and emulsifying agent. Algal extracts are also used for their emollient and hydrating effects on the epidermis, due to the high amount of polysaccharides.[6]

A main use of the alga is as a remedy against cellulite. The high content in mineral salts, iodine in particular, favors skin drainage and produces a slimming effect.

Side Effects and Toxicity

The use of algal extracts is not recommended to patients with hyperthyroidism or cardiovascular disorders. Allergic responses to the alga are very rare.

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OLIVE OIL

Scientific name: *Olea europaea* L.
Family: Oleaceae
Parts used: Olive oil

Features

The olive is an evergreen tree of medium size, which can live up to an age of hundreds of years. The trunk is twisted and the bark is grey and smooth. The wood is yellow-brown, fine textured, hard, and is used to manufacture valuable furniture. The roots are mainly superficial and adventitious. Leaves are opposite, entire, stiff, narrow-elliptical to lanceolate, coriaceous, and dark green on the upper surface and silver on the lower one, which is covered with scutiform hairs. Flowers are small, white, scentless, and grouped to form axillary bunches. The fruit is an oval, green, or purple drupe, having a fleshy pulp. This latter consists of 25–30% oil, which is stored within cells in the form of small lipid droplets. The seed is surrounded by an oval, woody, coarse, brown endocarp.[14]

The species is native to Asia Minor, from where it spread over the Mediterranean area 6,000 years ago. It has been cultivated since prehistoric times, e.g., by people from the Minoic culture around 3000 B.C. and by the ancient Egyptians around 2000 B.C. Thereafter, olive tree cultivation was diffused throughout Mediterranean countries by the Greeks and Romans.

FIGURE 4.40 Olive. (See color insert following page 40.)

The medicinal and cosmetic uses of the olive tree and its derivatives are very ancient practices and were originally associated with divinatory ceremonies. Ancient Greeks used to anoint themselves with olive oil, and in the *Odyssey* it is told that the silky skin of the goddess Aphrodite was rubbed with sacred oil. The plant was introduced to the American continent by Christian missionaries together with grapevine, while it was subsequently diffused to South America, Japan, Australia, and New Zealand.

Two varieties of the plant are currently known. *O. europaea* L. var. *europaea* is the cultivated olive tree, while *O. europaea* L. var. *sylvestris* is the wild one. The oil is mainly produced by pressure or by grinding the fruit and extracting the oil with mechanical methods.

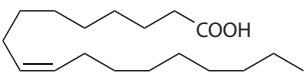
Constituents

Fresh olive oil is yellow-green in color, while it turns to golden yellow with time. It is chiefly composed of triglycerides (98–99%) containing oleic (78%), palmitic (11%), linoleic (9%), stearic, palmitoleic, arachic, and linolenic acids. Plants from relatively colder climates produce olives with a higher content in oleic acid than those from warmer climates.

Other oil constituents include phenols, peroxides, diacylglycerols (DAGs), monoacylglycerols (MAGs) and free fatty acids, pheophytin-a, and chlorophyll. In addition, high amounts of antioxidant compounds are also present, such as flavonic polyphenols.[7,15] The oil contains liposoluble vitamins (A, D, E, and K), while the fruit also contains hydrosoluble vitamins. The presence of chlorophyll makes the oil one of the richest sources of vitamin K, second only to green-leaf vegetables.

The oil unsaponifiable fraction (about 0.6–1.5%) is mainly composed of hydrocarbons (about 90% of the total), of which the unsaturated fraction consists of about 95% squalene. Other components of this fraction include hydrocarbons having 18 to 40 carbon atom chains, aliphatic alcohols (about 2%), sterols like β-sitosterol, campesterol, and stigmasterol (about 1.5%), and high-molecular-weight esters and aldehydes.[9] The unsaponifiable fraction yields a creamy butter, similar to karite butter, having a pleasant olive scent.

The alcoholic fraction contains linear alcohols, triterpenic cyclic alcohols, and low-molecular-weight terpenic alcohols. Oligoelements include relatively abundant amounts of iron, copper, zinc, manganese, and molybdenum.



oleic acid (ω-9)

Properties

The nutritional value of the oil is superior to that of animal fat due to the high content in unsaturated fatty acids with low atherosclerotic effects. The therapeutic properties include a laxative effect and the ability to stimulate the biliary function.

Clinical studies have shown that nutritional supplements containing synthetic vitamin E do not reach the same effectiveness of natural products as olive oil.

Flavonic polyphenols are natural antioxidants having different beneficial properties, such as burn healing, regulation of blood pressure and cholesterol blood content, and prevention of cardiovascular diseases.[3,4,16,17]

The polyphenol hydroxytyrosol has been shown to exert a chemopreventive action on tumors through the induction of apoptosis.[10] This compound also has cardioprotective, antiatherogenic, and anti-inflammatory properties, while in addition it exerts a photoprotective effect on the skin.[5,6,13] These therapeutic properties are mainly due to the very strong antioxidant power of hydroxytyrosol, which scavenges reactive oxygen species at higher rates than strong antioxidants like vitamin E.

Dermatologic and Cosmetic Use

The topical application of the oil results in a soothing action with beneficial effects on scabs, eczemas, and burns.[2,12] The presence of phytosterols and triterpenic compounds confers skin lenitive and revitalizing properties to the oil. The antioxidant action of vitamin E prevents skin irritation and aging, while the regenerating properties of vitamin A protect the skin against aging and maintain its softness, smoothness, firmness, and elasticity.

The oil is used in cosmetics as a lenitive and sweetening agent for dry and wrinkled skin, and also as a hair strengthener.[1] It is a component of hand lotions, lip balms, shampoo, and oils for bath and massage.

The unsaponifiable fraction contains various active principles with emollient, softening, and sebum-restorative properties. It is used in cosmetics (creams, milks, oleolites, gels, etc.) designed for the treatment of sensitive, dry, chapped, and aged skins, and as a makeup additive that renders makeups more easy to apply, soft, smooth, and well finished. The unsaponifiable fraction also exerts a photoprotective effect.

The butter is ideal for massage or as a vehicle for other active principles used in skin care. It contains high amounts of squalene, a sebumlike substance, waxes, and esters that ensure a high skin penetrability. The butter is also an emollient and hydrating agent; it promotes skin elasticity and prevents the formation of lines and wrinkles. It is used in antiage and photoprotective products, and is also used as a supplement in products for skin hygiene due to the ability to neutralize the aggressive action of detergents.

Side Effects and Toxicity

Cases of occupational allergic dermatitis caused by olive oil have been reported.[8,11,18]

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PERILLA

Scientific name: *Perilla frutescens* (L.) Britton
Family: Lamiaceae
Parts used: Seeds

Features

Herb standing up to 0.5–2 m high. The leaves are long-petiolate, with a wide-ovate lamina, rounded at the base, acuminate, curly, glossy, and downy-haired along the veins. The flowers are small, whitish, and grouped to form spikelike inflorescences born in the axils of triangular bracts. The calyx is campanulate and bilabiate, while the corolla is almost radial, with a short tube. The fruit is globose and the seeds are yellowish.

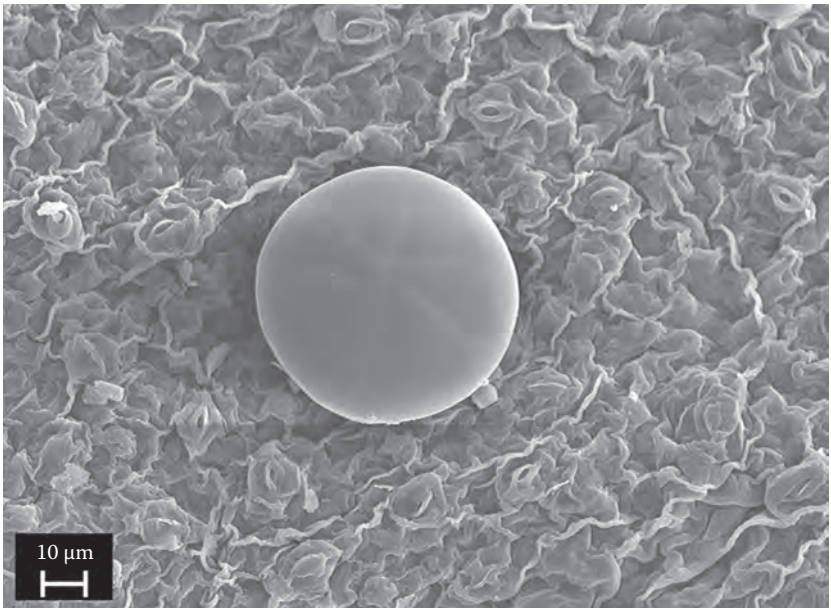
The species is native to the Far East. It has long since been cultivated in China and has been widely used in traditional Chinese and Japanese medicines. There are two varieties, one with green leaves and another with reddish leaves, due to anthocyanin accumulation. This latter has been studied in regard to processes of anthocyanin synthesis.[6]

(A)

FIGURE 4.41 (A) Perilla. (See color insert following page 40.)

Constituents

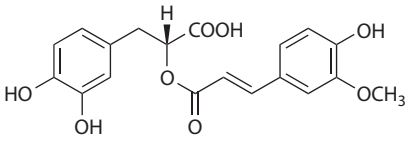
Leaf extracts contain the polyphenol antioxidant rosmarinic and 9′-methoxy-rosmarinic acid. They also contain caffeic and ascorbic acids, luteolin, and the



(B)

FIGURE 4.41 (B) Scanning electron micrograph of a glandular trichome.

glycoglycerolipids acylglycerylgalactosides. The oil extracted from the seeds is very rich in α-linolenic acid (50–60%), an ω-3 fatty acid similar to those abundantly present in fish.[3]



9'-methoxyrosmarinic acid

Properties

The plant is very popular as food and for its medicinal properties in China and Japan.[5] Plant extracts have immunomodulatory properties, which are probably responsible for their inhibitory effects on allergic rhinoconjunctivitis, a common chronic disorder in children, and atopic dermatitis.[8]

Different studies indicate that the oil can prevent cardiovascular diseases, cancer, arthritis, obesity, and asthma. The oil also has culinary uses as a condiment, and is used in the production of paints, inks, and dyes.[10]

The volatile monoterpenic derivatives perillaldehyde and perillyl alcohol have been studied for their antimicrobial and antiproliferative properties.[2,7]

Dermatologic and Cosmetic Use

The oil is employed in skin care as an antiage product or in treatments against hyperpigmentation.[1] Besides, it has antiseptic activity and can be used against *Propionibacterium acne*, the infective agent of acne.

Side Effects and Toxicity

Occupational dermatitis and positive patch test reactions to leaves have been observed in workers employed in the collection of the plant.[9] However, similar analyses carried out with the oil have proven positive in a very low number of cases, thus indicating that the oil is suitable to be used on sensitive skin.[4]

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POMEGRANATE

Scientific name: *Punica granatum* L.
Family: Lythraceae
Parts used: Bark, leaves, fruit, seeds

Features

Deciduous shrub or small tree native to Asia Minor, but now widespread in the Mediterranean region, Africa, southern Asia, South America, and Australia. Leaves are opposite, entire, and oval-lanceolate. Flowers have five to eight bright red petals and numerous stamens. The fruit is an apple-sized, round, yellowish-reddish, false berry, 6–12 cm in diameter, with a thick, bright red to brown skin. The interior of the fruit consists of a white, spongy tissue and of locules delimited by membranes. The locules host hundreds of seeds, each surrounded by a red, edible pulp called aril.

Due to the number of bright red seeds contained within the fruit, the pomegranate has become a symbol of fertility and wealth. The plant is cultivated for its fruit, but also as a park and garden plant. Fruits can be eaten fresh or used for making jam, juice, or syrup.[32]

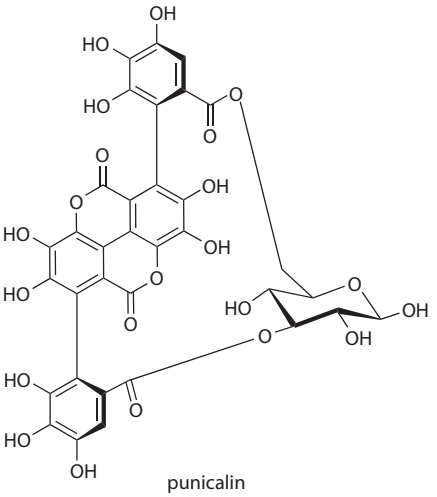
A tannic yellow dye can be extracted from the fruit skin. The dye has been used since ancient times, as evidenced by its presence in Egyptian tombs, and is still used in Asia Minor to stain tapestries and hairs.

FIGURE 4.42 Pomegranate. (See color insert following page 40.)

Constituents

The fruit contains abundant fructose, glucose, pectins, proteins, and vitamin C.[7] The most abundant minerals are potassium, sodium, calcium, and magnesium, while the main trace elements are manganese, copper, iron, zinc, lead, and cadmium. Tannins (gallotannins) are scarcely abundant in the edible portion, but represent about 10% of the fruit peel, consisting mainly of granatin, punicalin, and punicalagin.[12,35] The fruit peel also contains ellagic acid and flavonoids like quercetin and luteolin.[37] Tannins (e.g., punicalagin) and piperidinic alkaloids (pelletierine and pseudopelletierine) are present in branches and root bark.[30]

The seed endosperm yields an oil consisting of fatty acids, mono-, di-, and triglycerides. The main fatty acid of the oil is punicic acid (up to 70%), a conjugated trienic isomer of linolenic acid. Other constituents of the oil are the diunsaturated linoleic acid and the monounsaturated oleic and palmitoleic acids, while the saturated palmitic and stearic acids represent minor components.[10] The oil also contains phytosterols, such as campesterol, stigmasterol, β-sitosterol, γ-tocopherol, and 17α-estradiol.



punicalin

Properties

Pomegranate has great importance as a medicinal plant.[2,16,22,34] In various traditional medicines it is used as a remedy against infections due to parasites like the tapeworm and other cestodes. The pelletierines contained in the bark can act similarly to strychnine, by inducing a progressive contraction of the worm musculature that can reach tetanic spasm and cause the death of the parasite. The plant is also traditionally used as an astringent in the treatment of dysenteria and diarrhea. This latter property is due to the tannins present in high amounts in the bark, leaves, and fruit peel. Tannins are also abundantly contained in the flower extract, to which they confer antioxidant and hepatoprotective properties.[18,26]

In vitro studies on microglial cells preincubated with a fruit extract and stimulated with bacterial lipopolysaccharides have shown a lowering of the production

of pro-inflammatory interleukines, thus confirming anti-inflammatory properties.[15] The fruit extract can be used in the treatment of viral disorders and has shown the ability to reduce the infective potential of HIV.[31,33]

Ellagic acid and punicalagin have been shown to inhibit the enzyme β-secretase (BACE1), which is responsible for the formation of the β42 amyloid peptide involved in the pathogenesis of Alzheimer's.[21]

In Unani medicine, which is practiced in India, besides Ayurveda, abortive flowers (gulnar farsi) are used against diabetes. It has been shown that the extract of these flowers induces an improvement of glycemia in diabetic mice, while ellagic acid seems to be responsible for this effect.[4] It has also been assessed that the mechanism of action consists of a double activation of PPAR-α and PPAR-γ (peroxisome proliferator-activated receptor), which are known for their regulatory activity on lipid metabolism and for their ability to stimulate cell sensitivity to insulin.[11,23] The diabetic condition could also be alleviated by the ability of the flower extract to inhibit the enzyme α-glucosidase in the gut, thus reducing the levels of postprandial glycemia.[14,24]

Another important compound for the treatment of diabetes and obesity is punicic acid. Experiments carried out on obese rats have shown the ability of punicic acid to counteract weight increase.[4] These studies have also shown that ingested punicic acid is converted into rumeic acid, a typical compound of ruminants and diary products having remarkable antitumor properties.

In chondrocytes stimulated with interleukin 1β, the fruit extract inhibits the production of metalloproteinases and the activation of the p38 MAP kinase and NFkB, which are involved in metalloproteinase activation.[3]

The antimicrobial activity of various extracts has been ascertained by using different *Candida albicans* strains.[28] The fruit tannin punicalagin has shown antimicrobial activity against a strain of *Staphylococcus aureus* that is resistant to methicillin.[25,29]

Flavonoids and ellagic acid have been studied for their antitumor properties.[6,38] These compounds have shown antiproliferative, anti-invasive, and proapoptotic properties on breast and prostate cancer cells and lung carcinoma cells.[20] The treatment of A549 lung carcinoma cells with a fruit extract has inhibited the activation of MAP kinases, NFkB, and the PI3K/Akt pathway, and has also induced the arrest of cells at the G0/G1 phase of the cell cycle. The oral administration of the extract to athymic nude mice implanted with A549 cells has significantly inhibited the progression of the tumor, possibly through the inhibition of the above cellular factors and of the mTOR kinase, the target of the chemotherapeutic drug rapamycin. Other studies have shown the induction by flavonoids of leukemia cell differentiation, indicating their possible use in therapeutic strategies aimed at inducing cancer cells to differentiate into their nontransformed counterpart.[19]

Dermatologic and Cosmetic Use

Various cosmetic products contain fruit extracts or seed oil.[27] The fruit is used as an antioxidant due to the abundant polyphenolic fraction. The oil is used as a skin hydrating, antiwrinkle, and softener product.

It has been shown that the water extract of the fruit peel inhibits the expression of metalloproteinase 1 and induces the production of collagen type I in dermal fibroblasts, while it does not seem to exert relevant effects on keratinocytes.[5] Conversely, the oil stimulates keratinocyte proliferation but has a scarce effect on fibroblasts. It therefore seems that the dermal and epidermal effects of the plant reside in distinct fractions. Their combination could induce optimal skin regeneration and antiage effects, comparable to those induced by highly active compounds like retinoids.

It has been found that *in vitro* pre-treatment of HaCaT keratinocytes with a fruit polyphenol extract has protected these cells from UV-B damage, by preventing the reduction of viability, the lowering of intracellular glutathione, and lipid peroxidation.[1,36] The fruit extract has also inhibited the activation of metalloproteinases 1, 2, 7, and 9; the decrease of the MMP inhibitor TIMP-1; and the phosphorylation of MAP kinases and of the transcription factor c-jun.

Ellagic acid shows depigmenting properties that can be useful in the treatment of hyperpigmentations.[13,17]

Side Effects and Toxicity

The extracts generally do not induce negative effects if used at proper doses, although some risk could derive from the presence of piperidinic alkaloids.[39] Cases of food allergy due to fruit ingestion have also been reported.[8,9]

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PURPLE TEPHROSIA

Scientific name: *Tephrosia purpurea* (L.) Pers.
Family: Leguminosae
Parts used: Seeds, roots

Features

A many branched, erect, perennial herb, with a more or less hairy stem, growing to a height of up to 1.5 m. Leaves are imparipinnate, 5–15 cm long, with 9–21 leaflets, narrow, oblanceolate, glabrous above and silky below. Flowers are reddish purple, grouped in leaf-opposed racemes. The fruits are slightly recurved pods, glabrous or softly pubescent, containing 5–10 greenish grey, smooth seeds.

The plant originated from tropical Asia, but is now widely distributed all over the tropical zone. It grows wild as a common wasteland weed, and in many parts is under cultivation as a green manure crop.

Constituents

The main active principles are flavonoids like rutin, which is particularly abundant in the leaves; isoflavones; and rotenoids, such as rotenone, deguelin, and tephrosin.[1,3,4,10]

Properties

The plant has been used traditionally as folk medicine. It is used in Ayurveda for diseases affecting the heart, intestine, spleen, and bronchi. It is also a diuretic, tonic, and laxative, and a remedy against the obstruction of liver, spleen, and kidneys.[8] The roots are used as a vermifuge.

Clinical tests have shown that the plant improves the function of the liver in viral hepatitis and cirrhosis.[9] Accordingly, preclinical studies have shown that the plant extract has antioxidant properties and promotes liver tissue regeneration. Similar effects have been observed in other organs, such as the kidney.[12]

The ethanolic extract has shown antileishmanial properties in animal models.[16] It has also shown wound healing properties in the rat, with an increase in the presence of fibroblasts and collagen fibers, and the promotion of angiogenesis in the wounded area.[13]

The flavonoid fraction of the extract has been found to modulate the cellular and humoral components of the immune system in the mouse.[5] The flavonoid rutin acts against capillary weakness and hypertension.

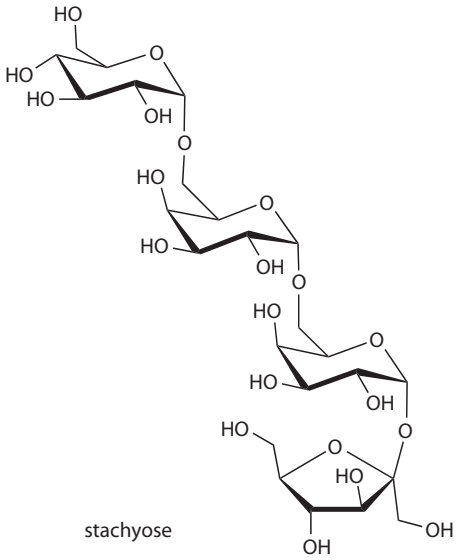
The plant is also known as an insecticide and fish poison.[18] In various tropical countries it is used for fishing, since it is able to stun fishes without seriously affecting mammals.[19] The toxic properties of the plant are due to rotenoids, like rotenone, which are able to block cellular respiration through the inhibition of the mitochondrial enzyme NADH-dehydrogenase.[20]

Dermatologic and Cosmetic Use

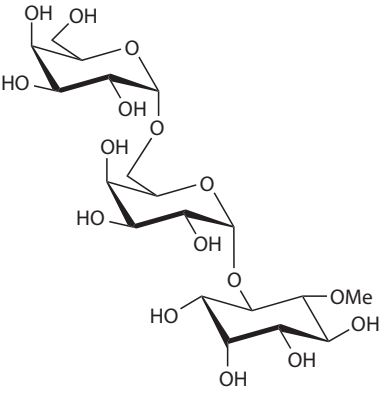
The seed extract is used as a neurocosmetic, since it can influence the nervous system through an action exerted on the skin.[6] The extract acts on keratinocytes by stimulating the release of β-endorphins, thereby inducing a general feeling of comfort and relaxation. β-Endorphins promote the relaxation of subcutaneous muscles, thus reducing wrinkle formation. Laboratory studies have shown that the neurocosmetic properties of the plant are due to the presence of two oligosaccharides, stachyose and ciceritol, which induce β-endorphin release.

Various plant extracts inhibit the development of tumors induced by phorbol esters in mouse skin and by 7,12-dimethylbenz(a)anthracene in hamster buccal mucosa, ensuring a good recovery of the levels of glutathione, glutathione-S-transferase, glutathione reductase, and catalase.[11,14,15]

Because of its cosmetic properties, the seed extract is used in various skin care products, such as lotions, massage ointments, and antistress, antiage, and after-sun creams.[2]



stachyose



ciceritol

Side Effects and Toxicity

No cases of allergy to the plant have been reported, while the ethanol extract is known to inhibit allergic reactions.[7]

Rotenoids are toxic compounds, and they must therefore be used with caution.[17] Rotenone is moderately toxic to humans, with an estimated lethal oral dose of 300–500 mg/kg. Fatal intoxication by ingestion is very rare, since the compound is sold in the market in low concentrations, and moreover its irritating action stimulates vomit. Local acute effects can include conjunctivitis, dermatitis, laryngitis, and congestion. Inhalation of high rotenoid amounts can induce breathlessness and convulsions.

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ROSA MOSQUETA

Scientific name: *Rosa* aff. *rubiginosa, (*syn. *Rosa canina* L.)
Family: Rosaceae
Parts used: Flower, fruit

Features

Rosa mosqueta is the common name used for at least three species: *Rosa* aff. *rubiginosa*, the main representative, *Rosa canina* and *Rosa moschata*.[3] *Rosa rubiginosa* is a bush with single, white, or pale yellow flowers and intensely red fruits. The species is native to Europe, but is naturalized and widely distributed in South America.

The fruits are used to manufacture food products like juice and jams, which have a pleasant taste and are particularly rich in vitamin C.

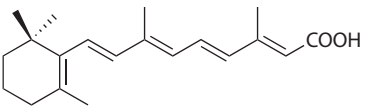
The seeds are used to obtain oil, and the annual seed production reaches a total of 20,000 tons, increasing the economic interest in this product.[12] The oil is produced mainly in Chile, and is marketed as an ingredient of cosmetic and pharmaceutical products.

FIGURE 4.43 Rosa x mosqueta. (See color insert following page 40.)

Constituents

The seeds contain about 8–10% oil, 0.3% essential oil, good levels of vitamin C, and proteins like glutelin 1, globulins, and albumins.[7,8,10] The oil is rich in polyunsaturated fatty acids (PUFAs), mainly linoleic (43–45%) and linolenic acid (34–37%), and also contains oleic, palmitic, stearic, and palmitoleic acids.[1,8,11] Other components include

antioxidants and pigments, such as all-*trans* retinoic acid; tocopherols; and carotenoids like β-carotene, lycopene, rubixanthin, gazaniaxanthin, β-cryptoxanthin, and zeaxanthin.[4,5] Minor quantities of violaxanthin, antheraxanthin, and γ-carotene are also present.



retinoic acid (tretinoin)

Properties

The fruit's rind has a high vitamin and mineral content and constitutes a good product for convalescence conditions. It also has refreshing and febrifuge properties, and can be used to prevent colds, due to its great amount of vitamin C. The presence of pectin, having a laxative action, helps in normalizing the intestinal function. The polyunsaturated fatty acids of the oil are essential to the human organisms. Linoleic and linolenic acids are important components of cell membranes and precursors of physiological mediators such as prostaglandins and leukotrienes.

Dermatologic and Cosmetic Use

The oil is suitable to treat skin ulcers, wrinkles, roughness, and hyperpigmentation.[9] Due to the presence of PUFA and all-*trans* retinoic acid, it is considered an important defense against skin aging, particularly if combined with borage (*Borago officinalis*) and black currant (*Ribes nigrum*).

The oil is also an excellent remedy against skin damage induced by excessive sun irradiation (photoaging). A product approved by U.S. FDA for the topical treatment of photodamage is tretinoin (all-*trans* retinoic acid). However, synthetic tretinoin can induce noxious effects and has to be used under medical surveillance. It has been shown in different studies that the oil of rosa mosqueta produces the same beneficial effects of synthetic tretinoin.[2] Moreover, the oil produces no undesirable effects, possibly due to a slow release of all-*trans* retinoic acid from the lipid mixture, which would avoid overdose problems. In addition, all-*trans* retinoic acid has been found to suppress matrix metalloproteinase activity and to increase collagen synthesis in diabetic human skin in organ culture.[6]

Side Effects and Toxicity

No undesirable effects are known for the oil.

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ROSEMARY

Scientific name: *Rosmarinus officinalis* L.
Family: Lamiaceae
Parts used: Leaves, twigs, flowering apices

Features

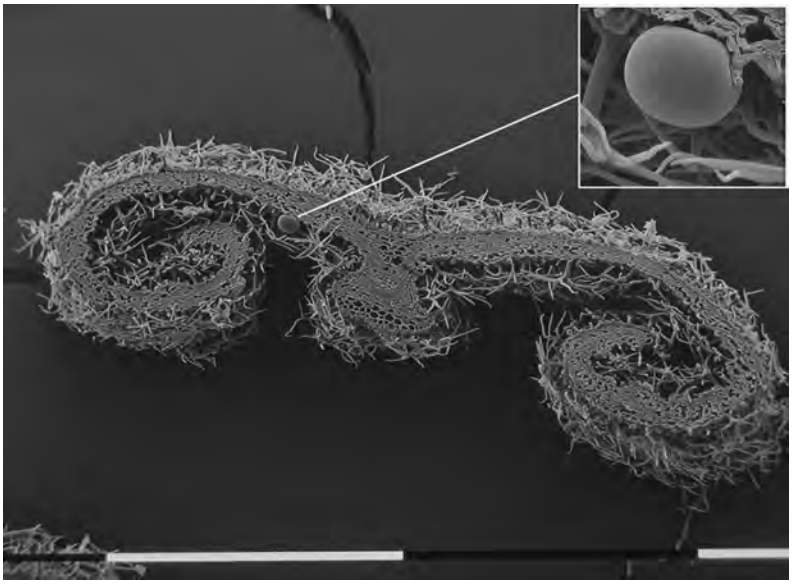
Evergreen shrub growing to a height of 1–2 m, commonly distributed, both wild and cultivated, from the Mediterranean region to Asia. The twig apices bear bluish labiate flowers grouped to form tomentose inflorescences. The leaves are opposite, 15–40 mm long, linear, coriaceous, and entire. Their lower surface is made grey and wooly by branched trichomes.

The medicinal properties of the plant were already known in ancient times, when the plant was also loaded with symbols. It was sacred to Egyptians, Jews, Greeks, and Romans, and in the Middle Ages it was cultivated in home gardens to keep evil ghosts and plagues away. In the past it was used as an ornament in weddings, funerals, feasts, and magic rituals, and was burned during religious ceremonies as a substitute for the more expensive frankincense. It was also burned in hospitals during pestilences, and used to scent beer and wine.[23]

Today the plant is used in cooking because of its aromatic properties, and to preserve food products due to the high content in antioxidants.

(A)

FIGURE 4.44 (A) Rosemary. (See color insert following page 40.)



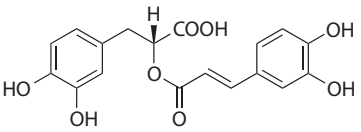
(B)

FIGURE 4.44 (B) Scanning electron micrograph of a leaf transversal section, and inset showing a glandular trichome. Bar = 100 μm.

Constituents

The plant contains various antioxidant polyphenols, mainly phenolic diterpenoids (carnosic acid, carnosol, and 12-O-methylcarnosic acid), caffeol derivatives like rosmarinic acid (an ester of caffeic acid and 3,4-dihydroxyphenylacetic acid), and flavones (isoscutellarein 7-O-glucoside and genkwanin).[7,14,17,19,20]

An essential oil is extracted from the twigs and flowering apices by steam distillation. This oil is transparent, has a low viscosity, and is mainly constituted by mono- and bicyclic terpenoids, such as pinene, borneol, camphor, bornyl acetate, camphene, 1,8-cineol (eucalyptol), and limonene.[4,6,22]



Rosmarinic acid

Properties

The plant has a very long tradition as a medicinal herb.[5] Hungary water is an infusion of flowering apices and wine that was allegedly formulated by Queen Elisabeth of Hungary in the eleventh century. The wine can be used as a cordial for palpitations, to stimulate kidney function, or as a remedy against headache caused by insufficient

circulation. A steamy infusion of flowering apices is a good remedy for colic, colds, and nervous depression.

The essential oil has several therapeutic properties.[1] It is an analgesic, antidepressant, astringent, carminative, stomachic, cholagogue, diuretic, stimulant, and tonic (nerve and general). It has a marked action on the nervous system, by reducing mental fatigue and stimulating memory. It is moreover a good anti-inflammatory, and can be used for headache, migraine, neuralgia, intestinal infections, colitis, diarrhea, liver dysfunction, rheumatisms, arthritis, muscle pain, and gout. It is also useful for vascular disorders such as atherosclerosis and varicose veins. Its diuretic and tissue draining properties reduce water retention.[11] The essential oil protects the respiratory system against asthma, bronchitis, cough, and catarrh.[2] It has antimicrobial properties against gram-positive and -negative bacteria and also has weak antifungal properties against pathogen strains.

Various studies have disclosed the properties of specific plants' compounds. Carnosic and rosmarinic acids and carnosol strengthen nerves, and have also been found to protect human lymphocytes against chromosome damage caused by radiations. In fibroblasts cultivated *in vitro*, diterpenoids like carnosol, rosmanol, and carnosic acids promote the expression of the enzyme γ-glutamylcysteine synthase, a limiting factor in the synthesis of the antioxidant compound gluthatione, and of the antioxidant enzymes superoxide dismutase and catalase.[12] In the same cells, carnosic acid prevents oxidative processes induced by exposure to hydrogen peroxide. These data suggest that the plant's diterpenoids can induce a physiological antioxidant response that renders cells more resistant to oxidative stress.[15] Rosmarinic acid has antiviral, antibacterial, anti-inflammatory, and antioxidant properties.[16]

Dermatologic and Cosmetic Use

Rosmarinic acid is an ingredient of various cosmetic formulations and perfumes, like, for instance, the well-known Eau de Cologne.[8,9,18] This compound is used for massage diluted in almond oil, and exerts a beneficial relaxing effect on muscles and nerves. It also improves the skin circulation, and therefore acts positively on congestion, swelling, and cellulite.[16] Because of its antimicrobial activity, it can be used for acne and other skin infections.

Rosmarinic acid is regularly used against hair loss, since it promotes blood circulation and consequently hair growth. However, it has been shown that the plant's extract protects hairs from external injurious agents also due to its antioxidant properties.[21] The plant is therefore useful against various hair and scalp disorders, such as early baldness or dandruff, and is frequently used as a component of shampoos and lotions.

Carnosic acid inhibits the expression of the tyrosinase gene, thus having an antimelanization effect.[13]

Side Effects and Toxicity

The essential oil should not be used during pregnancy or by people affected by epilepsy or hypertension. It is known that various essential oils contain neurotoxins that can induce convulsions. The plant can be the cause of contact dermatitis.[3,10]

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ROUND-HEAD BUSH CLOVER

Scientific name: *Lespedeza capitata* Michx.
Family: Leguminosae
Parts used: Leaves

Features

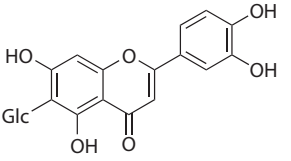
The genus *Lespedeza* was originally described by the botanist Vincent Manuel de Cespedes, Spanish governor of Florida at the end of the eighteenth century, whose name was probably mangled into "de Lespedez" by the publisher of the volume *Flora Borealis Americana*. This genus includes 152 species distributed in the eastern part of North America and in western and southern Asia.

L. capitata is a perennial shrub with hairy, thin, erect, or ascendent stems, which can reach a height of 60–100 cm. Leaves are pinnate with three leaflets, similar to clover. Flowers are white or dark in color and form terminal capitate heads. Fruits are short monosperm legumes.

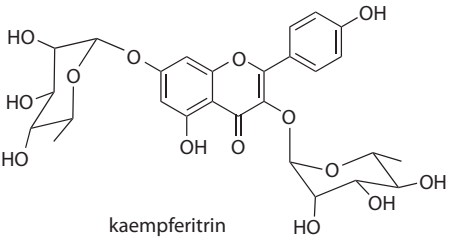
The plant is common in meadows and sparse woods. The seeds are used as food for aviary birds, while the dried plant is used as forage for livestock or for decorative purposes.

Constituents

The plant is rich in flavonoids (about 0.1% wet weight) and tannins, which are particularly abundant in young leaves.[1,3,7,13] A prominent flavonoid is lespecapitoside, a C-glycoside also known as homorientin. The binding of the sugar moiety to a carbon atom, instead of to an oxygen atom, confers to this compound a particular resistance to hydrolysis, allowing a more durable maintenance of biological effects in therapeutic uses. Another important flavonoid is the dirhamnosylflavonol lespedin, also known as kaempferitrin (kaempferol 3,7-dirhamnoside).[5,10] The leaves also contain other di-C-glycosylflavones, including shaftoside, carlinoside, and their derivatives, such as the uncommon isocarlinoside (1,6-C-α-L-arabinopyranosyl-8-C-β-D-glucopyranosyl-luteolin).[8]



lespecapitoside



kaempferitrin

Properties

The plant is mainly known for its effects on the kidney. Its use as a diuretic dates back to the traditions of Native American people who prepared a medicinal tea from

leaves. In North America the roots were also anciently used as an antidote against poisonings, while the stems were a remedy against rheumatisms. In the 1800s the plant was officially prescribed for nephritis in the United States, while it had been included for centuries in the traditional pharmacopoeia as a remedy for kidney diseases. In traditional Japanese medicine the plant was also known as a remedy against acute kidney insufficiency.

The diuretic effect of the plant has been assessed by scientific studies.[14] It has been shown that the plant promotes the renal excretion of urea and chloride anions, while the excretion of PO_3^-, HCO_3^-, NH_4^+, Na^+, and K^+ is not significantly affected. Kaempferitrin protects the kidney tissue against the noxious effects of nephritis, thus decreasing the presence of blood in urine.[15] In addition, this compound exerts an insulin-like effect, and is therefore able to correct blood glucose excess in diabetic patients and to promote glucose uptake by muscle cells in healthy subjects.[6]

The plant also induces hypoazotemic and hypocholesterolemic effects, mostly due to the presence of homorientin. This glycoside is also able to protect blood vessel walls against lipid infiltration, thus preventing the atherosclerosis syndrome.

The presence of a dimeric procyanidin induces a hypotensive action, due to the inhibition of the angiotensin I converting enzyme (ACE), resulting in a hindrance to the formation of the vasoactive hormone angiotensin II.[2,4,12]

Dermatologic and Cosmetic Use

The plant's flavonoids exert a free radical scavenging activity that protects collagen from the degradative processes induced by chronoaging and UV exposure. The plant extracts are therefore commonly included in antiage products.[9] Moreover, due to their draining and antiedematous activity, flavonoids are useful for combatting unaesthetisms of cellulite-like orange peel.[11]

Side Effects and Toxicity

Clinical studies have reported no toxic effect caused by plant extracts, showing fair tolerance limits. No contraindication exists at normal doses, except for specific cases of hypersensitivity. Gastric irritation and diarrhea can occur at excessive doses.

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SACHA INCHI

Scientific name: *Plukenetia volubilis* L.
Family: Euphorbiaceae
Parts used: Seeds
Other names: Inca peanut

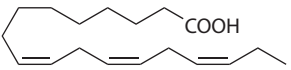
Features

Perennial vine growing in rain forests of Central and South America, notably the Amazon forest, up to an elevation of 1,700 m a.s.l. Leaves are alternate, heart shaped, and serrate. Inflorescences are formed by male flowers grouped in racemes and two female flowers located at the base. The fruits are capsules of 3–5 cm in diameter, with four to seven lobes, from green when immature to blackish brown at ripening, containing oval, dark brown seeds.

The plant has been cultivated since the pre-Inca age, about 3,000 years ago, and its importance in ancient times is evidenced by depictions on vessels found in Inca tombs. It continues to be an important food source for South American people. For instance, toasted seeds and cooked leaves are components of the diet of Chancas Indians. It is currently at the center of environmental and food projects aimed at a sustainable requalification of the Amazon forest and at providing economic sustainability to native populations.

Constituents

The plant has high oil (about 54%) and protein (about 30%) contents. The protein fraction is particularly rich in essential amino acids, viz., cysteine, tyrosine, threonine, and tryptophan, and is comparable to that of soy.[4] The oil fraction is the richest natural source of unsaturated fatty acids known so far.[3] It contains high levels of vitamins A and E. The most abundant fatty acids are the ω-3 α-linolenic (up to more than 50%) and the ω-6 linoleic (38%) acids, while fractions of ω-9 (9%) and saturated (6%) fatty acids are also present.[2] Iodine is particularly abundant among mineral salts.



α-linolenic acid (ω-3)

Properties

The seeds have a high nutritional value due to the presence of amino acids and essential fatty acids. They are particularly suitable for the diets of children and older people.

The omega fatty acids of the oil are an excellent dietary component for the control of blood cholesterol levels.

Dermatologic and Cosmetic Use

The oil has emollient properties, prevents water loss, particularly from irritated skin, and ensures skin rehydration.[1,5] It is therefore indicated for dry skins with atopic tendency, and is also used for rejuvenating treatments and wound care.

The two major oil constituents, α-linolenic and linoleic acids, are important components of cell membrane phospholipids and are effective in the reconstitution of the epidermal barrier. These fatty acids are prostaglandin precursors and can promote wound healing and keratinization processes.

Seed extracts containing albumin-like proteins confer elasticity to the skin and have anti-inflammatory and antiaging effects.[6]

Side Effects and Toxicity

No topical or food-related allergies can be attributed to the oil.

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SAUSAGE TREE

Scientific name: *Kigelia africana* (Lam.) Benth. (syn. *Kigelia pinnata* (Jacq.) DC.)
Family: Bignoniaceae
Parts used: Bark, leaves, fruits

Features

This species is distributed in the tropical belt of Africa. It is a tree growing up to 20 m that behaves like an evergreen in the rain forest and as a deciduous plant in regions where the climate includes a dry season.[17] Leaves are pinnate, 30–50 cm long, with 6–10 leaflets. Flowers and fruits are hanging from branches, and have thin, flexible petioles, which in the fruit can reach the amazing length of 2–6 m. Flowers open from August to November and are grouped in panicles. They are campanulate, about 10 cm in diameter, and orange, reddish, or purple-green in color. Flowers are visited by bats, birds, and insects, probably having a role in pollination. The fruit is a woody berry, 30–100 cm long, and can reach a weight of up to 5–10 kg.

FIGURE 4.45 Sausage Tree.

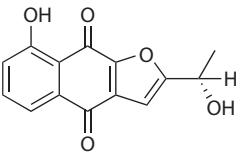
The common name of the tree is derived from the sausage-like fruits dangling from branches. Fruits are barely edible to humans, but are consumed by large African mammals and by insects.

Constituents

The Bignoniaceae family is characterized by the presence of iridoids and naphthoquinones. Iridoids (catalpol, specioside, verminoside, norviburtinal) have been isolated from different parts of the plant, either in free form or esterified with phenylpropanoids and their glycosides.[11,12,15] Other constituents include furanonaphthoquinones (kigelinone); monoterpenoid naphthoquinones (pinnatal, kigelinol), which are typical of this species; dihydroisocoumarins (kigelin); and in addition flavonoids, lignans, and triterpenes.[1,10,13,24]

Essential oils are also present in the leaves and fruits.[3] Polar extracts of the fruit and bark contain different polyphenols, like verminoside, and moreover verbascoside, caffeic acid, p-coumaric acid, and their derivatives.

Roots and bark mainly contain the naphthoquinone lapachol and kigelin, while other constituents of the bark include phytosterols like stigmasterol and β-systosterol.[19]



kigelinone

Properties

The plant is used in the traditional medicines of various African countries, usually as an anti-inflammatory, antimicrobic, antiparasite, and for skin care. The fruit is used for ulcers, as a purgative, and to stimulate milk production in the new mother. The bark is used as a remedy for venereal diseases, stomach ailments, and for tropical diseases like bilharziosis. The leaf decoct is used for jaundice.[8,14,25]

Studies aimed at clarifying the mechanisms of action of the plant principles have found that leaf and bark extracts possess antimicrobial activities against gram-negative and gram-positive strains.[2,9,21] These properties can be attributed to iridoids, like norviburtinal; to the naphthoquinones isopinnatal, kigelinone, dehydro-α-lapachone, and lapachol; and to the phenylpropanoids p-coumaric and ferulic acids. Some of these compounds are also responsible for the antibacterial and antifungal activities of the root bark, while caffeic acid and kigelinone confer antibacterial properties to the fruit.[5]

Iridoids and naphthoquinones, particularly norviburtinal, also show toxic effects against different parasitic protists. Amoebic dysentery is ubiquitary in tropical countries, rating as the second cause of death among parasitic diseases. Three known iridoids, viz., specioside, verminoside, and minecoside, isolated from the bark and root, have shown toxic activities to the agent of amoebic dysentery, the amoeba *Entamoeba*

histolytica.[4] Similar compounds, like isopinnatal and kigelinol, also isolated from the bark, have shown antiprotist activity against the parasites *Plasmodium falciparum*, the agent of malaria, and *Trypanosoma brucei*, the agent of sleeping sickness.[23,30] Molluscicidal activities have also been reported.[20]

Verminoside could be responsible for anti-inflammatory properties.[26] In macrophages stimulated *in vitro* with bacterial lipopolysaccharides, this compound inhibits the inducible form of the enzyme NO synthase, and the release of nitric oxide (NO), a compound involved in the process of inflammation. However, the anti-inflammatory properties of the plant could also derive from compounds present in the ethanol or ethanol-chloroform extracts of the fruit, which exert inhibitory effects on the inflammation-promoting enzymes cycloxygenases 1 and 2.

Compounds isolated from the bark, particularly lapachol, have shown antiproliferative activity to melanoma and renal carcinoma cell lines,[16] while norviburtinal and isopinnatal have exerted *in vitro* cytotoxicity to cancer cell lines.[18] The bark ethanolic extract is also able to inhibit the acetylcholinesterase enzyme, a property that is generally associated with the presence of alkaloids.

Dermatologic and Cosmetic Use

In traditional African medicine the fruits are used against eczema, psoriasis, and various skin irritations. The same properties are also exploited in Western countries for various dermatologic and cosmetic products.[27]

In certain African populations, women grind the fruit to a poultice, which is then spread on the breast to improve its firmness. The fruit active principles are known to induce a firming effect on the dermis and its musculature. Such an effect would be due to isoflavones and steroid saponosides present in the fruit. Isoflavones are phytoestrogens acting on tissues in a way similar to that of human estrogens. Saponosides induce skin drainage and exert a restitutive effect, thus restoring the elasticity and firmness of the dermis.

The mechanisms of these effects have not yet been fully clarified; however, it is known that steroid hormones can inhibit matrix metalloproteinases, the main agents of extracellular matrix degradation. In particular, it has been shown that 17-β-estradiol inhibits the expression of metalloproteinases 1, 2, and 9 in fibroblasts.[22] Hence, the plant could produce its effects, at least in part, through a protective action of its phytosteroids on skin matrix fibers.

Side Effects and Toxicity

Cases of intolerance to the plant have not been reported. The only notable element is the presence in the bark of lapachol, which is known to cause contact dermatitis.[28]

A specific point of concern arises from the use of the plant for breast treatments. It is known that estrogens are a risk factor for breast cancer in women. Studies have also been carried out on the role of phytoestrogens like isoflavones in the induction of breast cancer, although conclusive results have not been found yet.[29] The phytoestrogens that have been examined in these studies, e.g., the soy isoflavone genistein, usually do not increase the risk of breast cancer, while in some cases they

can even reduce it.[6,7] However, phytoestrogens from different botanical sources show a wide range in the magnitude of their pseudohormonal effects. Moreover, other factors can contribute to the variability of these effects. Phytoestrogens can induce different effects in pre- and postmenopausal women, while it is also known that the level of estrogens tends to increase in smokers or overweight women. Hence, even though various studies indicate a protective effect of phytoestrogens against breast cancer, care should be observed in the use of phytoestrogens by women who take anticontraceptives, or undergo postmenopausal treatments and antitumor therapies based on drugs like tamoxifen.

Leaving aside these latter cases, the use of phytoestrogens in skin and body care, or in the absence of medical advice, should always be carried out with compounds that are less powerful than human estrogens, and at doses comparable to those found in food plants.

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SAVORY

Scientific name: *Satureja hortensis* L., *S. montana* L.
Family: Lamiaceae
Parts used: Flowering apices (*S. hortensis*), aerial portions (*S. montana*)

Features

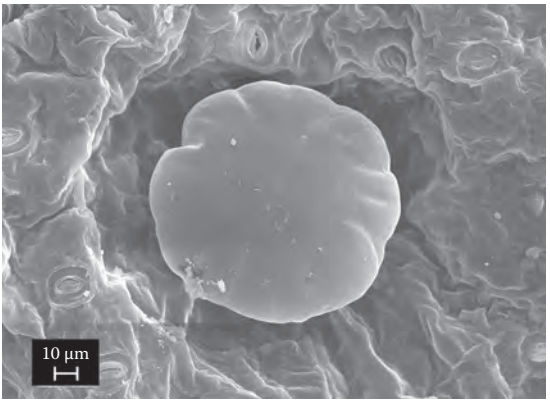
Annual (*S. hortensis*) or perennial (*S. montana*) herbaceous plant, growing to 10 to 40 cm in height, with a heavily branched stem. The leaves are crossed opposite, up to 3 cm long, lanceolate, and entire-marginate. The flowers are small, whitish, and grouped in axillary false whorls.

These plants are native to the Mediterranean region and grow in sunny, dry places. *S. hortensis* is distributed in the European continent and is widely cultivated. *S. montana* grows wild from North Africa to Russia and is rarely cultivated. Both species are collected two or three times a year, and the aerial parts are dried before use.

The Romans introduced savory in England, where it became popular as a medicinal and culinary plant. It has been used since the Middle Ages for its therapeutic properties and is very popular in the traditional medicines of Europe and Asia Minor. Due to their pungent aroma and spicy taste, these plants are used in cooking, the liquor industry, and perfumery, particularly *S. hortensis*, which has a relatively milder taste. The culinary use of the plant improves food digestion.

(A)

FIGURE 4.46 (A) Savory. (See color insert following page 40.)



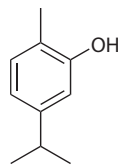
(B)

FIGURE 4.46 (B) Scanning electron micrograph of a glandular trichome on the leaf lower surface.

Constituents

The most abundant constituents are tannins; phenols; the fatty acids linoleic, linolenic, and stearic acids; sterols like β-sitosterol; triterpenes like ursolic acid; and polyphenols like rosmarinic acid.[3,12,15,23,25]

An essential oil is produced by secretory glands present in the leaves and inflorescences (1% in *S. hortensis*, 1.6% in *S. montana*).[17] The oil composition is different in the two species, and can vary with the season. More than 20 compounds can be identified in the oil, of which the most abundant are carvacrol (from 14 to 51% in *S. hortensis*), thymol (up to 46% in some *S. hortensis* chemotypes), γ-terpinene, and p-cymene.[5,6,9]



carvacrol

Properties

The plant has been reputed since ancient times for its aphrodisiac properties. This is accounted for by the genus name *Satureja*, meaning "satyr herb." In modern medicine, the plant has been shown to stimulate the brain and the corticoadrenal gland. It is also known as an antimicrobial, disinfectant, antispasmodic, antidiarrhetic, carminative, digestive, and tonic.[11,18,21] These properties have been ascribed to the plant because of its traditional uses, but in most cases they have not been verified in clinical trials. Moreover, in traditional medicine the plant is used to heal ulcers and wounds, owing to its cicatrizing properties. Because of its antibacterial activity, it is also suitable for infectious diseases of the respiratory tract.[24]

The total extract or its fractions containing phenols and tannins have a strong antioxidant power, as shown by *in vitro* experiments.[14,20] These properties may have a role in the traditional use of the plant as an analgesic and anti-inflammatory for muscle pain and arthritis.[10]

Different therapeutic properties are due to the essential oil. It has been experimentally shown that the oil activates the muscarinic acetylcholine receptor, thereby lowering intestinal muscle contraction and producing a spasmolytic effect. The whole oil and its component carvacrol have shown antimicrobial, fungicidal, and antioxidant properties.[1,7,16] An *in vitro* study on mammalian cells has shown that carvacrol can activate intracellular calcium and MAP kinases, hence revealing its ability to modify the cell's functional status.[4]

Dermatologic and Cosmetic Use

Both the extract and the essential oil are used in cosmetics. The essential oil can be used in aromatherapy, as an antibiotic for acne, and against psoriasis.[22] The oil is also a component of perfumes and soaps, although precautions have to be adopted for its dermatologic and cosmetic uses (see below).

The plant is traditionally macerated in water with other herbs, like lavender, St. John's-wort, rue, and rosemary, and then used for refreshing and tonifying baths with beneficial properties.[19]

Side Effects and Toxicity

The plant is considered safe for culinary uses. In contrast, the pure essential oil is caustic to the skin, but it induces no irritation if properly diluted.[13] Carvacrol, the main component of the oil, has shown a weak activity in mutagenicity studies, although a full toxicological screening is lacking. Methyleugenol is a terpenoid with recognized carcinogenic potential. Even though this compound is present in low amounts (less than 1%) in the essential oil of *S. montana*, the International Fragrance Association has set dose limits for the use of the oil in skin care, aromatherapy, and perfumery.[2,8]

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SHIITAKE

Scientific name: *Lentinula edodes* (Berk.) Pegler
Phylum: Basidiomycota (basidiomycete fungi)
Family: Tricholomataceae
Parts used: Fructiferous body
Other names: Oak mushroom

Features

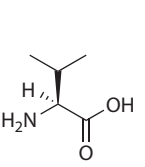
Wood-decaying, basidiomycete fungus, with delicious taste. The mycelium, formed by filamentous structures called hyphae, grows inside the wood of different trees, which is degraded by fungal enzymes such as manganese peroxidases and laccases for lignin, and cellulases for cellulose.[17] The fructiferous body of the mushroom develops at the surface of the wood in which the fungus is growing. It has a brown, convex cap, 12–15 cm in diameter, with white crevices. The stipe is bare, and the hymenium, developing on the underside of the cap, is formed by numerous gills bearing the spores.

The fungal species is native to eastern Asia, and has been grown in Japan and China since prehistoric times. The Japanese name *shiitake*, meaning "shii mushroom," accounts for the name of the oak tree that provides the dead logs on which the fungus is cultivated. In the 1970s its cultivation spread to Western countries, and it is currently one of the most consumed mushrooms in the world.[23,24]

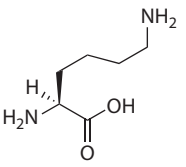
It has various culinary uses in Japanese and Chinese cuisines, but is also appreciated in many other countries for its characteristic aroma and taste.

Constituents

The mushroom contains the essential amino acids isoleucine, leucine, lysine, methionine, phenylalanine, threonine, and valine. The mineral fraction is constituted of 97–98% potassium, phosphorous, calcium, and magnesium.[30] Other important constituents are group B vitamins, such as thiamine, riboflavin, and niacin; terpenoids; steroids; phenols; and nucleotides. The main active principles include the (1–3)-β-D-glucan polysaccharide lentinan, the nonproteic amino acid eritadenine, a derivative of adenine, and the cyclic organosulfur compound lenthionin, which is similar to sulfur compounds of garlic and contributes to the typical aroma of the mushroom.[26] The lipid extract contains the steroid ergosterol.[6]



L-valine



L-lysine

Properties

The mushroom has a high nutritional value and has been known since antiquity for its medicinal properties. Many of these properties have been studied in laboratory and clinical researches, including antiviral, antibacterial, antitumor, immunostimulating, hypocholesterolemic, and hypoglycemic actions.[2,11–14]

The immunomodulatory effect of lentinan occurs through an increase of the complement factors C3 and C3b, and of various cytokines, like interleukin 1a, interleukin 1b, and TNF-α, and the stimulation of T lymphocytes and macrophages.[16,21] These properties also seem related to antitumor effects,[4] while fungal extracts have been found to inhibit the growth of cancer cells.[8,9] The inclusion of mushroom powder in the diet has stimulated the immune response and lowered the incidence of tumors in mice exposed to carcinogenic drugs.[15] Intraperitoneal injection of lentinan in mice has inhibited viral and chemical carcinogenesis, and strengthened the effect of chemotherapics.[3] The results of these studies in Japan have led to the use of lentinan in the clinical treatment of cancer.

Another consequence of the immunomodulatory effect of lentinan is the induction of resistance to viral and bacterial infections. A combination of lentinan and 3′-azido-3′-deoxythymidine (AZT) has been found to be more effective than AZT alone in repressing HIV replication in hematopoietic cells. The antiviral activity of lentinan seems related to the ability to stimulate interferon production. However, the compound has not yet been clinically tested in anti-HIV therapies.

Lenthionin has antibacterial and antifungal activities. It is also able to inhibit platelet aggregation, and its possible use in the treatment of thrombosis has been suggested.[28]

The fungus extract can lower blood cholesterol levels, thus preventing artery hardening and hypertension. The compound responsible for this effect is eritadenine, which can also lower blood homocysteine levels.[7]

Ergosterol, a main steroid of the fungus, is converted to vitamin D by UV rays during the process of mushroom drying. Vitamin D plays a fundamental role in the resistance of the organism to diseases, particularly cooling diseases, while it also exerts a repressive effect on breast and colon cancers.

The aminopolysaccharide chitin is a main component of the hyphal cell wall. This compound acts in the gut as a nondigested fiber, and seems to reduce cholesterol absorption.

Dermatologic and Cosmetic Use

The presence in the fungus of many essential amino acids stimulates the regeneration of skin tissue.[25] Moreover, the richness in glucans favors the maintenance of the proteoglycan component of the dermal matrix. Such a component binds ions that attract water by osmosis in the collagen fibrillar framework, thereby improving skin turgor and elasticity.

A fungal extract rich in oligosaccharides and uronic acids, used on cultures of human fibroblasts exposed to UV irradiation, has been reported to inhibit metalloproteinases 1 and 2, which degrade dermal matrix fibrils, and to increase the

production of TIMP-1, the tissue inhibitor of MMP-1.[22] The topical application of this extract to a group of volunteers has produced an improvement of the firmness and elasticity of the skin.

The lipid extract can be used to strengthen the skin-water barrier.

Side Effects and Toxicity

The mushroom is not toxic.[19] If ingested raw, however, it can induce food allergy in the form of an eczematous reaction known as shiitake dermatitis.[18,20] The mushroom can also cause contact dermatitis and asthma, particularly under occupational circumstances.[1,5,10,27,29]

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SOYBEAN

Scientific name: *Glycine max* (L.) Merr.
Family: Leguminosae
Parts used: Seeds

Features

Soybean, or soy, grows only under cultivation, while its congener *G. soja* grows wild in China, Japan, Korea, Taiwan, and Russia. It is an annual herbaceous plant indigenous to eastern Asia, which grows creeping on the ground or climbing. The aerial portions are thickly villous and the leaves are trifoliate, with leaflets ovate and entire-marginate. Leaves fall before fruit ripening. The flowers are small, white, pink, or purplish and are borne at the axils of leaves in three to eight clusters. The fruits are linear-oblong pods of about 10 cm, grouped in clusters of three to five and containing two to four pea-sized seeds.

The species is widely cultivated with different cultivars, some of which have been genetically engineered. It has been grown in Asia since prehistoric ages and was introduced to Western countries in the 1700s, and then to Africa.[19] It is currently one of the most important cultivations in the world. It is also important in agricultural practices because of its symbiotic relationships with soil bacteria, which form nodules on the roots and fix atmospheric nitrogen, a feature that is common to many legume plants.

Various food products are obtained from the plant's seeds, including a flour rich in proteins, oil, soy milk (used as an alternative to cow's milk in lactose intolerances), and soy sauce (which is produced by fermentation and is very popular in Eastern

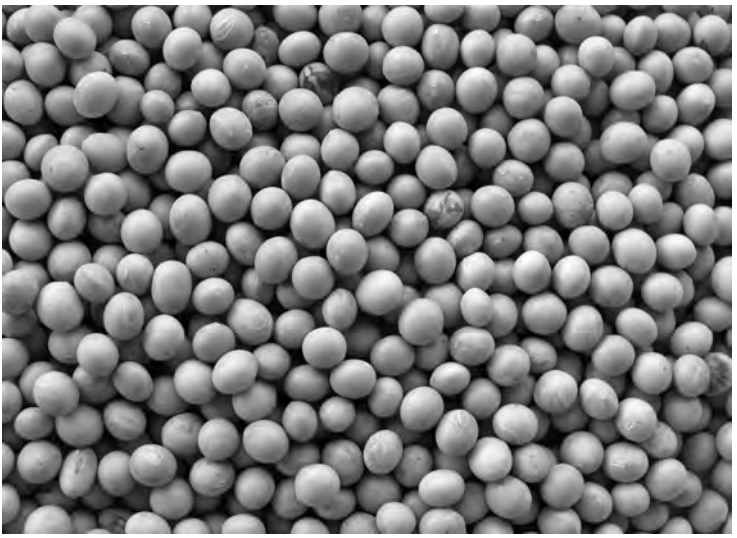


FIGURE 4.47 Soybean Seeds.

cooking).[38] The high protein content of the seeds allows food products having a nutritional value similar to that of meat to be obtained, such as soy bacon and hamburgers, which are very popular in North America.

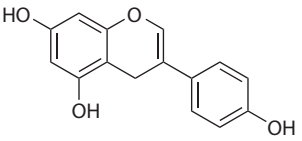
Constituents

Dry seeds consist of approximately 40% protein, 20% oil, and 35% carbohydrates. Main soluble sugars are sucrose, raffinose (sucrose + galactose), and stachyose (sucrose + galactose + galactose).[11] The fiber fraction includes insoluble carbohydrates like cellulose, hemicellulose, and pectin.

The oil extracted from seeds contains glycerides consisting of unsaturated fatty acids like linoleic, oleic, and linolenic acids, and saturated fatty acids like palmitic and stearic acids. The unsaponifiable fraction contains phytosterols like stigmasterol and sitosterol. An important constituent of the lipid fraction is lecithin, consisting of a mixture of phospholipids, of which the main ones are phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol.

The seeds contain isoflavones like genistein (4'5,7-trihydroxyisoflavone), daidzein, formononetin, and biocanin, and their glycosides, such as genistin and daidzin.[23,34] Other components are lignans, viz., matairesinol and secoisolariciresinol, and coumestans, mainly present in sprouts.

The seeds also contain bisdesmosidic saponins, having soyasapogenol A as aglycone (olean-12-en-3β,21β,22β,24-tetraol); monodesmosidic saponins, having soyasapogenol B and soyasapogenol E as aglycones (olean-12-en-3β,22β,24-triol and olean-12-en-3β,24-diol-22-one); and saponins conjugated to 2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP saponins).[77]



genistein (isoflavonoid)

Properties

Isoflavones, coumestans, and lignans have an affinity for estrogen receptors and are generally known as phytoestrogens.[64] Phytoestrogens bind preferentially to the estrogen receptor beta (ERβ), while physiological estrogens act mainly by binding to the estrogen receptor alpha (ERα). The mechanism of action of phytoestrogens seems therefore not completely overlapped with that of endogenous estrogens. This would explain the occurrence of both agonistic and antagonistic activities of phytoestrogens on estrogens.

Endogenous estrogens are used in the treatment of postmenopause syndrome. However, these treatments can increase the risk of breast and uterus cancer and of coronary disease. Hence, phytoestrogens have attracted much interest as alternative remedies against the problems of menopause.[14,32,33,42,47,60]

The soy is known to protect the bone from demineralization, while in clinical studies it has been shown that food rich in isoflavones can reduce menopause symptoms.[6,13,25,43] Long-term clinical studies on menopausal women have shown that soy isoflavones increase bone mineralization and reduce bone reabsorption.[3,10,44,62,67]

Studies carried out on rats have shown that genistein dietary intake reduces osteoporosis in trabecular bone tissue, prevents bone reduction, and increases the blood levels of osteocalcin and the number of osteoblasts in bone tissue.[5,9,50,58] Similarly to estradiol, genistein has been found to induce an increase of alkaline phosphatase in rat osteoblasts cultivated *in vitro.* Genistein has also inhibited the activity of chick osteoclasts that degrade the bone matrix by inhibiting their protein synthesis and acid secretion. Hence, genistein seems to stimulate the production of new bone tissue, instead of suppressing turnover like endogenous estrogens.[73]

Clinical studies have highlighted isoflavone effects on the gonads, consisting in a prolongation of the follicular phase of the menstrual cycle, a reduction of progesterone peaks in the luteal phase, and a reduction of LH and FSH production.[24,54] In animal experiments it has been observed that phytoestrogens cause a reduction of estrogen plasma levels, combined with an increase of sex hormone binding globulin (SHBG), a protein that regulates the concentration of circulating estrogens and protects organisms from the onset of breast cancer.[22] The estrogen decrease caused by isoflavones is also probably due to the inhibition of aromatase, the P450 enzyme that converts testosterone to 17-β-estradiol.

Isoflavones are also interesting for possible use in the prevention and treatment of cancer.[32,47,51,59,60,69] About 20% of scientific papers concerning genistein are addressed to the study of cancer, including phase I and II clinical trials. Studies of Asian, European, and American people have found an inverse correlation between the blood levels of genistein deriving from soy diet and the incidence of sex-related cancer, particularly prostate and breast cancer.[1,53] Genistein acts as an antitumor drug by inhibiting various cellular activities, like tyrosine kinases involved in cellular proliferation, topoisomerase II involved in DNA replication, and metalloproteinase 9 involved in tumor invasiveness, and the expression of different genes, including the vascular endothelial growth factor (VEGF) gene involved in angiogenesis.[2,21,29,55–57] Genistein can therefore contrast cell growth, proliferation, tissue invasion, and angiogenesis, which are essential processes for the development and progression of cancer.[16,17,75]

Despite a body of evidence on the tumor-protective effects of phytoestrogens, their use on women at high risk for breast cancer should be carefully evaluated for the possible occurrence of negative consequences.[12,15,37,66] *In vitro* studies have shown that genistein induces cell cycle arrest and apoptosis in prostate carcinoma cells. However, its real effectiveness at physiological doses has not been assessed. Genistein can act synergistically with chemotherapics like tamoxifen and cisplatin, and with radiotherapy. It can strengthen the calcitriol-induced inhibition of prostate cancer cell proliferation, occurring through a reduction in the levels of prostaglandin E2 (PGE2).[68] Such an effect of genistein is due to the inhibition of the calcitriol-degrading enzyme cytochrome CYP24. Moreover, genistein inhibits the enzyme COX-2, thereby inducing a reduction of PGE2 production. Phytoestrogens also inhibit the enzyme 5α-reductase, involved in androgen metabolism, whose

activity seems correlated with the occurrence of prostate cancer. A reduction of cholecystokinin and pancreatic polypeptide has also been observed in animals, suggesting a possible protection exerted by soybean against gastroenteric cancer.

The antitumor action of genistein can also be addressed to specific targets by conjugation to antibodies against antigens displayed by cancer cells, such as the overexpression of CD19 in leukemic B lymphocytes or the EGF receptor in other tumors. However, genistein has a biphasic activity on cells, consisting of inhibitory effects at higher concentrations and stimulatory effects at lower concentrations. Hence, therapeutic doses should be carefully determined.[66] Also, despite experimental data concerning the effects of soy and its phytoestrogens on menopause syndrome and sex-related cancer, there is no conclusive evidence about the real therapeutic effectiveness of the dietary intake of isoflavones.[51]

Some studies indicate that postnatal consumption of soybean could affect sexual development.[66] It has been assessed in rodents that treatment with genistein at the pre- or neonatal age enhances the development of mammary glands and activates tumor suppressor genes.[35,48] In another study on neonatal female mice it has been observed that subcutaneous injection of genistein leads to alterations of ovary development and menstrual cycle, accompanied by reduced fertility.[27] The plant has also been put in relationship with autoimmune disorders of the thyroid gland. However, there are no conclusive data about the consequences for humans of soy dietary uptake during the neonatal period.[66]

The plant has also attracted some interest in the treatment of cardiovascular diseases.[4,20,32,47,60] Clinical studies have shown that soy intake causes a reduction of LDL cholesterol and blood triglycerides, and an increase of HDL cholesterol.[7,40] Genistein stimulates nitric oxide production in endothelial cells through the activation of the adenylate cyclase–cAMP–PKA pathway, thereby inducing blood vessel relaxation.[65] Such an effect increases the dilatatory response of atherosclerotic arteries to acetylcholine and activates peroxisome proliferator-activated receptors (PPARs), which regulate vascular functions. However, genistein also seems able to inhibit nitric oxide formation induced by cytokines, thus reducing inflammatory conditions like prostatitis.[72] Such an anti-inflammatory action exerted on blood vessels and the inhibition of platelet aggregation are further mechanisms by which genistein can prevent the pathogenesis of atherosclerosis.[52] Soy isoflavones and proteins have been shown to act synergistically in reducing the concentration of plasma lipids in hypercholesterolemic subjects. Isoflavones also seem able to protect LDL proteins from oxidation and to improve the endothelial function. It is not clear, however, if these effects can successfully reduce the risk of cardiovascular diseases.

Lecithin is used to prevent hyperlipidemia and hypercholesterolemia, and exerts a beneficial action on mental and physical fatigue. It has also been hypothesized that the prolonged use of soybean could reduce the risk of diabetes.

Genistein has also been shown to induce hepatoprotective effects. Daidzein is an inhibitor of the enzymes aldehyde dehydrogenase and alcohol dehydrogenase, involved in alcohol metabolism and the consequent possible damage to liver tissue.[26] Total parenteral nutrition (TPN) induces cholestasis and hepatic steatosis, which are frequently lethal in childhood. It has been shown in an animal model that the addition of soy oil to TPN prevents these disorders.[49]

Some soy components behave like antinutrients or interfere with digestive processes. Clinical studies indicate that the presence of soy in the diet interferes with the intestinal absorption of orally administered thyroid hormone used in hypothyroidism. Moreover, soy diet could compromise the thyroid function in subjects affected by latent thyroid alterations or insufficient iodine absorption.[45] Group A sapogenins confer to soy bitter and astringent properties that can be organoleptically unpleasant. Saponins form micellae with bile salts in the gut, thereby reducing the absorption of these latter compounds, and presumably also of cholesterol. Soyasaponins B have shown antitumor properties, particularly when combined with isoflavones, while DDMP saponins behave as oxyradical scavengers.

The plant also contains protease inhibitors, known as Bowman-Birk and Kunitz inhibitors, which can interfere with digestive processes. Their administration at high doses to laboratory animals leads to pancreatic hypertrophy with an increased production of pancreatic proteases, probably mediated by cholecystokinin.[61] Increases in cholecystokinin and pancreatic secretion have been observed in humans following the ingestion of raw soybean flour. Lactose-intolerant infants fed with soy milk, or individuals regularly consuming high doses of legume proteins, are exposed to risks of digestive disorders due to the residual presence of Bowman-Birk and Kunitz inhibitors in these products.[66]

Phytates are soy antinutrients interfering with the absorption of calcium, magnesium, zinc, and iron. The oligosaccharides raffinose and stachyose, which in the plant protect the seed from dehydration, are degraded in the gut by the intestinal flora with production of gases like CO_2, H_2, N_2, and CH_4, which can induce flatulence. Such an inconvenience does not occur after ingestion of soy sauce, since oligosaccharides are degraded by fermentation processes used in sauce preparation.

Similarly to estrogens, isoflavones can induce immunomodulatory effects via ERβ.[18,47,60] *In vitro* studies have shown that genistein lowers the production of nitric oxide by mouse macrophages, inhibits the proliferation and motility of T lymphocytes and their production of leukotriene B4 and interleukins, and inhibits the tumor-killing activity of cytotoxic T lymphocytes, the adhesivity of leukocytes, and the activation of natural killer cells induced by bacterial lipopolysaccharides. These effects have been obtained at genistein doses that are higher than those deriving from the diet, but mice injected with genistein have shown alterations of the immune system, and these effects have been partially observed at concentrations similar to those produced by dietary intake. Physiological doses of genistein have also induced in mice the inhibition of interferon-γ production induced by bacterial infection. The immunosuppressing properties of genistein could be useful in the treatment of autoimmune diseases or after organ transplantation.

In contrast with these findings, other animal studies have reported the activation of the immune system, with an increase in the size of the thymus and an increased resistance to tumor cells. *In vivo* and *in vitro* studies have suggested immunostimulatory effects of daidzein in the mouse, and it has also been observed that soy diet increases the levels of interleukin 6 in women. However, contrasting data have been reported concerning the immunomodulatory effects of soy diet during childhood. A DNA microarray analysis in the mouse has been used to evaluate the regulation of a large number of genes by estradiol and genistein, including genes involved

in DNA transcription, apoptosis, cell cycle, and immune self-tolerance. The results have shown a wide overlapping of the genes regulated by the two compounds, with a prevalence of upregulations by estradiol and downregulations by genistein. However, it has been also found that some genistein-regulated genes are not influenced by estradiol, suggesting that genistein may also act through pathways different from those of estradiol.

Because of the importance of genistein in the medical and pharmaceutical field, different studies have been addressed to the mechanisms of synthesis of this compound. Genistein is synthesized by the plant starting from the flavanone naringenin. However, it can also be chemically obtained via the deoxybenzoin or chalcone route. The enzyme responsible for natural genistein production is isoflavone synthase (IFS), a P450 cytochrome whose genes have been cloned and transfected into nonlegume plants through DNA recombinant techniques.

Dermatologic and Cosmetic Use

Genistein exerts protective effects on the skin against photocarcinogenesis and photoaging.[70] This isoflavone inhibits in the mouse the pathogenesis of skin tumors induced by UV irradiation, while in humans it reduces photoinduced skin damage. These effects seem to occur through various mechanisms, including DNA protection from photodynamic damage, inhibition of phosphorylation cascades induced by UV-B, and stimulation of antioxidant defense.[74] The topical application of a soybean extract to UV-irradiated nude mice has reduced collagen degradation through the inhibition of metalloproteinases, which are one of the main causes of photoaging.[30]

The genistein metabolite equol has reduced inflammatory edema and suppression of contact hypersensitivity induced by UV radiations in a murine model. This compound has also shown antiphotoaging, anti-inflammatory, immunoprotective, and anticarcinogenic properties against the effects of sun radiation in laboratory animals, suggesting its use in sun products for skin care.[76]

In a murine model, a diet based on soy oil has reduced the incidence of alopecia areata.[39] The peptide soymetide 4 is able to inhibit the onset of alopecia in neonatal rats through the activation of NFkB and COX and the stimulation of PGE2 production, which would suppress the apoptosis of hair bulb cells.[71]

Genistein stimulates tyrosinase activity and melanin production, thereby protecting melanocytes and preventing the pathogenesis of melanoma induced by UV-B radiations. However, it has also been reported that soy extracts would have inhibitory properties on tyrosinase activity, hence suggesting their use in depigmenting treatments.

Modified soy proteins have also been used to obtain films for skin hydration and protection from environmental irritating agents.[63] Soy protein hydrolysates and lecitin are also used in cosmetics for their foaming and emulsifying properties.

Side Effects and Toxicity

The plant belongs to a limited group of foods that are responsible for approximately 90% of food allergies. Soy allergens are generally of protein origin. A total of 16 have

been characterized, but many more are likely to be present.[36] Because of the wide diffusion of soy food products, techniques aimed at reducing the content of allergens have been developed. Besides food allergies, the plant is also known to induce respiratory allergies.[8]

The use of soy should be avoided by subjects with hypothyroidism or disturbed sodium absorption. Soy must be used carefully in the presence of hyperpotassemia, due to its high content in potassium, and during childhood, since animal studies suggest possible interferences with sexual development.[41,46]

Experimental studies suggest that the plant could reduce the effects of tamoxifen.[28] Soy phytoestrogens have also been shown to induce *in vitro* genotoxic effects involving apoptosis and cell growth inhibition.[31] However, these findings have been obtained using higher concentrations with respect to the physiological or pharmacological doses to which the human organism can be exposed.

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SPIRULINA

Scientific name: *Arthrospira platensis* (Nordstedt) Gomont
Phylum: Cyanobacteria
Family: Oscillatoriaceae
Parts used: Biomass

Features

Spirulina is a helical member of the Oscillatoriaceae cyanobacteria, once classified in the genus *Spirulina*, consisting of cylindrical, filamentous, multicellular trichomes.[22] It occurs naturally in tropical and subtropical temporary ponds and lakes and is cultivated in various regions of the world.

It is believed to have been a food source for the Aztecs and other Mesoamerican peoples until the sixteenth century. Its harvesting from Lake Texcoco (near today's Mexico City) was described by one of Cortés's soldiers. Spirulina has also been used since prehistoric times by African people living on the shores of Lake Chad.[1]

The largest commercial producers of spirulina are located in the United States and in Asian countries. It is regularly used as a dietary supplement and is marketed in the form of tablets, flakes, and powder.[9]

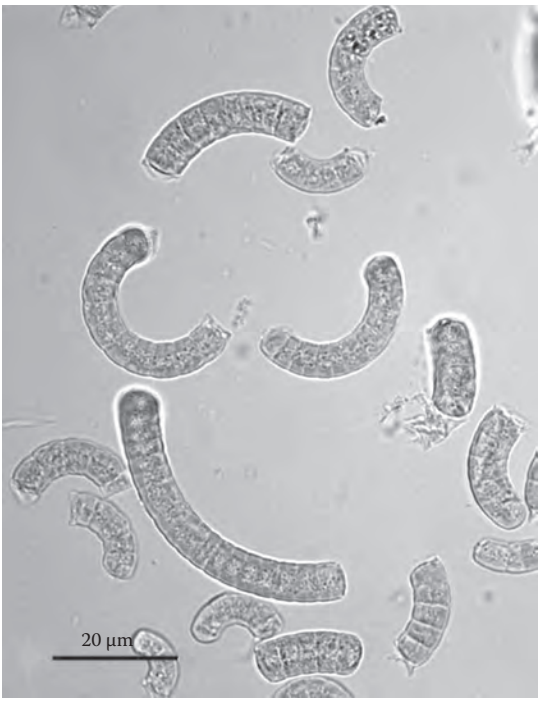


FIGURE 4.48 Spirulina.

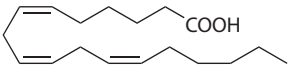
Constituents

Spirulina has a high protein fraction (55–77% dry weight), containing all essential amino acids.[18] The proteins of spirulina have lower levels of methionine, cysteine, and lysine with respect to milk and meat proteins, but their nutritional value is higher than that of plant proteins.[4,21]

Spirulina also contains good amounts of the essential lipid γ-linolenic acid (GLA), which are inferior only to those of the richest botanical sources, like borage oil.[19] Other fatty acids are α-linolenic, linoleic, stearidonic, eicosapentaenoic, docosaesaenoic, and arachidonic acids.

Main carbohydrates include glucose, rhamnose, mannose, xylose, and galactose. These bacterial organisms have no cellulose in the walls of their cells, and this increases their nutritional value with respect to plants, since cellulose forms a nondigestible dietary fraction.

Spirulina contains high amounts of mineral salts and vitamins, including vitamin A, in the form of β-carotene, and vitamins D, K, E, B1, B2, and B12.[14,24] The high presence of carotenoids is responsible for the plumage color of flamingos, which eat these cyanobacteria in African lakes.



γ-linolenic acid

Properties

In vitro experiments have shown that spirulina extracts inhibit HIV-1 virus replication in various human cells, probably due to the presence of polysaccharides.[3] Clinical trials and animal studies have shown a therapeutic action against viral and bacterial infections, anemia, tumor growth and starvation, a reduction of the hepatotoxicity of drugs and heavy metals, and a mitigation of inflammatory and allergic responses.[7,11–13,15,17,20]

The high content in vitamin B12 is important in the treatment of pernicious anemia, while the richness in iron is suitable for the therapy of other kinds of anemia. The iron contained in spirulina is more easily absorbed by the intestine than the iron of plants.

The high amount of β-carotene confers good antioxidant properties to the extract.[10,23] Therefore, spirulina has been successfully used to mitigate the injurious effects of gamma radiations on a group of children exposed in the Chernobyl disaster.

Spirulina's high-molecular-weight polysaccharides have immunostimulatory properties. Selenium-containing C-phycocyanin, extracted from selenium-enriched spirulina cultures, has shown strong antioxidant and antiproliferative properties on melanoma and adenocarcinoma cells.[5] C-phycocyanin has induced apoptosis through an increase of DNA fragmentation and nuclear condensation and a reduction of the mitochondrial membrane potential.[8]

The dietary ingestion of spirulina can reduce cholesterol blood levels and body weight within a few weeks, without causing adverse effects. The body weight reduction depends on an increase in lipid metabolism, while the lowering of cholesterol is due to GLA and C-phycocyanin, which inhibit the absorption of cholesterol and bile acids in the intestinal tract.[2,16]

Dermatologic and Cosmetic Use

The topical application of spirulina extracts to the skin tonifies and revitalizes the epidermis, improves the draining of dermal tissue, and induces a reduction of the subdermal adipose tissue, thereby favoring the elimination of cellulite.[6]

Side Effects and Toxicity

No toxicity of spirulina has been detected in chronic and subchronic animal studies.

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ST. JOHN'S WORT

Scientific name: *Hypericum perforatum* L.
Family: Clusiaceae
Parts used: Inflorescences, apical leaves

Features

Herbaceous biennial of about 30 to 100 cm in height**,** growing from sea level up to the mountains, in dry places, clearings, and high mountain prairies. The stem is erect, hairless, and has two raised edges. Leaves are opposite, entire and elliptic, and possess several essential oil glands. Glands are translucent and make the leaves appear perforated when observed against the light, which accounts for the plant's latin name *Hypericum perforatum*. Various kinds of secretory structures are present, including light glands, dark glands, and secretory canals. Flowers have five golden yellow petals with black dots on the margins, and are disposed in branched corimbs borne at the tip of the plant. They start to open in May, and reach maximum blooming by June 24, which accounts for the common name St. John's-wort.

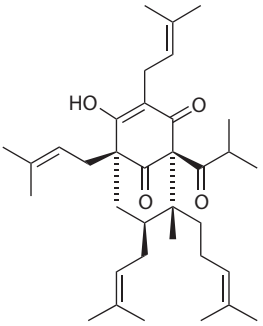
FIGURE 4.49 St. John's Wort. (See color insert following page 40.)

Constituents

The plant's active principles include flavonoids (up to 11% in the flowers), such as oligomeric procyanidins, phenolic acids, and flavonols; tannins (6.5–12%); and naphtodianthrones (up to 3%), mainly hypericin, having a typical red color, pseudohypericin, and its oxidized derivative cyclopseudohypericin. These latter compounds derive from the photoconverison of protohypericin and protopseudohypericin.[19]

Other constituents include the phloroglucinols hyperforin and adhyperforin (up to 3%), an essential oil (0.3–0.6%), amino acids, coumarins, xanthones, choline, carotenoids, and vitamin C.[2] The percent amounts of these constituents can vary depending

on the geographical origin of individuals, probably due to different environmental factors, such as soil, altitude, and sun exposure.[9]



hyperforin

Properties

The plant has long been used in traditional medicine as a remedy for anxiety, depression, wounds, burns, rheumatism, gout, inflammations, and ulcer. In Western countries, its therapeutic use can be traced back to the seventeenth century, while it was already used by North American indigenous people before the arrival of Europeans, to heal fever, snakebites, and skin diseases. It is now included in the official pharmacopoeias of different countries.[1,4]

The plant is of great interest in the medical field, owing to its distinctive therapeutic properties as an antidepressant, antimicrobic, antiviral, anti-inflammatory, and topical agent.[12]

The efficacy of the plant in the treatment of mild to moderate depression has been assessed in clinical studies, and its mechanism of action has been also deeply investigated.[5,10,17,23] It has been ascertained that hyperforin, one of the main lipophilic compounds of the plant, is effective in inhibiting serotonin and norepinephrine reuptake in synapses, whereas hypericin and kaempferol do not exert this kind of action. It seems that this effect is responsible for the antidepressive properties of the plant, possibly together with the synergistic actions of other active constituents.[7] For instance, the flavonoid amentoflavone can interact with benzodiazepine binding sites of GABA-A receptors, thereby inducing a state of relaxation. An important property of the plant extract is the limited induction of side effects typical of antidepressant drugs, such as a reduction of cognitive performance, sleep disorders, and a strengthening of sympaticomimetic activities, possibly leading to heart failures.

The procyanidin fraction can induce coronary vasodilation, thus exerting a protective effect against hypertension.

Other properties of the plant include antiviral and antiretroviral activities, which depend on the action of hypericin. In addition, the plant shows vulnerary and antibacterial activities, which seem due to the presence of essential oil, phloroglucynols, flavonoids, and tannins.

Hypericin has also been investigated as a possible antitumoral agent. It has been suggested, in particular, that hypericin could be used in photodynamic therapy (PDT),

since it becomes particularly toxic to cancer cells after photochemical activation.[3,8] However, the use of this compound in the treatment of skin tumors is hindered by its scarce penetration through the corneal skin layer.

A lipophylic extract containing amentoflavone, hypericin, hyperforin, and adhyperforin has shown a very strong anti-inflammatory activity, comparable to that of indometacin, suggesting that the antiflogistic properties are best expressed by the plant phytocomplex.

Dermatologic and Cosmetic Use

The extract can be used to soothe inflamed or sensitive skins, and as a remedy for sunburns.[22]

The plant extraction in oil yields a red infusion, known as St. John's-wort oil, which can be used for the healing of superficial wounds and burns.

Hyperforin is active on different bacterial strains, including particularly resistant ones, such as *Staphylococcus aureus*.[21] This renders this compound particularly interesting as a preservative in cosmetic production. Moreover, hyperforin can be a valid alternative to essential oils, since these latter add a strong scent to cosmetic preparations. Hyperforin can also be used for the disinfection of wounds and to remove bad scents.

The extraction of the plant's aerial parts in CO_2 allows the separation of hyperforin from hypericin.[20] Such a technique is very important in the preparation of dermatologic and cosmetic products, since hypericin can induce photosensitization in prone subjects. The supercritical CO_2 extract contains up to 40% of hyperforin, and can be used in the treatment of decubitus ulcers, acne, and atopic dermatitis.[18] It is also indicated as an additive to preparations with strong hydrating properties.

Formulations containing supercritical St. John's-wort extracts (39% of hyperforin) and the lichen *Usnea barbata* (96% of usnic acid) have been developed for the treatment of dermatitis, fungal skin infections, acne, and rosacea.[15]

Side Effects and Toxicity

Topical use of the plant is considered relatively safe since adverse reactions are rare. However, ingestion of high amounts of hypericin can induce photodermatitis (hypericism).[6,11,16] Cases of photosensitization through topical application have not been reported, but use of the plant is not recommended in allergic or photosensitive individuals.

Plant extracts should also be avoided during pregnancy and lactation.[13] High doses of plant extracts can induce interactions with drugs like cyclosporins, digoxin, HIV reverse transcriptase inhibitors, chemotherapeutics, and anticoagulants (e.g., warfarin).[14]

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WAKAME

Scientific name: *Undaria pinnatifida* (Harvey) Suringar
Class: Phaeophyceae (brown algae)
Family: Alariaceae
Parts used: Thallus

Features

Large brown kelp having a heteromorphic life cycle, with alternation of a diploid sporophyte and a haploid gametophyte. The sporophyte is the most conspicuous form, reaching an overall length of 1–3 m. It has a branched holdfast and a stipe with wavy edges, giving it a corrugated aspect. The stipe gives rise to a broad, flattened, and lanceolate blade having a distinct midrib and wavy margins.[19]

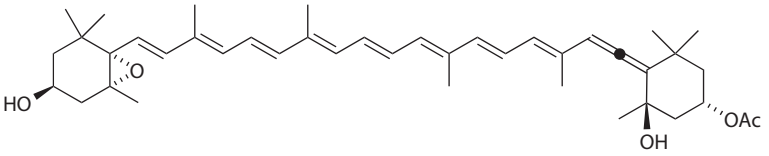
In its natural environment, the alga grows on rocks and reefs at 1–8 m below low tide, forming dense stands and a thick canopy. It is native to temperate regions of Japan, China, and Korea, but has been spread around the world through shipping and mariculture activities.[17]

Wakame has been grown by Japanese and Korean sea farmers for centuries, is collected in the spring, and is marketed fresh or dried. It is a popular food in Far Eastern countries and is most widely used in the Japanese miso soup.

Constituents

The total dry weight consists approximately of 50% carbohydrates, 20% proteins, 1% lipids, and 25% mineral salts. The main carbohydrates are sulfated polysaccharides like alginic acid, a polymer consisting of D-mannuronic and L-galacturonic acids, and fucoidan. This latter is a complex polysaccharide that is present in two distinct forms: F-fucoidan, consisting of 95% fucopyranoside, and U-fucoidan, consisting of 20% glucuronic acid.[9,15]

The main carotenoid is fucoxanthin, which confers to brown seaweed its typical color. The alga is rich in calcium, magnesium, and iron, and has a high content in vitamin A, B group, C, K, H, E, PP, and folic acid.



fucoxanthin

Properties

Sulfated polysaccharides have anticoagulant and antibiotic properties. The structure of alginic acid is similar to that of pectin, and the compound forms a gel upon contact with water. When this polysaccharide is ingested, it produces a

covering that protects the stomach wall against gastritis and ulcer. Moreover, alginic acid is not degraded by digestive hydrolases and does not represent a caloric source in the diet, but instead acts as fiber bulk stimulating food transit in the digestive tract.

Fucoidan induces immunostimulation and protects against viral infections, including HIV.[2,7,18] This polysaccharide, used in combination with the oseltamivir drug, has shown a strong ability to suppress the replication of type A influenza virus (IFV). Fucoidan is also known to lower cholesterolemia, to improve liver function, and to induce growth inhibition and apoptosis in tumor cells.[3] In HS-sultan cells, it has induced apoptosis coupled to caspase 3 activation and ERK pathway downregulation.[1] It also binds heavy metals and radionuclides, and the alga is therefore able to contrast the noxious effects of contaminations caused by these toxic agents.

The vitamins present in wakame produce noteworthy synergistic actions, such as a combined effect of vitamin E and vitamin A that favors the excretion of excess cholesterol from the body.

In clinical tests, oral intake of wakame has led to antihypertensive effects.[6] It has also been assessed that hydrolyzed proteins of the extract induce the inhibition of ACE, an enzyme that promotes vasoconstriction through the conversion of angiotensin I to angiotensin II.[16]

Other studies have shown that the alga induces a consumption of body fat stores, hence being effective against obesity and its closely related diabetes.[10] These properties are likely to be due to fucoxanthin, which seems to promote fat degradation in adipocytes through the induction of uncoupling protein 1 (UCP1), a brown fat protein that uncouples mitochondrial respiration and thereby leads to a rise in energy consumption.[11] Fucoxanthin is also able to arrest *in vitro* prostate cancer cell growth.

Dermatologic and Cosmetic Use

The topical application of algal extracts gives rise to a synergistic action of folic acid, iodine, and fucoidan that is particularly beneficial for skin, nails, and hairs.[8] Fucoidan maintains the smoothness and hydration of the skin, and prevents the formation of lines and wrinkles, thus producing an antiaging effect.[4,5,13] These properties seem to derive from a protective effect against the oxidative degradation of collagen and hyaluronic acid.

The ability of fucoxanthin to stimulate the metabolism of fat reserves is particularly useful in the treatment of cellulite, since it favors the removal of subcutaneous fat.[14] The algal antihypertensive properties also act favorably in this respect, since they promote the reabsorption of the edematous component of the cellulitic tissue.

Side Effects and Toxicity

No allergic reactions to wakame have been reported. Moreover, fucoidan has been found to lower the response of type 2 helper T lymphocytes in BALB/c mice, hence showing its ability to moderate the pulmonary inflammatory response triggered by allergic reactions.[12]

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WATERCRESS

Scientific name: *Nasturtium officinale* R. Brown
Family: Brassicaceae
Parts used: Aerial portions

Features

Perennial herbaceous plant with angular, hollow, decumbent, and branched stem, growing up to a height of 90 cm. The leading and side shoots bear terminal corymbus-like racemes, consisting of small white flowers. Leaves are fleshy, alternated, imparipinnately compound, with entire, elliptical lateral segments and rounded-cordate terminal segments. The fruit is a peduncled, oblong-linear silique containing many seeds arranged in two series.

The species lives in wetlands, still waters, streams, and springs. It is spread from the sea level up to 1,500–2,000 m altitude. Its original area spans from Europe to Central Asia, but it is currently ubiquitous. It is also cultivated in many countries as a source of food for humans and livestock.

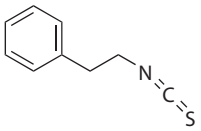
The leaves and aerial parts must be collected before flowering, since thereafter they tend to acquire a bitter taste. They can be served fresh in a salad or used to prepare soups and sauces. The presence of isothiocyanates confers to the plant a moderately spicy taste and renders its organoleptic and medicinal properties similar to those of yellow mustard. Consumed fresh, it is an excellent source of vitamins and minerals.

FIGURE 4.50 Watercress. Courtesy of Dr. Marco Castelli. (See color insert following page 40.)

Constituents

The plant contains glucosinolates, of which the main one is gluconasturtiin, which upon enzymatic degradation releases phenylethyl isothiocyanate (PEITC).[3] Other glucosinolates include glucotropeolin, releasing benzyl isothiocyanate, 7-methyl thioheptyl glucosinolate, and 8-methyl thiooctyl glucosinolate.

The plant also contains flavonoids and is rich in potassium, calcium, iron, folic acid, and vitamins A and C.[11] Besides iron, other heavy metals tend to accumulate in the plant's tissues. Such a feature has attracted some interest for a possible use of this species in environment phytoremediation.[8,9]



phenylethyl isothiocyanate

Properties

The plant has been used since ancient times for its nutritional, organoleptic, and medicinal properties. Glucosinolates do not have significant biological effects, but through the activation of the enzyme myrosinase, they give rise to isothiocyanate compounds able to perform a marked pharmacological action. Such a process occurs, for instance, during feeding after the rupture of tissue cells by chewing and digestion. The enzyme is inactivated by cooking, but some level of isothiocyanates can be detected in the human body even after the eating of cooked watercress, probably due to enzymatic conversions performed by the gut flora.[4]

Isothiocyanates confer expectorant, secretolytic, and antibiotic properties, while diuretic effects derive from the high presence of potassium. Topical applications of extracts produce a revulsive effect that is suitable for rheumatisms, neuralgia, and lumbago. Application to the chest relaxes the bronchial tree and aerial ways, while a similar action occurs on the gastrointestinal system following ingestion. Moreover, inhibitory effects on high blood pressure have also been reported.[12]

The plant is an important source of nutrients and vitamins. It is in particular a good antiscorbutic thanks to the high presence of vitamin C, and exerts an antioxidant action producing positive effects on the blood and lymphocytes.[5]

An *in vitro* study has shown that PEITC inhibits the enzyme metalloproteinase 9 (MMP-9) produced by breast cancer cells.[14] Due to the importance of MMP-9 for tumor invasiveness, the above results suggest that the use of the plant could prevent, at least to some extent, the metastasization of breast cancer.

Isothiocyanates can also inhibit the production of nitric oxide and prostaglandin E2 by macrophages, suggesting their possible use in the therapy of chronic inflammations.[15] Another important effect of isothiocyanates is the inhibition of phase I detoxification enzymes, which are responsible for the activation of several carcinogens.[10] By contrast, isothiocyanates can activate phase II enzymes, which are instead involved in the inactivation and excretion of various toxic compounds, including carcinogens.[13]

It is believed that watercress exerts a preventive effect against the development of tumors in smokers through an increase of the urinary excretion of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a carcinogenic metabolite of nicotine that is formed in the liver and in other tissues.[6,7]

Dermatologic and Cosmetic Use

Watercress-based lotions containing PEITC provide a rubifacient effect that stimulates hair growth. However, such an effect is lower in baldness conditions that do not derive from ischemic causes, such as in androgenic alopecia and alopecia areata.

Isothiocyanates give the extract a particular scent, similar to yellow mustard, which renders it an interesting ingredient in the perfume industry.

Plant extracts exert on the skin an antiseptic and detergent action that can be useful for acne. The plant can also be used as a hydrating nutrient able to reduce TEWL. A study has provided a scientific basis to this property, by showing that in cultures of human keratinocytes, the extract induces the expression of aquaporin 3, a protein that is essential for skin hydration.[16]

Side Effects and Toxicity

The release of isothiocyanates renders the plant's extracts potentially irritant for the skin and able to induce contact dermatitis.[2] Their systemic use is also contraindicated in the presence of inflammation of the urinary tract.[1]

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WHEAT

Scientific name: *Triticum aestivum* L.
Family: Poaceae
Parts used: Seeds

Features

Annual grass native to Asia Minor. The stem is hollow, regularly divided into nodes and internodes, and can reach a height of between 60 and 180 cm, according to the different varieties. The leaves originate at nodes, are linear and rough to the touch, and clasp the stem at the base. Flowers are born in spikes at the apex of culms. Spikes are formed by spikelets, consisting of two glumes embracing a few simple flowers, each containing one ovary. The fruit is an oval caryopse, the wheat grain, consisting almost exclusively of the seed that contains the embryo, also known as wheat germ.

The first records about wheat cultivation date back to the early civilizations of the Mesopotamian area, about 11,000 years ago. Among the different species of wheat selected by humans through the course of millennia, the one that became widespread

FIGURE 4.51 Wheat. (See color insert following page 40.)

is *Triticum aestivum*, a hexaploid strain derived from a spontaneous hybridization between *T. turgidum* and *Aegilops tauschii*. A number of different cultural varieties have been obtained from the original strain, while in recent times transgenic lines have also been developed.[37,40]

The wheat is an ideal crop to grow, due to its suitability for harvesting, transport, storage, and uses in food industries. Moreover, wheat flour allows the production of raised bread thanks to the process of agglutination through mixing with water. For these reasons, wheat has become the most cultivated crop on a worldwide scale, and constitutes the alimentary basis for the human population in many regions of the world.

Constituents

The seed contains about 70–75% carbohydrates, of which the main component is starch, 12–13% protein, and 2% lipids. Important bioactive components include lignans, such as secoisolariciresinol and pinoresinol, group B vitamins (thiamine, riboflavin, and niacin), and minerals like iron, magnesium, phosphorous, potassium, and zinc.[14,21]

Wheat flour contains four kinds of proteins: albumins (15%), which are soluble in water; globulins (5%), which are soluble in saline solutions; and gliadin (40%) and glutenin (40%), which are insoluble in aqueous solutions. The gluten is a mixture of gliadin and glutenin.

The wheat germ is a source of oil containing both unsaturated fatty acids, such as linoleic (50%), oleic (25%), and linolenic (6%), and saturated fatty acids, like palmitic and stearic. An unsaponifiable fraction is also present, which contains phytosterols and is particularly rich in tocopherols (vitamin E), mainly γ- and δ-tocopherol.

Properties

A number of studies have been directed to investigate wheat effects on the metabolism of the human body, mainly of the liver. The seed contains many proteins, some of which can inhibit amylases present in saliva and in the pancreatic juice.[29] Wheat extracts can stimulate DNA synthesis in cultures of fibroblast and mouse lymphocytes, and promote the *in vitro* growth and activity of ornitine decarboxylase in BALB/c 3T3 mouse fibroblasts.[16–18,38] A wheat fraction has trophic effects on CACO-2 cells,[12] while wheat gliadins have been found to induce apoptosis on the same cells.[20] A 3–10 kDa oligosaccharidic fraction of the aqueous extract, combined with human EGF, can promote endothelial cell growth and protect mouse tail tissue from ischemic necrosis.[8]

Wheat germ and bran have raised some interest in the prevention and therapy of tumors.[6,7] These properties are probably due to the presence of benzoquinones and agglutinins in the wheat germ, and of fibers, lipids, and phytates in the bran.

A Hungarian pharmaceutical preparation, known as Avemar, has attracted much interest for its antitumor properties.[4] This product is obtained from wheat germ fermentation, a process that causes the release of benzoquinone aglycones from their glycosylated forms. It has been clinically tested in association with standard

therapies and seems able to prolong the survival of patients affected by different malignant diseases by inhibiting tumor propagation and metastasization.

Various *in vitro* studies have allowed the pointing out of some of Avemar's molecular targets. The wheat germ derivative inhibits leukemic cell growth by inducing apoptosis through caspase 3 activation, which in turn causes the degradation of poly-ADP-ribose polymerase (PARP), thus leading to genomic instability. Moreover, the product does not induce the same level of apoptosis in peripheral blood mononuclear cells. By using T and B cell lymphoid tumors, it has been shown that Avemar stimulates protein tyrosine phosphorylation and calcium entry. These mechanisms seem involved in a decrease of major histocompatibility complex (MHC) I proteins at the cell surface, and such a process would abrogate the ability of tumor cells to elude the immune system, thus exposing them to the action of natural killer cells.[15] These effects seem to depend chiefly on the activity of 2,6-dimetoxy-p-benzoquinone.

The endothelial cells of tumor blood vessels express low amounts of the intercellular adhesion molecule 1 (ICAM-1) factor, thus hindering the infiltration of leukocytes in the tumor tissue. However, Avemar can increase the expression of ICAM-1 in these endothelial cells, thereby rendering more effective the activity of leukocyte-attracting chemokines.[35]

In a study on Jurkat leukemic T cells, it has been observed that Avemar can affect metabolic pathways that direct glucose metabolism to the synthesis of nucleic acids, such as the enzymes glucose-6-phosphate dehydrogenase and transketolase, thereby hindering cell cycle and consequently cell growth.[11] The shunt of glucose degradation from pathways controlling nucleic acid synthesis and cell proliferation to pathways providing energy to the organism could explain such *in vivo* effects of Avemar as slower tumor progression, prolonged survival of patients, and improved quality of life following training after acute surgical operations and chemo- or radiotherapy. Another effect of this kind seems to be the inhibition of ribonucleotide reductase, an enzyme involved in DNA synthesis.[31]

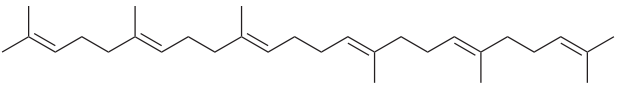
Avemar has also shown therapeutic effects on rheumatoid arthritis, both in the rat and in humans.[2,34] *In vitro* studies suggest that these properties should be put in relation with the ability of inhibiting the COX-1 and COX-2 cycloxygenase enzymes. Such an inhibitory activity is also considered a preventive factor against colorectal cancer.[24] It has also been shown in the rat that consumption of wheat bran, and particularly of its component phytic acid, can reduce the occurrence of early markers of colon carcinogenesis.[25,41]

Dermatologic and Cosmetic Use

Seed extracts rich in phospholipids, glycolipids, and sugars are used as skin hydrating products for the reduction of TEWL, due to their sebum-like properties.[13] Protein hydrolysates are used for skin hydration, due to the capability of peptides to retain water in skin and hair interstices. Protein hydrolysates are also used in detergent products in order to limit the irritant properties of surfactants. The amino acid cysteine, of which some seed proteins are particularly rich, forms disulfide bridges with hair keratins, thus conferring brightness, softness, and volume to hairs.[1,19]

Wheat germ oil has high antioxidant and anti-UV power, due to the abundant presence of vitamin E.[28] The oil also contains unsaturated fatty acids that have a particular affinity for sebum. The oil is suitable for dry skin, skin exposed to sun or bad weather conditions, or aged skin. Squalene is an oil component that stimulates cell proliferation and tissue regeneration in the skin tissue, while it also shows bactericidal properties.

The seed is also a source of the antioxidant enzyme superoxide dismutase (SOD), which is used in skin care to reduce skin damage induced by free radicals.[9] SOD is also able to prevent processes of fibrosis in skin tissue, probably through the induction of myofibroblast redifferentiation back to fibroblasts.[5,39]



squalene

Side Effects and Toxicity

Wheat and its derivates can induce allergic reactions.[3,30] Wheat flour causes airway allergies, mainly of an occupational type. More common allergies are due to wheat consumption.[26] Wheat allergies are among the fifth most common food allergies. Symptoms include gastroenteric irritation, dermatitis, eczema, angioedema, rhinitis, and asthma.

Food allergies can also be triggered by gluten protein hydrolysates, involving serious consequences, up to anaphylactic reaction.[27] This latter kind of allergies can also occur after the use of cosmetics containing wheat protein hydrolysates.[10,22,32,36] The blood of individuals allergic to wheat can contain immunoglobulins binding either gluten proteins or albumins and globulins.

Celiac disease is an autoimmune disorder affecting the small intestine, which results from a genetic predisposition and is triggered by the introduction of gluten.[23,33] This syndrome is quite common and affects about 1% of the entire human population.

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WILD YAM

Scientific name: *Dioscorea villosa* L.
Family: Dioscoreaceae
Parts used: Roots, rhizome

Features

Periannial vine native to North and Central America. The rhizome is long, twisted, yellowish, and hard. The stem is thin, wooly, reddish brown, and can measure 12 m in length. The leaves are alternating, cordiform, and pedunculated. The flowers are dioecious, small, whitish-greenish or yellowish. Male flowers are grouped to form panicles, while female flowers form spicate racemes. The fruit is a winged capsule.

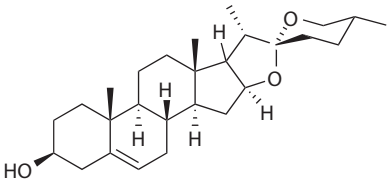
The rhizomes and roots are harvested in autumn, before the flowering season.

Constituents

The main constituents of roots and rhizomes are furostanic and spirostanic saponins, primarily digoxin and dioscorin.[19] After hydrolysis under strong acid or basic conditions, these glycosidic compounds release their aglycone moiety consisting of the steroid sapogenin diosgenin. Other constituents are catecholamines, phytosterols such as β-sitosterol, carotenoids, phytic acid, flavan-3-ol glycosides, and tannins.[20]

Carbohydrates include starch, mannose, glucose, and galactose. Main vitamins are ascorbic acid, riboflavin, and niacin. Chief mineral elements are calcium, magnesium, potassium, and phosphorous, while micronutrients include iron, aluminum, cobalt, manganese, zinc, sodium, chrome, selenium, and tin.

FIGURE 4.52 Wild Yam.



diosgenin

Properties

Ancient American people like Aztecs and Mayans used wild yam for various ailments, such as internal spasms and women's diseases. The plant has also been traditionally used for inflammation and bronchial asthma. Modern herbalists have used the plant for treating menstrual cramps and labor complications.

The discovery of diosgenin opened the way to the synthetic production of steroid hormones and led to the development of the contraceptive pill. Diosgenin is a steroid compound that represents a natural source for the industrial production of various steroid hormones, like progesterone, androgens, estrogens, and corticosteroids. Even though the conversion of diosgenin to progesterone can be obtained artificially, it is still unclear whether diosgenin undergoes the same kind of transformation in the human body. Also, no clear evidence exists to support the idea that diosgenin exerts an effective action on sexual disturbances. Doubts also arise from the fact that the plant extracts are sometimes integrated with progesterone.

Extracts are nevertheless used successfully to treat women's disorders like premenstrual syndrome, menopause, and osteoporosis.[11,21,25] Therefore, it is possible that diosgenin mimics the effect of progesterone, though with a minor efficiency, and that it could amend syndromes of estrogen dominance.[2,3,9] It seems that steroid saponins and their metabolites are able to bind estrogen receptors present in the hypothalamus, which are involved in a negative feedback control of estrogens. Phytosteroids could then mimic high blood estrogen levels, thereby inducing a reduction of estrogen production. Other effects related to the binding of diosgenin to estrogen receptor have been detected in osteoblasts.[26] Diosgenin activation of ion currents in cortical neurons has also been pointed out.[24]

The plant is also an antispasmodic, diaphoretic, anti-inflammatory, antirheumatic, and expectorant. It can also be used for gastrointestinal inflammatory conditions and for biliary colics. An explanation of the antispasmodic effect can derive from a study in which diosgenin has been shown to induce a relaxation of blood vessel walls through the activation of muscarinic receptors in the endothelium, followed by a release of myorelaxant factors such as NO and prostaglandins.[4]

Other studies have shown that diosgenin induces a hypocholesterolemic effect, most likely linked to a reduction of intestinal cholesterol absorption and to an increase of cholesterol hepatic secretion in the form of biliary acids.[12,18,22] Hepatoprotective effects have also been shown, possibly related to antioxidant properties.[1]

Diosgenin has also been found to induce apoptosis in a number of tumor cell types, and it is therefore investigated as a possible anticancer drug.[8] In human leukemia cells

it has induced the arrest of the cell cycle followed by apoptosis due to an alteration of calcium homeostasis.[16] In HeLa cells diosgenin has caused apoptosis through a reduction of the mitochondrial membrane potential.[10] In osteosarcoma cells it has induced COX-2 activity and cell cycle arrest in the G phase followed by apoptosis.[17] Finally, in rheumatoid arthritis synoviocytes diosgenin has increased the activity of cycloxigenase 2 (COX-2), causing higher production of prostaglandin E2, loss of mitochondrial membrane potential, activation of caspase 3, and DNA fragmentation.[15]

Dermatologic and Cosmetic Use

The anti-inflammatory properties of the plant make it suitable for dermatologic products used in the treatment of irritated or aged skins.[23] The extracts also show anticollagenase activity, suggesting a possible use in antiaging products and more in general for skin degenerative syndromes.[6]

Diosgenin has a depigmenting effect and can therefore be used in melasma, melanodermatitis, and sun lentigo.[5] A study carried out on melanoma cells has shown that the depigmenting effect is linked to the activation of the cellular PI3 kinase pathway.[14]

Diosgenin is also used for breast cosmetic lifting since it seems to induce an increase of adipocyte volume resulting in an increase of breast turgor.

Side Effects and Toxicity

Toxicity cases or unwanted side effects have not been reported following therapeutic or cosmetic uses.[7] However, diosgenin can interfere with other drugs by increasing their excretion, or alter the effects of synthetic estrogens.

The plant's active principles should be avoided during pregnancy and lactation or by women undergoing hormone therapies.

The species *Dioscorea batatas*, which is close to *D. villosa*, can cause occupational contact dermatitis and asthma.[13] People allergic to *D. batatas* can show sensitivity to other *Dioscorea* species.

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WITCH HAZEL

Scientific name: *Hamamelis virginiana* L.
Family: Hamamelidaceae
Parts used: Bark, leaves

Features

Small tree that can reach, and in some cases exceed, a height of 6 m. The branches are thick, and in young individuals the lowest ones grow from the base of the stem. The bark is of a light brown color; it is smooth at first and then becomes scaly and furrowed. The twigs grow in a zigzag shape and are covered at first by grey hairs, while subsequently they become smooth. Leaves are alternate, oval, with a lobed, toothed margin, dark green superiorly and light green on the lower surface. Flowers open in the winter, after the shedding of leaves, and are variable in color, ranging from light to intense yellow. The fruit is a capsule of 1–1.5 cm, having a woody, hard pericarp, which at maturity explosively bursts open at the apex, thus throwing the seeds it contains at a distance of up to 10 m from the plant.

This species is native to the central-eastern regions of North America and has been used for centuries by Native American people.

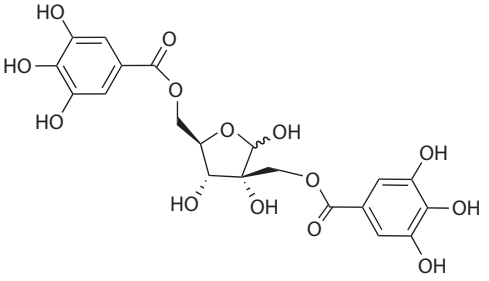
FIGURE 4.53 Witch Hazel.

Constituents

The bark and the leaves are rich in hydrolyzable tannins (about 3%), among which the main one is hamamelitannin (2'5-di-O-galloyl-hamamelose).[11] The molecular structure of this compound consists of two residues of gallic acid and of a monosaccharidic

unit of hamamelose, a typical sugar of this plant.[28] Hamamelo-furanoso-gallates and proanthocyanidins are also present, including prodelphinidin, catechins, and gallocatechins.[2,13]

The plant contains flavonoles, like kaempferol and quercetin, and their glycosides astragalin, quercitrin, afzelin, and myricitrin. There are also essential oils, whose main components are hexene-2-ol, α- and β-ionone, eugenol, safrole, and sesquiterpenes.[6] In addition, saponins, resins, and waxes are also present.



hamamelitannin

Properties

The plant has an old tradition of medicinal use among the indigenous people of North America. It has astringent, antihemorragic, and anti-inflammatory properties, and in popular medicine is used for hemoptisis, inflammations, hemorrhoids, diarrhea, burns, and skin irritations.[8,16,22,31]

Clinical studies have shown the effectiveness of the bark extract on hemorrhoids, and of the leaf alcoholic extract in the reduction of skin temperature.[23] In other studies, a leaf ethanolic extract has reduced the rat paw inflammation induced by carragenan,[4] while a bark ethanolic extract, rich in proanthocyanidins, has acted against *Herpes simplex* virus type 1.[7] This latter extract has also shown free radical scavenging properties, and the ability of inhibiting such enzymatic activities as β-glucosidase and leucocyte elastase.

The therapeutic properties of the plant can be primarily ascribed to the presence of tannins and proanthocyanidins. Antihemorrhagic properties have been explained, at least partially, by an *in vitro* experiment where hamamelitannin inhibited the death of endothelial cells induced by tumor necrosis factor (TNF) without altering the induction of endothelial cell adhesion to monocytes.[12]

Hamamelitannin and galloylated proanthocyanidins can also inhibit 5-lipoxygenase, an activity that could explain the anti-inflammatory effects of the plant.[14] Finally, hamamelitannin is a potent scavenger of free radicals,[24,25] and it is then able to inhibit the mutagenicity induced by nitroaromatic compounds.[1]

Dermatologic and Cosmetic Use

The plant extracts find therapeutic applications in various skin disorders and are used in a number of cosmetic formulations.[5,9,15,18,29] The plant has been approved

by German Commission E for the treatment of inflammations of the skin and mucosae, and for hemorrhoids and varicose veins. The extract is a skin refreshing agent, moderate astringent, tonic, sedative, and anti-inflammatory and also acts as a regulator of the sebaceous secretion and skin barrier.[20] It is particularly indicated for the treatment of eczemas, ulcers, wounds, burns, couperose, and atopic dermatitis, and is also useful for the treatment of greasy skin, especially on the face.

Some of these properties have been assessed in clinical tests, where plant extracts have reduced the erythema caused by UV-B radiation, and contrasted skin aging induced by free radicals.[17,19] As for the treatment of eczema, various clinical trials using creams containing a leaf distillate have shown an effective reduction of irritation and itching in case of atopic dermatitis, while in contact dermatitis the treatment has been less effective.[21,27] In a dermatologic test carried out on children, the extract has produced an improvement of eczema, small wounds, and localized skin inflammation.[30]

The effects of the plant on the skin can be ascribed to the high levels of polyphenolic compounds. It has been experimentally shown that hamamelitannin protects skin cells from cellular death induced by UV-B rays, probably due to its high antioxidant power.[26] In another study, proanthocyanidins extracted from the bark have stimulated *in vitro* the proliferation of keratinocytes, while *in vivo* they have limited both erythema and transepidermal water loss (TEWL) following skin irritation induced by lauryl sulfate.[3]

Side Effects and Toxicity

There are no contraindications to the use of the plant, although the ingestion of discrete amounts should be avoided due to the conspicuous presence of tannins. It is also advisable to avoid oral ingestion during pregnancy and lactation, while no problems can be envisaged for topical use, even under these latter conditions. Skin irritations have been rarely reported. For instance, one case of periorbital dermatitis is known to have occurred after topical use of a witch hazel–containing gel.[10]

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YELLOW SWEET CLOVER

Scientific name: *Melilotus officinalis* (L.) Lam.
Family: Leguminosae
Parts used: Flowering apices, leaves

Features

Biennial herbaceous plant growing to between 60 and 180 cm in height. The stem is hollow, thin, ramified, and the leaves are composed of three leaflets (trifoliate) with a saw-toothed margin. Flowers are small, pale yellow, papilionate, and arranged in terminal racemes bearing 30–70 flowers. The fruit is a small, brown-black, obovate and laterally compressed pod, which at ripening has transversal veins and contains one seed.

The species is native to Europe and Asia and grows in meadows, pastures, uncultivated fields, and path margins. The plant is frequently grown as forage and has a

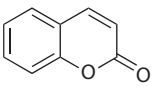
FIGURE 4.54 Yellow Sweet Clover. (See color insert following page 40.)

strong sweet smell due to the presence of coumarin. The Latin name *Melilotus* is accounted for by the fact that the plant smell attracts bees and other insects, which provide pollination.

The herb consists of dried and crushed flowering apices. It has both medicinal and domestic uses. It is used, for instance, to scent dried fruit, beverages, and clothes. Fresh leaves are also used as food.

Constituents

The main active principles are coumarin and its derivatives (about 0.5%), e.g., melilotin (hydroxycoumarin) and melilotoside (hydroxycinnamic acid glucoside), which during the drying process releases glucose and coumaric acid.[2,10,19,29] Other constituents are flavonoids, e.g., quercetin, kaempferol and their glycosides, saponins, triterpenes, resins, tannins, and essential oils.[9,30,31,34]



coumarin

Properties

The plant has anti-inflammatory, antioedematous, phlebotonic, diuretic, and sedative properties. In traditional medicine it has also been used as a hepatoprotector, expectorant, balsamic, and against kidney spasms. The infusion has a pleasant flavor and can be taken after meals as a digestive, or before going to bed as a sleep aid. The spasmolytic and sedative effects of the plant can alleviate neurosis, neuralgia, headache, and gastrointestinal ailments.

Coumarin can be used as an antispastic or in the therapy of limphedema, thrombophlebitis, hemorroids, and varicose veins.[3,4,6,12,20,21,25] Its effect on blood vessels is similar to that of escin, a principle from horse chestnut, and consists of an increase of capillary permeability.[16,17] Coumarin promotes the proteolytic activity of macrophages, which degrade proteins accumulated in the interstitial spaces and lymph vessels of inflamed tissues.[22] These proteins exert an osmotic pressure that causes limphedema by hindering the draining of tissue operated by blood vessels. Coumarin also reduces the catabolism of epinephrin, thus improving blood vessel contractility. It has also been used in the therapy of some tumors.

Flavonoids act complementarily to coumarin by increasing the resistance of blood vessel walls. The combined action of coumarin and flavonoids produces an antioedematous effect with a lowering of water retention by tissues.

These properties have been confirmed by clinical trials and laboratory studies on animal models of acute inflammation. In addition, *in vitro* tests have shown that a plant extract antagonizes the effect of pro-inflammatory cytokines and stimulates the production of anti-inflammatory mediators.[23] A possible use of the extract in the reduction of postsurgical edema has been envisaged.[35]

It has also been shown that polysaccharides isolated from the plant have immunomodulating, antianemic, and adaptogenic properties,[24] and that isocoumarins act as gastroprotectors, probably due to an increase of prostaglandin production.[11]

Dermatologic and Cosmetic Use

Coumarin is used in cosmetics, detergents, and perfumes as a fragrance.[7] The improvement of tissue draining is important in the treatment of cellulite or of venous insufficiency of the lower limbs.[32] Distilled water from yellow sweet clover is a refreshing, soothing, and relaxing lotion, particularly indicated for dry and exhausted skins.

The plant is also used as a skin decongestant, astringent, and mild soother. The infusion is used for the decongestion of eyelids and of the periocular zone; for anti-inflammatory treatments of the oral mucosa, nostrils, and throat; and to rinse wounds, abrasions, papules, and pimples.

Side Effects and Toxicity

The plant has been associated with hemorrhages affecting cattle and humans, but it has been shown that the effect is due to a compound that is not directly produced by the plant. This compound was initially discovered at the end of the 1800s, when the plant was introduced in the United States and Canada to improve forage production. In the United States around 1920, there was a severe cattle syndrome, characterized by subcutaneous hemorrhages and bleedings. After this episode, other cases were registered in various countries.[26,27,33,36] By the end of the 1930s, the biochemist K. P. Link and his colleagues succeeded in isolating the chemical compound that was responsible for the disease[18]; dicoumarol (3,3'-methylenebis 4-hydroxycoumarin), which originates from the transformation of coumarin operated by molds belonging to the genus *Aspergillus*, a process that takes place when forage is stored in humid places.[28] Dicoumarol is structurally similar to vitamin K and inhibits the enzyme vitamin K–epoxide reductase. This enzyme is involved in the formation of various coagulation factors, mainly prothrombin and factor VII. Dicoumarol has been used as an anticoagulant until the introduction of its analogue warfarin, also widely used as a rodenticide.[15]

Besides the above side effect, therapeutic uses of the plant can produce temporary conditions of nausea and diarrhea. Coumarin can also cause hepatic intoxication[1,5,8] and induce contact dermatitis.[14] The plant can enhance the effect of anticoagulants, particularly those derived from dicoumarol, and must be avoided during pregnancy and lactation.[13] It is not particularly allergenic, but is reported as an allergen by EU guidelines on cosmetics.[14]

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Açai Palm

Aloe

Bearberry

Bilberry

Burdock

Buriti Palm

Butcher's Broom

Chamomile

Chasteberry

English Ivy

European Elder

Ginkgo

Grape

Green Tea

Hops

Horse Chestnut

Indian Coleus

Lemonbalm

Linden

Mango

Coffee

Murumuru

Neem

Olive

Perilla

Pomegranate

Rosa x mosqueta

Rosemary

Savory

St. John's Wort

Watercress

Wheat

Yellow Sweet Clover