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Synergistic use of bioactive agents for the management of different skin conditions: an overview of biological activities

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Abstract. **Recently, many plant-derived bioactive agents have been included in dermo-cosmetics formulations. This leads to an extensive portfolio of innovative products with an expanded range of benefits, including anti-aging, antioxidant, hydrating and depigmenting. Although different technologies drawing on science and nature are used to create these high-performing molecules, there remains some debate about the mechanism of action of the natural bioactive ingredients within dermo-cosmetics. This review recapitulates the main biological mechanisms underlying the activity of natural active ingredients, with a specific focus on their synergistic use for the management of common, yet quite specific, skin conditions.**

A total of 28 plant-derived bioactives were selected from the Givaudan Active Beauty (Argenteuil, France) portfolio, a multinational company specializing in innovative natural actives research. An extensive literature review about their biological activity was conducted by a PubMed search using different keywords. No language or publication date restrictions were used. Givaudan Active Beauty data on file were also considered. The bioactive ingredients were described according to the pathogenetic mechanisms underlying 10 common skin conditions that dermo-cosmetics may address.

Literature data have shown that plant-derived bioactives are involved in a wide range of biological mechanisms showing anti-inflammatory, antioxidant, and moisturizing properties, along with skin barrier protection and collagen synthesis activities. As a result, different combinations of bioactives within dermo-cosmetics can be defined to counteract simultaneously the different pathogenetic mechanisms underlying different skin conditions.

Available literature supports the synergistic use of plant-derived bioactive agents within dermo-cosmetics as a viable and safe option for managing the most common skin conditions.

Key Words:
Dermo-cosmetics, Bioactive agents, Skin conditions, Biological activities, Natural health products.

Introduction

Increased knowledge of skin physiology, recent technological advances, and greater demand for green, natural, and effective health products have propelled cosmetics into a biomedical revolution involving scientifically designed products containing biologically active ingredients[1]. These improved formulations targeting specific skin needs are globally called dermo-cosmetics.

To qualify as dermo-cosmetic, a product must contain bioactive ingredients whose effectiveness in restoring skin health or adjuvant treatment of a wide range of skin phenotypes and disorders has been established through rigorous laboratory testing[2]. Dermo-cosmetics are not intended to cure diseased skin. Consequently, they avoid pharmaceutical regulation and scrutiny; otherwise, they may be designed to satisfy specific skin needs linked to defined skin conditions[3].

Recently, an increasing number of plant-derived bioactive agents have been included in dermo-cosmetic formulations[4]. This leads to the creation of an extensive portfolio of innovative and natural active ingredients with an expanded range of benefits, including anti-aging, antioxidant, anti-wrinkle, soothing, hydrating, depigmenting and cooling[5]. Different technologies from science and nature are used to create these high-performing molecules. Nevertheless, there remains some debate surrounding the active ingredients found within dermo-cosmetics, particularly regarding

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their mechanism of action, formulation, penetration, and retention in the skin[1,3].

Givaudan Active Beauty (Argenteuil, France) is a multinational company specializing in researching innovative cosmetic active ingredients. These may be crafted by green fractionation (extraction of secondary metabolites from plants) as well as originating from its innovative biotech know-how. All comprise sustainable technologies to produce natural active ingredients. In particular, biotechnologies have been classified according to the type of processing: white biotechnology identifies active ingredients crafted by fermentation and biocatalysis; green biotechnology identifies plant cell cultures and phytopeptides technologies; blue or marine biotechnology identifies algae (both macro- and micro-algae) as the starting point for processing.

This review aims to provide information on the main biological mechanisms of natural active ingredients derived from the Givaudan Active Beauty experience, with a specific focus on their synergistic use for the management of different common skin conditions that dermo-cosmetics may address.

Methodology

A group of 28 different plant-derived bioactives was selected in the Givaudan Active Beauty (Argenteuil, France) portfolio, representing different technologies. A literature search was carried out without date restrictions, up to January 2022 in the PubMed scientific databases using different search terms to describe the biological activities of all active ingredients. Several scientific articles from *in vitro* and *in vivo* studies were selected and considered. Givaudan Active Beauty data on file were also included. The description of active ingredients fit was provided according to the pathogenetic mechanisms underlying common skin conditions; the most common skin specificities were identified based on epidemiological data and were restricted to conditions for which dermo-cosmetics represent a viable treatment option.

Ten common skin conditions were identified as the most frequently treated with dermo-cosmesis, namely: acne, atopic dermatitis and eczema, alopecia, dark spots and melasma, seborrheic dermatitis and dandruff, venous insufficiency and microcirculation impairment, redness, and overreacting skin, stretch marks, chronic itch, radiodermatitis (**Appendix 1**). The main biological activities of 28 active ingredients that can be exploited and combined in cosmetic formulations are described in the following paragraphs.

Acne

Acne is estimated to affect 9.4% of the global population, making it the most common chronic inflammatory disease of the skin[6]. Although it is not a life-threatening or physically debilitating disease, it can cause substantial discomfort and pain, impacting patients' quality of life (QoL) and self-confidence[7]. Acne lesions develop after abnormal desquamation of the keratinocytes lining the sebaceous follicle, resulting in hyperkeratinization and microcomedone formation. Increased sebum secretion rate is another major feature, along with quantitative and qualitative modifications of sebum[8]. In addition, the hair follicle can be infected with bacteria, which trigger an immune reaction. Among them, *Cutibacterium acnes* (*C. acnes*, formerly known as *Propionibacterium acnes*) is considered the main bacterium responsible for acne[9].

Actives for the Treatment and Prevention of Acne

Therapeutic approaches focus on hyperkeratinization, androgen-mediated sebogenesis, follicle obstruction, colonization with *C. acnes,* and inflammation related to innate and adaptive mechanisms[10]. Figure 1 summarizes the different actives that can be combined to manage the pathogenetic factors related to acne.

18ß-glycyrrhetinic acid [International Nomenclature Cosmetic Ingredient (INCI): glycyrrhetinic acid], BisaboLife™ (INCI: bisabolol) and Masknyl™ (INCI: glycerin, water, glycosylrutin, rutin) are active components with proven anti-inflammatory activity. Glycyrrhetinic acid is a natural triterpenoid from licorice root. It is obtained after hydrolyzation of glycyrrhizic acid. Its structure is similar to those of the mineral-corticoid and glucocorticoid hormones secreted by the adrenal cortex, and this supports its anti-inflammatory activity[11,12]. In particular, the 18β-glycyrrhetinic acid potentiates the anti-inflammatory activity of cortisol by inhibiting its intracellular inactivation. 18β-glycyrrhetinic acid has additionally been shown to inhibit 5-lipoxygenase and cyclooxygenase activity [Scientific files (SF) – Soothex, data on file][13], attenuate the generation of excessive nitric oxide, prostaglandin E2 (PGE2), and reactive oxygen species (ROS) and suppress the expression of pro-inflammatory genes

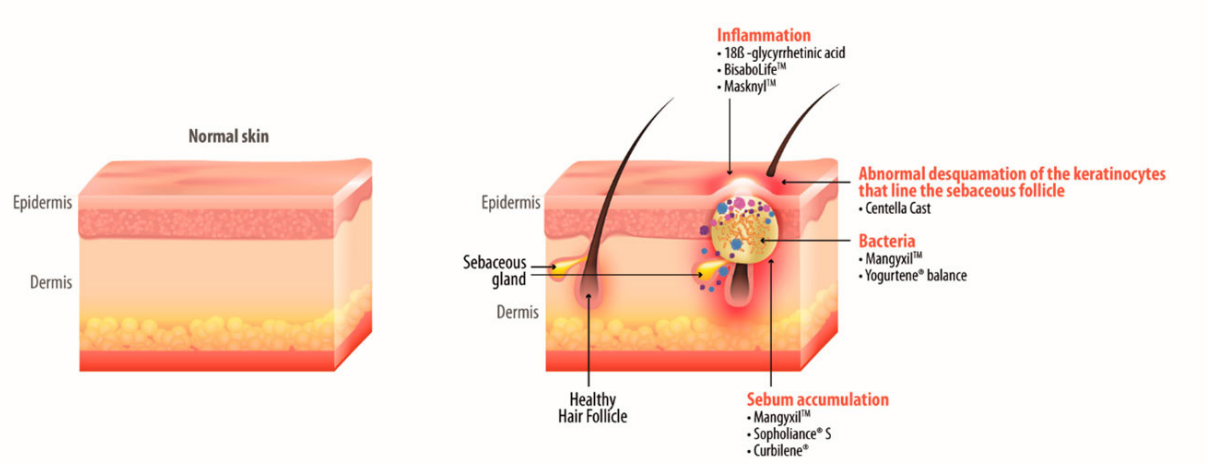

Figure 1. Actives that can be combined to manage the different pathogenetic factors related to acne.

through the inhibition of NF-κB and PI3K activity[13,14], all mechanisms contributing to its anti-inflammatory properties.

BisaboLife™ is identical to native wild chamomile and candeia tree (-)-α-bisabolol. It is crafted through a white biotechnology process, enabling this active isomer's sustainable production by using natural plant sugars as a carbon source. During the first phase of the fermentation process, plant sugars are used as a renewable substrate for fermentation. Then, the crude oil is distilled to obtain (-)-α-bisabolol. This process guarantees a purity higher than 99% (Bisabolife, data on file). The (-)-α-bisabolol has been studied thoroughly for decades and is well-known for its antioxidant and anti-infective properties[15-17]. The antioxidant activity has been determined by investigating the property of (-)-α-bisabolol to interfere with ROS. The anti-inflammatory activity is partly due to the inhibition of leukotriene synthesis[15]. In particular, (-)-α-bisabolol reduced pro-inflammatory cytokine production and ameliorated skin inflammation[18]. Clinical investigations on BisaboLife™ demonstrated that this active ingredient has the same anti-inflammatory activity on proinflammation cytokines inhibition as plant and chemical bisabolol (Bisabolife, data on file).

Masknyl™ is a phytoactive ingredient crafted from sophorin (phytomelin), a flavonoid of plant origin, quite ubiquitary in the botanical kingdom, with well-documented benefits in terms of antioxidant action, soothing, and wound healing[19]. Sophorin is widely used in the cosmetic industry at a limited dosage due to its poor solubility. Through glycosylation, the bioavailability of sophorin has been improved within Masknyl™. This compliant molecule is activated by the skin microflora and provides a rapid effect in terms of soothing and anti-redness activity (Masknyl, data on file).

Mangixyl™ (*Mangifera indica*) [INCI: mango leaf extract (and) propanediol (and) water], Sopholiance™ S [INCI: *Candida bombicola*/glucose/methyl rapeseedate ferment (and) water], Curbilene [INCI: *Cucurbita pepo* (pumpkin) seed oil] and Yogurtene® Balance [INCI: inulin (and) yogurt powder] are actives that can regulate the sebum overproduction and improve its composition, thus restoring the normal skin condition and the physiological barrier function. In addition, these actives can fight against the bacteria responsible for acne, maintaining microbiome-friendly properties and an overall balance of skin microbiome.

Mangixyl™ is crafted from the green fractionation of *M. indica* leaves and contains active phytochemical compounds, mainly polyphenols; in particular, mangiferin, C-benzophenones, and penta-O-galloyl-β-D-glucose. Preclinical studies[20-22] denoted that the ethanol fraction obtained from *M. indica* leaves and kernel was a potential anti-acne agent due to its activity against *C. acnes* and its potent free-radical scavenging and inhibitory effects on acne-related pro-inflammatory cytokines. Mangixyl™ can act on *C. acnes* metabolism, more precisely on lipase activity, which is involved in the virulence of *C. acnes* (Mangixyl, data on file).

Sopholiance™ S is a sophorose-lipid belonging to the glycolipid family, crafted through white biotechnology that exploits the fermentation *via* a microorganism, *C. bombicola*. Sopholiance™ S prevents specific bacterial proliferation present in acne (*Propionibacterium acnes*) and prevents papules and pustules formation (Sopholiance S, data on file).

Curbilene® is a lipophilic extract from *C. pepo L.* (pumpkin) seeds prepared with a specific process in CO_2 supercritical conditions, which gives extracts devoid of residual solvent[23]. Its main components are oleic acid, linoleic acid (30-50%), and fatty acids, and its composition is quite similar to human sebum. Curbilene® does not influence the sebum secretion rate; otherwise, it decreases the sebum brilliance (matting effect; 15% reduction after 8 hours from skin application) and viscosity (32% reduction after 8 hours from skin application)[24], providing a mattifying effect without affecting sebum quantity or skin barrier function, nor inducing a rebound effect due to excessive sebum depletion.

Yogurtene® Balance is crafted through white biotechnology and combines the skin benefits of yogurt powder with the prebiotic activity of inulin, a vegetable fructose polysaccharide derived from chicory. This combination can reduce the growth of pathogenic bacteria in favor of friendly microorganisms naturally present on the epidermis. It has no antibacterial properties and remains gentle for the skin. It also provides the skin with all the benefits of yogurt: non-hydrolyzed proteins, lactose, vitamins, and minerals (Yogurtene Balance, data on file).

Centella asiatica is a perennial, creeping herbaceous plant belonging to the Apiaceae (Umbelliferae) family. It has been widely used in Indian ayurvedic medicine and as a traditional herbal medicine in Asia. *C. asiatica* derivatives are available with different characteristics. Centella CAST (*C. asiatica* selected triterpenes) is characterized by a defined combination of pure terpenoids. It has been demonstrated to stimulate fibroblast activity, enhance collagen and fibronectin production, and stimulate collagen synthesis[25]. Centella CAST is used in skin care products to restore firmness and elasticity and improve skin appearance[26]. In this perspective, Centella CAST qualifies to restore and repair skin lesions and help minimize the formation of keloids.

Alopecia, Hair Thinning, and Hair Loss

Alopecia is generally used to indicate all types of hair loss, localized or diffuse, from the scalp or any part of the body. Androgenetic alopecia (AGA) is the most common form of alopecia. It affects both genders and is characterized by excessive shedding of hair with a distinctive and reproducible pattern[27]. The prevalence of AGA increased with age from 31% (age 40-55 years) to 53% (age 65-69 years)[28,29].

AGA is mainly caused by telogen *effluvium*, triggered by several factors, such as drugs, trauma and emotional and physiological stress[30,31]. AGA is characterized by a progressive reduction in hair's diameter, length, and pigmentation. Hair thinning results from the effects of the testosterone metabolite dihydrotestosterone, catalyzed by the enzyme 5-alpha-reductase, on androgen-sensitive hair follicles[32].

Actives for the Treatment and Prevention Of AGA

AGA needs long-term treatment, and there are side effects and toxicities associated with conventional FDA-approved drugs. Consequently, bioactives framed in the cosmetic/dermo-cosmetic sector can provide beneficial treatment and minimum side effects compared with the conventional marketed drugs[33].

AGA usually starts with an increase in telogen hair (loss), paralleled by a decrease in anagen hair (regrowth) or an increase in the dystopic anagen (not fully formed hair). Consequently, therapeutic approaches can focus on increasing anagen hair and decreasing telogen hair (dystopic anagen hair to improve the hair density).

Redensyl™ [INCI: glycerin (and) water (and) *Larix europaea* wood extract (and) glycine (and) zinc chloride (and) *Camellia sinensis* leaf extract] is a hair care ingredient crafted through green fractionation and white biotechnology that acts as a hair growth galvanizer by reactivating hair follicle stem cells and dermal papilla fibroblasts. It comprises patented molecules [dihydroquercetin-glucoside (DHQG) and epigallocatechin gallate-glucoside (EGCG2), two stabilized polyphenols] targeting the outer root sheath bulge stem cells and the fibroblasts located in the dermal papilla. Glycine and zinc, two other components of Redensyl™, are also involved in hair metabolism. Glycine is a major constituent of specific hair proteins called keratin-associated proteins (KAP)[34]. Zinc is essential for cystic incorporation into keratin[35]. Clinical investigation has shown that Redensyl® is efficient in treating androgenic alopecia male patterns and, more generally, treating hair loss (Redensyl, data on file). Redensyl® has also been shown to boost hair growth and decrease hair loss with visible results in 3 months by promoting the conversion of hair follicles into the anagen phase (Redensyl, data on file).

Prevention measures can also be implemented by stimulating hair growth through the stimulation of keratinocyte mitosis, the protection of the hair bulb, and the increase in the hair resistance to traction. Maca (*Lepidium meyenii*) is a plant that grows in the high Andes mountains of Peru. Maca root contains secondary metabolites, such as macaenes and macamides (alkaloids), mainly responsible for hair growth properties and protective activities against external stress. Seveov™ [glycerin (and) water (and) *L. meyenii* root extract] is a 100% derived natural maca extract that stimulates hair growth by promoting keratinocyte mitosis and protecting the hair bulb. It has been shown to increase cell proliferation in hair bulbs and the epithelial sheaths by 169% and 36%, respectively, demonstrating its protective benefits (Seveov, data on file). It also increased collagen density in the underlying dermal tissue, promoting hair adhesion to the scalp, thus preventing hair loss.

Centerox™ [INCI: madecassoside (and) *C. asiatica* leaf extract (and) asiaticoside] is a purified extract from *C. asiatica,* an Ayurvedic medicinal herb of the *Umbelliferae* family originating from the Indian Ocean and typical of eastern medicine. *C. asiatica* targets the production of key components of the dermo-epidermal junction, such as laminin-5 and fibronectin, forming the basis of skin structural support and thus increasing hair resistance. A lotion based on Centerox™ showed effectiveness in increasing hair resistance to traction as well as decreasing the number of hairs lost during the washing (-41.2%)[36]. Centerox™ also showed positive effects on laminin-5 production, with a 33% (p<0.05) increase compared to placebo[36].

Sabalselect™ [INCI: *Serenoa serrulata* fruit extract] is extracted from palm tree berries, also known as saw palmetto (or *Serenoa repens*). The mechanism of action of *Serenoa* is the inhibition of 5-alpha-reductase, which converts testosterone to metabolite dihydrotestosterone responsible for AGA[33,37,38]. The influence of Sabalselect™ on hair growth was assessed in different studies, which showed an increase in average hair count and terminal hair count[39-41].

Atopic Dermatitis and Eczema

Atopic dermatitis (AD), also called atopic eczema, is a common chronic or recurrent inflammatory skin disease and affects 15-20% of children and 1-3% of adults worldwide. It is characterized by acute flare-ups of eczematous pruritic lesions over dry skin[42,43]. AD usually starts in early childhood and may represent the initial step of the so-called 'atopic march,' which represents the natural history of atopic manifestations preceding the development of other allergic disorders (typically asthma) later in life[43-45]. In total, 50% of AD patients develop other allergic symptoms within their first year of life, and probably as many as 85% experiences an onset below 5 years. Patients usually outgrow the disease in late childhood: about 70% with disease onset during childhood have spontaneous remission before adolescence. However, early childhood AD is often the initial indication that a child may later develop asthma and/or allergic rhinitis (hay fever)[46,47].

Actives for the Treatment of Atopic Dermatitis and Eczema

AD and eczema can be considered chronic or recurrent inflammatory skin diseases with acute flare and pruritic lesions over dry skin and skin barrier disruption. As a protective response, the interested skin areas are usually much thicker than unaffected skin and present crusts.

Actives with proven anti-inflammatory activity (18β glycyrrhetinic acid, BisaboLife™, Bosexil™) can be used to manage eczema AD.

Bosexil™ (Boswellia Phytosome®) [INCI: *Boswellia serrata* resin extract (and) lecithin (and) microcrystalline cellulose (and) silica] is a new boswellic acid formulation between soy lecithin and a highly purified *Boswellia* extract, crafted through white technology[48]. The two compounds form a non-covalent adduct in a 1:1 weight ratio, and one part of microcrystalline cellulose is added to improve the formulation, with an overall content of boswellic acids of at least 25%. The Phytosome® form is a delivery system aiming to improve the skin affinity of boswellic acids. *Boswellia* properties are widely recognized, mainly for the treatment of inflammatory conditions, through the inhibition of the production of inflammatory cytokines Il-6, IL-8, TNFα, and ROS, as well as for wound healing and its antimicrobial activity[49,50].

Dysfunction of the epidermal barrier also has a pathogenic role in AD and eczema[51] and could trigger multiple downstream pathways, resulting in pruritus. Therefore, epidermal barrier protection and proper skin hydration maintenance play a key role in managing these skin conditions.

More specifically, using a cream with boswellic acids and 18-β-glycyrrhetinic acid allows an

amelioration of the skin condition. It may provide adjunctive benefits as restoring the skin barrier function acting on complementary mechanisms, thus suggesting a supportive use in the remission phase, prolonging the remission times between clinical relapses with an overall improvement of the QoL[52].

Hydreïs™ [INCI: water (and) hydrolyzed beta glucan (and) citric acid] and Xylogel™ [INCI: tamarind seed polysaccharide] are polysaccharides that can be used to promote proper skin hydration. Hydreïs™ is crafted through white biotechnology from a Martinique exotic bacteria strain, found in soil subject to extreme hydric stresses. This strain produces an exopolysaccharide that maintains organic stocks and water content. Hydreis™ is obtained by selective hydrolysis of the exopolysaccharide and has a controlled molecular weight between 1 and 15 kDa, facilitating its penetration and activity in the skin. It can stimulate the repair of the involucrin and the filaggrin, responsible for the structure of the stratum corneum and the natural moisturizing factors[53]. Moreover, it stimulates the synthesis of the components of intercellular hydration canals called the aquaporin-3[53].

The main component of Xylogel™ is a branched polysaccharide from the tamarind seed consisting of a cellulose-type backbone (β-(1→4)-D glucose) which carries xylose and galactoxylose substituent. Its high molecular weight allows the formation of viscous gels with a unique sensory feeling. Thanks to its branched structure, it exerts a moisturizing effect comparable to hyaluronic acid. In particular, it increased skin hydration and improved overall skin elasticity rapidly (Hydreïs, data on file). Xilogel™ was also shown to provide a tendential increase in filaggrin on human epidermis reconstructed models (Hydreïs, data on file).

Besides hydration and maintaining a healthy skin barrier function, lipids are also essential. The skin barrier is based on essential lipids[54]. To reintegrate and maintain the skin barrier in good shape, it is crucial to supply it with essential PUFA (e.g., omega-3-like alpha-linolenic acid and omega-6-like linoleic acid). This, in turn, leads to ceramides formation (constituting the lipids mortar of the stratum corneum), keratinocytes differentiation, and activation of PPAR (peroxisome proliferator-activated) receptors for the restoration of homeostasis. Omegablue™ [INCI: *Vaccinium myrtillus* seed oil] and Vetivyne™ (INCI: propanediol (and) water (and) *Vetiveria zizanoides* root extract) actives can protect the skin barrier by acting on the lipid metabolism of the skin. Omegablue™ is crafted through green fractionation, upcycling the bilberry seeds left after juice extraction. It represents a source of essential fatty acids like linoleic acid and a-linolenic acid[55]. It has been tested on keratinocytes to demonstrate its ability to stimulate cellular proliferation and improve PPAR-α activation, which is deeply involved in the formation and repair of the epidermal skin barrier, thus ameliorating the skin barrier function (internal data)[56]. Omegablue™ has also been shown to act in soothing challenged skin by forming a protective barrier from external agents due to its content of essential PUFA relevant for the anti-inflammatory cascade[57].

Vetivyne™ is made from a water-soluble extract of exhausted vetiver roots through green fractionation. It acts on the skin's three main lipids sources through a potent lipid synthesis activity, which improves sebum production, keratinization, and the adipocytes' capacity to store fat. Internal data supported this biological mechanism and showed that Vetivyne™ improved the epidermal barrier through the modulation of lipid metabolism of the skin (Indene, data on file).

Eczema is normally associated with an itchy sensation, itching resulting from skin nerve over stimulation that several factors may trigger. Zanthalene™ [INCI: oleyl alcohol (and) *Zanthoxylum bungeanum* fruit extract] is based on a typical alkylamide (α-hydroxy-sanshool) from Sichuan pepper, and it is obtained through green fractionation. Zanthalene™ can induce a tingling sensation through chemestesis (triggering some skin receptors normally responding to a physical stimulus *via* a chemical stimulus). It was found to deplete the neurotransmitter and induce a state of numbness (temporarily blocking the Na^+ channels) (Vetivyne, data on file). It can interact with sensory receptors at low dosages, removing skin discomfort, such as itch[58].

Figure 2 reports the different actives that can be used to manage clinical manifestations related to AD and eczema.

Seborrheic Dermatitis and Dandruff

Seborrheic dermatitis (SD) and dandruff are common dermatological problems affecting the body's seborrheic areas. SD incidence peaks during three age periods - in the first 3 months of life, during puberty, and in adulthood with an apex between the ages of 40-60 years (Zanthalene, data on file)[59-61]. In infants up to 3 months of

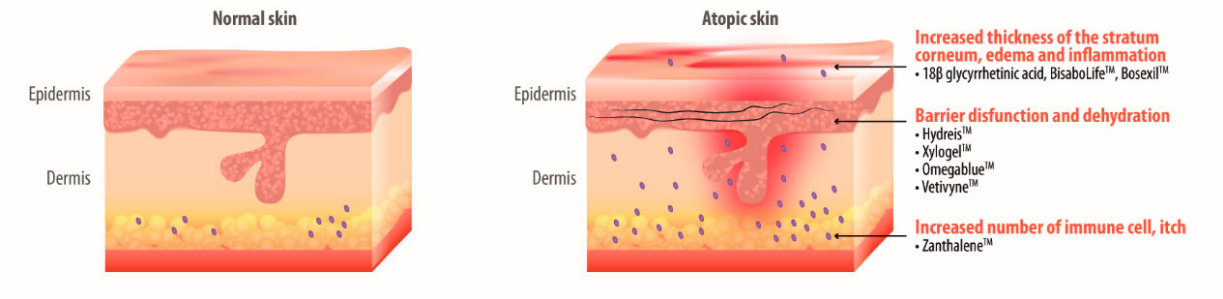

Figure 2. Actives that can be combined to manage the different clinical manifestations related to atopic dermatitis and eczema.

age, the incidence can be up to 42%[61-63]. In adolescents and adults, SD affects the scalp and other seborrheic areas on the face, upper chest, axillae, and inguinal folds[61,64,65]. Incidence is 1-3% of the general adult population[60,66]. Men are affected more frequently than women (3.0% *vs.* 2.6%) in all age groups, suggesting that SD may be associated with sex hormones such as androgens (Zanthalene, data on file)[60,65]. No apparent differences were observed in SD incidence between ethnic groups[60].

Dandruff shows many common features, such as SD in histology, such as epidermal hyperplasia, parakeratosis and *Malassezia* yeasts surrounding the parakeratotic cells[67]. Whereas inflammatory cells, such as lymphocytes and NK cells, may be present in great numbers in SD, dandruff shows subtle neutrophil infiltration or no infiltration[67].

Actives for the Treatment of Seborrheic Dermatitis and Dandruff

One of the key targets for oily skin is an enzyme, the 5-α-reductase, which is responsible for the over-secretion of sebum at certain stages of life, such as during puberty or other hormonal changes. Sopholiance™ S, K-phyto™ GHK [INCI: water (and) caffeoyl tripeptide-1] actives can counteract this sebaceous activity. Conversely, Patchoul'Up™ [*Pogostemon cablin* leaf/stem extract (and) water] counteracts dry flakes associated with itching and dry scalp.

Caffeic acid is one of the main phytochemicals in coffee, well known for its antioxidant and soothing benefits. Tripeptide GHK is a naturally occurring plasma peptide belonging to the matrikine family, stimulating collagen production. Through green biotechnology, these molecules were combined into a new phytopeptide called K-phyto™ [PP] GHK offers different actions, starting with the antioxidant and antiaging activities conserved over the initial phytochemical (caffeic acid) and peptide (matrikine GHK), enhanced by additional inhibition of sebum production obtained through inhibition of the 5-α-reductase production up to -40% (K-Phyto [PP] GHK, data on file)[68].

Patchoul'Up™ is a 100% upcycled active ingredient able to rebalance sebum production, eliminate dry flakes from the scalp and normalize the scalp microbiome. It is crafted through green fractionation from distilled patchouli leaves after their use as a raw material in fragrance creation. Patchoul'Up™ contains specific botanical oligosaccharides and proteoglycans able to act on keratinocytes to reduce their excessive migration while reducing the thickness of the stratum corneum (-35%), which contributes to decreased scalp over-exfoliation at the origin of dry flakes. Patchoul'Up™ has also been shown to trigger skin barrier function by boosting keratohyalin, filaggrin, and caspase 14 and stimulating the Natural Moisturizing Factor up to +35% (Patchul'up, data on file).

Dandruff is often associated with itching, and the chemestesis sensorial modulation provided by Zanthalene can be exploited to manage this clinical manifestation.

Melasma and Dark Spots

Melasma is a common pigmentary disorder characterized by asymmetrical, hyperpigmented macules and dark, patchy skin that develops in sun-exposed areas, especially the face and neck[69,70]. The exact prevalence of melasma is unknown in most countries and varies according to ethnic composition, skin phototype, and intensity of sun exposure[71].

While the pathogenesis of melasma remains unclear, certain risk factors are known, such as exposure to UV light, female gender, a genetic predisposition, hormonal changes, such as pregnancy, use of oral contraceptives, and hormone replacement therapy[72,73].

The emotional and psychological effects of this disorder can severely impact the patient's QoL[74]; moreover, the treatment of melasma can be challenging because long-term therapy is often required, and reoccurrence is common[74].

Dark spots (or aging spots, brown spots, etc.) are one of the most important aging concerns[75], appearing mainly on the face and hands, the most UV exposed areas; they are the consequence of an overproduction of melanin during skin pigmentation. The uncontrolled pigmentation process can have several causes: aging process (senile lentigo), UV overexposure (solar lentigo), inflammatory or wound healing processes (scars), pollution, among many others. Whitening agents or exfoliating compounds represent to date the only strategies to counteract hyperpigmented spots. However, they are often aggressive for the skin or with an impact on the skin tone, as they not specifically act on the spots.

Recently, a new biological pathway has been described to explain how the loss of communication between senescent fibroblasts and melanocytes represents the main cause of uncontrolled pigmentation. Within this pathway, a key protein (SDF-1) has been described as crucial messenger in our skin, but its production decreased drastically in senescent conditions[76].

Actives for the Management of Melasma and Dark Spots

Pigmentation of the skin is related to melanin, the colored substance responsible for our skin color. Pigmentation occurs *via* the transfer of melanin produced from melanocytes to keratinocytes. This process can be affected by a variety of factors. Active ingredients can focus on the normalization of melanin production, the melanocytes-keratinocytes transfer, the reactivation of cellular communication, and the regulation of the inflammatory/oxidative pathways without having the side effects of hydroquinone, whose usage remains limited to the prescription drugs field. Antioxidants are a particularly interesting addition because they participate in reducing cutaneous inflammation and efficiently complete the action of the other components of a depigmenting formula[77].

THBG [trihydroxy benzoic acid; Brightenyl™ (INCI: glycerin (and) water (and) diglucosyl gallic acid)] is perfectly stable and highly water-soluble active, crafted through green fractionation and white biotechnology as a safe whitening and skin complexion agent. Once applied to the skin, the enzymatic activity partially converts THBG into two molecules (trihydroxybenzoic acid [THBA] and trihydroxybenzoic acid glucoside) of the stratum microbial layer. Delivered *in situ*, THBA and THBG act in synergy on seven different biological targets to regulate and optimize the skin complexion. In detail, THBA and THBG have been shown to capture UV-induced free radicals (ROS), prevent UV-induced DNA damages, reduce PGE2 production, control the NF-κB pathway, control melanocyte-inducing transcription factor (MITF) expression, saturate keratinocytes receptors for melanosomes and block melanin synthesis even under UV conditions (Brightenyl, data on file)[78].

B-Lightyl™ (INCI: glycerin (and) water (and) ascorbic acid (and) *Himanthalia elongata* extract) is an active ingredient based on a macroalgae extract (*H. elongata*) obtained through marine biotechnology, able to re-establish the communication between fibroblasts and melanocytes (reactivating SDF-1 production in senescent skin conditions or under over-exposure to UV). In addition, B-Lightyl™ enables it to take back control of the skin pigmentation process, both in a preventive and curative way, thanks to its antioxidant properties. Three clinical studies were carried out on various ethnicities. On Caucasian volunteers, B-Lightyl™ demonstrated a significant reduction of the melanin content on hyperpigmented spots on hands after 28 days of application, reporting a 103% reduction compared with placebo ($p<0.05$). On Asian volunteers, B-Lightyl™ visibly reduced face spots after 28 and 56 days of twice-daily application, showing -156% ($p<0.01$) and -292% ($p<0.05$) of reduction, respectively. On African volunteers, B-Lightyl™ reduced on the hyperpigmented face spot the melanin content, showing -91% ($p<0.01$) and -327% ($p<0.01$) after 28 days and 56 days, respectively (B-Lightyl, data on file).

Skin and Microcirculation

Venous insufficiency (VI) defines a state of alteration of the venous wall, with an increase in lateral pressure and permeability and a reduction in flow[79]. These microcirculatory disturbances lead to evident tissue damage in some districts, such as lower limbs. Frequently reported symptoms are telangiectasia or reticular veins and varicose veins, edema, leg pain, and heaviness. More advanced symptoms comprise trophic disorders

(pigmentation or eczema), skin fibrosis, and venous ulceration, which can become a chronic wound in the advanced forms of the disease[80-82]. An abnormal venous flow of the lower extremities is observed in up to 50% of individuals. Up to 17% of men and 40% of women may experience a chronic form of VI in their lifetime, significantly impacting their QoL[82-84].

Actives for the Management of Microcirculation Impairment

Different actives can act on the vein walls, increasing their tonus and thus reducing pain, stabilizing capillary permeability, and increasing lymphatic drainage[85,86]. This activity provides a hemodynamic effect (which improves venous return) and an anti-inflammatory venous impact[87,88].

Visnadin™ (INCI: Visnadin) active is obtained from the seeds and aerial parts of *Ammi visnaga* L., widely used in Egyptian medicine as an antispastic and vasodilator[89]. It can improve the pumping action of the arterioles by increasing the release of prostacyclin, which induces vessels' rhythmic contractions. The vasodilating properties are associated with its two major γ-pyrones, khellin and visnagin, and the pyranocoumarin and visnadin. Both khellin and visnadin have been proven to possess calcium antagonistic activity, which, in turn, yields vasodilating activities[90]. Visnadin™ also has anti-phosphodiesterase activity, thus increasing lipolysis[90].

Escin is a mixture of triterpenic saponins extracted from horse chestnuts. The main molecular mechanism of escin is selective vascular permeabilization: it produces a selective sensitization of vascular smooth muscles to Ca^{2+} ions, increasing venous tone and capillary sealing. Capillaries become less permeable to water, thus performing microcirculation-boosting and anti-edematous activity[91]. Escin provides anti-oedematous properties, also inhibiting neutrophil adherence[91]. Additionally, it has been observed that escin can act on different pathways to counteract the release of pro-inflammatory mediators (PGE2) at the vascular level and the NF-κB pathway. It inhibits catabolic enzymes, such as hyaluronidase, elastase, collagenase and cyclooxygenase[92,93].

C. asiatica derivatives effectively improve some venous wall alterations (including thickening and swelling) in varicose veins and chronic venous insufficiency[94]. *Centella asiatica* is also considered active in connective tissue modulation (i.e., in venous ulcerations) and may improve the organization of collagen and other tissue proteins, such as elastin, by modulating the growth and action of fibroblasts in the vein wall and stimulating collagen remodeling in and around the venous wall (Centella CAST, data on file)[95].

Redness, Overreacting, Sensitive Skin

Sensitive skin is a clinical condition defined by the self-reported facial presence of different sensory perceptions, including stinging, tightness, burning, pain, tingling, and pruritus[96]. These symptoms suggest the involvement of cutaneous nerve fibers and neuronal and epidermal thermos channels.

Sensitive skin may occur in individuals with normal skin, with skin barrier disturbance, or as a part of the symptoms associated with facial dermatoses, such as rosacea, AD and psoriasis[97]. There is an increase in the reported number of individuals with sensitive skin, especially in the female population, 50% of which describe their skin as very sensitive[98].

Actives for the Management of Redness, Overreacting, Sensitive Skin

Redness and sensitive skin management mainly focuses on treating inflammation and protecting the skin barrier (Figure 3). The combined use of the anti-inflammatory actives Bosexil™, 18β glycyrrhetinic acid, and BisaboLife™ can be combined with Omegablue™ and Vetivyne™.

Ocaline™ [INCI: seawater (and) *C. pepo* (pumpkin) seed extract (and) citric acid] is an optimized blend of spring seawater and a vegetable extract from the seeds of *C. pepo* L. fruits obtained through green fractionation, which can favor the inhibition of the release of inflammatory neuro-mediators, such as substance P. This neuropeptide stimulates histamine release by mast cells leading to extravasation and, consequently, to a leak of plasma and proteins from microcirculation, which is responsible for erythema[5]. The anti-inflammatory effect of Ocaline™ PF was evaluated on 10 adult women; erythema, dryness, roughness, and subjective symptoms were assessed after the application of an irritating agent. Ocaline™ significantly decreased the erythema, roughness, and dryness within 3 hours, providing an immediate soothing effect compared with the control treatment (Ocaline, data on file). Moreover, Ocaline™ showed the ability to soothe skin with preventing effect within 7 days of daily use (Ocaline, data on file).

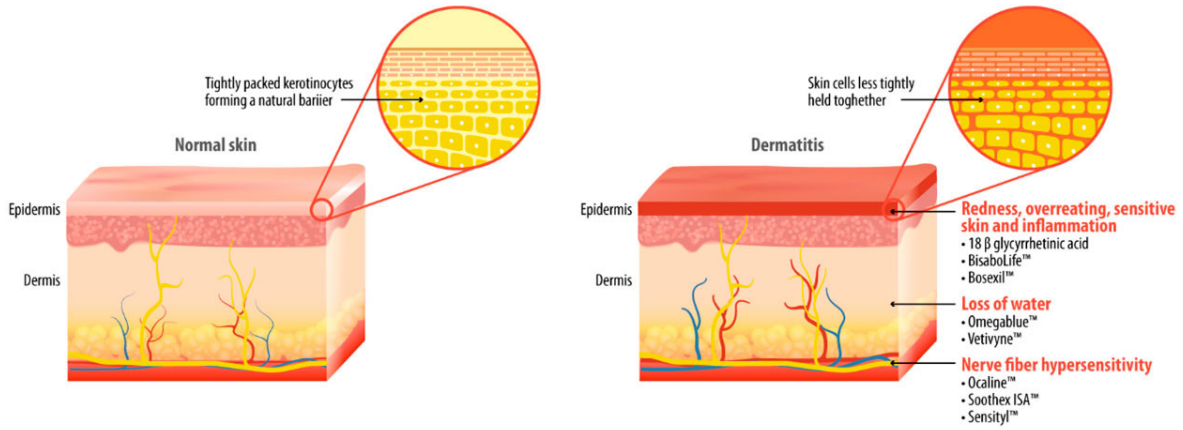

Figure 3. Actives that can be combined to manage redness, overreacting, sensitive skin.

1. Soothex ISA™ [purified *Olibanum gum* resin at 10%, green fractionation – INCI: isostearyl alcohol (and) *Boswellia serrata* gum] and Sensityl™ [*Phaeodactylum tricornutum* from the diatom, the dominant class of marine phytoplankton, marine biotechnology – INCI: water (and) *Phaeodactylum tricornutum* extract (and) pentylene glycol] offer soothing and calming actions to the skin by rebalancing sensitive skin microbiota and taking control over the whole inflammation process. Soothex ISA™ inhibits the 5-lipoxygenase (inflammatory leukotrienes) and the human leukocyte elastase (protease enzyme that causes tissue degeneration and further inflammation], thus providing a double anti-inflammatory and anti-aging effect [Scientific files (SF) – Soothex, data on file). Sensityl™ showed protection of skin microbiota against sensitive skin conditions, restoration and protection of sensitive skin and improvement of cutaneous reactivity (Sensityl, data on file)[5].

Stretch Marks

Stretch marks, or *striae distensae* (SD), are the lesions of the dermis caused by its linear atrophy at stretching sites. They occur in more than 70% of pregnant women and adolescents due to cutaneous stretching[99].

Early- and late-stage SD can be distinguished by s*triae rubrae* and s*triae albae*. Histopathology of s*triae rubrae* reveals excessive fine elastic fibers in the papillary dermis with thicker tortuous fibers in the periphery, perivascular lymphocytes, dilated dermal vessels, and edema. There is reduction and reorganization of elastin and fibrillin fibers and structural changes in collagen fibers, which are thicker and densely packed in parallel rows. Histopathology of *striae albae* shows epidermal atrophy, loss of rete ridges, less vascularity, and densely packed, thin, and scar-like horizontal collagen bundles[100].

Actives for the Management of Stretch Marks

Treatment of stretch marks aims to reduce redness, swelling, and irritation in *striae rubrae*, increase collagen and elastic fiber production, ameliorate collagen organization, improve hydration, and reduce inflammation in *striae albae* (Figure 4)[101].

Actives with proven anti-inflammatory activity (18 β glycyrrhetinic acid, BisaboLife™, Bosexil™) and able to reduce redness and swelling (Sensityl™, Quercevita™) and promote hydration (Hidreis, Xilogel HS, PrimalHyal™) and collagen reorganization (*C. asiatica* derivatives, such as Centella CAST and Centerox) can be used to manage stretch marks.

Quercetin is one of the most abundant natural flavonoids in fruits and vegetables. It shows superior antioxidant activity within the flavonoid family and acts mainly by scavenging oxygen radicals, protecting lipids against peroxidation, and chelating metal ions[102]. In addition, it displays anti-inflammatory properties, including inhibition of cytokine production, such as TNF-α and IL-8[103,104]. Quercevita™ (INCI: lecithin, quercetin) is characterized by a phospholipids-based delivery system used to increase the ability of quercetin to permeate the skin. In a monocentric,

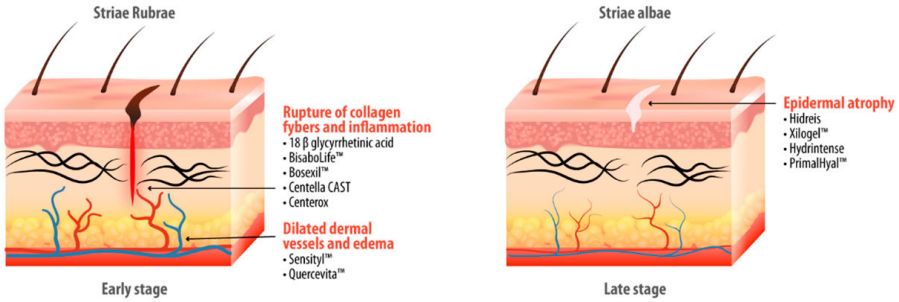

Figure 4. Actives that can be combined to manage stretchmarks.

single-blind trial, the use of Quercevita™ showed a significant soothing effect against skin inflammation induced by different insults, including UV radiation, histamine prick test, and skin barrier disruption[105]. The soothing effect was visible as reduced redness (erythema), wheel diameter, and itching sensation. In addition, the results suggest the ability of Quercevita™ to help restore skin barrier functions, given the increase in hydration and the reduction in trans-epidermal water loss (PrimalHyal 50, data on file).

PrimalHyal™ 50 (INCI: hydrolyzed hyaluronic acid) is a patented grade of low-molecular-weight hyaluronic acid (MW: 20-50 KDa) crafted through white biotechnology, able to stimulate tight junction to reinforce skin cohesion and prevent trans-epidermal water loss, increase pro-collagen I synthesis and reduce skin roughness (-66% in 29 days, *in vivo* test)[106].

Chronic Itch

Chronic itch is an itch occurring for 6 weeks or longer[107]. It is an unpleasant symptom affecting many dermatological patients. The frequency and the causes of chronic itch depend on age, predisposition, such as atopy, underlying diseases, ethnicity, climate/humidity, and especially access to the regional healthcare system[107,108]. The lifetime prevalence of chronic itch is 22% in the general population, demonstrating that more than one out of five people experience it once in their lifetime[109].

Actives for the Management of Chronic Itch

Acute, chronic, or recurrent inflammatory skin diseases can cause itching, mainly due to dry skin and breakdown of the skin barrier. Consequently, a combination of actives able to modulate sensoriality and itch perception acting on the skin receptors (Zanthalene), calm inflammation (18ß-glycyrrhetinic acid, BisaboLife™, Bosexyl™), protect the barrier (Omegablue™, Vetyvine™), promote hydration (Xilogel™), can be used to manage the chronic itch.

Radiodermatitis

Radiotherapy, specifically on the delicate breast area but generally all over the body, induces a skin reaction in up to 95% of patients. This is due to the local increase in free radicals that damage skin tissues and trigger an inflammatory response involving tissues and blood vessels. This leads to vasodilation, edema, and the production of pro-inflammatory cytokines[110].

The damage can result from several processes, including reduced endothelial cell changes, inflammation, and epidermal cell death[111].

Actives for the Management of Radiodermatitis

Radiation-induced skin reactions (Figure 5) are often characterized by swelling, redness, pigmentation, fibrosis, and skin ulceration[112].

Bosexil™ (*B. serrata*) was tested in women under radiotherapy for breast cancer diagnosis in multiple studies, showing a soothing and lenitive effect[113,114]. Formulations additionally containing Omegablue™ and Xylogel™ can be useful to protect the skin barrier and promote hydration. Zanthalene™ can be useful to manage itch, and 18β glycyrrhetinic acid can be exploited to manage burning consequent to the inflammatory reaction.

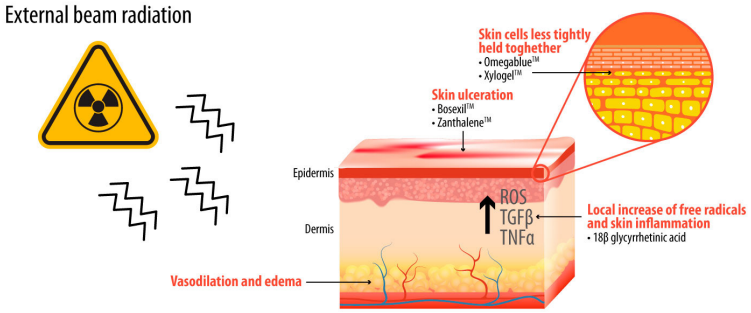

Figure 5. Actives that can be combined to manage radiodermatitis.

Discussion

Currently, chronic disturbances in skin homeostasis are common among all age groups. They are mainly associated with extrinsic factors exposure to microbes, biological toxins, and chemical agents, and intrinsic factors like individual predisposition. They can develop pathological conditions, such as acne vulgaris, AD, eczema, seborrheic dermatitis, dandruff, melasma, dark spots, redness, and stretch mark[115,116]. Though these are not life-threatening diseases, these pathologies strongly and negatively influence the QoL of affected people and may have serious psychological consequences. Patients are often embarrassed about the appearance of their skin, and the long-term therapy and social costs of these conditions have a major impact on healthcare systems and society in general[117-120]. Since therapeutic modalities to manage these skin conditions are still extremely limited and often accompanied by relevant side effects, the treatment with dermo-cosmetics is increasingly widespread. In particular, dermo-cosmetic formulation, including active principles of natural origin, can protect the skin against exogenous or endogenous harmful agents and help remedy many skin conditions[3]. Moreover, even when dermo-cosmetics are not intended to improve or cure diseased skin, their use has been associated with reducing drug use and skin disease flares[10]. Since the pathogenesis of skin diseases is extraordinarily complex and given the growing interest in plant-derived dermo-cosmetic products among patients, the knowledge of the main biological mechanisms underlying the activity of natural active ingredients is crucial in the identification of the therapeutic targets and correctly defining the combination of actives that can be used to manage different skin conditions[3]. Scientific data show that plant-derived bioactives are involved in many biological mechanisms showing anti-inflammatory, antioxidant, and moisturizing properties, along with skin barrier protection and collagen synthesis activities. Emollient natural remedies often contain polysaccharides, complex sugars, and starch derivatives that relieve dryness mostly with biomimetic mechanisms and provide a soothing membrane that covers the skin (eg., Hydreis™, Xylogel™). Protection of skin hydration is achieved using seed oils rich in fatty acids and triglycerides that reduce epidermal water loss and biologically contribute to the protection and repair of the skin barrier by different mechanisms involving PPAR receptors and ceramide precursors (e.g., Omegablue™). Actives with antioxidant properties often have a high level of flavonoids, engineered with technologies to make flavonoids more bioavailable (e.g., glycosylation in Maskynl™, phytosome in Quercevita); in case of infection, using plants with selective antimicrobial and antifungal biocides can be beneficial (e.g., Mangixyl™).

Different combinations of bioactives within dermo-cosmetics can be defined to simultaneously counteract different pathogenetic mechanisms underlying various skin conditions, considering the complexity of the skin disease pathogenesis. At the same time, helping patients understand the degree of improvement that can be achieved with dermo-cosmetics should remain a primary responsibility of the physician.

As technology advances, dermo-cosmetics continue to become more sophisticated and widely used. To enhance the effectiveness of molecules and to allow a better delivery and a lower risk of side effects, different biotechnology solutions are constantly being developed and applied. For example, the glucosylation by biocatalytic reaction of poorly soluble substances has shown to be a valid solution to obtain stable, water soluble

and easy to formulate derivatives. Improvement of polyphenol properties upon glucosylation has been observed within Redensyl® (composed of dihydroquercetin-glucoside and epigallocatechin gallate-glucoside, two stabilized polyphenols) and Brightenyl™ (trihydroxy benzoic acid), as well as in other examples from the literature[121,122]. At the same time, plant cell culture technology has the potential to meet the continuously growing demand for bioactive natural compounds in the near future. In line with this tendency, in the last years an exponential increase in the number active substances obtained by plant cell culture technology has been observed (eg., K-phyto™ [PP] GHK)[123]. A further opening towards the plant cell culture technology will be prosecuted with the aim to achieve a more sustainable development, restricted access to fresh water, limited food supply and energy demand, since these all are critical global challenges[123]. The development of high-quality active ingredients and reproducible production methods also represent fundamental aspects to overcome doubts regarding the safety of plant-derived ingredients. For instance, standards for testing dermo-cosmetic products are continuously evolving, and trials to test their efficacy and safety adhere to strict methodologies that are reproducible, scientifically sound and comply with the latest approved guidelines[2]. In particular, all safety assessments and post-marketing surveillance for a given cosmetic formulation are conducted using a process similar to that for medical products and devices. In addition, since 2013, the Platform of European Market Surveillance Authorities for Cosmetics has been established to facilitate cooperation and coordinate all activities in the field of cosmetics market surveillance[124].

Conclusions

Available literature evidence suggests that the synergistic use of natural-derived bioactive agents (be it plants, algae or biotech engineered active ingredients) within dermo-cosmetics can be a viable and safe option for managing the most common skin conditions. As technology advances and dermo-cosmetics continue to become more sophisticated and widely used, the medical profession must continue to play an active role in familiarizing themselves with these products and educating patients about the expected benefits of their use.

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Conflicts of Interest

RR, FL, MF, AS, and GM are employees of Givaudan Active Beauty.

Authors' Contributions

All Authors contributed to the definition and contextualization of paper contents, critically edited the manuscript, and approved its final version for submission.

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