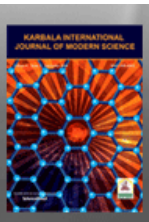
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Abstract

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Keywords

Skin microbiome, Cosmeceuticals, Prebiotics, Probiotics, Postbiotics, Bioactive compounds

REVIEW ARTICLE

Skin Microbiome: Current Target for Cosmeceuticals

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Abstract

Skin acts as a barrier to the external environment and perform various functions like maintaining internal homeostasis, sensations to touch based stimuli, vitamin D production and defence against foreign pathogens, prevent dehydration. Skin has its own diverse microbiota like bacteria, virus, fungi that is collectively called as skin microbiome. Skin microbiome balance is disturbed (condition called dysbiosis) by both internal and external factors which lead to skin problems like acne, psoriasis, dandruff. It is important to maintain the healthy skin ecosystem. Cosmeceuticals i.e., combination of cosmetic and pharmaceuticals, is a recent trend in the skin care industry where we add extract or bioactive compounds in the form of lotions, creams, mists to increase the supply of nutrition to the skin. Being hybrids of cosmetics and pharmaceuticals, they are applied topically as cosmetics but also contain the ingredients that influence the biological functions of the skin. Prebiotics (to stimulate the growth of favourable bacteria), Probiotics (good bacteria to skin) and Postbiotics (adding by-products of bacteria) are added into the product to enhance the skin flora. Bioactive compounds like minerals/vitamins (e.g., selenium, Vitamin E), phytochemicals (polyphenols) and microbial metabolites like hyaluronic acid) and peptides are used as an ingredient in cosmeceuticals. They act as antioxidants, anti-hyperpigmentation, anti-inflammatory, anti-ageing, anti-wrinkles, and UV protection. Developing product that can improve the healthy eco-system of skin is a new trend in dermatological products which are the future generation skin care products.

Keywords: Skin microbiome, Cosmeceuticals, Prebiotics, Probiotics, Postbiotics, Bioactive compounds

1. Introduction

Skin acts as a barrier to the external environment and performs various functions like maintaining internal homeostasis, sensations to touch based stimuli, vitamin D production and defence against foreign pathogens, and prevents dehydration [1]. Epidermis is outermost layer composed of stratum corneum (horny layer), Stratum lucidum (only present in thick skin), stratum granulosum (granular layer), stratum spinosum (prickle cell layer), stratum basale (germinative layer), selectively permeable membrane majorly made of keratinocyte cells comes in contact with the external environment [2]. Maintaining moisture is the function of stratum corneum [1]. This layer holds moisture of the skin as corneocytes can swell up becoming pliable and elastic thus preventing cracking in the skin [2]. Internal factors include change in the enzyme activity that can lead to decrease in the natural moisturizing factors that cause dehydration of stratum corneum. This can also lead to corneodesmolysis, where the protein complex responsible for binding adjacent corneocytes does not undergo enzymatic break down and forms powder like flakes at the surface of skin. In contrast, external factors like dry environment are the cause for gradual dehydration of stratum corneum followed by deeper layers. Dehydration of epidermal layer leads to liberation of inflammatory agents, triggering an increase in keratinocyte production. and disruption of epidermal differentiation and ultimately disrupt the natural barrier function of stratum corneum [3–5].

Skin of each individual has its own specific microbiota like bacteria, virus, fungi that gets stabilized from birth to adulthood and collectively known as skin microbiome [6,7]. The Human Microbiome Project revealed the existence of three

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primary types of bacteria residing on the Healthy skin surface: *Cutibacterium* (23%) (formerly known as *Propionibacterium*), *Staphylococcus* (16.8%), and *Corynebacteria* (22.8%). In addition to bacteria, various fungal strains (mycobiome) and viral fractions (Virome) such as *Malassezia spp* and *Papillomaviridae* and *Poxviridae* families are also known to reside on the skin [8,9]. Skin microbiome helps in maintaining skin homeostasis, barrier function, protection from pathogen [10]. For example, *Staphylococcus epidermidis* strain found in the skin, produces 6-N-hydroxyaminopurine which protect the skin from pathogen [11]. Any disruption in skin microbiota makes the skin vulnerable to various diseases like cutaneous infection which could lead to transition from eubiosis to dysbiosis [12]. Skin is considered as neuroendocrine organ which interact with both external environment and microbiome [13]. This endocrine system of the skin helps in maintaining skin integrity, homeostasis, functionality [14]. Cutaneous microbial endocrinological studies has shown that skin microbiota can synthesise various neurotransmitters and neuromodulators like γ-aminobutyric acid histamine and glutamate, and, etc. Glutamate which is a neurotransmitter is synthesised by skin microbes like *Corynebacterium*. It is important for the bidirectional communication between skin and microbes [13]. Skin microbiome balance is disturbed by both internal (aging, gender, ethnicity) and external factors (pollution, diet, antibiotic, cosmetics, lifestyle, geographical location) which lead to skin problems. It is important to maintain the healthy skin ecosystem [10].

Cosmeceutical is a vast and fastest growing personal care industry. Raymond Reed, founder of US society cosmetic chemist coined the term cosmeceuticals and which gained further recognition through the efforts of American dermatologist Albert Kligman, referred to as the father of cosmeceuticals [15]. He developed the anti-aging and UV-protection cream using retinoic acid as an active ingredient [16]. Cosmeceuticals which are combination of cosmetic and pharmaceuticals, is a recent trend in the skin care industry where natural extracts or bioactive compounds can be added in the formulations to increase the supply of nutrition to the skin [17]. They bridge the gap between cosmetics and drugs by not only enhancing beauty but also give medical standards to the products without harming the human well-being [16]. The new cosmeceutical is evaluated on three terms (i) its skin's bioactive attributes, (ii) its ability to penetrate the stratum corneum and maintain delivery concentration over time, and (iii) its effectiveness and safety, ensuring absence of cytotoxic effects [18].

Skin care products have been developed after lots of research and development for skin rejuvenation like, moisturizers, sunscreams, serum, facial oils, anti-wrinkles, skin cleansers (16). Cosmetic formulations include bioactive compounds capable of impacting skin functions such as immunity, thermoregulation, and protective mechanisms. Bioactive compounds that are used as an ingredient in cosmeceuticals include phytochemicals (polyphenols), microbial metabolites (e.g. Lactic acid, hyaluronic acid) and minerals/vitamins (e.g., selenium, Vitamin E), peptides [19]. These compounds when added in the product can act as antioxidants, anti-hyperpigmentation, anti-inflammatory, anti-ageing, anti-wrinkles, and UV protection [20]. The skin microbiome is a vital ecosystem affecting skin health and disease, yet its potential as a target for cosmeceuticals remains underexplored. Limited understanding of microbial interactions with skin physiology hinders the development of effective cosmetic and therapeutic products. Skin disorders like acne, eczema, and psoriasis are common and impact quality of life, with traditional treatments often failing to address microbiome imbalances. The practical application of microbiome research in cosmeceuticals is still developing, with insufficient examination of how cosmetic ingredients affect the microbiome and a lack of long-term studies on microbiome-targeted products. This study aims to bridge this gap by investigating the skin microbiome's composition, there role in immunity, and dysbiosis and the role of various components used in the cosmeceutical formulations. Targeting the skin microbiome by adding probiotic, prebiotic, postbiotic in the formulation is a new approach in skin care market as shown in Fig. 1. The market of the skin care product has been estimated to reach 200.25 billion USD by 2026 using natural products and the market of probiotics to be grow at 12% rate by the next ten years [21,22]. Each individual has a unique microbiome and this approach will help in development of a personalized product according to their own skin ecosystem. This review focus on relationship of skin microbiome to immunity, Dermatological disorders, components to improve skin health like peptides, growth factors, antioxidants, natural botanical product, pre-, pro, postbiotic formulations, used in the cosmeceuticals.

2. Skin microbiome linked to host immunity

Skin is considered as primary immunological barrier and serve as a first line defence to pathogens. A robust symbiotic connection exists among skin cells, immune cells, and the skin microbiota,

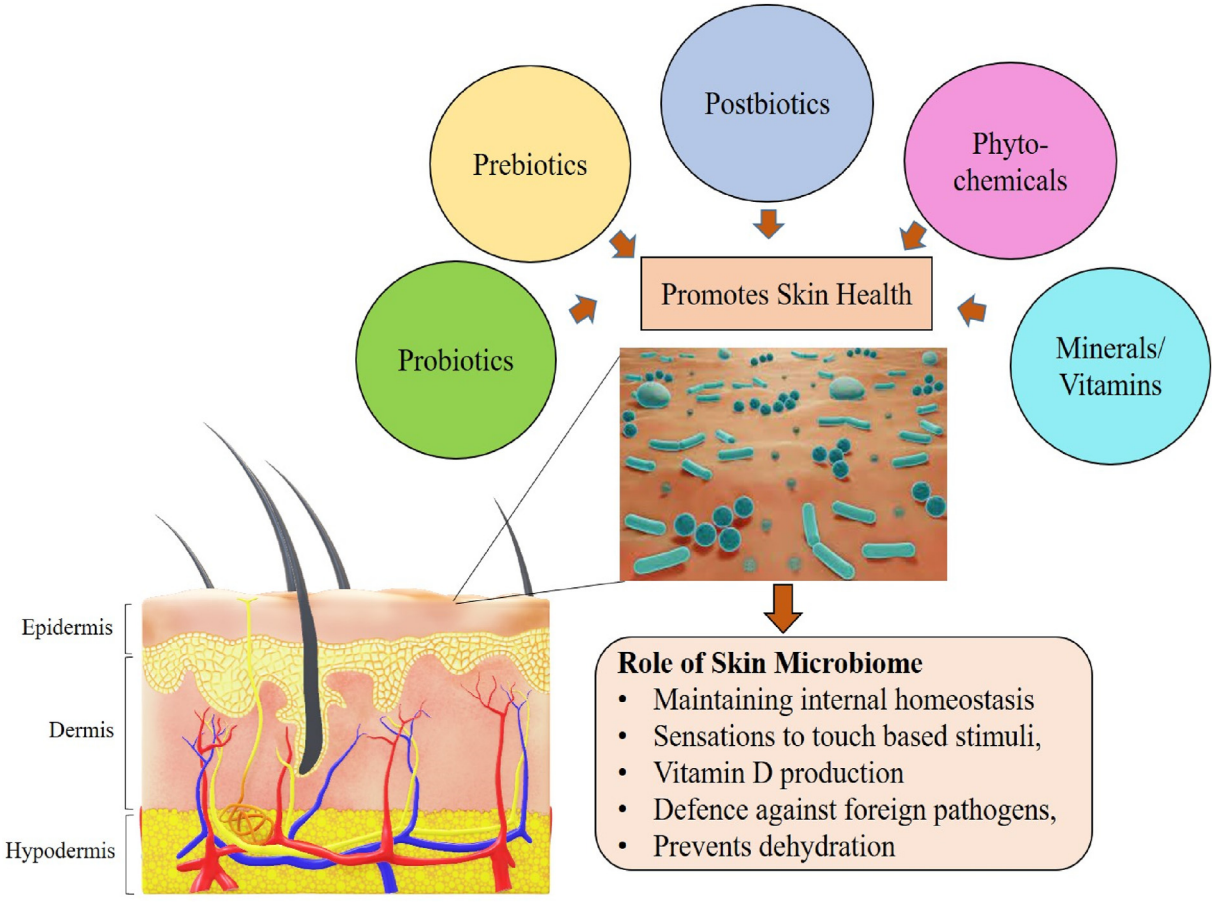

Fig. 1. Role of skin microbiome and components to improve its health.

collaborating to uphold skin health. Any dysbiosis in the system lead to the compromised skin barrier function [23]. Homeostasis between the external environment and skin is maintained by physical barrier, chemical barrier, skin microbiome and skin residing immune cells [24]. Macrophages, dendritic cells, natural killer cells, and other immune cells within the skin communicate with epithelial cells, collectively forming the cutaneous immune system [25].

Compromised skin microbiome leads to various skin diseases and increase the risk of pathogenic infection. Toll-like receptor-bearing cells, keratinocytes and Langerhan's cells fight against the pathogen by regulating immune responses like antimicrobial production, activating innate immune cells (natural killer cells), phagocytosis [26]. Skin microbiome enhance skin barrier function and homeostasis by producing various metabolites like antimicrobial peptides (AMPs), keratinocytes, lipid antimicrobial agents and cytokines [9]. Commensal tolerance in the host is developed during the neonatal state where T-cells (Tregs) start accumulating in the skin and develop immune tolerance to skin microbiota [27,28]. Host immune system can differentiate between the commensal bacteria and pathogenic bacteria through interleukins signalling as toxins produced by pathogen *Staphylococcus aureus* reduces the pathogen specific tregs (21). *S. epidermidis*, a commensal bacterium produces various ligands to inhibit tumor necrosis factor-α and IL-6 responsible for false immune activation [29] and ligands that work as TLR2 and EGFR agonists which stimulate the production of antimicrobial peptides (AMPs) against *Streptococcus* and *S. aureus* [30–32]. Pattern recognition receptors (PRRs) that are present on the immune cells and keratinocytes interact with the molecular patterns like peptidoglycan and lipopolysaccharide that are present on the pathogenic bacteria. These interactions lead to the activation of inflammatory cytokines and macrophages to kill pathogens [33,34]. Skin keratinocytes produce antimicrobial peptides (AMPs) majorly β-defensin and cathelicidin that have antimicrobial effects against foreign pathogens. Commensal microbes like *S.*

epidermidis and *Propionibacterium spp.* have shown the ability to control the expression of AMPs production [24,35]. *S. epidermidis and Propionibacterium acnes* helps in maintaining homeostasis by one producing antimicrobial substances and other utilize the lipids present on the skin to form short chain fatty acids exerting ani-inflammatory effect. Epidermal bacteria and *Corynebacterium* inhibit the colonization of *S. aureus* by producing porphyrins [9].

3. Skin disorders linked to dysbiosis

Alteration in the skin microbiome composition affects lead to the increased colonization of pathogenic bacteria on the skin. This dysbiosis results in various dermatological disorders and diseases like acne, psoriasis, atopic dermatitis as shown in Fig. 2 [36].

3.1. Acne vulgaris

Acne vulgaris or acne is a chronic skin condition linked to sebaceous glands and hair follicles. Acne majorly occurs on the sites rich in sebaceous gland and at the time of puberty. Sebum production at the time of puberty is high which makes it optimal environment for bacteria to thrive [37]. *Cutibacterium acnes*, a commensal bacterium is responsible for acne formation by mediating crosstalk with androgen-dependent hyperseborrhea, follicular keratinocyte hyperproliferation, and inflammation. It increases the local inflammation by regulating the production of pro-inflammatory cytokines, tumor necrosis factor-α (TNFα), interleukin (IL)-6, IL-8, IL-12, through Toll-like receptor 2 (TLR2) *S. epidermidis* helps in maintaining C. acnes homeostasis by displaying anti- C. acnes activity [38]. Treatment of acne was classically done by application of antibiotics like macrolides, clindamycin, and tetracyclines either oral of topical but it faces challenges of antibiotic resistance [39].

3.2. Psoriasis

Psoriasis, a chronic inflammatory skin condition arising from dysbiosis, manifests as red papules and plaques covered in silver scales. It has been suggested that environment factors including Koebner's phenomenon, sunburns, medications such as beta-blockers or ACE inhibitors, emotional stresses, HIV infection, alcohol and smoking triggers the T-cells which in turn causes hyper-proliferation of keratinocytes and inflammatory response [40]. *S. aureus* and *Streptococcus pyogenes* are the primary bacteria

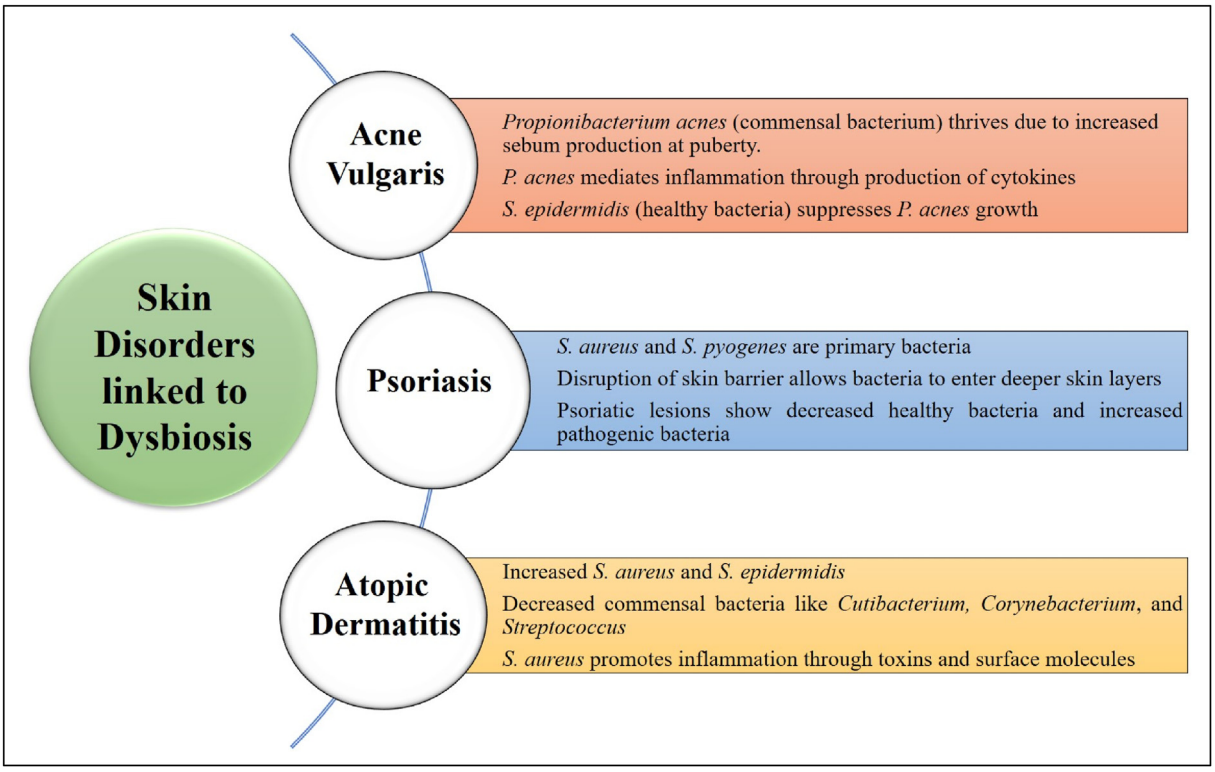

Fig. 2. Skin disorders linked with microbial imbalance.

associated with psoriasis. The pathogenesis of psoriasis is intricate; intense itching of psoriatic lesions can lead to skin wounds, facilitating the migration of bacteria into the deep dermis layer and potentially the bloodstream [41,42]. On comparing the healthy skin and psoriatic lesions, it was seen that the psoriatic skin has heterogenous diversity of bacteria with decrease in *Actinobacteria, Cutibacterium, C. acnes, S. epidermidis* and *P. acnes* and increase in *S. pettenkoferi, Proteobacteria, S. aureus, Propionibacterium genera* and *Firmicutes* whereas healthy skin has shown stable homogenous variety of microbes. Studies have focused on the importance of skin microbiota identification of patients with psoriasis for the better treatment [36].

3.3. Atopic dermatitis

Atopic dermatitis (AD), commonly known as eczema, is a chronic skin inflammation disorder that makes the skin dry, itchy and swollen. It usually starts in infancy or early childhood and may persist into adulthood [7]. AD is caused by microbial disruption [7], transepidermal water loss due to barrier disruption [37], Genetic factors, and environment factors [43]. Immune system dysfunction: AD is an autoimmune disease associated with an exaggerated immune response of IL-24 and IL-13 cytokines that results in skin inflammation and barrier dysfunction [44]. People who have family history of AD, asthma or allergic rhinitis are more prone to have this disease suggesting that there's a genetic predisposition. Environmental factors: Exposure to certain allergens such as dust mites, pet dander and pollen; irritants like strong soaps, detergents and woollen clothes as well as climatic conditions such as coldness/dryness can trigger symptoms. Skin barrier dysfunction: This is often found in AD patients since their epidermal layer tends to be compromised allowing moisture out while increasing the penetration of irritating substances into the dermis hence causing drying up; itching leading to inflammations. Microbial factors: The deviations within dermal microbiome including excessive multiplication of specific bacteria or fungi may be responsible for its development [7,37,43]. AD is commonly caused by colonization of *S. aureus, S. epidermidis* which results in the decrease of commensal bacteria like *Cutibacterium*, *Corynebacterium,* and *Streptococcus. S. aureus* is also responsible for the inflammation in AD patients by releasing toxins, phenol-soluble modulins, proteases, and other virulence factors [7]. Additionally, *S. aureus* produces various surface molecules like clumping factors A &B, fibronectin binding protein which helps in adherence to stratum corneum layer of skin [9].

4. Components for promoting skin health

Ingredients found in the cosmeceutical formulations include natural/botanicals, vitamins, peptides, growth factor, microbial metabolites and phytochemicals as shown in Table 1. These are the active ingredients found in concentrated levels for their effective delivery in the cosmeceuticals. The cosmeceutical product formulations are majorly categorized on properties like moisturizing agents, sunscreen, antioxidants, anti-hyperpigmentation, anti-aging, anti-wrinkles, and anti-pimples.

Consumers are paying much attention to the ingredients of skin care products while buying, where natural or organic products containing botanical extracts have gain much space in the marketplace [45]. Botanical extracts which have found wide application in cosmetics include *Aloe vera*, Bearberry, mulberry, *Calendula* spp (marigold), *Centella asiatica* (tiger grass, cica), bamboo, licorice, *Camellia sinensis* (green tea), Ginseng, lotus, pomegranate, red rice bran, *Curcuma longa* (turmeric), *Azadirachta indica* (Neem), *Cocos nucifera* (coconut), *Carica papaya*, *Cymbopogon spp* (lemongrass), *Emblica officinalis* (amla), *Ginkgo biloba* [46,47].

4.1. Antioxidants

Antioxidants are the substances that inhibit the cellular damage caused by free radicals. Free radicals are formed as an intermediate product of enzymatic and non-enzymatic reactions like reactive oxygen species (ROS); superoxide radical ($O2\ \cdot -$), peroxyl ($ROO\cdot$), alkoxyl ($RO\cdot$), and hydroxyl ($HO\cdot$) and need to be stabilised by reacting further with nitric oxide ($NO\cdot$) to form reactive nitrogen species (RNS) [66]. The need of antioxidants in cosmeceuticals is due to generation of free radicals which leads to a condition known as oxidative stress [62]. The possible targets for oxidative damage in skin include biomolecules including lipids, proteins, carbohydrates, and nucleic acids. Reactive singlet oxygen has the capability to interact with all DNA bases. For example, when Guanine reacts with singlet oxygen it produces 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) which pairs with adenine unlike guanine, resulting in point mutation [67]. Free radicals can also stimulate the release of metalloproteinases formation (MMP-1, MMP-3, MMP-8, and MMP-9), and various enzymes like collagenase, elastase, tyrosinase, and xanthine oxidase which can degenerate the collagen, elastin and connective tissue of the skin causing premature aging [68,69]. The most susceptible target for free radicals includes polyunsaturated fatty acids (PUFA) present within the

Table 1. Components that promotes skin health.

Components	Activity	Reference
Peptides		
Acetyl Hexapeptide-3 (Argireline) Ac-Glu-Glu-Met-Gln-Arg-Arg-NH_2	Increases skin permeation and reduces wrinkles	[48]
Copper Tripeptide-1 (Cu-GHK) Cu(II)H-Gly-His-Lys-OH	MMP inhibitory effect and UVB exposure skin protection	[49]
Palmitoyl Tripeptide-5 (Syn®-Coll) Pal-Lys-Val-Lys-OH	Stimulating growth factor TGF-β, which stimulates collagen biosynthesis, and inhibits matrix metalloproteases degrading collagen.	[49,50]
Lipospondin, Elaidyl-Lys-Phe-Lys-OH	Inhibits MMPs mRNAs and stimulates growth factor TGF-β, upregulates collagen and tissue MMP-1 inhibitors production (TIMP-1), and downregulates MMP-1 in fibroblasts	[51]
Botanical Extracts		
Centella asiatica	Stimulate Smad pathway, skin fibroblast proliferation, collagen synthesis and decrease metalloproteinase, Neuroprotective, stretch marks	[52,53]
Licorice	Anti-inflammatory, antimelanogenic, antimicrobial, and anti-carcinogenic properties	[46,47]
Seaweed (Macroalgae)	Tyrosinase inhibitor activity, photoprotection, UV protection, anti-aging, antioxidant, depigmentation agent, collagenase inhibitor, Hyaluronidase inhibitor	[54,55]
Cannabis sativa, Aegopodium podagraria, Betula pendula, Kadsura coccinea, Helianthus annuus,	Moisturizing, anti-aging, antimicrobial, antioxidant, anti-inflammatory	[56]
Algal extracts *C. vulgaris, Nostoc, Spirulina, Fucus vesiculosus, Nannochloropsis, Isochrisis*	Anti-aging, Moisturizing, anti-wrinkle, UV protection,	[57]
Growth Factors		
Epidermal growth factor (EGF), Fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), granulocyte-colony stimulating factor, platelet-derived growth factor, keratinocyte growth factor, and hepatocyte growth factor	cell proliferation, differentiation, immune responses, organ development, angiogenesis, wound healing and stimulates collagenesis	[58–61]
Antioxidants		
Enzymatic- glutathione peroxidase, catalase, superoxide dismutase	Inhibit the cellular damage caused by free radicals	[62]
Non-Enzymatic-Vit C, Vit E, Carotenoids, albumin, transferrin, lactoferrin, haptoglobin, and ceruloplasmin, phenolic compound		
Prebiotic, Probiotics, Postbiotics		
Prebiotics- Galacto-Oligosaccharide, Xylitol (XYL), Inulin, Lactulose, Polydextrose, Fructo-OligoSaccharides (FOS), IsoMalto-Oligosaccharides (IMO), AraboinoGaLactan (LAG) and dextran	Species-specific antibacterial/antibiofilm action, helps in maintaining the skin microbiome by inhibiting the growth of pathogens	[63]
Probiotics- *Bifidobacterium* and *Lactobacillus*	Antiaging, Antioxidants, spot-removing, properties, enhanced skin barrier, anti-wrinkle, anti-inflammatory	[64,65]
Postbiotics- metabolites of probiotics (butyrate)	Anti-inflammatory, antioxidant, immunomodulatory, antimicrobial, and anti-ageing/anti-senescence activities	[65]

cell membranes which lead to a destructive self-perpetuating chain reaction (this oxidative damage by free radicals is known as lipid peroxidation). Vitamin C, Vitamin E, phenolic compounds etc. are the compounds with antioxidant activity [62].

4.2. Peptides

Peptides are chain of amino acids that are linked together by peptide bond. They act as a signalling molecule in various physiological processes like stress, immunity, growth, homeostasis, defence [70]. Both intrinsic and extrinsic factor that are responsible for aging results in increased degradation and decreased production of matrix proteins like collagen, elastin, fibronectin, hyaluronic acid, loss of structural protein led to less firmness of skin, less water retention capacity, loss of barrier function and antimicrobial function [71,72]. Bioactive peptide can be used in the cosmetic formulations to increase skin health. A study showed that hydrolysed biomass of protein with pepsin and subtilisin A obtained from spirulina (*Arthrospira maxima*) has collagenase inhibitory activity with IC50 = 32.5 μg $mL^{-1}$and anti-

hyaluronidase activity with IC50 = 0.92 mg mL^{-1} [73]. Peptide isolated from microalgae *Dunaliella tertiolecta* showed 32.5% elastase inhibition activity at 0.0026 μg μL^{-1} while peptides from *Tetraselmis suecica* and *Nannochloropsis sp.* showed IC50 values of 0.038 and 0.025 μg μL^{-1} respectively [74]. Overproduction of tyrosinase causes increased melanogenesis i.e., hyperpigmentation of skin (17). Skin collagen peptide obtained from squid (*Todarodes pacificus*) show copper chelating (present at active site for catalysing the oxidation reaction) and 39.65% of anti-tyrosinase activity [75]. Bioactive peptides from rice bran have anti-microbial, anti-inflammatory, angiogenic activities [76]. Topical peptides have been classified into five categories: signal peptide, neurotransmitter inhibiting peptide, carrier peptide, enzyme inhibitor peptide, structural peptide [77]. Neurotransmitter inhibiting peptides are designed to block the release of acetylcholine to the neuromuscular junction [78]. Acetylcholine is released from the vesicles due to reaction cascade mediated by SNAP (Synaptosome-Associated Protein) receptor protein which further binds to the receptor to cause muscle cramp resulting in fine lines and wrinkles, thus forming SNARE (Soluble N-ethylmaleimide-sensitive factor Activating protein Receptor) complexes [79]. Acetyl Hexapeptide-3, a neurotransmitter inhibiting peptide interrupts the formation of SNARE complex causing inhibition of Ca2+-dependent catecholamine release by covering the N terminal of SNAP-25 [48]. Pentapeptide-3 derived from snake venom induce muscle relaxation. It prevents unwanted cramps and disables nerve function by acting as an antagonist of acetylcholine receptors [80]. Copper is an essential metal ion that is involved in many processes like angiogenesis, wound healing, and many enzymatic reactions. It can be stabilised and delivered into the system via carrier peptides [78]. Copper intake reduces the activity of MMPs (Matrix metalloproteases) and collagenase and prevents premature aging [48,81]. Copper plays a vital role as a cofactor in several enzymes: lysyl oxidase, essential for the synthesis of collagen and elastin; superoxide dismutase, involved in reducing free radicals; and cytochrome c oxidase, which contributes to antioxidative processes in endothelial cells. They all show anti-aging effects as collagen production improves the skin texture, reduces oxidative stress caused by free radicals and improves blood circulation in skin [78].

4.3. Growth factor

Growth factors are naturally secreted proteins that binds to the receptor and activates cascade of biochemical reactions involved in cell proliferation, differentiation, immune responses, organ development, angiogenesis, wound healing and stimulates collagenesis [59,61]. Use of growth factors in cosmetic formulation related to anti-aging products and skin rejuvenation medicine is increasing due to studies that reported their role in tissue regeneration, prevention of photoaging [58]. Growth factor like, Epidermal growth factor (EGF), Fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), granulocyte-colony stimulating factor, platelet-derived growth factor, keratinocyte growth factor, and hepatocyte growth factor along with cytokines (TGF-β, interleukin (IL)-6, and IL-8) directly affect the biosynthesis of elastin, collagen, extracellular matrix [60,61]. Synergistic effect of Epidermal growth factor with various protein molecules (Quercetin, Matrikines, Perfluorocarbons, Cell-penetrating peptides, hyaluronic acid (HA)has shown better effects on skin repair. For example, EGF with Matrikines increased skin elasticity, procollagen production, anti-wrinkle [61].

4.4. Prebiotics, probiotics and postbiotics

For improving skin health prebiotics (to stimulate the growth of favourable bacteria), probiotics (good bacteria), postbiotics (metabolites) and synbiotics (combination of prebiotics and probiotics) can also be used in the formulation. Prebiotics are the non-digestable food products that are used to stimulate the growth of beneficial commensal microorganisms [82–84]. These can be used in the cosmetic formulations to treat the imbalance in the skin microbiome in two ways of action either by killing the pathogen or by downregulating the quorum-sensing-regulated gene expression [82,85]. There are many established prebiotics like Fructo-OligoSaccharides (FOS), IsoMalto-Oligosaccharides (IMO), Galacto-Oligosaccharide, Xylitol (XYL), Arabino-GaLactan (LAG), Inulin, Lactulose, Polydextrose, and dextran [83]. For instance, Xylitol has the potential to inhibit the growth of pathogenic bacteria, improves skin moisture and also improves skin barrier function by up-regulating the expression of various proteins filaggrin, loricrin, involucrin [86]. A study has shown that when FOS, IMO, LAG combined with XYL at 1% concentration show selective species-specific antibacterial/antibiofilm action, helps in maintaining the skin microbiome by inhibiting the growth of pathogens [63]. It has been proven that 1% of colloidal oat as a prebiotic has direct effect on the growth of microorganism, metabolism, increase in the production of lactic acid and upregulation of certain genes like dltA, dltB,

dltC and dltD that are responsible for metabolism of bacterial cell component D-alanine [87].

According to the Food and Agriculture Organization of the United Nations and the WHO, Probiotics are the living microorganisms when added in an adequate amount can promote host health. In cosmetic formulations, instead of living bacteria, semi-active, non-replicating bacteria, killed or lysates are preferred for topical application [88]. Probiotics helps in maintaining homeostasis, produce various regulatory T cells and cytokines to exert anti-inflammatory effect, antibacterial substances that blocks the interaction of opportunistic bacteria to epithelial cells [88,89], competitive inhibition of binding sites and inhibition of biofilm formation [90], antioxidant effect against UV radiation induced oxidative stress and hyperpigmentation [91]. Most commonly used probiotic bacterias are *Bifidobacterium* and *Lactobacillus* whose secretory molecules are responsible for the activation of many pathways needed for healthy skin [92]. *Lactobacillus* has antibacterial effect on pathogenic bacteria like *Escherichia coli, Pseudomonas aeruginosa,* and pathobionts (resident microbes with pathogenic potential) [90]. Probiotics are also used in the treatment of skin diseases including Atopic dermatitis (AD), Acne vulgaris, Seborrhoeic dermatitis, Wound healing [93]. *Lactobacillus plantarum* increases the collagen synthesis, upregulation of serine palmitoyltransferase (rate limiting step in ceramide synthesis) gene expression, and reduce melanin synthesis, inhibit the biofilm formation of *S. aureus,* improves skin quality [94]. *Vitreoscilla filiformis,* used in many cosmetic formulations for its properties like immunomodulatory, anti-inflammatory, improves skin barrier, and stimulates skin defence, keratinocyte proliferation. It upregulates the expression of TNFAIP3 (A20) gene in keratinocytes which causes anti-inflammatory effect. It also stimulates mitochondrial manganese superoxide dismutase 2 (MnSOD2) at both mRNA and protein levels exerting antioxidant effects [88]. Treating inflammatory skin conditions using oral and topical probiotics has demonstrated promising outcomes, positively impacting wound healing and potentially mitigating skin cancer risks. Research in this area is still needed to verify the findings [36].

Synbiotic formulation, a mixture of prebiotic and probiotic is a new concept of topical application. A study has shown that in combination prebiotics has the potential to increase the survival and retention period of probiotic strains by experimenting on mice with mixture of soybean oligosaccharide (SOS), FOS or inulin and *Lactobacillus acidophilus* LAFTI L10 (L10), *Bifidobacterium lactis* LAFTI B94 (B94) or *Lactobacillus casei* L26 LAFTI (L26) [95]. A research study shown that symbiotic formulation of selenium nanoparticles and probiotic biomass (*Lactobacillus rhamnosus*) has SPF effects of 29.77 and neutralize free radical mediated toxicity. Probiotics protect the skin from UV radiations and prebiotics preserve the viability and increase the therapeutic effect of probiotics [96]. Postbiotics are the metabolites that are either secreted or derived after the lysis of probiotics with similar properties like probiotic. These are used in the formulations to avoid the risk of adding live microorganisms and benefits of probiotics. For example, butyrate, a postbiotic helps in intestinal growth and anti-inflammatory [97].

5. Challenges

The development of probiotics requires proper isolation and characterization techniques with phenotypic and genotypic tests. Phenotypic test includes phenotypes related to antioxidant activity, antibacterial activity, genotypic test studies genetic potential of probiotic strain and adaptability. The genetic and phenotypic basis of probiotic characteristics is still largely unknown with respect to cosmeceuticals. Delivery of probiotics is also a major concern as skin act as a barrier to the external environment. Stability of probiotics in the cosmeceutical formulation is hard to maintain and results in additional expenses to maintain the efficacy of products [37]. The major concern related to the growth factor and bioactive peptides is maintaining their stability and bioactivity during formulation, manufacturing, storage. Their activity can be affected by many factors like pH, water activity, temperature, concentration, encapsulation, packaging and bioengineering is required for topical treatment. Due to low permeability of the growth factor and biopeptides through stratum corneum special delivery systems are required like liposomal delivery, penetration enhancer, Scaffolds, Particulate systems. The high technology requirement for growth factors makes the product expensive [19,50,61].

6. Conclusion

Cosmeceutical research is developing in leaps and bounds, with the skin microbiome emerging as a significant focus. A better understanding of the interaction between skin health and the skin microbiome reveals the potential for revolutionary changes in skincare through microbiome-targeted cosmeceuticals. So, Microbiome-targeted cosmeceuticals are skincare products designed to balance the skin's microbiome to improve skin health. These

products often incorporate prebiotics, probiotics, and postbiotics to nourish beneficial microorganisms, introduce live beneficial bacteria, and utilize bacterial metabolites, respectively. When combined with other active ingredients such as growth factors, peptides, botanical extracts and algal extracts, these cosmeceuticals can enhance skin barrier function, reduce inflammation, improve hydration, and provide anti-aging benefits. Therefore, enhancing the balance of healthy skin microbes is a promising approach to addressing dysbiosis and improving overall skin health. Nevertheless, further studies should focus on finding out how skin physiology works, how pathological changes occur due to the influence that a microbiome has on it as something like a drug in order to fully elucidate these relationships and also optimize such approaches for skincare purposes. However, even though there still needs more research with regards to this subject matter; the future looks bright for personalized skincare approaches based on microbiomes that would promote healthy looking skin in terms of wellness and attractiveness.

Conflicts of interest

The authors declare that they have no conflict of interest.

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References

[1] S. Osseiran, J. dela Cruz, S. Jeong, H. Wang, C. Fthenakis, C. L. Evans, Characterizing stratum corneum structure, barrier function, and chemical content of human skin with coherent Raman scattering imaging, Biomed. Opt. Express 9 (12) (2018) 6425–6443, https://doi.org/10.1364/boe.9.006425.

[2] S. Lawton, Skin 1: the structure and functions of the Skin, Nurs. Times 115 (2019) 30–33, https://doi.org/10.1097/00000441-183411000-00032.

[3] A.V. Rawlings, C.R. Harding, Moisturization and skin barrier function, Dermatol. Ther. 17 (2004) 43–48, https://doi.org/10.1111/j.13960296.2004.04S1005.x.

[4] C.R. Harding, A. Watkinson, A. V Rawlings, I.R. Scott, Dry skin, moisturization and corneodesmolysis, Int. J. Cosmet. Sci. 22 (2000) 21–52, https://doi.org/10.1046/j.1467-2494.2000.00001.x.

[5] A. V Rawlings, P.J. Matts, Stratum corneum moisturization at the molecular level: an update in relation to the dry skin cycle, JID 124 (2005) 1099–1110, https://doi.org/10.1111/j.1523-1747.2005.23726.x.

[6] I. Cho, M.J. Blaser, The human microbiome: at the interface of health and disease, Nat. Rev. Genet. 13 (2012) 260–270, https://doi.org/10.1038/nrg3182.

[7] Y. Chen, R. Knight, R.L. Gallo, Evolving approaches to profiling the microbiome in skin disease, Front. Immunol. 14 (2023) 1151527, https://doi.org/10.3389/fimmu.2023.1151527.

[8] T.M. Santiago-Rodriguez, B. Le François, J.M. Macklaim, E. Doukhanine, E.B. Hollister, The skin microbiome: current techniques, challenges, and future directions, Microorganisms 11 (2023) 1222, https://doi.org/10.3390/microorganisms11051222.

[9] X.E. Zhang, P. Zheng, S.Z. Ye, X. Ma, E. Liu, Y.B. Pang, Q.Y. He, Y.X. Zhang, W.Q. Li, J.H. Zeng, J. Guo, Microbiome: role in inflammatory skin diseases, J. Inflamm. Res. 17 (2024) 1057–1082, https://doi.org/10.2147/JIR.S441100.

[10] M. Boxberger, V. Cenizo, N. Cassir, B. la Scola, Challenges in exploring and manipulating the human skin microbiome, Microbiome 9 (2021) 1–14, https://doi.org/10.1186/s40168-021-01062-5.

[11] T. Nakatsuji, T.H. Chen, A.M. Butcher, L.L. Trzoss, S.J. Nam, K.T. Shirakawa, W. Zhou, J. Oh, M. Otto, W. Fenical, A commensal strain of Staphylococcus epidermidis protects against skin neoplasia, Sci. Adv. 4 (2018) eaao4502, https://doi.org/10.1126/sciadv.aao4502.

[12] K. Findley, E.A. Grice, The skin microbiome: a focus on pathogens and their association with skin disease, PLoS Pathog. 10 (2014) e1004436, https://doi.org/10.1371/journal.ppat.1004436.

[13] P. Racine, X. Janvier, M. Clabaut, C. Catovic, D. Souak, A.M. Boukerb, A. Groboillot, Y. Konto-Ghiorghi, C. Duclairoir-Poc, O. Lesouhaitier, N. Orange, S. Chevalier, M.G.J. Feuilloley, Dialog between skin and its microbiota: emergence of "cutaneous bacterial endocrinology", Exp. Dermatol. 29 (2020) 790–800, https://doi.org/10.1111/exd.14158.

[14] D. Pinto, T. Ciardiello, M. Franzoni, F. Pasini, G. Giuliani, F. Rinaldi, Effect of commonly used cosmetic preservatives on skin resident microflora dynamics, Sci. Rep. 11 (2021) 8695, https://doi.org/10.1038/s41598-021-88072-3.

[15] N. Wanjari, J. Waghmare, A review on latest trend of cosmetics-cosmeceuticals, Int. J. Pharm. Rev. Res. 4 (2015) 45–51.

[16] P. Morganti, G. Morganti, A. Gagliardini, A. Lohani, From cosmetics to innovative cosmeceuticals—non-woven tissues as new biodegradable carriers, Cosmetics 8 (2021) 65, https://doi.org/10.3390/cosmetics8030065.

[17] O. Taofiq, F. Rodrigues, L. Barros, M.F. Barreiro, I.C. Ferreira, M.B.P. Oliveira, Mushroom ethanolic extracts as cosmeceuticals ingredients: safety and ex vivo skin permeation studies, Food Chem. Toxicol. 127 (2019) 228–236, https://doi.org/10.1016/j.fct.2019.03.045.

[18] J. Levin, S.B. Momin, How much do we really know about our favorite cosmeceutical ingredients? J. Clin. Aesthet. Dermatol. 3 (2010) 22–41. PMID: 20725560; PMCID: PMC2921764.

[19] J.E. Aguilar-toalá, A. Hernández-mendoza, A.F. González-córdova, B. Vallejo-cordoba, Potential role of natural bioactive peptides for development of cosmeceutical skin products, Peptides (N.Y.) 122 (2019) 170170, https://doi.org/10.1016/j.peptides.2019.170170.

[20] K. Arora, S. Singh, C. Saxena, L. Chaurasia, The trends and development in the cosmetic technology: a review, Int. J. Res. Pharm. Nano Sci. 7 (2018) 161–169.

[21] J.L. Boyajian, M. Ghebretatios, S. Schaly, P. Islam, S. Prakash, Microbiome and human aging: probiotic and prebiotic potentials in longevity, skin health and cellular senescence, Nutrients 13 (2021) 4550, https://doi.org/10.3390/nu13124550.

[22] S. Puebla-Barragan, G. Reid, Probiotics in cosmetic and personal care products: trends and challenges, Molecules 26 (2021) 1249, https://doi.org/10.3390/molecules26051249.

[23] M.H. Swaney, L.R. Kalan, Living in your skin: microbes, molecules, and mechanisms, Infect. Immun. 89 (2021) 10–1128, https://doi.org/10.1128/IAI.00695-20.

[24] M. Coates, M.J. Lee, D. Norton, A.S. MacLeod, The skin and intestinal microbiota and their specific innate immune systems, Front. Immunol. 10 (2019) 2950, https://doi.org/10.3389/fimmu.2019.02950.

[25] C. Bangert, P.M. Brunner, G. Stingl, Immune functions of the skin, Clin. Dermatol. 29 (2011) 360–376, https://doi.org/10.1016/J.CLINDERMATOL.2011.01.006.

[26] R. Feuerstein, J. Kolter, P. Henneke, Dynamic interactions between dermal macrophages and Staphylococcus aureus, J. Leukoc. Biol. 101 (2017) 99–106, https://doi.org/10.1189/jlb.3MR0316-097RR.
[27] T.C. Scharschmidt, K.S. Vasquez, M.L. Pauli, E.G. Leitner, K. Chu, H.A. Truong, M.M. Lowe, R. Sanchez Rodriguez, N. Ali, Z.G. Laszik, J.L. Sonnenburg, S.E. Millar, M.D. Rosenblum, Commensal microbes and hair follicle morphogenesis coordinately drive treg migration into neonatal skin, Cell Host Microbe 21 (2017) 467–477.e5, https://doi.org/10.1016/j.chom.2017.03.001.
[28] T.C. Scharschmidt, K.S. Vasquez, H.A. Truong, S.v. Gearty, M.L. Pauli, A. Nosbaum, I.K. Gratz, M. Otto, J.J. Moon, J. Liese, A.K. Abbas, M.A. Fischbach, M.D. Rosenblum, A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes, Immunity 43 (2015) 1011–1021, https://doi.org/10.1016/j.immuni.2015.10.016.
[29] Y. Lai, A. di Nardo, T. Nakatsuji, A. Leichtle, Y. Yang, A.L. Cogen, Z.-R. Wu, L. v Hooper, R.R. Schmidt, S. von Aulock, K.A. Radek, C.-M. Huang, A.F. Ryan, R.L. Gallo, Commensal bacteria regulate Toll-like receptor 3–dependent inflammation after skin injury, Nat. Med. 15 (2009) 1377–1382, https://doi.org/10.1038/nm.2062.
[30] I. Wanke, H. Steffen, C. Christ, B. Krismer, F. Götz, A. Peschel, M. Schaller, B. Schittek, Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways, J. Invest. Dermatol. 131 (2011) 382–390, https://doi.org/10.1038/jid.2010.328.
[31] D. Li, H. Lei, Z. Li, H. Li, Y. Wang, Y. Lai, A novel lipopeptide from skin commensal activates TLR2/CD36-p38 MAPK signaling to increase antibacterial defense against bacterial infection, PLoS One 8 (2013) e58288, https://doi.org/10.1371/journal.pone.0058288.
[32] Y. Lai, A.L. Cogen, K.A. Radek, H.J. Park, D.T. MacLeod, A. Leichtle, A.F. Ryan, A. di Nardo, R.L. Gallo, Activation of TLR2 by a small molecule produced by Staphylococcus epidermidis increases antimicrobial defense against bacterial skin infections, J. Invest. Dermatol. 130 (2010) 2211–2221, https://doi.org/10.1038/jid.2010.123.
[33] S.R. Krutzik, B. Tan, H. Li, M.T. Ochoa, P.T. Liu, S.E. Sharfstein, T.G. Graeber, P.A. Sieling, Y.-J. Liu, T.H. Rea, B. R. Bloom, R.L. Modlin, TLR activation triggers the rapid differentiation of monocytes into macrophages and dendritic cells, Nat. Med. 11 (2005) 653–660, https://doi.org/10.1038/nm1246.
[34] S.E. Doyle, R.M. O'Connell, G.A. Miranda, S.A. Vaidya, E.K. Chow, P.T. Liu, S. Suzuki, N. Suzuki, R.L. Modlin, W.-C. Yeh, T.F. Lane, G. Cheng, Toll-like receptors induce a phagocytic gene program through p38, J. Exp. Med. 199 (2004) 81–90, https://doi.org/10.1084/jem.20031237.
[35] Y. Yamazaki, Y. Nakamura, G. Núñez, Role of the microbiota in skin immunity and atopic dermatitis, Allergol. Int. 66 (2017) 539–544, https://doi.org/10.1016/j.alit.2017.08.004.
[36] V. Celoria, F. Rosset, V. Pala, P. Dapavo, S. Ribero, P. Quaglino, L. Mastorino, The skin microbiome and its role in psoriasis: a review, Psoriasis Targets Ther. 13 (2023) 71–78, https://doi.org/10.2147/PTT.S328439.
[37] I.J. McLoughlin, E.M. Wright, J.R. Tagg, R. Jain, J.D.F. Hale, Skin microbiome—the next frontier for probiotic intervention, Probiotics Antimicrob. Proteins (2021), https://doi.org/10.1007/s12602-021-09824-1.
[38] C. Dessinioti, A. Katsambas, The microbiome and acne: perspectives for treatment, Dermatol. Ther. 14 (2024) 31–44, https://doi.org/10.1007/s13555-023-01079-8.
[39] C. Dessinioti, A. Katsambas, Antibiotics and antimicrobial resistance in acne: epidemiological trends and clinical practice considerations, Yale J. Biol. Med. 95 (2022) 429–443. PMID: 36568833; PMCID: PMC9765333.
[40] M. Vičić, M. Kaštelan, I. Brajac, V. Sotošek, L.P. Massari, Current concepts of psoriasis immunopathogenesis, Int. J. Mol. Sci. 22 (2021) 11574, https://doi.org/10.3390/ijms222111574.
[41] X. Zhou, Y. Chen, L. Cui, Y. Shi, C. Guo, Advances in the pathogenesis of psoriasis: from keratinocyte perspective, Cell Death Dis. 13 (2022) 81, https://doi.org/10.1038/s41419-022-04523-3.
[42] Z. Gao, C. Tseng, B.E. Strober, Z. Pei, M.J. Blaser, Substantial alterations of the cutaneous bacterial biota in psoriatic lesions, PLoS One 3 (2008) e2719, https://doi.org/10.1371/journal.pone.0002719.
[43] M.-L. Clausen, S.M. Edslev, P.S. Andersen, K. Clemmensen, K.A. Krogfelt, T. Agner, Staphylococcus aureus colonization in atopic eczema and its association with filaggrin gene mutations, Br. J. Dermatol. 177 (2017) 1394–1400, https://doi.org/10.1111/bjd.15470.
[44] C. Callewaert, N. Knödlseder, A. Karoglan, M. Güell, B. Paetzold, Skin microbiome transplantation and manipulation: current state of the art, Comput. Struct. Biotechnol. J. 19 (2021) 624–631, https://doi.org/10.1016/j.csbj.2021.01.001.
[45] A.F. Stallings, M.P. Lupo, Practical uses of botanicals in skin care, J. Clin. Aesthet. Dermatol. 2 (1) (2009) 36–40. PMID: 20967187; PMCID: PMC2958188.
[46] A.N.M. Alamgir, Classification of drugs, nutraceuticals, functional food, and cosmeceuticals; proteins, peptides, and enzymes as drugs, in: Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1. Progress in Drug Research, Springer, Cham. 2017, pp. 125–175, https://doi.org/10.1007/978-3-319-63862-1_5, vol 73.
[47] J.K. Nguyen, N. Masub, J. Jagdeo, Bioactive ingredients in Korean cosmeceuticals: trends and research evidence, J. Cosmet. Dermatol. 19 (2020) 1555–1569, https://doi.org/10.1111/jocd.13344.
[48] C. Blanes-Mira, J. Clemente, G. Jodas, A. Gil, G. Fernández-Ballester, B. Ponsati, L. Gutierrez, E. Pérez-Payá, A. Ferrer-Montiel, A synthetic hexapeptide (Argireline) with anti-wrinkle activity, Int. J. Cosmet. Sci. 24 (2002) 303–310, https://doi.org/10.1046/j.1467-2494.2002.00153.x.
[49] F. Errante, P. Ledwoń, R. Latajka, P. Rovero, A.M. Papini, Cosmeceutical peptides in the framework of sustainable wellness economy, Front. Chem. 8 (2020) 1–8, https://doi.org/10.3389/fchem.2020.572923.
[50] V. Pai, P. Bhandari, P. Shukla, Topical peptides as cosmeceuticals, Indian J. Dermatol. Venereol. Leprol. 83 (2017) 9–18, https://doi.org/10.4103/0378-6323.186500.
[51] J.-H. Cauchard, A. Berton, G. Godeau, W. Hornebeck, G. Bellon, Activation of latent transforming growth factor beta 1 and inhibition of matrix metalloprotease activity by a thrombospondin-like tripeptide linked to elaidic acid, Biochem. Pharmacol. 67 (2004) 2013–2022, https://doi.org/10.1016/j.bcp.2004.01.028.
[52] C. Boira, M. Meunier, M. Bracq, A. Scandolera, R. Reynaud, The natural Centella asiatica extract acts as a stretch mark eraser: a biological evaluation, Cosmetics 11 (2024) 15, https://doi.org/10.3390/cosmetics11010015.
[53] W. Bylka, P. Znajdek-Awiżeń, E. Studzińska-Sroka, A. Dańczak-Pazdrowska, M. Brzezińska, Centella asiatica in dermatology: an overview, Phytother. Res. 28 (2014) 1117–1124, https://doi.org/10.1002/ptr.5110.
[54] L. López-Hortas, N. Flórez-Fernández, M.D. Torres, T. Ferreira-Anta, M.P. Casas, E.M. Balboa, E. Falqué, H. Domínguez, Applying seaweed compounds in cosmetics, cosmeceuticals and nutricosmetics, Mar. Drugs 19 (2021) 552, https://doi.org/10.3390/md19100552.
[55] H.S. Kalasariya, C.E. Maya-Ramírez, J. Cotas, L. Pereira, Cosmeceutical significance of seaweed: a focus on carbohydrates and peptides in skin applications, Phycology 4 (2024) 276–313, https://doi.org/10.3390/phycology4020015.
[56] M. Michalak, Plant extracts as skin care and therapeutic agents, Int. J. Mol. Sci. 24 (2023) 15444, https://doi.org/10.3390/ijms242015444.
[57] K. Chauhan, N. Tiwari, P. Patani, C. Author, Alage: an extensive analysis of its role in the cosmetic landscape, J. Popul. Ther. Clin. Pharmacol. 30 (2023) 7807–7817, https://doi.org/10.53555/jptcp.v30i1.3830.

[58] R. De Araújo, M. Lôbo, K. Trindade, D.F. Silva, N. Pereira, Fibroblast growth factors: a controlling mechanism of skin aging, Skin Pharmacol. Physiol. 32 (2019) 275–282, https://doi.org/10.1159/000501145.
[59] A.C. Mitchell, P.S. Briquez, J.A. Hubbell, J.R. Cochran, Engineering growth factors for regenerative medicine applications, Acta Biomater 30 (2016) 1–12, https://doi.org/10.1016/j.actbio.2015.11.007.
[60] C. Aldag, D. Nogueira Teixeira, P.S. Leventhal, Skin rejuvenation using cosmetic products containing growth factors, cytokines, and matrikines: a review of the literature, Clin. Cosmet. Invest. Dermatol. 9 (2016) 411–419, https://doi.org/10.2147/CCID.S116158.
[61] O. Eskens, S. Amin, Challenges and effective routes for formulating and delivery of epidermal growth factors in skin care, Int. J. Cosmet. Sci. 43 (2021) 123–130, https://doi.org/10.1111/ics.12685.
[62] S.B. Nimse, D. Pal, Free radicals, natural antioxidants, and their reaction mechanisms, RSC Adv. 5 (2015) 27986–28006, https://doi.org/10.1039/c4ra13315c.
[63] S. Di Lodovico, F. Gasparri, E. Di Campli, P. Di Fermo, S. D'ercole, L. Cellini, M. Di Giulio, Prebiotic combinations effects on the colonization of staphylococcal skin strains, Microorganisms 9 (2021) 1–15, https://doi.org/10.3390/microorganisms9010037.
[64] J. Dou, N. Feng, F. Guo, Z. Chen, J. Liang, T. Wang, X. Guo, Z. Xu, Applications of probiotic constituents in cosmetics, Molecules 28 (2023) 6765, https://doi.org/10.3390/molecules28196765.
[65] C.V. De Almeida, E. Antiga, M. Lulli, Oral and topical probiotics and postbiotics in skincare and dermatological therapy: a concise review, Microorganisms 11 (2023) 1420, https://doi.org/10.3390/microorganisms11061420.
[66] G. Petruk, R. del Giudice, M.M. Rigano, D.M. Monti, Antioxidants from plants protect against skin photoaging, Oxid. Med. Cell Longev. 2018 (2018), https://doi.org/10.1155/2018/1454936.
[67] J. Ravanat, C. Saint-Pierre, P. di Mascio, G.R. Martinez, M.H. G. Medeiros, J. Cadet, Damage to isolated DNA mediated by singlet oxygen, Helv. Chim. Acta. 84 (2001) 3702–3709, https://doi.org/10.1002/15222675(20011219)84:12<3702::AID-HLCA3702>3.0.CO;2-Y.
[68] B. Bose, H. Choudhury, P. Tandon, S. Kumaria, Studies on secondary metabolite profiling, anti-inflammatory potential, in vitro photoprotective and skin-aging related enzyme inhibitory activities of Malaxis acuminata, a threatened orchid of nutraceutical importance, J. Photochem. Photobiol. B 173 (2017) 686–695, https://doi.org/10.1016/j.jphotobiol.2017.07.010.
[69] L. Chen, J.Y. Hu, S.Q. Wang, The role of antioxidants in photoprotection: a critical review, J. Am. Acad. Dermatol. 67 (2012) 1013–1024, https://doi.org/10.1016/j.jaad.2012.02.009.
[70] T. Uhlig, T. Kyprianou, F.G. Martinelli, C.A. Oppici, D. Heiligers, D. Hills, X.R. Calvo, P. Verhaert, The emergence of peptides in the pharmaceutical business: from exploration to exploitation, EuPA Open Proteom. 4 (2014) 58–69, https://doi.org/10.1016/j.euprot.2014.05.003.
[71] B. Reddy, T. Jow, B.M. Hantash, Bioactive oligopeptides in dermatology: Part I, Exp. Dermatol. 21 (2012) 563–568, https://doi.org/10.1111/j.1600-0625.2012.01528.x.
[72] K.O. Shin, H.S. Park, Antiaging cosmeceuticals in korea and open innovation in the era of the 4th industrial revolution: from research to business, Sustainability 11 (2019) 898, https://doi.org/10.3390/su11030898.
[73] G.E.B. Montalvo, V. Thomaz-Soccol, L.P.S. Vandenberghe, J. C. Carvalho, C.B. Faulds, E. Bertrand, M.R.M. Prado, S.J.R. Bonatto, C.R. Soccol, Arthrospira maxima OF15 biomass cultivation at laboratory and pilot scale from sugarcane vinasse for potential biological new peptides production, Bioresour. Technol. 273 (2019) 103–113, https://doi.org/10.1016/j.biortech.2018.10.081.
[74] C.D. Norzagaray-Valenzuela, A. Valdez-Ortiz, L.M. Shelton, M. Jiménez-Edeza, J. Rivera-López, M.A. Valdez-Flores, L.J. Germán-Báez, Residual biomasses and protein hydrolysates of three green microalgae species exhibit antioxidant and anti-aging activity, J. Appl. Phycol. 29 (2017) 189–198, https://doi.org/10.1007/s10811-016-0938-9.
[75] L. Nakchum, S.M. Kim, Preparation of squid skin collagen hydrolysate as an antihyaluronidase, antityrosinase, and antioxidant agent, Prep. Biochem. Biotechnol. 46 (2016) 123–130, https://doi.org/10.1080/10826068.2014.995808.
[76] M. Taniguchi, M. Kameda, T. Namae, A. Ochiai, E. Saitoh, T. Tanaka, Identification and characterization of multifunctional cationic peptides derived from peptic hydrolysates of rice bran protein, J. Funct. Foods. 34 (2017) 287–296, https://doi.org/10.1016/j.jff.2017.04.046.
[77] F. Gorouhi, H.I. Maibach, Role of topical peptides in preventing or treating aged skin, Int. J. Cosmet. Sci. 31 (2009) 327–345, https://doi.org/10.1111/j.1468-2494.2009.00490.x.
[78] H. Husein, R.F. Castillo, Cosmeceuticals: peptides, proteins, and growth factors, J. Cosmet. Dermatol. 15 (2016) 514–519, https://doi.org/10.1111/jocd.12229.
[79] T.N. Lima, C.A. Pedriali Moraes, Bioactive peptides: applications and relevance for cosmeceuticals, Cosmetics 5 (2018) 21, https://doi.org/10.3390/cosmetics5010021.
[80] S.K. Schagen, Topical peptide treatments with effective anti-aging results, Cosmetics 4 (2017) 16.
[81] M.P. Lupo, A.L. Cole, Cosmeceutical peptides, Dermatol. Ther. 20 (2007) 343–349, https://doi.org/10.1111/j.1529-8019.2007.00148.x.
[82] M. Maguire, G. Maguire, The role of microbiota, and probiotics and prebiotics in skin health, Arch. Dermatol. Res. 309 (2017) 411–421, https://doi.org/10.1007/s00403-017-1750-3.
[83] L. McCabe, R.A. Britton, N. Parameswaran, Prebiotic and probiotic regulation of bone health: role of the intestine and its microbiome, Curr. Osteoporos. Rep. 13 (2015) 363–371, https://doi.org/10.1007/s11914-015-0292-x.
[84] H. Akiyama, T. Oono, W.-K. Huh, O. Yamasaki, S. Ogawa, M. Katsuyama, H. Ichikawa, K. Iwatsuki, Actions of farnesol and Xylitol against Staphylococcus aureus, Chemotherapy 48 (2002) 122–128, https://doi.org/10.1159/000064916.
[85] S.W. Hong, E.-B. Choi, T.-K. Min, J.-H. Kim, M.-H. Kim, S.G. Jeon, B.-J. Lee, Y.S. Gho, Y.-K. Jee, B.-Y. Pyun, Y.-K. Kim, An important role of α-Hemolysin in extracellular vesicles on the development of atopic dermatitis induced by Staphylococcus aureus, PLoS One 9 (2014) e100499, https://doi.org/10.1371/journal.pone.0100499.
[86] K. Salli, M.J. Lehtinen, K. Tiihonen, A.C. Ouwehand, Xylitol's health benefits beyond dental health: a comprehensive review, Nutrients 11 (2019) 1813, https://doi.org/10.3390/nu11081813.
[87] F. Liu-Walsh, N.K. Tierney, J. Hauschild, A.K. Rush, J. Masucci, G.C. Leo, K.A. Capone, Prebiotic colloidal oat supports the growth of cutaneous commensal bacteria including s. Epidermidis and enhances the production of lactic acid, Clin. Cosmet. Invest. Dermatol. 14 (2021) 73–82, https://doi.org/10.2147/CCID.S253386.
[88] A. Gueniche, M. Liboutet, S. Cheilian, D. Fagot, F. Juchaux, L. Breton, Vitreoscilla filiformis extract for topical skin care: a review, Front. Cell Infect. Microbiol. 11 (2021) 747663, https://doi.org/10.3389/fcimb.2021.747663.
[89] M.-C.J. Huang, J. Tang, Probiotics in personal care products, Microbiol. Discov. 3 (2015) 5, https://doi.org/10.7243/2052-6180-3-5.
[90] E.G. Lopes, D.A. Moreira, P. Gullón, B. Gullón, A. Cardelle-Cobas, F.K. Tavaria, Topical application of probiotics in skin: adhesion, antimicrobial and antibiofilm *in vitro* assays, J. Appl. Microbiol. 122 (2017) 450–461, https://doi.org/10.1111/jam.13349.
[91] J. Rong, C. Shan, S. Liu, H. Zheng, C. Liu, M. Liu, F. Jin, L. Wang, Skin resistance to UVB-induced oxidative stress and hyperpigmentation by the topical use of Lactobacillus helveticus NS8-fermented milk supernatant, J. Appl. Microbiol. 123 (2017) 511–523, https://doi.org/10.1111/jam.13506.

[92] M.M. Ramsey, M.O. Freire, R.A. Gabrilska, K.P. Rumbaugh, K. P. Lemon, Staphylococcus aureus shifts toward commensalism in response to Corynebacterium species, Front. Microbiol. 7 (2016) 212804, https://doi.org/10.3389/fmicb.2016.01230.
[93] Y. Yu, S. Dunaway, J. Champer, J. Kim, A. Alikhan, Changing our microbiome: probiotics in dermatology, Br. J. Dermatol. 182 (2019) 39–46, https://doi.org/10.1111/bjd.18088.
[94] W.H. Tsai, C.H. Chou, Y.J. Chiang, C.G. Lin, C.H. Lee, Regulatory effects of lactobacillus plantarum-GMNL6 on human skin health by improving skin microbiome, Int. J. Med. Sci. 18 (2021) 1114–1120, https://doi.org/10.7150/ijms.51545.
[95] F.H. Al-Ghazzewi, R.F. Tester, Impact of prebiotics and probiotics on skin health, Benef. Microbes 5 (2014) 99–107, https://doi.org/10.3920/BM2013.0040.
[96] K. Kaur, G. Rath, Formulation and evaluation of UV protective synbiotic skin care topical formulation, J. Cosmet. Laser Ther. 21 (2019) 332–342, https://doi.org/10.1080/14764172.2019.1658878.
[97] R. Knackstedt, T. Knackstedt, J. Gatherwright, The role of topical probiotics in skin conditions: a systematic review of animal and human studies and implications for future therapies, Exp. Dermatol. 29 (2020) 15–21, https://doi.org/10.1111/exd.14032.