

RECENTLY EMERGED BIOACTIVE COSMECEUTICALS FOR SKIN REJUVENATION: A REVIEW.

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Abstract

Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. Cosmeceuticals are commonly used in skincare regimens to maintain healthy skin and improve visible signs of aging. A review of the biomedical literature was conducted using a peer-reviewed journal articles to identify laboratory, animal, and clinical studies that evaluated the most recent breakthroughs in the biological properties and potential dermatologic uses of the different bioactive ingredients used in cosmeceuticals. Bioactive ingredients in cosmeceutical products are derived from various sources including food, herbs, tissue engineering and stem cell therapy. Their bioactive components and pharmacologic activities have been shown to provide dermatologic benefits with potential applications for skin rejuvenation, photo protection, wound healing, and more. The information provided by this article is valuable to get the picture of the latest trends and also helpful for clinicians and related manufacturing companies. Despite several developments in this field, extensive research is required for performing successful and precise clinical trials in the future. Further improvements would enable the researchers to develop new products in this field.

Keywords: *Bioactives, cosmeceutical, skin aging, skin rejuvenation*

Introduction

The term cosmeceuticals refer to the substances that exerted both cosmetic and therapeutic benefits (1). Cosmeceuticals affects the biological functioning of the skin (medicinal or drug like benefits) depending upon the ingredients present in them. Like cosmetics, cosmeceuticals are applied topically; they contain ingredients that influence the skin's biological function (2).

Cosmeceuticals include most of the bioactive food components such as milk peptides certain vitamins and minerals, phytonutrients, various oils and botanical extracts. Different kinds of cosmeceuticals have been introduced like anti-wrinkle creams, sunscreens, moisturizers, bleaching agents, antidandruff shampoos, eye wrinkle creams, etc. In general cosmeceuticals are often used in the field of dermatology to improve skin tone/whitening, increase skin radiance, decrease the appearance of skin wrinkling, and provide anti-aging benefits (3,4,) and (5).

The area in which cosmeceuticals have shown the most promise is the treatment of skin aging. Photoaged skin typically develops coarse wrinkles, uneven pigmentation, atrophy, whereas naturally aged skin is characterized by finer wrinkles. Both types of aging are partially the result of decreased production of new collagen, a target of many cosmeceuticals (6), while other agents reverse signs of aging skin via regulation of fibroblast proliferation, metalloproteinase activity, and elastotic fiber turnover.

Thousands of chemical substances obtained either naturally or synthetically have been tested and or investigated as potential to use as an active compounds in cosmeceutical products (3). However, naturally occurred cosmeceuticals have a larger market value over the synthetic cosmeceuticals (3) and (5). Currently, natural ingredients are becoming more attractive for the industries such as functional food, nutraceuticals, cosmeceutical and pharmaceutical industries as people starting to believe naturally occurring compounds are safer to humans than artificial compounds.

Intrinsic versus extrinsic skin aging

Aging is a complex process comprised of two distinct components: (A) intrinsic aging and (B) extrinsic aging (7). During the intrinsic aging production of

cytokines and extracellular matrix-modifying enzymes such as elastase, collagenase, stromelysin, and interleukin-1 (IL-1) within the dermis are increased (8,9). These enzymes disrupt normal tissue integrity, resulting in: wrinkling, dermal fragility, and dermal thinning (10,11,12).

Dermal collagen production declines in adult life, and there is an associated decrease in elastin production as well. This results in a decrease in dermal thickness, which may play a role in the dermal fragility and delayed wound healing seen in elderly skin. Impaired skin barrier function is related to a deficiency in lipid synthesis, particularly in cholesterologenes, which leads to decreased lipid content in the stratum corneum. To inhibit and restore skin aging, a number of peptide-derived cosmeceutical ingredients are being developed (13).

Extrinsic aging can be considered as an accelerated intrinsic aging. Smoking and photo damage exacerbates many of these changes (14,15). UV radiation produces reactive oxygen species (ROS), which lead to increased expression of pro-inflammatory cytokines (15). The accumulation of large collagen degradation products inhibits new collagen synthesis. Collagen type I is the main component of skin layers.

The amount of collagen is important to sustain the elasticity and strength of the skin (16,17). In the dermis, UVB exposure has been shown to stimulate dermal fibroblast production of collagenase. This induces the degeneration of collagen and deposition of altered elastic tissue, which presents as wrinkles (18,19). Photo damaged skin has specific histologic findings. The epidermis may be atrophied or thickened with atypical keratinocytes. The most significant findings are seen in the dermis with collagen and elastin degeneration. Melanocyte density and activity has been found in some studies to be decreased while other studies have found increased melanocyte density (20).

Recent advances in Cosmeceuticals

Here is a review of the biomedical literature that is mainly restricted to the year 2019 and above using a peer reviewed journal articles to identify a new possible bioactive cosmeceuticals and their potential dermatologic uses in skin rejuvenation. Bioactive ingredients that are listed below are derived from various sources including food (walnut protein hydrozylate), plants (*Plantago lanceolata* L.), tissue

engineering and stem cell therapy (adipose derived stem cells).

Fibroblast growth factors (FGF) (Fibroblast Growth Factors)

Fibroblast growth factors are regulatory proteins that mediate important signaling pathways and act on cell regeneration so they have a role in repair of the dermis during the skin anti-aging process. FGF acts primarily through binding to tyrosine kinase receptors, promoting the phosphorylation of serine, threonine, and tyrosine residues of specific target proteins such as Raf-1, MAPK/Erk kinase, and extracellular signal-regulated kinase-1, which are part of the cascade of MAP kinases (mitogen-activated protein kinase). In addition, the FGF has a relevant role in anti-aging therapy because it is related to collagen and elastin synthesis activation responsible for skin resistance and elasticity (21).

Adipose-derived stem cells (ADSCs)

Adipose-derived stem cells (ADSCs) have intense interest in fields of dermatological medicine. As a major component detected in ADSCs secretome, platelet-derived growth factor AA (PDGF-AA) has been reported mediating extracellular matrix deposition and remodeling, thus might contribute to its anti-aging effect. Treatment of human dermal fibroblasts (HDFs) with ADSC-conditioned medium (ADSC-CM) have been done to explore the preventive effects of ADSCs secretome against aging damages. Cellular proliferation; β -galactosidase stain; mRNA expressions of MMP-1, MMP-9, and TIMP-1; and protein expressions of collagen I, collagen III, and elastin have been detected. Generally, ADSC-CM we prepared demonstrates a certain degree of positive role in preventing HDFs from intrinsic and extrinsic aging damages and that PDGF-AA may contribute to making it become effective with some other components in ADSC-CM (22).

Novel topical dermal repair

Topical antiwrinkle cream (Ultrascript Dermal Regeneration, Montclair, NJ) and a topical evening DNA repair serum (Dermal DNA Repair Serum with the active ingredient AC-11 from Optigenex INC) have been evaluated. The evening agent was to be applied to improve the overall youthful appearance of the face. This novel anti-wrinkle cream is a safe and

effective topical treatment for the immediate, but short-term improvement of wrinkles. Prolonged use of the cream and continued follow-up may show additional long-term benefits. This novel approach provides an effective option for the immediate, but temporary reduction in skin wrinkles in females of skin types I-III (23).

Glutathione (GSH)

GSH is master antioxidant which can be used as the main constituent for the formulation of cosmeceutical preparations. The effects of GSH on melanocytes make it a good candidate for using in whitening formulations with minimum side effects and tyrosinase inhibition rebound. Because of antioxidant property and induction of re-epithelization of this molecule, it can be exploited as anti-aging and wound healer. Moreover, GSH can be used in after-sun preparations due to its protective effects on keratinocytes (24).

Grammatophyllum speciosum extract.

Grammatophyllum speciosum is a giant-sized orchid which is widespread throughout the tropical rainforests in Southeast Asia. A study has provided scientific evidence supporting the use of *G. speciosum* ethnolic extract as a novel anti-aging ingredient for skin care products. Gastrodin, a phenolic glycoside found as a major active component in *G. speciosum*, is a potent antioxidant. The ethanolic extract of *G. speciosum* pseudobulb has potential to increase stem cell phenotypes of human keratinocyte cells, which are an essential factor in the regeneration process. The ethanolic extract of the pseudobulb of *G. speciosum* exhibited a potent elastase inhibitory activity and a protective effect against ($O_2\bullet^-$) at $10\mu\text{g/mL}$ in human fibroblast cells. The *G. speciosum* pseudobulb extract with known amount of gastrodin, utilized as an active quality control marker, was further developed into a cosmetic product as a stable serum. The studies with volunteers revealed that the serum could effectively and safely increase the firmness and smoothness of the skin as well as improve the appearance of skin wrinkles (25).

Pradosia mutisii extract

Pradosia mutisii is a member of the Sapotaceae family whose oil has traditionally been used to cure skin scars. The free radical scavenging, and moisturizing

effects of a methanol extract of *Pradosiamutisii* (Pm-ME) in keratinocytes (HaCaT cells), melanocytes (B16F10 cells), and fibroblasts (human dermal fibroblasts (HDFs)) at non-cytotoxic concentrations have been determined. Coumaric acid as a major component, and the extract exhibited protective activity against UVB- and H₂O₂-induced cytotoxicity. The Pm-ME also upregulated the expression levels of hyaluronic acid synthase (HAS) and transglutaminase-1 (TGM-1) in HaCaT cells, indicating a putative moisturizing activity. The expression of collagen type 1 (Col1A1) gene and its promoter activity, Similarly, Pm-ME helped recover collagen levels after UVB and H₂O₂ treatment in HDFs as well as decreased the synthesis and secretion of melanin from B16F10 melanoma cells, which may indicate a beneficial whitening cosmetic value (26).

Galangin

Galangin is a natural flavonol that recently known to have many pharmacological effects such as anti-viral, anti-inflammatory, anti-atopic dermatitis and anti-oxidative activities. Galangin showed down-regulation of intracellular reactive oxygen species, 4-hydroxynonenal, and matrix metalloproteinases and showed a protective effect against skin fibroblasts under oxidative stress caused by UVB irradiation. This lead to up-regulation of fibroblast growth factor 2 and type 1 pro-collagen (27).

Plantago lanceolata L. extract.

Plantago lanceolata L. is a perennial herb belonging to the plantain family (Plantaginaceae). The extract derived from narrow leaf plantain herb is a source of many bioactive substances. The most important of them are flavonoids, phytosterols, phenylethanoid glycosides, and iridoids. The strong antioxidant properties of the extract obtained from narrow leaf plantain herb are mainly attributable to flavonoids, which neutralize free radicals and participate in the process of metal chelation.

Substances present in the narrow leaf plantain, particularly luteolin and apigenin, contribute to a decrease in the oxidation of lipid substances and counteract the harmful effects of UV radiation. The UV protecting and fibroblast growth-stimulating agents properties of *Plantago lanceolata* extracts have been evaluated. *Plantago lanceolata* extracts are potential new multifunctional ingredients of

cosmetics and pharmaceutical products. Moreover, the extracts have high antioxidant properties combined with the ability to absorb UV radiation (prevention of skin aging processes) which makes them potential components of natural sunscreen cosmetics.

The extracts have also characterized by the stimulation of skin regeneration (increase in fibroblast proliferation) so, they can be used in natural cosmetics (28).

Collagen hydrolysate (CH) and peptides

CH prepared with papain from skin of certain species might be beneficial on protecting fibroblast from photo aging. Bovine CH inhibited matrix metalloproteinases (MMP)-1 synthesis. Tilapia CH promoted cell viability and pro-collagen I production, while inhibited the generation of reactive oxygen species (ROS) and MMP-1 in UVA-exposed HDF cells. Hen CH improved viability and pro-collagen I production, alleviated the expression of apoptotic genes, reduced ROS, MMP-1, and MMP-9 production, induced discoidin domain receptor 2 (DDR2) phosphorylation, and inhibited UVA-induced Akt and ERK1/2 phosphorylation in HDF cells, an effect largely comparable with a collagen-derived tripeptide Gly-Pro-Hyp. Hen skin CH is superior to porcine, bovine, and tilapia skin CH on the protection of UVA-induced damage in fibroblast (29).

Kojic acid

Kojic acid (KA) is a natural metabolite produced by fungi that has the ability to inhibit tyrosinase activity in synthesis of melanin. In addition, KA and its derivatives are used as anti-oxidant, anti-proliferative, anti-inflammatory, radio protective and skin-lightening agent in skin products. KA has the ability to act as a UV protector, suppressor of hyperpigmentation in human and restrainer of melanin formation, due to its tyrosinase inhibitory activity (30).

Bioactive peptides loaded on hyaluronic acid microneedle patches

The dermal tolerability and efficacy of hyaluronic acid-based microneedles (HA-MNs) loaded with bioactives for restoration of the skin properties was evaluated. The test product of HA-MNs comprises arginine/lysine polypeptide, acetyl octapeptide-3,

palmitoyl tripeptide-5, adenosine, and seaweed extracts. The composition of the microneedle patches works in a multi-targeted manner and all ingredients might possibly be acted synergistically for the improvement of skin structure, function, and appearance. The product was tolerated excellently. The fine lines/wrinkles showed a noticeable decrease; the skin hydration was improved; the skin density and thickness in the dermis increased (31).

Cross linked hyaluronic acid gel (VYC-12)

VYC-12 is a cross-linked HA injectable gel that was designed to treat superficial cutaneous depressions, such as fine lines, and provides additional improvements in skin hydration. VYC-12 belongs to a family of versatile HA gels based on the Vycross® technology platform (Allergan plc), which combines low and high molecular weight HA to improve the cross-linking efficiency of the HA chains. The tightly cross-linked HA network yields a cohesive gel with an improved duration of response. Treatment with VYC-12 significantly improved satisfaction with skin in the majority of subjects (32).

A crosslinked hyaluronic acid with a cohesive poly densified matrix

CPM®-HA20G, a poly densified filler containing a single phase of HA cross-linked continuously and manufactured with cohesive poly densified matrix (CPM) technology. CPM®-HA20G significantly increased gross elasticity, firmness, tone radiance, and hydration of the skin. Significant reduction of skin fatigue, skin roughness, and redness was also observed. CPM®-HA20G is considered to be an effective and safe HA injectable for skin revitalization in patients suffering from signs of skin aging and loss of skin elasticity (33).

Alpha Ionone

Alpha Ionone, an aroma compound found in herbs, fruits, roasted almonds, carrots, and raspberries led to a robust increase in procollagen content of human dermal fibroblasts. In human dermal fibroblasts, Alpha Ionone inhibited UVB-induced loss of collagen, and this effect was accompanied by upregulating the molecules

participating in the TGF- β -SMAD pathway, but downregulating the molecules involved in the MAPK-AP-1 signaling pathway. Alpha Ionone treatment also

increased hyaluronic acid contents, and this effect was accompanied by an upregulation of mRNA expression of genes (HAS1 and HAS2) involved in hyaluronic acid synthesis. Thus, Alpha Ionone is effective in the prevention of UVB-induced decrease of collagen and hyaluronic acid in human dermal fibroblasts. Alpha Ionone -ionone may prove beneficial for the prevention of UV-induced wrinkle formation and skin damage (34).

A novel anti-aging sun care formulation.

A product was designed to prevent and repair skin damage resulting from exposure to solar radiation and pollution. This product offers a very high sun protection factor (SPF50) and UVA protection. It contains the DNA repair enzyme photolyase, derived from plankton extract, to complement the skin's inherent DNA repair mechanisms. In addition, to provide protection against pollution and anti-aging or skin rejuvenation benefits, the product contains hyaluronic acid, palmitoyl tripeptide-38, and pentapeptide-34 trifluoroacetate (35).

Walnut protein hydrolysate (WPH).

Based on the food-derived bioactive peptides, the walnut protein hydrolysate (WPH, rich in peptides) proved that their functional ingredients are used for anti-photoaging foods development. The elasticity improvement of WPH against skin photoaging process can be attributed to regulating the components metabolism and repairing the damaged mechanical structure of extracellular matrix (ECM) (36).

Tranexamic acid

Tranexamic acid ameliorate the development of signs of skin aging. Treatment with tranexamic acid can lead to the synthetic inhibition of plasmin. Also, Tranexamic acid causes synthetic reinforcement of hyaluronic acid by an increase in the number of epidermal cells and the degradative inhibition of extracellular matrix (ECM) by metalloproteinase (MMP) suppression. Therefore, amelioration of wrinkles on the skin and improvement in skin moisture were achieved (37).

Zingiber cassumunar Roxb. extracts

Zingiber cassumunar Roxb. is a medically important plant with extensive traditional medicinal functions

and bioactivities. The extracts and components from rhizome of *Z. cassumunar* were investigated for their 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, HDFa (human dermal fibroblasts-adult) collagen secretion promotion, tyrosinase inhibition, and NO generation inhibition activities for the purpose of identifying ingredients with potential anti-aging, skin-whitening, and anti-inflammation for use in cosmetics. Extract of the plant showed significant NO generation inhibition, DPPH radical scavenging, tyrosinase inhibitory activities, and weak promoting collagen secretion activity. These results suggest that medicinal plant *Z. cassumunar* possesses potential application value in the development of natural cosmeceutical products for anti-aging, skin-whitening, and anti-inflammation activity (38).

Zanthoxylum piperitum extracts

Zanthoxylum piperitum extracts is an aromatic medicinal plant. Five phytochemical compounds (Quercitrin, afzelin, hydroxy- α -sanshool, α -sanshool and hyperoside) were isolated and screened for their biological activities. In the activity tests, the extracts showed inhibitory activity against inflammation response and melanin synthesis, and induction of procollagen type I C-peptide (PIP). Among the isolated compounds, hydroxy- α -sanshool and α -sanshool displayed significant anti-inflammatory response. The above results demonstrate that *Z. piperitum* active compounds are considered as cosmeceutically active agents for enhancing skin quality (39).

Conclusion

The biologic activity of the most recent bioactive skin rejuvenators has been elucidated, providing mechanisms for how these compounds may protect skin against aging. Cosmeceuticals show much promise for the treatment of both aging and photoaged skin. Further randomized, placebocontrolled, double-blind studies are needed to substantiate many of the claims made about cosmeceuticals. Elucidating the diverse pathways targeted by different cosmeceuticals highlights the need to study combinations of several classes of cosmeceuticals, which will likely reveal synergistic effects on reversing signs of aging.

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