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Current Topical Strategies for Skin-Aging and Inflammaging Treatment: Science versus Fiction

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Synopsis

Aging is a natural phenomenon that affects the whole body, including the skin. As we age, endogenous and exogenous factors cause our skin to become thinner, paler, and wrinkled. Although the underlying mechanisms of the pathogenesis of skin aging are not entirely known, multiple pathways have been proposed. Inflammaging has recently emerged as a pathway that correlates aging and age-related diseases with inflammation. This review discusses the role and pathways of inflammaging that lead to skin aging. Moreover, strategies and current topical approaches for skin-aging treatment are discussed. Studies over the past 10 years suggested that DNA damage and oxidative stress are the most critical mechanisms in skin aging, and both are interlinked with inflammaging. Several treatments for skin aging have been considered such as antioxidants, hormone replacement therapy, and vitamins. To deliver anti-aging agents topically, researchers adopted numerous approaches to enhance skin penetration including physical, chemical, or biomaterial enhancers and carrier-based formulations. In recent years, consumers' demands for anti-aging products have considerably risen, leading to robust growth in the anti-aging market. Therefore, further in-depth studies are necessary to understand skin-aging mechanisms and evaluate the efficacy of anti-aging products to protect consumers worldwide by providing them safe and effective over-the-counter skin-aging formulations.

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INTRODUCTION

Biologists have defined aging as "age-dependent or age-progressive decline in intrinsic physiological function, leading to an increase in age-specific mortality rate (i.e., a decrease in survival rate) and a decrease in age-specific reproductive rate" (1). As we age, our skin becomes thinner, paler, and wrinkled with irregular pigmentation (2). Different clinical parameters are used for estimating apparent age such as under eye lines, forehead lines, crow's feet, and age spot. Other biophysical parameters, such as skin texture, and firmness evaluation instrument and biochemical parameters (glycation and proliferation) are also used to determine apparent age (3).

Being the most visible part, the skin receives our greatest attention and care, especially from women (4). Ancient civilizations have already aimed to control and prevent skin aging (5), such as ancient Egyptians who used sour milk baths, oils, and fruit acids for skin renewal or types of sandpaper to remove and smoothen scars (6). Nowadays, Americans' expenditure on products for skin care amounts to around $43 billion/year (4). This continued interest fueled research into skin-aging processes and treatments.

First introduced by Giacomoni and D'Alessio as a model to describe skin aging (7), inflammaging is a field of research that was imagined by Franceschi et al. (8) to extend the study of the role of inflammation in the aging of different organs, and age-related diseases and processes, including skin aging (8). It differs from inflammation, which is a natural body response to injury, infection, or trauma. Inflammation is a complicated process which facilitates source removal and tissue repair based on the release of proinflammatory mediators and cells, such as neutrophils, macrophages, and monocytes, until it reaches a resolved state (hemostasis) (9). However, if the stimulus is low grade and persistent, a chronic, nonresolving inflammation (inflammaging) will occur (10). There is a strong, but complex, correlation between inflammaging and age-related disease, including skin aging. This review focuses on the mechanisms of inflammaging that lead to skin aging.

Moreover, strategies and topical approaches for skin-aging treatments are discussed. Immune cells in the dermis release singlet oxygen and matrix metalloproteinases (MMPs), causing connective tissue damage. During this immune response, other cells are damaged, releasing proinflammatory mediators and repeating the cycle (11). The microinflammatory theory could explain a number of skin-aging features such as loss of elasticity, and dermal flexibility. Moreover, this theory accounts for wrinkle appearance and epidermal thinning with age (12). Bhattacharyya et al. (13) assessed the histological changes in intrinsic aged mice. Results showed that there was a notable epidermal thinning and reduction in the pilosebaceous unit associated with aging (13). In addition, DNA damage plays a critical role in skin aging and can be caused by endogenous and exogenous factors. Endogenous agents are mainly reactive-oxygen species (ROS) resulting from different metabolic processes, while exogenous agents include UV radiation and chemicals (14).

TYPES OF SKIN AGING

Similar to other organs, skin aging is considered a progressive multifactorial process (15,16) based on a gradual decline in physiological integrity and cellular functions (15). It is often classified as intrinsic or extrinsic aging (2).

INTRINSIC AGING

Intrinsic aging represents the inevitable and genetically determined aging of all tissues (17). It is shaped by endogenous physiological determinants, including gender, ethnicity, anatomical differences, and hormonal fluctuations (18). Clinical signs of intrinsic skin aging include xerosis, fine lines, decreased elasticity, and subepidermal atrophy (17). These changes are based on reduced cellular proliferative capacity and genetic abnormalities (19). In addition, the dermis of older skin is characterized by fewer mast cells, fibroblasts, elastic fibers, and lower amounts of collagen compared with younger skin (20). Moreover, signs of intrinsic skin aging not only include declines in fibrous extracellular matrix components, such as elastin, fibrillin, and collagens but also degeneration of oligosaccharides, which influence the skin's capacity to preserve bound water (21). Although these structural changes are natural aspects of skin aging, environmental and individual factors, such as UV exposure and diet, can dramatically influence the rate of skin aging (22).

EXTRINSIC AGING

Extrinsic aging is referred to as photoaging, as it is shaped by environmental causes, especially UV exposure (22). In fact, UV radiation exposure is considered the key determinant of extrinsic skin aging and attributable to 80% of facial skin aging (2). Whereas intrinsic aging causes epidermal thinning, photoaging is characterized by epidermal thickening based on impaired keratinocyte differentiation in the epidermal layer and basal cells (23). In addition, keratinocyte proliferation is impaired in both stratum corneum (SC) and basal cells (24). Furthermore, accelerated skin aging is associated with increased levels of MMPs (an enzyme family responsible for the decay of collagen and extracellular matrix proteins) (25).

Although elastic fiber degradation is a characteristic feature associated with aging, photoaging exhibits enormous accumulation of dystrophic elastin in the dermis known as solar elastosis (26). Elastin degradation in photoaging could be due to MMP activation, specifically human macrophage metalloelastase secreted by keratinocytes, fibroblasts, and inflammatory cells (27). Mora Huertasa et al. (28) investigated the molecular changes in elastin associated with normal aging and photoaging. The study revealed that the elastin cleavage pattern is different in both types and is more pronounced in photoaging. Moreover, the N-terminal of tropoelastin becomes more susceptible to enzymatic degradation due to photoaging (28).

Moreover, air pollution has detrimental effects on skin. Air pollutants (ozone, volatile organic compounds, oxides, and others) alter skin homeostasis and induce aging and other inflammatory diseases. This influence could be attributed to different mechanisms including free radical production, inflammatory mediator release, and skin barrier damage (29).

MOLECULAR PATHWAYS AND PROCESSES OF SKIN INFLAMMAGING

It is important to identify molecular mechanisms, which are likely complementary and interconnected, that control skin aging to find beneficial approaches for prevention and treatment. Inflammaging plays a crucial role in age-related diseases, such as osteoporosis,

Alzheimer's disease, diabetes type II, and skin aging. Chronic exposure to intrinsic and extrinsic factors by itself generates the release of inflammatory mediators, causing inflammation as well as dermal and extracellular matrix damage (2). The next section highlights the main pathways of skin inflammaging, considering DNA damage and oxidative stress as key players in the process.

OXIDATIVE STRESS

Oxidative stress, which occurs because of a mismatch between ROS production and the cell's ability to detoxify these species (30), is a key contributor to skin aging (31). ROS are generated by-products of oxygen metabolisms in every cell from different sources, including mitochondria, peroxisomal activity, oxidase activity, and endoplasmic reticulum (ER) (32). ROS at normal levels have beneficial functions for the body, including cellular structure synthesis, fighting pathogens, and numerous signaling pathways (30). However, if ROS levels increase, oxidative stress occurs, harming cellular structures and immune responses and accelerating skin aging (30).

Under normal conditions, receptor protein tyrosine phosphatases (RPTPs) inhibit receptor tyrosine kinase (RTK) activity on the cell surface through dephosphorylation (33). However, under oxidative stress, ROS bind to cysteine of RPTPs, inhibiting its activity and increasing phosphorylated RTKs levels. Consequently, numerous downstream signaling pathways are triggered, such as initiation of mitogen-activated protein kinase, transcription factor activator protein-1 (AP-1), and nuclear factor-κB (NF-κB) (34). The process inhibits collagen production and increases MMP gene transcription (2,35). Collagen degradation by MMPs leads to a build-up of fragmented and disorganized collagen fibrils, which downregulate new collagen synthesis (25). MMP-1, MMP-3, and MMP-9 collectively account for most of the type I and III dermal collagen degradation (36). In addition, reduced collagen content is attributable to AP-1's suppression of type I and III procollagen gene expression in the dermis (37).

Different studies have reported a strong correlation between oxidative stress and inflammation, as continued exposure to ROS induces cell damage and, subsequently, a proinflammatory signaling response. Oxidative damage to cells triggers TNF-α release, which in turn binds to cell surface receptors, activating the NF-κB inflammasome. NF-κB inflammasome generation results in an overproduction of other proinflammatory cytokines, which can be detrimental to health (38,39). In addition, UV radiation activates inflammatory mediators, such as neutrophils, to remove damaged cells. Moreover, macrophages infiltrate the exposed area, release ROS, and degrade the extracellular matrix (2,35). This is accompanied by fibroblast deterioration and an inability to repair the extracellular matrix, leading to skin aging (40). Therefore, NF-κB inflammasome is considered the major etiology of inflammaging.

MICROINFLAMMATORY THEORY

The microinflammatory theory describes skin aging as a number of events in a repeated cycle that occurs because of cell exposure to intrinsic or extrinsic factors. (i) Damaged cells secrete proinflammatory signals such as prostaglandins and leukotrienes. (ii). These

signals bind to mast cells, causing TNF-α and histamine release. (iii) TNF-α and histamine stimulate intercellular adhesion molecule-1 (ICAM-1) synthesis in endothelial cells of the blood vessels. (iv) ICAM-1 binds to circulating immune cells that release hydrogen peroxide to perform diapedesis and enter the dermis. (v) Immune cells in the dermis release singlet oxygen and MMPs, causing connective tissue damage. (vi) Immune cells reach the damaged cell, release hydrogen peroxide, and digest the damaged cell. (vii) During the three oxidative bursts, other cells are damaged, proinflammatory mediators are release, and the inflammatory cycle is maintained (11).

The microinflammatory theory could explain a number of skin aging features such as loss of elasticity, and dermal flexibility. Moreover, this theory accounts for wrinkle appearance and epidermal thinning with age (12). Bhattacharyya et al. (13) assessed the histological changes in intrinsic aged mice. Results showed that there was a notable epidermal thinning and reduction in the pilosebaceous unit associated with aging (13).

DNA DAMAGE

UV radiation creates pyrimidine dimers, resulting in DNA mutations. Moreover, UV radiation generates ROS, which accelerate telomere shortening and interfere with enzymes required for DNA repair (41).

Continuous DNA damage responses cause replicative cell senescence and aging processes, as illustrated by Xia et al. (10). DNA damage in aging cells contributes to a surge in the proinflammatory secretory phenotype, which in turn induces further DNA damage and proinflammatory secretion in adjacent cells. Ultimately, local inflammation becomes systemic, resulting in an inflammaging exacerbation (10).

Telomeres refer to nucleotide sequences at the ends of chromosomes that protect them from degrading (42). With each cell division, telomeres shorten because of replication problems. Accordingly, the proliferation capacity of the cell deteriorates, and eventually, cellular aging occurs (2,43). However, telomerase is an enzyme that retains telomere length by adding telomere repetitions to the end (44). Therefore, regulation of telomerase activity is a key factor in DNA repair and antiaging therapy.

Goyarts et al. (45) conducted a study to investigate the molecular mechanism associated with morphological changes in age spots. mRNA in skin biopsies was analyzed, and results revealed that 23 genes were upregulated, whereas 17 genes were downregulated. For instance, peptidase gene and genes responsible for keratinization and basement membrane synthesis were downregulated. Moreover, genes related to inflammation were upregulated, including MMP3, which is responsible for elastic fiber degradation in the dermis. Both upregulated and downregulated genes were highly linked to inflammation, confirming the role of microinflammation in age spots (45).

OBESITY

Obesity, especially central obesity, is closely correlated with a proinflammatory state (39). This state is attributable to declines in subcutaneous adipose tissue and increases in visceral adipose tissue (VAT), which produces more inflammatory cytokines with age (46,47). Elevated quantities of visceral fats are accompanied by higher levels of inflammatory

markers circulating in the blood, in addition to high amounts of proinflammatory cells in their tissues (47). Also, a number of T-cell lymphocytes grow, and macrophages differentiate into M1 macrophages, with increased proinflammatory cytokine production (46). Because of its anatomical position, VAT provides venous blood directly to the liver through the portal vein, consequently controlling the metabolism of the whole body (47). As a result, VAT may be a source of circulating low-grade inflammation (inflammaging).

GUT AND SKIN MICROBIOTA

A new theory links inflammaging to permeability and changes occurring in the gut microbiota (39). Those microorganisms are known for their role in counteracting pathogenic organisms and retaining the intestinal barrier integrity (48). Different studies have confirmed that beneficial normal gut flora is markedly reduced with aging (49). Reduced microbiota permits other bacteria to inhabit, including symbiotic bacteria that could be pathogenic under certain conditions. Moreover, gut microbiota imbalance has been hypothesized to increase the permeability of the mucosal barrier, allowing bacteria and their products to reach systemic circulation, resulting in a chronic proinflammatory state (39). This imbalance is clearly noticeable in people suffering from chronic diseases that aggravate with aging (39). Nonetheless, there is no definite evidence of heightened intestinal permeability and release of proinflammatory agents in older people who are not suffering from chronic inflammatory diseases (50).

Shibagaki et al. (51) correlated skin aging to skin microbiome. The study involved characterization and comparison of skin bacterial communities in 2 age-groups. Results showed that in older adults, there was a reduction in genus *Propionibacterium* in the cheek, forearm, and forehead microbiomes (51).

TREATMENT APPROACHES OF INFLAMMAGING

An intervention to solve inflammaging should be safe, efficient, nontoxic, and suitable for long-term use (10). Several treatment strategies for inflammaging are being assessed, such as antioxidants, ways of increasing adaptive immunity, lifestyle changes, and pro-/prebiotics use (10).

ANTIOXIDANTS

Antioxidants, which are either endogenous or exogenous, neutralize the harmful effects of pro-oxidants and minimize physiological disorders (52). Endogenous antioxidants are further categorized as enzymatic or nonenzymatic (52). Exogenous antioxidants are dietary supplemented, such as vitamins, flavonoids, and others. Defensive effects of antioxidants are based on different mechanisms, including prevention or elimination of free radicals and repair of damaged biomolecules (53). Antioxidants have clinical potential for antiaging (52).

Several studies have addressed how antioxidants help in chronic inflammatory states. Masaki (54) discussed how antioxidants, such as tocopherols, ascorbic acid, and polyphenols, can reduce skin diseases and photoaging (54). Lee et al. (55) performed an *in vivo*

antiwrinkle study using an animal model to evaluate an extract of *Veronica officinalis*, showing an 18% reduction in wrinkles after cream usage for 56 d. Curcumin, a natural extract from turmeric, has demonstrated anti-inflammatory and antineoplastic activity (56). A study among 28 women was performed to evaluate the-antiphotoaging effect of curcumin using Tricutan, a herbal extract of rosemary, turmeric, and gotu kola (57). The product improved photoaging based on skin firmness and general self-assessment after 1 mo of usage (57). Another clinical randomized double-blind study with 47 subjects focused on the effect of curcumin on inflammatory mediators was conducted (56). The study confirmed anti-inflammatory effects of water extract of *Curcuma longa* as evidenced by a decline in inflammatory mediators. Quantities of TNF-α and IL-1β were markedly decreased in mRNA and proteins. The enhanced hyaluronan production with increased skin water content had a moisturizing effect (56).

In sum, studies support curcumin as a potential intervention for inflammaging. Although curcumin suffers low oral bioavailability and first-pass metabolism, these drawbacks can be overcome through IV administration and current formulations (56).

Naringenin (NGN) is a flavanone that is abundant in many fruits and is characterized by antioxidant and anti-inflammatory properties. A study by Martinez et al. (58) investigated the efficacy of NGN for antiphotoaging in hairless mice (58). *In vitro* antioxidant activity was first assessed through ability of ferric reduction, scavenging hydroxyl radicle, 2,20 azinobis (3 -ethylbenzothiazoline- 6 sulfonic acid (ABTS) assay, and inhibition of lipid peroxidation (58). The efficacy of NGN topical formulation *in vivo* was evaluated through skin edema measurement and several antioxidant assessments (58). The authors concluded that NGN reduces skin edema, inhibits cytokine production, maintains cellular antioxidant production, and promotes heme oxygenase-1 mRNA expression in the skin, thereby providing skin protection from ultraviolet-B irradiation (Supplementary Table 1) (58).

Yap evaluated the efficacy of a topical nano-emulsion tocotrienol-rich fraction (TRF) on skin erythema (inflammation due to UV) in an *in vitro* study, using immortalized human keratinocyte cell line (HaCaT) (59). ROS measurement showed a significant decrease in oxidative damage caused by UV (59). Furthermore, Yap tested TRF effects on outer lobes of pig ears, measuring skin antioxidative potentials and sun protection factors (59). TRF was found to reduce free radicals in *ex vivo* models and decrease UV-induced erythema and tanning in human subjects in a clinical trial (Supplementary Table 1) (59).

ROLE OF HORMONE IMBALANCE ON AGING

Hormonal status and imbalance play a role as an internal-only inducer of aging. As detailed by Giacomoni and D'Alessio (7), hormonal imbalance has a direct effect on vascular aging progression and, subsequently, skin aging. Moreover, it is well-documented that immunity declines with age (60). Inflammaging in elderly subjects is characterized by elevated proinflammatory mediators, such as IL-6 and TNF-α (61). Furthermore, postmenopausal women recognize a decline in estrogen hormones (60). Several studies support that hormone replacement therapy improves immunological parameters (60). Estrogen therapy in postmenopausal women has decreased proinflammatory cytokine levels, such as IL-6 (60).

Hormones, such as estrogens, have a weighty impact on the skin structure, function, and physiological state. This could be attributed to the abundance of estrogen receptors in the

skin. Estrogen has a substantial influence on the skin-aging process as it enhances the collagen content, production, and quality; increases skin thickness; enhances skin vascularization; and further enhances the extracellular skin matrix, which is responsible for the tone and appearance of the skin (62). Subsequently, estrogen replacement therapy reverses the harmful effect of estrogen deprivation on the skin. In a study by Brincat et al. (63), 41 postmenopausal women treated with estradiol (100-mg) subcutaneous implants exhibited significantly increased skin thickness and metacarpal index over 1-y period of estrogen therapy.

Stout et al. (64) explored the effect of 17α-estradiol in old mice (64). 17α-Estradiol improved metabolic disorders and inflammaging through better nutrient sensing and alteration of lipid redistribution related to age. These effects improved liver function and glucose homeostasis (64). 17α-Estradiol may be a promising intervention for inflammaging because of its improvement of leptin signaling (64).

Despite the advantages of using HRT in postmenopausal women, further studies are needed to examine HRT side effects. Serious problems could be associated with HRT. Some studies reported that such treatment could induce breast cancer (60,61,65). Moreover, users of HRT are at risk of venous thromboembolism (66). As supported in the previous studies, HRT can be used in low doses for anti-inflammaging in advanced age (60).

STEM CELLS

Embryonic stem cells have the ability to form differentiated cells and may help in treatment of several disorders (67). Aging is associated with reduced tissue regeneration, which is highly related to impaired functions of stem cells. Epidermal stem cell capacity to proliferate is suppressed with age. Therefore, transplantation of stem cells could be a promising approach to the treatment of skin aging (2).

Doles et al. (68) investigated the involvement of stem cells in skin inflammaging using a mouse model. Stem cells increased during aging, with impaired function and ineptitude to endure stress. Moreover, an *in vivo* study by Mojallal et al. (69) using an animal model showed that fat grafting stimulated collagen synthesis and improved skin volume and quality (69).

In addition, adipose-derived stem cells can be a successful treatment against skin aging along with its potentials for wound healing. Zhang et al. (70) tested the effect of adipose-derived stem cells on skin aging because of D-galactose using an animal model (Supplementary Table 1). These stem cells inhibited D-galactose–induced skin aging, as confirmed by reduced levels of glycation products and increased levels of superoxide dismutases with antioxidant properties. Moreover, adipose stem cells released a vascular endothelial growth factor, thereby promoting skin regeneration (70). However, concerns about stem cells limit its application in cell-based therapy. Stem cell senescence affects their subpopulation dynamics, ruins their proliferation, and diminishes their functions (71).

RETINOIDS

Retinoids are types of compounds with chemical similarity to vitamin A (2). They are used as topical application to decrease MMP expression and collagen degradation through

AP-1 inhibition (2,72). Retinoids also increase epidermal thickening, thereby alleviating skin aging (2,72).

A protein called cysteine-rich angiogenic inducer 61 (CCN1/Cyr61) plays a vital role in regulating inflammation and fibrogenesis (73); thus, interventions that affect CNN1 activity play an important role in senescence (73). An *in vivo* study using vitamin A (retinol) as a topical treatment observed a decline in CNN1 expression in both natural and photoaged skin (72). This study inferred that retinoids improve skin aging through downregulation of CNN1 and collagen production (72).

Kafi et al. (74) investigated the effectiveness of retinol as an intervention for skin aging in a randomized, double-blind study over 24 weeks, showing that retinol improves wrinkles due to induction of glycosaminoglycan and increased collagen production (74).

NOVEL FORMULATIONS FOR SKIN AGING

Topical and transdermal drug delivery systems (TDDSs) eliminate risks associated with intravenous routes and drawbacks associated with oral therapy, such as altered gastric pH and hepatic metabolism (75). Moreover, the TDDS is a noninvasive method to deliver drugs, avoiding trauma and infection risks (76).

However, SC consists of dead keratinocyte layers surrounded by a lipid matrix, making the passage of drug molecules through the skin a troublesome issue (75). Few drugs can be delivered through the TDDS (exceptionally, small and highly lipophilic drugs could be delivered via passive diffusion at therapeutic levels). In addition, most drugs are transported through the skin very slowly, with lag times exceeding several hours to reach steady-state flux (76). Finally, the TDDS and dermal transport suffer poor skin penetration of drugs (77).

There are multiple approaches to enhance drug penetration through skin layers, such as penetration enhancers and carrier-based formulations. There are chemical, physical, and biomaterial penetration enhancers.

CHEMICAL PENETRATION ENHANCER

Chemical penetration enhancers are a promising way to overcome SC barrier and permit drug permeation across the skin in adequate rates (78). A good penetration enhancer must be nonirritant, nontoxic, and inert with adequate cosmetic acceptability (79). Polyunsaturated fatty acids, polymers, nonionic surfactants, pyrrolidones, and terpenes are commonly incorporated in topical formulations for chemical enhancers.

Curcumin applications as antioxidants are limited because of poor absorption and excessive hepatic metabolism after oral administration (78). Patel et al. (78) developed a topical gel to deliver curcumin, using menthol as a chemical penetration enhancer, showing that menthol markedly increased percutaneous flux as well as the enhancement ratio of curcumin across excised rat epidermis (Supplementary Table 1) (78).

PENETRATION ENHANCER

Different approaches have been used to facilitate drug penetration through the skin based on physical principle (80).

Biomaterials as penetration enhancers. Different biomaterials have recently emerged as safer skin penetration enhancers. For example, cell-penetrating protein, such as arginine, magainin, and lysine, facilitates the delivery of various cosmeceuticals through the skin (81). Arginine-rich peptide improves transdermal delivery of proteins into skin tissue (Supplementary Table 1) (82). Moreover, Li et al. (83) used trypsin as a biochemical enhancer to enhance insulin transdermal delivery (83).

Nasrollahi et al. (84) studied the ability of cell-penetrating peptides to transport elastin into fibroblast as skin-aging treatment. The study confirmed the transport of the elastin–peptide complex across fibroblast cell culture via a fluorescent microscope, which occurred by physical interactions between the peptide and the membrane (Supplementary Table 1) (84).

Carrier-based formulations. Vesicular systems of nanometer size are commonly used to enhance skin penetration of drugs and other cosmeceuticals. Nanocarriers have received researchers' attention because of their various advantages, such as improving drug pharmacokinetics, prolonging its half-life, and reducing its metabolism. In addition, nanocarriers protect the drug *in vitro* and *in vivo* (85).

Liposome. First introduced in 1961, liposomes are spherical vesicles with phospholipid bilayers that carry portions of the surrounding solvent within (86). This allows for the incorporation of hydrophilic, hydrophobic, and amphiphilic drugs. Natural and synthetic phospholipids are used in liposome formation along with cholesterol and surfactants (87). It was hypothesized that liposomes enhance cosmeceutical delivery by increasing skin barrier permeability and changing the intracellular lipids (88). Because of liposomes' rapid partition, the cosmeceutical agent is carried to the SC, and as the vesicle remains in this layer, the drug passes to deeper layers (89). However, liposomes are greatly limited by their instability, aggregation, and molecule leakage. Also, their diffusion into the skin is heterogenous and inhibited by the skin barrier (90).

Tsai et al. (91) developed and investigated NGN-loaded elastic liposomal formulations via an *ex vivo* study (91). The NGN accumulation in different skin layers in case of elastic liposomes was significantly higher relative to Tween 80 and saturated aqueous solutions. Furthermore, elastic liposome formulations caused less skin irritation when applied to rat skin than a standard irritant, indicating that elastic liposomes can be considered a good carrier for topical formulations of NGN (91).

Caddeo et al. (92) created liposomal formulation to deliver two different phenols: resveratrol (lipophilic) and gallic acid (hydrophilic), both of which have protective skin effects against oxidation and inflammation (92). The formulation's ability to protect fibroblasts from oxidative damage of H_2O_2 was evaluated *in vitro*. In addition, therapeutic efficacy was evaluated in mice based on capability to inhibit chemically induced edema and myeloperoxidase activity (Supplementary Table 1) (92).

Niosomes. Niosomes are vesicles consisting of nonionic surfactants such as Span 60, Span 80, Tween 60, and Tween 80, which are safe and cheap for pharmaceutical applications. They are good carriers of hydrophilic and hydrophobic cosmeceutical agents (93). Niosomes have advantages over liposomes, as they are more stable, cheaper, and easier in production (85). However, they showed reduced molecule fluxes compared with liposomes (94).

Gallic acid derived from *Terminalia chebula* showed antiaging effects because of its antioxidant properties. However, its extract suffers chemical instability and inactivity on exposure to environmental conditions (95). Manosroi et al. (95) developed elastic and

nonelastic niosomal gel formulation of gallic acid to enhance both its stability and skin penetration. An *in vivo* study was conducted to assess skin irritation effects via closed patch tests and evaluate antiaging effects based on skin elasticity, hydration, erythema, and pigmentation. The results indicated that niosomal formulation enhanced the stability and antiaging efficacy of gallic acid (Supplementary Table 1). In another study, Gupta et al. (96) developed liposomes, niosomes, and curcumin–phosphatidyl choline (phytovesicles) vesicles to enhance curcumin topical bioavailability. They found that vesicular systems improved antiaging effects and phytovesicles were the most effective (Supplementary Table 1).

Proniosome, Ethosome, and Transfersome. Proniosomes are flowable, dry formulations composed of surfactant-coated carriers, which form multilamellar niosomes on hydration (97). Proniosomes have been developed to overcome niosomes' drawbacks, such as aggregation and leaking (97).

Protection of coenzyme Q_{10} (CoQ_{10}) against photoaging is related to its antioxidant efficacy. Yet, its lipophilicity and high molecular weight hinder its topical applications (98). Yadav et al. (99) developed proniosomal formulation of CoQ_{10} to solve these problems as listed in Supplementary Table 1. An *in vivo* study exposed the skin to UV radiation followed by a 4-week formulation application, assessing skin sagging via a pinch test visually for wrinkles, striation, and inflammation. The study showed that pronisomes could be an efficient way to deliver CoQ_{10} (99).

Ethanol is an efficient permeation enhancer. When added in 20–50% to phospholipid, it yields an elastic nanovesicular system known as ethosome (100). The improved penetration of ethosome over liposome is because of ethosomes' interaction with skin lipids. It has been hypothesized that ethanol reduces transition temperature, fluidity, and density of skin lipids, causing deeper penetration of cosmeceutical agents into skin layers (100).

Transfersomes are bilayered, deformable vesicles formed by phospholipids, ethanol, and surfactants. Transfersomes penetrate SC because of their flexibility and ability to squeeze between intracellular lipids. Moreover, the skin hydration gradient permits further vesicle penetration into deeper hydrated layers (101).

Kaur et al. (102) encapsulated curcuminoids extract in liposomes, ethosomes, and transfersomes to evaluate their photoprotection and skin hydration effects. The study showed improvement in skin characteristics, indicating enhanced penetration and photoprotection effects (Supplementary Table 1).

Saraf et al. (103) developed curcuminoid-loaded transfersomes formulation for antiwrinkle treatment, which was incorporated into cream and evaluated for their irritation. Furthermore, antiwrinkle effects were assessed by measuring skin elasticity of six female volunteers. Results revealed increased skin deposition with enhanced skin elasticity and firmness (Supplementary Table 1).

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs). In 1991, SLNs were introduced as a substitute for other colloidal carriers. They are a carrier system consisting of a solid core (lipid with a high melting point) and an aqueous surfactant coat (104). Solid lipids constitute about 0.1–30% w/w, whereas surfactant constitutes 0.5–5% to enhance stability. Particle size, drug encapsulation, stability, and release are influenced by the types of lipids and surfactants (105). For better stability and loading capacity, NLCs were produced, which are modified SLNs consisting of solid and liquid fats (105).

Farboud et al. (106) formulated SLNs as an efficient carrier of CoQ_{10} to enhance its stability. It was then incorporated into oil/water cream to improve skin hydration. A double-blind clinical study was conducted among 25 females to assess antiaging effects of developed formulations. Skin hydration and elasticity assessment confirmed enhanced penetration, and antiwrinkle and antiaging effects (Supplementary Table 1) (106).

In another study, Yue et al. (107) developed CoQ_{10}-loaded NLCs to enhance their antioxidant effect on photoaged skin (107). The protective effect of CoQ_{10}-loaded NLCs was enhanced compared with emulsion formulation, indicated by UV-irradiated fibroblast viability and inhibition of lipid peroxidation. The *in vivo* study showed better SC penetration and dermal accumulation with the NLC formulation compared with emulsion (Supplementary Table 1) (107).

Retinaldehyde, a precursor of retinoic acid, is a useful photoaging treatment. Moreover, retinaldehyde is less irritating to the skin on topical application (108). Nayak et al. (109) coloaded retinaldehyde and CoQ_{10} in NLCs to improve their photoaging treatment. An *ex vivo* study showed a negligible permeation but greater accumulation in skin layers (109). A wrinkle model induced by UV was developed in mice and demonstrated effectiveness of coloaded NLCs as antiwrinkle treatment (109).

COSMETIC ACTIVES AND ANTIAGING PROPERTIES

Vitamin C, vitamin E, polyphenols, green tea, silymarin, and others are known for their antioxidant potentials (110). The skin antiaging effect of green tea compounds (catechin and (–) epigallocatechin gallate) were investigated on human dermal fibroblasts. Results demonstrated that (–) epigallocatechin gallate enhanced the cell viability and has dose-dependent antioxidant activity. Furthermore, (–)-epigallocatechin gallate decreased MMP expression and other inflammatory signaling pathways (111).

Mammone et al. (112) investigated different plant extracts and discovered that *Dianella ensifolia* extract has antioxidant potential and decreases skin hyperpigmentation. This extract contained (1-(2,4-dihydrophenyl)-3-(2,4-dimethoxy-3-methylphenyl) propane) which inhibits free radical and lipid oxidation induced by UV. Moreover, the reduction in skin discoloration was clinically assessed in human volunteers. Results showed that topical formulation contained extracted compound the increased the rate of tan fading compared with hydroquinone formulations (112).

Different traditional dosage formulas involved different antiaging mechanisms, including anti-inflammatory antioxidant properties, increase in skin barrier strength, rejuvenation, and others (113). Sundaram et al. (114) designed an antiaging cream that consisted of the extract of *Aegle marmelos* fruit pulps, *Nyctanthes arbor-tristis* leaves, and the terminal meristem of *Musa paradisiaca* flowers. The formula was evaluated for its antioxidant and anti-elastase activity, and results proved the herbal cream was a strong candidate for antiaging (114).

Vitamin E protects against UV-induced hyperpigmentation, whereas vitamin C reduces the production of melanin (115,116). Raspberry reduces loss of transepidermal water and enhances gene expression that allows for hydration and moisturization of the skin via hyaluronic acid synthesis. A randomized controlled study by Rattanawiwatpong et al. (117) among 50 Thai females with Fitzpatrick skin type III or IV evaluated the synergistic,

antiaging effect of the encapsulated serum of vitamin C, vitamin E, and cell culture extract of raspberry leaves based on different skin parameters. Results showed the serum had synergistic antiaging effects, such as improvements in elasticity, wrinkles, radiance, smoothness, and skin darkening (117).

Centella asiatica is widely used in Indian herbal medicine and known for its beneficial skin effects. Maramaldi et al. (118) evaluated antiglycation and anti-inflammaging of *Centella asiatica* in oil-in-water emulsion formulation (Supplementary Table 1). Triterpenes contained in the extract promote collagen synthesis; moreover, both triterpenes and polyphenolics have shown a synergistic action for normalization of keratinocyte hyperproliferation, inflammation, and generation of the natural epidermal homeostasis. This study showed *C. asiatica* extract promoted collagen synthesis, reduced DNA damage by UV, decreased photodimerization of thymine and expression of interleukin-1α, inhibited carboxymethyl lysine synthesis, and densified epidermal collagen network in the papillary dermis (118).

TOPICAL COLLAGEN FORMULATIONS

For a substance to be delivered via the skin, many physicochemical properties need to be considered, including molecular weight, solubility, and partition coefficient (119). Importantly, topically applied collagen seems ineffective as it cannot be absorbed through the skin because of its high molecular weight, and only naturally produced collagen can be effective (120). Commercial products such as Collagen Hydrating Serum produced by Wilma Schumann (121) and Matricol Caviar Deluxe Collagen produced by Matricol (Medskin Solutions Dr. Suwelack AG, Billerbec, Germany) (122) whose unit price exceeds $200 and $300, respectively, contain collagen (Table 1). Thus, their claims of delivering pure natural collagen in high concentration through the skin and promoting new collagen are highly doubtful. Other commercial products are listed in Table 1.

On the other hand, palmitoyl pentapeptide-4, with the trade name of Matrixyl (DECIEM Company, Toronto, Canada) is an active peptide of small size that is based on collagen type I propeptide (132). It was reported that Matrixyl promotes collagen type I synthesis in both *in vitro* cell culture and clinical studies (132). For example, controlled two double-blind clinical studies conducted in females revealed that the product improved wrinkle depth (133).

Recently, hydrolyzed collagen has gained a lot of fame in the cosmetic industry; because of its low molecular weight, it can penetrate the skin and produce antiaging properties. Zhang et al. (134) conducted an *ex vivo* study to investigate collagen hydrolysate penetration and found that only 8% penetrated mouse skin. Moreover, *in vitro* and *ex vivo* studies cannot reflect the *in vivo* bioavailability of these products, and there are limited studies that evaluate the *in vivo* permeation and efficacy of such peptides (135).

Unfortunately, numerous drawbacks, concerns, and challenges are associated with nutraceutical products. In addition, both topical and oral antiaging formulations have not been compared with Food and Drug Administration approved injected collagen or hyaluronic acid products, such as Evolence and others (136).

Consequently, the market is currently flooded with expensive antiaging products that suffer from questionable safety and efficacy profiles. Hence, valid, well-established, and common regulations for antiaging nutraceuticals along with in-depth clinical, *in vivo*, and *in vitro* studies are required to monitor emerging trends and demands of antiaging nutraceuticals in the global market (137).

Table I
Commercial collagen-based nutraceutical formulations sold online

Brand	Ingredients	Formulation type	Claims	Company	Refs.
BioCell	Hydrolyzed collagen type II Hyaluronic acid	Capsules	Reduces fine lines and wrinkles Reduces 76% of skin dryness Reduces joint discomfort and stiffness	Health Logics	(135)
Japanese Beauty Suppliment Meiji Amino collagen Premium collagen	Amino collagen	Powder	–	Meiji	(132)
3 Bio-Mask 24k Gold Collection Peel Off + Serum 24 K – Kit	Hydrolyzed collagen Hyaluronic acid *Saponaria pumila* callus culture extract *Khaya Senegalensis* bark extract and others	Mask and serum	Prevents and treats premature aging Antioxidant Slows the glycation	Bioage Skincare Solutions	(134)
Collagen Hydrating Serum	Native collagen fluid Glycerin Panthenol Lactic acid	Serum	Antiaging, provides hydration, and decreases wrinkles and fine line appearance Promotes new collagen in skin	Wilma Schumann	(130)
Matricol Caviar Deluxe	Pure natural collagen Caviar extract	Mask sheets	Active prevention against skin aging Provides optimum skin moisture	Matricol	(131)
Collagen Moisture Filler/ Combleur Hydrant	Natural collagen	Cream	Provides intense hydration Helps fill in lines and wrinkles	L'Oreal	(133,138)

Table I
Continued

Brand	Ingredients	Formulation type	Claims	Company	Refs.
Pure Gold Collagen	Collagen Zinc Copper Biotin Vitamin C Vitamin E Vitamin B6	Supplement drink	Preserves skin elasticity Maintains normal hair, skin, and nails Maintains normal pigmentation of skin and hair Antioxidant	Gold Collagen	(139)
Rousselot Fish Collagen Hydrolyzed	Fish hydrolyzed collagen Wild Mexican yam extract Hyaluronic acid	Dietary supplement powder	Increases skin mechanical strength Hydrates the skin and prevents wrinkle Maintains permanent youthfulness	Peptan	(136)
Collagen Peptides Powder	Hydrolyzed collagen Digestive enzymes	Dietary supplement powder	Improves skin elasticity Prevents wrinkles and aging signs Enzymes digest proteins for proper body utilization	NutraChamps	(137)
Medicube Triple Collagen Essential Serum	Hydrolyzed collagen Atelo collagen Soluble collagen	Serum	Improves skin elasticity	Medicube	(140)

CONCLUSION

People's demands for young appearance is growing as life expectancy in developed countries increases. Skin as the first indicator of aging has received the greatest attention to understand causes and find solutions. In this review, we summarized the endogenous and exogenous factors of skin aging and assessed the role, underlying molecular pathways, and treatment strategies of skin inflammaging. Moreover, we discussed novel formulations and nutraceutical products for skin aging. Although the aging process seems multifactorial where different mechanisms are interconnected, oxidative stress, microinflammation, and DNA damage are highly influential. Despite increasing efforts to find therapeutic treatments, their effectiveness remains questionable. Nutraceuticals' reputation as being effective and safe highly attracts consumers. Collagen-containing products are gaining a lot of attention from both researchers and consumers. Because of limited global restrictions, expensive antiaging products of questionable safety and efficacy profiles dominate the market. More research is needed to further understand skin-inflammaging mechanisms and find effective treatments.

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Supplementary table I
Current approaches for topical skin Anti-aging formulations

Title	Formulation type	Drug	Evaluation	Refs.
Formulation and evaluation of curcumin gel for topical application	Conventional (gel)	Curcumin	Viscosity measurement was determined by using a Brookfield viscometer Franz diffusion cells was used for *in vitro* skin permeation study Visual assessment of skin irritation in Wistar albino rats was performed by using visual scoring scale Evaluation of the anti-inflammatory effect of the optimized formulations was detected by using carrageenan-induced rat paw edema method	(70)
Preparation and evaluation of submicron carriers for NGN topical application	Submicron emulsion	Naringenin	Viscosity measurement was determined by a cone-and-plate rheometer Measurement of the droplet size was measured by the DLSa technique *In vitro* skin permeation studies were conducted via Franz diffusion cells Drug deposition in SC[b], epidermis, and dermis was determined via HPLC[c] after layer separations: (the SC was removed using an adhesive tape, and theepidermis was separated from the dermis by heat) Histological evaluation of skin irritation in male Sprague–Dawley rats was performed. Physical, chemical, and thermodynamic short-term stability studies had been conducted	(92)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
CoQ_{10} and retinaldehyde co-loaded nanostructured lipid carriers for efficacy evaluation in wrinkles	Gel containing nanostructured lipid carriers (NLCs) loaded with CoQ_{10} and retinaldehyde	CoQ_{10} and Retinaldehyde	*In vitro* physicochemical characterization: Examining the NLCs[d] colloidal system morphology was performed by SEM[e] Evaluating both the free gel and the NLCs containing gel; spreadability and rheological behavior were determined by the cone-and-plate viscometer HPLC-based stability study A comparative drug release study was performed from NLCs and NLCs-gel *In vitro* cell culture studies were carried out for both cellular uptake and viability *Ex vivo* studies were carried out for assessment of skin permeation, distribution and dermal pharmacokinetics *In vivo* study was conducted by using animal model The skin irritation test on Sprague-Dawley rats was performed by using a vapometer to measure trans epidermal water loss Evaluating the therapeutic efficacy of the optimized formulations on female Swiss albino mice after wrinkles induction	(141)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
Development of herbal cosmetic cream with Curcuma longa extract–loaded transfersomes for antiwrinkle effect	Transfersomal cream	Curcumin from *Curcuma longa* extract	*In vitro* characterization of curcumin containing transfersomes: Morphological examination of the vesicles using transmission electron microscopy (TEM[f]) Spectrophotometric determination of the entrapment efficiency Particle size and zeta potential measurement by a Malvern Zetasizer Storage stability over 6 months *In vitro* skin permeation and deposition studies were carried out by using 2-stage modified Franz diffusion cells. Characterization of curcumin incorporated transfersomal cream Physicochemical evaluation of the cream (color, odor, content, pH, acid, ash, and saponification value) The irritation test on human volunteers was carried out with determination of the erythemal score established by the Indian standards *In vivo* studies were carried out on female human volunteers to evaluate the skin elasticity using a cutometer	(104))
Topical formulation containing NGN: efficacy against ultraviolet B irradiation-induced skin inflammation and oxidative stress in mice	Conventional topical formulations	NGN	*In vitro* evaluation of NGN antioxidant activity was performed by using FRAP[g], ABTS[h], hydroxyl, iron-dependent and iron independent lipid peroxidation tests Physicochemical characterization of the developed topical formulations was detected *In vivo* evaluation of the efficacy of the NGN containing topical formulations in sex matched hairless mice subjected to UVB[i] radiation of measured intensity was performed by using various measurements (skin edema, cytokine measurement, FRAP, ABTS, catalase assay, lipid peroxidation, superoxide anion production, glutathione assay and others)	(50)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
In vitro and *in vivo* skin antiaging evaluation of gel containing niosomes loaded with a semi-purified fraction containing gallic acid from *Terminalia chebula* galls	Gel containing niosomes	Semi-purified fraction containing gallic acid	*In vitro* biological antioxidant activity of gallic acid and the semi purified fraction incorporated into the optimized elastic and non-elastic niosomes was estimated via the free-radical scavenging Cytotoxicity assay was performed via MTT[j] assay MMP-2[k] inhibition activity by gelatinolytic zymography (gelatinolytic activities of MMP-2 was assessed by SDS-PAGE[l] zymography using gelatin as a substrate) Evaluating the physicochemical stability of the gel containing niosomes loaded with the semi-purified fraction was carried out Skin irritation tests on male rabbits (irritation index depends on erythema and edema degree) Efficacy investigation of the antiaging potential of the optimized gel in human volunteers was detected via determination of skin elasticity, surface microstructure, hydration, erythema and pigmentation	(96)
Development and evaluation of vesicular system for curcumin delivery	Phyto-vesicles, liposomes and niosomes	Curcumin	Characterization of curcumin–phosphatidyl choline complex was performed via TLC[m], DSC[n], melting point, and FTIR[o] Characterization of the vesicular systems Morphological study by TEM Vesicles size and PDIp by Malvern Zetasizer Spectrophotometric determination of the entrapment efficiency Assessment of the anti–aging capability of the developed vesicular systems in UV-radiated Swiss albino mice was carried out by examining certain biochemical markers, moisture content, and histological analysis	(97)
Effects of skin penetration enhancers in topical antiaging products containing α-hydroxyacids and hyaluronic acid	Conventional lotion	α-Hydroxyacids Hyaluronic acid	Evaluating the effect of different permeation enhancers on transdermal penetration was performed by using skin permeation tests via diffusion cells	(72)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
Transdermal delivery of functional collagen via polyvinylpyrrolidone microneedles	Polyvinylpyrrolidone microneedles	Collagen type 1	Examination of the microneedle morphology was detected via SEM and CLSM[q]. Collagen type 1 was separated via SDS-PAGE electrophoresis Functional collagen concentration was determined via ELISA[r] Microneedle penetration through the porcine skin and human foreskin was evaluated via a fluorescence microscope	(77)
Transdermal delivery of proteins mediated by non-covalently associated arginine-rich intracellular delivery peptides	Arginine-rich intracellular delivery (AID) peptides	Protein	Transdermal delivery assay on mice (histological examination) Protein internalization on human A549 cells[s](confocal microscope) Cytotoxicity in Human A549 cells (MTT assay)	(83)
A peptide carrier for the delivery of elastin into fibroblast cells	Amphipathic cell–penetrating peptide carrier	Elastin	The SDS-PAGE technique was used to determine protein/peptide complex formation Particle size distribution by DLS Particles morphology was determined via SEM. Cytotoxicity study in NIH-3T3[t] cells (MTT assay) Internalization of the complex in NIH-3T3 cells was evaluated using a fluorescent microscope	(85)
CoQ_{10} enhances dermal elastin expression, inhibits IL-1α production and melanin synthesis *in vitro*	O/W Nano emulsion	CoQ_{10} (CoQ_{10})	Investigation of CoQ_{10} anti-aging effect in multiple adult fibroblast cell lines was performed by using a cell proliferation assay. Illustrating the effect of CoQ_{10} on ROS[u] production by radiating fibroblast cell lines with UV radiation followed by measuring the intracellular ROS level Evaluating the depigmentation potential of CoQ_{10} was detected via melanin assay, tyrosinase activity measurement and DOPA[v] staining	(99)
Systematically optimized CoQ_{10}-loaded proniosomal formulation for treatment of photo-induced aging in mice: characterization, biocompatibility studies, biochemical estimations and anti-aging evaluation	Proniosomal gel formulation	CoQ_{10}	*In vitro* characterization of the proniosomal gel: The % drug entrapped was determined by using HPLC method Particle size analysis was measured by using a Malvern zetasizer Morphological studies were detected by using TEM Rheological studies were determined by using a cup-and-bob viscometer. *Ex vivo* evaluation of the drug permeation and retention was performed. *In vivo* evaluation of the drug antiaging effect in female Swiss albino mice after exposure to UV radiation was carried out via visual, histopathological and other evaluations	(100)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
Current formulation and evaluation of a Q10-loaded SLN cream: in vitro and in vivo studies	SLNs–loaded cream	CoQ_{10}	Particle size analysis and zeta potential measurement of SLNs[w] were detected by using photon correlation spectroscopy Drug–excipient compatibility was determined by differential scanning calorimetry Visualization of the colloidal dispersion was performed by TEM *In vitro* release study was conducted by using an automated, temperature-controlled continuous flow diffusion cells. *In vivo* antiaging capabilities of developed formulation were evaluated in 25 female volunteers by assessment of skin hydration and viscoelasticity	(107)
The advantages of a CoQ10 delivery system in skin photo-protection	NLCs	CoQ_{10}	Particle size and shape of NLCs were determined via Zetasizer and TEM, respectively Cell viability testing was detected by using Human embryo skin fibroblasts via MTT assa Antioxidant assessment through lipid peroxidation products and intracellular ROS assays was performed by using the photometrical method Biochemical evaluation of the antioxidant parameters and enzymes activity Cell apoptosis was determined by fluorescence microscopy In vivo skin permeation was conducted by using female Sprague–Dawley rats via fluorescent microscopy	(108)
TRF attenuates UV-induced inflammaging: A bench to bedside study	Nanoemulsion	TRF	*In vitro* studies: Determination of cell viability in HaCat[x] cell line using MTT assay Quantification of certain oxidative and inflammatory markers in HaCat cell line after UVB exposure using the ELISA technique. ROS measurement by flow cytometry and fluorescence plate reader *Ex vivo* studies to investigate the drug permeability and a antioxidant effect were conducted by the skin antioxidative potential method and radical sun protection factor test using skin samples from the external lobe of a fresh pig ear Clinical studies on healthy human volunteers involving UV irradiation and skin color measurements were carried out	(52)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
Anti-inflammaging and antiglycation activity of a botanical ingredient from African biodiversity (Centevita™)	Conventional (solution)	Extract from Madagascar, and Centella asiatica	Biological activity on human skin explants through determination of several parameters: Thymine photodimerization induced by UV Interleukin (IL)1-α, ROS scavenging properties Antiglycation activity Antiwrinkle effect was evaluated via a clinical trial on healthy volunteers and skin parameters such as skin replicas, firmness, elasticity and collagen density	(142)
Topical vesicular formulations of Curcuma longa extract on recuperating the ultraviolet radiation–damaged skin	Liposomes, ethosomes, and transfersomes in cream	Curcuma longa extract	Physicochemical characterizations of the vesicular systems including particle size analysis, TEM imaging, and entrapment efficiency determination were conducted Physicochemical evaluations of creams pH, viscosity, stickiness, smoothness, stability, spreadability and microbial count were carried out Clinical study on human volunteers was performed and skin hydration and sebum content were determined	(103)
Functional response of bioprotective poloxamer-structured vesicles on inflamed skin	Nanovesicles (liposomes and glycerosomes modified by poloxamers)	Resveratrol and gallic acid	Vesicles size and shape were evaluated via photon correlation spectroscopy, and cryogenic transmission electron, respectively. Viscosity measurement was performed by the cone-and-plate rheometer Stability studies *In vitro* skin permeation through Franz diffusion cells Drug deposition study was conducted using tape stripping to remove the stratum corneum followed by HPLC analysis of drug content Cell viability testing and protection against oxidative stress on mouse embryonic fibroblasts (3 T3) using MTT assay were evaluated *In vivo* antinflammatory effect was evaluated in female CD-1 mice through edema and myeloperoxidase inhibition	(93)

Supplementary table I
Continued

Title	Formulation type	Drug	Evaluation	Refs.
An approach based on lipid nanoparticles (SLN) for topical delivery of α-Lipoic acid	SLNs	α-Lipoic acid	Particle size was determined by photon correlation spectroscopy Drug–excipient compatibility was evaluated by differential scanning calorimetry analysis Rheological analysis was performed by oscillation frequency sweep tests	(143)

[a]Dynamic light scattering
[b]Stratum corneum
[c]High-performance liquid chromatography
[d]Nanostructured lipid carriers
[e]Scanning electron microscope
[f]Transmission electron microscopy
[g]Ferric reducing ability of plasma
[h]ABTS
[i]Ultraviolet B radiation
[j]3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
[k]Matrix metalloproteinase-2
[l]Sodium dodecyl sulfate- polyacrylamide gel electrophoresis
[m]Thin layer chromatography
[n] Differential scanning calorimetry
[o]Fourier transform infrared spectroscopy
[p] Polydispersity index
[q]Confocal laser scanning microscopy
[r]Enzyme-linked immunosorbent assay
[s]Adenocarcinomic human alveolar basal epithelial cells
[t]Fibroblast cell line
[u]Reactive oxygen species
[v]3,4-Dihydroxy-L-phenylalanine
[w]SLNs
[x]Immortalized human keratinocyte cell line