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Topical anti-aging agents: state-of-the-art review

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ABSTRACT

Skin aging can be divided into intrinsic and extrinsic aging. Even though it is inevitable, symptoms of skin aging are a common concern for patients. As a result, there is a surge in the making of anti-aging cosmeceuticals. However, there is a lack of evidence-based data to support the usage of topical preparations as anti-aging treatments. Therefore, further studies are needed to explore topical treatment options for skin aging. This literature review discusses the mechanism of commonly used topical anti-aging agents and their adverse reactions.

ABSTRAK

Penuaan kulit dapat diklasifikasikan menjadi penuaan intrinsik dan ekstrinsik. Meski tidak bisa dihindari, gejala penuaan kulit menjadi gejala yang umum dilaporkan oleh pasien. Hal ini menyebabkan industri berlomba-lomba menciptakan preparat kosmetik untuk mengurangi efek penuaan. Namun, terdapat kekurangan data berbasis bukti untuk mendukung penggunaan preparat topikal sebagai perawatan antipenuaan. Oleh karena itu, penelitian lebih lanjut diperlukan untuk mengeksplorasi pilihan pengobatan topikal untuk penuaan kulit. Tinjauan pustaka ini membahas mekanisme agen antipenuaan topikal yang umum digunakan dan efek sampingnya.

Keywords:
anti-aging;
intrinsic;
extrinsic;
topical;
adverse reactions

INTRODUCTION

As people age, their skin undergoes changes influenced by various factors. In general, skin aging can be divided into two categories, intrinsic and extrinsic aging. Intrinsic aging occurs as the individual ages and is characterized by fine wrinkles and thinning of the epidermis. In contrast, extrinsic aging is characterized by deep wrinkles, skin laxity, and hyperpigmentation. Extrinsic aging is mostly caused by sun exposure. Regardless of the type of aging, wrinkling and decreased elasticity are characteristic phenomena of skin aging and result from progressive atrophy of the dermis.[1,2] Physiological changes in the aging skin include structural and biochemical changes as well as changes in neurosensory perception, permeability, response to injury, and an increased incidence of skin diseases. Although the number of cell layers remains stable, the skin thins progressively during adult life at an accelerating rate, especially in the epidermis. Thickness decreases on average by about 6.4% per decade, associated with a decrease in the number of epidermal cells.[3]

Over the last decade, there has been a surge in scientific interest in

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anti-aging treatments. This is because aging face skin is one of women's most popular cosmetic concerns. Wrinkles, sagging, uneven skin tone, dull, and dry skin are just a few apparent indicators that can harm self-esteem and social interactions.[4,5] The rising interest is closely linked to the increased use of cosmeceuticals. The term cosmeceutical refers to a non-prescription product that significantly impacts the look and function of the skin.[6] The industry offers a wide variety of cosmeceuticals to lessen the effects of skin aging. There is a scarcity of evidence to support their use. For the most recent developments in topical anti-aging agents, proper mechanisms and side effects should be followed.[7]

This article evaluates the evidence in the published literature that supports the use of the most commonly found components in cosmeceuticals, focusing on topical anti-aging agents and their adverse reactions.

DISCUSSION

Retinoids

Retinoids are common anti-aging agents used in commercial or over-the-counter (OTC) cosmetical products to treat skin problems such as acne and rosacea and decrease early signs of skin aging such as wrinkles and photoaging.[8,9] Retinoid refers to a compound derived from vitamin A or showing structural or functional similarities to vitamin A. Retinoids are available in many forms. Retinol or retinaldehyde is included in the precursor form group and is widely used in cosmeceuticals because of its fewer side effects than tretinoin, the active form. Meanwhile, consumption of tretinoin should be used under prescription, considering its side effects such as erythema, xerosis, desquamation, pruritus, and burning sensation.[10,11] Nonetheless, because retinol must be transformed into tretinoin, it is thought to be less effective than tretinoin.[8] Oxidation process of retinol starts when retinol enters the cell, binds with the cytosolic receptor, and induces retinol dehydrogenase to catalyze the oxidation to retinaldehyde which is later oxidized into the active form of retinoic acid (tretinoin).[12] Retinoids are lipophilic and can penetrate the stratum corneum effectively. After penetrating the epidermis, retinol reaches keratinocytes and binds to an appropriate receptor. This action has been shown to influence the secretion of transcription and growth factors that induce the living layer of the epidermis and reduction in trans epidermal water loss (TEWL).[8]

The anti-aging properties of retinoids are based on their effects such as enhanced collage production activities in the dermis, keratinization of the epidermis, prevention matrix metalloproteinases (MMPs) production induced by UV rays, and tyrosinase inhibition to reduce hyperpigmentation.[13] Tretinoin is commonly used in the topical anti-acne treatment and varies in concentration, from 0.01% to 0.4% in gel or cream form. Meanwhile, retinoic acid is commonly found as an OTC drug with various concentrations from 00.01%, 0.025%, 0.05%, and 0.1% in gel, cream, or liquid form.[8] Retinol is frequently used in cosmeceutical treatment, with concentrations varying between 0.0015% and 0.3%.[14] Other forms of retinoids are adapalene and tazarotene. Adapalene is a derivative of naphthalene carboxylic acid with a retinoid-like activity that binds with nuclear receptors of retinoic acid and changes gene expression and mRNA synthesis. Thus, it acts as a potent modulator of keratinization of hair follicle cells by modifying keratinocyte metabolism, increasing proliferation, and showing a keratolytic effect.[15] Tazarotene is a synthetic retinoid (prodrug) used in the topical treatment of plaque psoriasis, acne vulgaris, and

photodamaged skin (hyperpigmentation, wrinkles, and benign facial lentigines) with a concentration of 0.05% to 0.1%.[16]

Retinol's limitations as a cosmetic ingredient are related to its irritating and unstable properties. A suitable vehicle, such as creams, gels, or serums, must be used to shield them from light and air to maintain efficacy.[14] Retinoids should not be administered to pregnant or attempting women.[17]

Hyaluronic acid

Hyaluronic acid (HA) has been widely used in esthetic medicine to improve skin hydration due to its water-retention properties. HA is one of the extracellular matrix (ECM) molecules produced mainly by mesenchymal cells and widely distributed, with a total of 50% found in the skin.[18] Histological change in aging skin marked by the disappearance of epidermal HA leads to the loss of the ability of the epidermis to bind and retain water molecules, resulting in loss of skin moisture.[19]

Antioxidant properties of HA could promote cell regeneration and induce collagen production. The topical application of HA should consider the molecular weight and the HA's chain length.[13] Recent studies reported that intermediate-size HA fragments (50-400 kDa) could induce cellular proliferation within the epidermal and dermal compartments.[20] Nevertheless, other studies showed better penetration abilities in low-molecular-weight HA, reducing wrinkle depth.[21,22] Hyaluronic acid is non-toxic and non-sensitizing; thus, its safe and has been commonly used as a dermal filler to restore skin volume and minimize the appearance of wrinkles.[18]

Hyaluronic acid has been used for a topical treatment to treat actinic keratosis and inflammatory skin conditions as a moisturizer by improving the retention and localization of the active component in the epidermis as well as the penetration of the active ingredient through the stratum corneum (SC).[19,23] Furthermore, HA could be used in all Fitzpatrick skin types and result in improvement of skin plumping and 55% hydration as measured by corneometry.[19]

Vitamin C

Vitamin C or ascorbic acid is one of the most potent antioxidant agents in the skin and the most abundant.[24] This hydrophilic six-carbon molecule can be found in its oxidized form (dehydroascorbic acid or DHA) and its reduced form (ascorbic acid or ascorbate).[25] Although abundant and essential in metabolic activity, humans cannot synthesize vitamin C due to the lack of L-gulono-γ-lactone oxidase, the enzyme responsible for catalyzing the last step of vitamin C biosynthesis. Hence, the supply of vitamin C relies on diet and external supplementation.[26]

The systemic bioavailability of vitamin C depends on intestinal absorption and renal excretion. In the intestine, vitamin C is absorbed through an active transport system via a transporter called sodium-dependent vitamin C transporter 1 (SVCT1).[27] Vitamin C is readily absorbed in the small intestine at a low concentration. However, SVCT1 is downregulated when there is a high level of vitamin C. Thus, limiting vitamin C's bioavailability when its supplementation is given by oral route.[28,29]

The pharmacological concentration of vitamin C can be achieved by parenteral administration in contrast to the physiological concentration by oral administration.[30] However, it is well-known that The regulation of SVCTs and their different concentration between organs lead to nonlinear pharmacokinetics of vitamin C.[27] Hence, the plasma concentrations of vitamin C do not affect specific tissue distribution

beyond physiological saturation, and the distribution of vitamin C differs in various tissue.[31] Thus, topical application of vitamin C may be desired in dermatology practice.[24]

Vitamin C can be delivered into the epidermal layer via a topical route, with its efficacy depending on the serum's formulation. However, L-ascorbic acid, the most common form of vitamin C, is repelled by the membrane of the stratum corneum due to its hydrophilicity and charged state.[1,9] Thus, a variety of derivatives and preparation of vitamin C have been developed and evaluated. Magnesium ascorbyl phosphate (MAP), an ester of vitamin C, is its most stable derivate. Unlike L-ascorbic acid, the MAP molecule is lipophilic and stable at neutral pH.[29] Other derivatives of vitamin C include ascorbyl-6-palmitate, tetraisopalmitoyl ascorbic acid, ascorbic acid sulphate, and isostearyl 2-0 L-ascorbyl phosphate.[24]

Ascorbic acid is essential for collagen synthesis. It acts as a cofactor for prolyl 4-hydroxylase, prolyl 3-hydroxylase, and lysyl hydroxylase, an enzyme that plays a pivotal role in stabilizing and cross-linking collagen fibers.[33] Furthermore, ascorbic acid also activates the gene expression of collagen synthesis and the factor that inhibits its degradation.[34]

Ascorbic acid is a strong antioxidant with an effect mediated through an electron transfer process. In regards to its antioxidative effect, the molecule is capable of reducing reactive species oxygen (ROS), nitrogen, as well as sulfur radical.[25] Ascorbic acid is also reported to prevent peroxide radicals-induced lipid peroxidation.[35] Vitamin C is also known for its effect on replenishing tissue vitamin E, a lipophilic antioxidant.[34] Deficiency of vitamin C levels results in various skin problems such as early symptoms of scurvy, poor wound healing, skin fragility, and corkscrew hairs.[32]

Previous evidence from a systematic review reported that ascorbic acid is also an effective treatment of hyperpigmentation.[36] Ascorbic acid exerts its anti-hyperpigmentation effect through interference with tyrosinase, an enzyme involved in melanogenesis. Another meta-analysis showed that ascorbic acid was effective in preventing pigmentation induced by UV daylight in a dose-dependent manner.[37]

Topical vitamin C is generally safe for regular use over a long period with a concentration range between 8-20%.[24,29] It can also be used safely with other products such as retinol and sunscreen. Erythema and dryness are rarely listed as vitamin C adverse effects. These adverse effects can be prevented by applying a moisturizer after using topical vitamin C.[29]

Vitamin E

Vitamin E, which exists as eight compounds (4 tocotrienols and 4 tocopherols), is a lipophilic antioxidant with anti-lipoperoxyl radical scavenging activity. The most common form of vitamin E is α-tocopherol (αT).[38] Tocotrienols and tocopherols share a basic structure, such as a chromanol ring. They differ in the C16 side chain, in which tocotrienols' are composed of three double bonds rather than a saturated isoprenoid chain.[39]

Plants are the primary source of vitamin E. Seeds and oils are well-known to be rich in vitamin E, such as peanuts, sesame seeds, sunflower, and safflower oils.[38,40] In addition, vitamin E coexists with lipids and fat in many dietary sources; this vitamin intake is associated with specific fatty acids.[39]

Vitamin E has a bioavailability of 50-80%. It follows the absorption pathway of fats and its uptake in the small intestines is increased by fat consumption.[41] After an oral route of administration, vitamin E will be packed into chylomicrons that either be sent to tissue or excreted in bile.[42] Vitamin E was shown to be evenly

distributed in the body, particularly in the liver, adipose tissue, plasma, and skin.[43,44]

Naturally occurring vitamin E in the form of αT will be oxidized when exposed to the atmosphere. However, vitamin E's stability may be enhanced with the use of conjugate, such as the esterified form of tocopherols. The ester of αT is resistant to oxidation and able to penetrate the skin layer.[45]

Many topical products claim that they contain vitamin E. However, they contain different forms and dosages of vitamin E. The most common form of marketed vitamin E is αT, with a 5% or less concentration. In addition, products with a concentration of less than 0.001% have been reported.[46]

Vitamin E plays an essential role in defense against lipid peroxidation.[45] It is considered to be the most important lipophilic antioxidant, protecting the membrane from oxidation by scavenging lipid radicals.[47] Vitamin E prevents the propagation of free radicals in the cell membranes, thus called a chain-breaking antioxidant. It reacts approximately 1000 times faster with peroxyl radicals compared to the radical with polyunsaturated fatty acids in the membrane.[40]

When there is a peroxyl radical, vitamin E is involved in a reaction to form a vitamin E radical.[47] Vitamin E attack the radical of peroxyl lipid to form lipid hydroperoxide. Vitamin E radicals may also undergo a reaction with other antioxidant agents. It may react with a reducing agent such as vitamin C to replenish vitamin E.[48]

Vitamin E also inhibits the production of ROS.[45] The combination of vitamin E and ascorbic acid increases the antioxidative effect compared to the monotherapy of either agent.[49] In addition, vitamin E's antioxidative property is dependent on other agents such as vitamin C and glutathione.[50]

Topical vitamin E could improve burns, surgical scars, wounds, granuloma annulare, and skin aging. Patients who have coagulation problems or are taking anticoagulants need to be aware of the increased risk of bleeding.[45] Topical application of vitamin E is safe including in pregnancy with very few side effects. The most common adverse effect is mild irritation and allergy, although these are rarely reported.[45,50] However, a single case report described adverse effects such as contact dermatitis and erythema multiforme-like eruption.[51]

Peptides

Peptides, whether it is polypeptides or oligopeptides, are composed of amino acids. They are similar to a peptide sequence of a specific compound in the human body. Topical peptides are known to be capable of stimulating the dermal metabolism and the synthesis of collagen.[52] Gorouhi and Malibach further classified topical peptides into four groups; namely signal peptides, enzyme inhibitor peptides, neurotransmitter-inhibitor peptides; and carrier peptides.[53]

Signal peptides can stimulate the signal of extracellular matrix synthesis, especially collagen.[54] They also can promote the synthesis of glycosaminoglycan, proteoglycan, and elastin. As collagen production increases, the skin will look younger and firmer.[53] The example of signal peptides are palmitoyl tripeptide, palmitoyl pentapeptide, palmitoyl hexapeptide, lipospondin, and tripeptide-10 citrulline.[53,54]

Enzyme inhibitor peptides act via direct or indirect inhibition of an enzyme. It includes silk fibroin peptide, soy oligopeptide, and rice peptide. They inhibit various enzymes such as proteinase and superoxide dismutase. However, there are only a few in vivo studies, thereby the evidence is very limited.[55]

Facial wrinkles and fine lines

are formed through the activity of muscle contraction. During muscle contraction, acetylcholine has to be released in the neuromuscular junction. Neurotransmitter inhibitor peptides can inhibit the transmission of acetylcholine at the neuromuscular junction. Thus, inhibiting the formation of fine lines and wrinkles.[53,55] Neurotransmitter inhibitor peptides include acetyl hexapeptide-3, acetyl tripeptide-30 citrulline, pentapeptide 3, tripeptide-3, and pentapeptide-18.[54,56]

Carrier peptides act to deliver important trace elements required for an enzymatic process.[55] In the case of skin aging, copper is a cofactor for lysyl oxidase, an enzyme that plays a pivotal role in the synthesis of collagen.[57] In addition, copper ion (Cu^{2+}) reduces the secretion of MMP-2,[58] an enzyme that is known to be capable of digesting collagen type I and IV.[59] An example of carrier peptides include copper tripeptide-1 and manganese tripeptide-1.[54]

α-Hydroxy acids (AHA)

α-Hydroxy acids (AHAs) are a group of hydrophilic organic acids with one hydroxyl group attached to the alpha position, including glycolic acid and lactic acid, which are known to have anti-aging benefits.[60,61] α-Hydroxy acids remove calcium ions from epidermal cell adhesions and give exfoliating effect by causing the shedding and flaking of dead and dry cells. α-Hydroxy acids also promote further cell growth, thereby lessening the appearance of wrinkles and making the skin look younger.[60]

α-Hydroxy acids hydrate the skin by increasing gene expression of collagen and hyaluronic acid. α-Hydroxy acids' anti-aging role was accompanied by the effects of vitamins B, C, and E.[61] Sugarcane (glycolic acid), sour milk (lactic acid), and fruits are all sources of AHAs in nature and created synthetically and utilized in dermatological and cosmetic goods. The effectiveness of AHAs depends on pH, concentration, and exposure time. Further, the use of AHAs needs to be controlled carefully.[61,62] Low concentrations of AHAs can be advantageous for the skin due to epigenetic improvements of inflammasome complex. On the contrary, high concentrations of AHAs as peeling agents could disturb the cohesiveness of the corneocytes lead to instability of the skin barrier and irritation of the skin.[61]

α-Hydroxy acids use to treat photoaging, acne, ichthyosis, rosacea, pigmentation disorder, and psoriasis by reducing roughness, discoloration, sun keratoses, and pigmentation also increasing collagen density and improving the quality of elastic fiber.[63,64] High concentrations of AHAs develop dryness, burning sensation, erythema, and photosensitization but it is also more tolerable than retinoids.[60]

Niacinamide

Nicotinamide (niacinamide) is the amide form of water-soluble vitamin B3 (nicotinic acid, niacin) that have essential nutrient for the whole body and the skin.[65] As humans age, the integrity of the skin is changed or disturbed, which can be seen by thinning of the epidermis and dermis, increased water loss, fragmentation of collagen and elastin, and alteration of the skin's immune composition.[66] Nicotinamide upregulates the synthesis of ceramide by activating the mRNA expression of serine palmitoyl transferase and could improve skin composition.[67] Depending on its concentration, topical niacinamide has antimicrobial, antipruritic, photo-protective, vasoactive, sebostatic, and lightening effects.[68]

One study showed that using topical nicotinamide alone or combined with other substances could increase fibroblast proliferation, collagen synthesis, and revascularization, which could help tissue regeneration.[69] Nicotinamide could play a role as a

photo-protective and anti-inflammatory agent. Nicotinamide significantly affects various conditions related to hyperpigmentation by increasing melanin synthesis and melanosome biogenesis. It also induces intercellular melanosome transfer.[65,70,71]

The skin's structure changes as we age due to UV radiation exposure, unhealthy lifestyle choices, and environmental pollution.[72] Ultraviolet light radiation could increase ROS production and pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IFN-γ, granulocyte colony-stimulating factor (C-GSF), macrophage inflammatory protein (MIP-β) and TNF-α that led to inflammation and cell death.[73,74] Nicotinamide has been shown to enhance skin barrier function and increases the amount and rate of DNA excision repair in UV-induced cell damage.[71,74] Without having any negative side effects, nicotinamide promotes the health and attractiveness of the skin.[65]

Antioxidant

Skin aging could occur due to oxidative stress caused by multiple factors, including intrinsic and extrinsic factors.[75] The primary cause of skin aging processes is redox imbalance marked by excessive formation of oxidative stress in dermal fibroblast.[76] Accumulation of ROS during oxidative stress can lead to lipid, protein, nucleic acid, and organelle damage that mediates skin aging.[77]

Vitamins and minerals that have antioxidant properties are the key elements of an anti-aging diet.[78] Antioxidants have a role in preventing and treating skin aging by scavenging the ROS and alleviating oxidative skin damage.[79] Antioxidants such as tocopherol, ascorbic acid, and their derivatives have been used as active ingredients in anti-aging cosmetics.[80] The DNA damage leading to skin aging could be reduced by oral administration of antioxidants.[78,79]

Vitamin and minerals topical that contain antioxidant properties such as zinc, vitamin E, polyphenols, vitamin C, and selenium could protect against DNA damage, harmful ROS-induced photo-aging, scavenge free radicals or reduce free radicals to less reactive compounds.[81-84] To prevent skin aging, it is important to use phytochemical properties that could promote the capacity of fibroblasts to combat oxidative stress.[76] Topical antioxidants could be useful as long as it administered rationally.[85]

CONCLUSION

Anti-aging products are a skincare category that will constantly expand due to its increasing interest. It is essential for health care workers, primarily dermatologists and primary care physicians, to understand the basic mechanisms of anti-aging agents and their potential side effects that commonly used in the market.

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