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## Topical Pharmacological Agents That Have Anti-Aging Properties

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### ABSTRACT

Aging of the skin is a common problem today, the effects of aging skin cause insecurity due to changes due to various factors. Aging is the process of progressively reducing the function and capacity of the skin. Effects of aging such as wrinkles, fine lines, hyperpigmentation, sagging skin and dark blemishes. The method used in this study is a search of relevant literature collected from various studies that have been published in google scholar, Elsevier, and pubmed related to anti-aging. To reduce the effects of aging on the skin, cosmetic pharmaceutical products are developed known as anti-aging, so writing this review article is carried out with the aim of knowing the types of topical ingredients that act as anti-aging agents. Anti-aging can take the form of creams, serums and gels. Anti-aging is formulated with topical ingredients that are able to reduce the effects of aging on the skin, for example retinol, vitamin C, niacinamide, and vitamin E. Topical ingredients that are commonly used as anti-aging agents and are effective in reducing the effects of aging are retinol and niacinamide.

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## Introduction

The skin is a human integument organ that is easily observed for changes. The skin often undergoes changes caused due to various factors. One of the problems that is often found in the skin is skin aging. Skin aging is a process of progressively decreasing skin function and capacity. Indonesia as a country with a tropical climate gets enough sunlight, becoming one of the triggering factors for aging on the skin. Sunlight is divided into three types based on its waves, namely UVA, UVB and UVC rays. Exposure to UV (ultraviolet) rays can cause redness of the skin, skin that feels like burning, erythrim, cataracts, has the potential to grow cancer cells, the skin experiences premature aging and loses its elasticity<sup>1</sup>.

Ultraviolet light has a major effect on the occurrence of premature aging of the skin. Wrinkles are one of the signs of premature aging, in this case there is a decrease in collagen and elastin productivity in the dermis layer of the skin, causing the epidermis layer to change texture.

Ultraviolet rays have a major effect on the occurrence of premature aging of the skin. Wrinkles are one of the signs of premature aging, in this case there is a reduction in collagen and elastin productivity in the dermis layer of the skin, causing the epidermis layer to change texture. In addition to ultraviolet rays, aging that occurs on the skin is caused due to intrinsic and extrinsic factors. Intrinsic factors include genetic, cell metabolism, and hormonal, while extrinsic factors include UV radiation, infrared, and environmental carcinogens<sup>2</sup>. Changes in morphology and physiology caused by intrinsic factors include dry skin, sagging, wrinkles and slower healing due to wounds. Meanwhile, changes caused by extrinsic factors such as the skin experiences deep wrinkles, the skin loses elasticity, and the skin surface becomes rough.

Anti-aging is used as a technique to inhibit damage to the skin, so that signs of aging on the skin can be inhibited. In addition, anti-aging beauty products have many other benefits, namely making the skin healthier, brighter, and youthful<sup>3</sup>. Anti-aging treatments are performed to disguise wrinkles, sagging skin, and fine fold lines on the face. Because of the importance of anti-aging in efforts to repair skin damage, it is necessary to collect more in-depth information regarding active ingredients that are often used as anti-aging agents. In this review article, we will discuss related to skin aging, skin aging mechanisms, and topical ingredients that have anti-aging properties or anti-aging agents.

## Method

In this review article, a search of relevant literature collected from various studies that have been mentioned in Google Scholar, Elsevier, and Pubmed is carried out. The number of literature obtained was 20 journals, but those included in the inclusion criteria were 14 journals. The inclusion criteria in writing this article are journals in the range of publication years > 2000 with keywords using English such as anti-aging for skin, anti-aging agent, niacinamide effect, niacinamide for Skin, retinol effect, vitamin C effect, etc. The selected journals are English and Indonesian-language journals that discuss premature aging, skin aging effects, anti-aging, and topical ingredients that can be used as anti-aging.

## Results and Discussion

### 1. Skin Aging

Skin aging is a physiological process that changes the physiology and structure of the skin caused by various factors. Aging of the skin can be seen from the appearance of wrinkles, sagging skin, fine fold lines on the face and the appearance of black spots. This aging leads to reduced skin barrier function, slowed epidermal cell turnover, as well as decreased vascularity of the skin. The aging process in the skin also causes a decrease in the number of Langerhans cells and melanocytes which are the cause of decreased pigmentation in the skin, the amount and collagen, elastin fibers, mast cells and macrophages that can cause changes in skin texture<sup>4</sup>.

Skin aging is divided into two types, namely intrinsic aging and extrinsic aging. Intrinsic aging occurs due to the thinning epidermal layer of the skin and causes the surface contact of the dermis and epidermis to also thin out and the exchange of nutrients can also be reduced. This causes the skin to be easily injured and torn after minor trauma, so the proliferation of basal cells also decreases, so that in the layers of the dermis, the number of mast cells and fibroblasts decreases compared to young skin and causes the same to occur in elastin and collagen fibers. Intrinsic aging can be seen from skin thinning, fine wrinkles, dry skin, sagging skin, as well as benign tumors such as seborrheic keratosis<sup>2</sup>.

Extrinsic aging occurs due to external factors such as ultraviolet light radiation. Ultraviolet light increases elastin expression fourfold, causing elastosis. Elastosis is a characteristic of skin aging characterized by abnormal buildup of elastin fibers in the layers of the dermis<sup>2</sup>.

## 2. Anti-aging agent

Anti-aging is used as a technique to inhibit damage to the skin, so that signs of aging on the skin can be inhibited. In addition, anti-aging beauty products have many other benefits, namely making the skin healthier, brighter, and youthful<sup>3</sup>. Anti-aging treatment is done to disguise wrinkles, sagging skin, and fine fold lines on the face.

Anti-aging agents are divided into two large groups developed as components of anti-aging creams, namely the antioxidant group and the cell regulatory group. Antioxidants consist of vitamins, polyphenols and flavonoids, reduce collagen degradation by reducing the concentration of FR in the tissues. Antioxidants function to protect cells from free radical damage by donating one free electron to free radicals so that they become stable, stop chain reactions and prevent damage to lipids, proteins and DNA<sup>5</sup>. The vitamins often used in anti-aging care products are usually vitamin C, vitamin A, vitamin E, and vitamin B3. Meanwhile, cell regulatory groups (cell regulators) can be retinol, peptide and growth factor (GF) which have a direct effect on collagen metabolism and producing collagen<sup>6</sup>.

### Vitamin A

Vitamin A or retinol is a polyisoprenoid compound containing a cyclohexanil ring. Vitamin A is a fat-soluble vitamin (fat soluble) and is somewhat stable against high temperatures<sup>7</sup>. Vitamin A or retinol is one of the topical agents that is often used in cosmetic industry. Vitamins cannot be synthesized on their own by the body, vitamin A can be obtained from the consumption of foods containing retinoids (animal sources) and rubberenoids (vegetable sources) in the diet. In our body retinol will be converted into all-trans retinoic acid (tretinoin) via retinaldehyde. The application of retinoids on the face has been shown to be used as an agent to treat acne. Retinoids are agents that have a similar way of working and structure to retinol. Retinoids will decrease systemic and topical retinoids, namely nanoromatics (retinol, tretinoin, and isotretinoin), monoaromatics (etretinate and acitretin) and polyaromatics (arotinoids, adapalene and tazarotene)<sup>8</sup>.

Retinoids are widely used in the treatment of acne in cosmetic products. Vitamin A can induce collagen biosynthesis and reduce MMP1 (collagenase 1). Retinol is currently the most commonly used ingredient as an anti-aging compound compared to tretinoids which can cause irritation to the skin. Topical retinol can improve the fine wrinkles associated with natural aging. Significant induction of cosaminoglycan gly, which is known to retain substantial water, as well as increase the productivity of colaen that plays a role in crossing wrinkles<sup>9</sup>. Retinol can help reduce the effects of intrinsic and extrinsic aging by using collagen metabolic processes<sup>9</sup>.

With various studies and its commonly used use in facial anti-aging products, retinol is known to be the most frequently used ingredient to overcome skin aging, it's just that it is important to note that the use of retinol cannot be done every day because it will be bad for the skin. Retinol cannot be used every day because it can have an effect on the skin, especially for sensitive skin, there are often cases of side effects due to excessive use of retinol resulting in too tight skin, peeling and irritation.

### Vitamin C

Vitamin C is an ingredient that can be consumed by humans, can be found in public places such as markets, supermarkets, and so on. Sources of Vitamin C can be fruits, vegetables, fish, and some other processed products<sup>10</sup>. Vitamin C or L-ascorbic acid is the most abundant antioxidant found in the skin. L-ascorbic acid (vitamin C) which is soluble in water and does not withstand heat at concentrations between 5-15% has been shown to

have an anti-aging effect on the skin by producing Col-1 and Col-3 as enzymes, collagen and matrixmetalloproteinase inhibitors<sup>6</sup>. Vitamin C is generally used as an antioxidant antidote to free radicals, vitamin C can be soluble in water so that it can donate electrons, and neutralize free radicals, as well as protect intracellular structures from oxidative stress<sup>11</sup>.

Oxidative stress is one of the causes of aging of the skin. Oxidative stress is a condition of imbalance between reactive oxygen species (ROS) formed and antioxidant defense mechanisms. ROS is a reactive oxygen compound that is a secondary component of aerobic metabolism. ROS imbalances are caused by increased reactive oxygen species (ROS) production and reduced antioxidant production or both. Due to oxidative stress, oxidative damage will occur in various cellular components, disrupt the communication process between cells, stimulate apoptosis and be involved in various diseases related to aging<sup>2</sup>. Vitamin C plays a role in collagen biosynthesis, recent studies prove that vitamin C affects collagen synthesis independently from hydroxylation by activating transcription and stabilizing ribonucleic acid carriers of procollagen pesara. In addition, vitamin C can also inhibit elastin biosynthesis so that it supports the care of aging skin<sup>12</sup>.

A derivative of vitamin C called magnesium ascorbyl phosphate in a study is known to be used in cosmetics and the results show a brightening effect on the skin. The use of vitamin C in facial cosmetics can help the synthesis of collagen, a hyperpigmentation brightening agent, and has anti-inflammatory and photoprotective properties<sup>11</sup>. Seeing the role of vitamin C as an ingredient that can help collagen synthesis, it is important to know that increased collagen production can repair damaged skin structures such as aging, although vitamin C is not so often known as an anti-aging ingredient in the cosmetics industry.

### **Vitamin B3**

Vitamin B3, or nicotinamide or niacinamide, is a derivative of niacin obtained through food from meat, fish, milk, eggs, and nuts. Niacinamide deficiency can cause pellagra. Niacin has been used in medicine, most often to lower cholesterol. Nicotinamide is part of the coenzyme nicotinamide adenine dinucleotide (NAD), NAD phosphate (NADP), and its reduced forms are NADH and NADPH. These molecules are important in many reactions of cellular metabolism enzymes. Niacinamide is in the form of a white crystalline powder that has no color, has no smell and has a salty and bitter taste. Niacinamide is a water-soluble vitamin. The molar weight of niacinamide is 122.12 g/mol. Currently, niacinamide is only produced synthetically<sup>13</sup>.

Niacinamide is also commonly used in the cosmetic industry as an active anti-aging ingredient for the skin. Niacinamide can regulate metabolism and cell regeneration, and is commonly used at concentrations below 5% as an anti-aging agent. Nicotinamide increases collagen production in fibroblast cultures, and this effect may be responsible for increased skin elasticity and reduction of fine wrinkles. All of these effects can help reduce some of the signs of aging skin, and effectively concentrations at 3,5% to 5%. Niacinamide does not irritate the skin of the face, is easily formulated, chemically stable, and compatible with other components, hence niacinamide is considered ideal for use as an anti-aging agent<sup>14</sup>. Niacinamide which is effectively used in various cosmetics is known to be safe at a concentration of 4%. Niacinamide is often used to treat various skin problems such as hyperpigmentation, aging, acne psoriasis, pruritus, dermatitis, epidermal melasma, and

other skin problems. Other studies have shown that niacinamide has lightening properties against the skin by improving melanic hyperpigmentation caused by melasma<sup>15</sup>.

Clinical trials show 5% niacinamide can provide 35%-68% melanosome inhibition, with a decreased hyperpigmentation effect and thinning of the skin after 4 weeks of application<sup>16</sup>). In the application of in vitro, niacinamide can affect the viability of melanocytes and keratinocytes to reduce hyperpigmentation lesions and be able to stop the transfer of melanosome and induce skin lightening<sup>17</sup>. Various studies have proven that niacinamide is able to overcome various skin problems, ranging from aging, acne, to skin problems such as epidermal melasma. Unlike retinol which cannot be applied to the skin every day, niacinamide is actually safe to use every day regularly on the skin with a concentration level of no more than 5% in skincare and cosmetic mixtures.

### Vitamin E

Vitamin E is a group of compounds consisting of tocopherol. Vitamin E was first discovered by Bishop and Evan in 1922, is the main lipophilic antioxidant in plasma, membranes, and tissues. This vitamin is insoluble in water as well as being known as an antioxidant agent. Food sources that contain vitamin E are vegetable oils, nuts, seeds, meat and milk<sup>18</sup>.

Vitamin E(-tocopherol) is commonly used as an ingredient in cosmetic products that have anti-inflammatory and antiproliferative effects in the concentration range of 2-20%. Vitamin E can work by smoothing the skin and improving the ability of the stratum corneum to retain its moisture, accelerate epithelialization, and contribute to skin photoprotection, although its effects are not as strong as vitamin C<sup>6</sup>. Vitamin E has the characteristic of being able to absorb UV rays and is responsible for the damaging biological effects of the sun. Vitamin E is an antioxidant compound that can dissolve in body fat in the form of 4 tocopherols and 4 tocopherols. Alpha tocopherol is the most active compound in protecting cell membranes from lipid peroxidation by free radicals.

Vitamin E is often formulated as a topical agent at concentrations of 1% to 5%<sup>11</sup>Vitamin E ( $\alpha$ -tocopherol) used as a component of skin products has anti-inflammatory and antiproliferative effects in concentrations between 2 and 20%. It works by smoothing the skin and increasing the ability of the stratum corneum to retain its moisture, accelerate epithelialization, and contribute to skin protection in photopels<sup>19</sup>. The use of vitamin E in the in vitro method has shown the effect of alpha tocopherol in reducing the dose of minimal erythema and the number of sunburn cells which is a marker of skin damage due to oxidative stress. The use of vitamin E in nanoemulsion formulations of anti-aging gels is known to increase water content, shrink pores, reduce blemishes and the number of wrinkles on the skin<sup>20</sup>).

Of the four topical ingredients that are often used as anti-aging agents, retinol and niacinamide are the most commonly used ingredients in the pharmaceutical industry as anti-aging agents. The use of retinol in various studies has proven to be able to reduce various effects of aging such as disguising wrinkles, fine lines, hyperpigmentation as well as dark blemishes. The same has been proven niacinamide because it is able to reduce wrinkles, fine lines, brighten the skin and treat skin disorders such as melasma. Vitamin E and vitamin C are also known to reduce the effects of aging skin but are not as effective as retinol and niacinamide. Retinol cannot be used every day because it can have an effect on the skin, especially for sensitive skin, there are often cases of side effects due to excessive use of retinol resulting in too tight skin, peeling and irritation. In contrast to niacinamide which is safe to use every day.

## Conclusion

Anti-aging agents are a topical ingredient commonly used in the pharmaceutical industry to address problems related to aging skin. Anti-aging agents are divided into two large groups developed as components of anti-aging creams, namely the antioxidant group and the cell regulatory group. Antioxidant groups that are often used as anti-aging agents include vitamin A, vitamin B3, vitamin C, and vitamin E. Among these four ingredients, retinonol (vitamin A) and niacinamide (vitamin B3) are very commonly used as anti-aging agents that not only overcome aging problems but also overcome skin problems such as acne, melasma, hyperpigmentation and others. It's just that it should be noted that the use of vitamin A cannot be done every day, and it is much safer to use vitamin B3 which can be used daily and has minimal side effects.

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