Potential Of Natural Products In Inhibiting Premature Skin Aging

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Review Article

REVIEW ARTICLE: POTENTIAL OF NATURAL PRODUCTS IN INHIBITING PREMATURE SKIN AGING

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ABSTRACT

The objective of this article is to review the phytochemicals that serve as anti-aging materials by developing in vitro activity screening test methods. The method used is a literature study from national and international journals, including the original article, research article, etc., with a total of over 40 journals. Secondary metabolite compounds from natural ingredients such as flavonoids, polyphenols, alkaloids, and terpenes have antioxidant activity and have the potential to be anti-aging substances for the skin. The initial stage of searching for natural ingredients that have anti-aging activity can be done by developing in vitro activity screening test methods, such as inhibition of collagenase, elastase, hyaluronidase, and tyrosinase enzymes. This enzyme plays an important role as one of the causes of premature aging of the skin. From the literature search, it was found that many plant extracts to active compounds and cosmetic preparations from the extracts can inhibit these enzymes. The group of compounds that are known to have acted as enzyme inhibitors is polyphenolic compounds, especially those with multimerver properties, flavonoids, especially those with ortho-0H groups, triterpenes (especially pentacyclic), essential oils, and others. This shows that natural ingredients are one source of potential compounds as raw materials in the formulation of anti-aging cosmetic preparations.

Keywords: Premature skin aging, In vitro test, Plant extract, Elastase enzyme, Collagenase enzyme

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INTRODUCTION

The skin is the most visible outermost organ; this makes us pay more attention to the condition of the skin. An aging process is a natural event that occurs in all living things. Irreversible skin aging begins at the age of 20 y, although the signs are not visible for a long time. Aging of the skin is a complex biological process that results from intrinsic aging (from within the body, such as genetics) and changes that develop over time and extrinsic effects caused by environmental factors. Bad environmental conditions and lifestyles can cause premature aging. Extrinsic factors that play a role in premature aging are repetitive facial expressions, poor sleeping positions, smoking, etc. External signs of skin aging include fine wrinkles, thin skin, pigmented spots, loose skin, dry skin with or without itching, inability to sweat enough, grey hair, hair loss, etc. Of all these factors, the free radical theory is the theory that is often associated with the cause of premature aging factors. UV radiation is a very potent trigger in the formation of free radicals ROS (Reactive Oxygen Species) on the skin. In the skin, free radicals that are produced in excess will damage the collagen in the skin cell membranes, so the skin loses its elasticity and causes wrinkles [1,2].

Indonesia is a tropical country with year-round sunshine. UV radiation from the sun is absorbed by the skin and becomes one of the causes of premature skin aging to prevention and dermcare efforts are needed, such as the use of anti-aging cosmetics. Human desire is to live longer but looks younger so that they can be socially and physically active longer. In the 21st century, with the development of science and technology, plastic surgery techniques and other skin rejuvenation techniques have developed. But there is a tendency for some people to avoid invasive procedures to reduce risks and complications. Humans naturally want to look younger and with as few scars as possible. This has led to increased research on synthetic and natural cosmetic ingredients [3].

MATERIALS AND METHODS

This review focuses on natural ingredients or phytochemicals that serve as anti-aging materials by developing in vitro activity screening test methods. The article was used literature studies from Indonesian and international journals, including the original articles, research articles, patents, etc., with a total of over 40 journals.

RESULTS

Skin and premature skin aging

The aging process in humans causes a decrease in various organ functions, including the skin, and also causes several health problems in the elderly. The skin plays an important role as a barrier to the internal and external environment. Other functions of the skin are to maintain homeostasis, regulate body heat, maintain water, electrolyte, and protein balance, sensory perception, and immunological protection. In elderly skin, there is a thinning of the epidermis, a decrease in the supply of blood, fluids, and nutrients to the skin, a slowing of the wound healing process and immune response, disruption of thermoregulation, and a decrease in the number of oil and sweat glands. At the cellular level, there is a decrease in the production of lipids and natural moisturizing factors in the stratum corneum. In addition to these changes, there are also cerebral diseases that affect the function of the skin [4].

The skin is the largest organ in the human body with the main functions of protection, heat regulation, and the sense of touch. The skin is also the largest organ exposed to ultraviolet radiation and can cause various balance disorders in the skin, such as an increase in the amount of melanin, mild dermatitis, rough texture, wrinkles, premature aging to skin cancer. Nowadays, the awareness to look better with healthy and youthful skin is a necessity and has an impact on a person’s quality of life. The aging process in living things will naturally occur over time and the most visible impact of aging is the aging process on the skin because the skin is the most visible external organ. The aging process can also be accelerated by oxidative stress. There are two categories, namely intrinsic and extrinsic oxidative stress. Intrinsic causes are the result of metabolic processes in the body that produce free radicals such as unhealthy foods and unhealthy lifestyles. Extrinsic causes are mainly exposure to solar radiation (photaging), air pollution, and the effects of global warming [5-7].

The skin consists of 3 layers, namely the epidermis, dermis, and subcutaneous. In the dermis, there is an extracellular matrix which is the main component and plays a very important role in the growth and elasticity of the skin. The extracellular matrix contains proteoglycans bound to metalloproteins such as collagen, elastin, and fibrinogen produced by fibroblasts. Collagen is the main protein...
in the extracellular matrix that is responsible for the strength and elasticity of the skin, connective tissue, hair, and nails. Elastin is an important protein in maintaining skin elasticity to keep it firm and supple. Hyaluronic acid and glycosaminoglycans are important in maintaining skin moisture and thus are linked to skin elasticity [8]. Elastase is a serine protease (EC protease) and the only enzyme that can break down elastin. When the skin is exposed to UV radiation, the enzymes collagenase and elastase will increase so that they break down collagen and elastin, causing premature aging. Naturally, the amount of collagen will decrease by about 1% per year. Likewise, with elastin, naturally, the amount of elastin will decrease [9].

**Effects to reduce the effects of premature skin aging**

There are several ways to reduce the process of premature aging caused by UV rays of the sun, which is avoiding exposure to excessive UV, using clothing that is UV protection, the use of cosmetics containing sunscreen, vitamin A or its derivatives, or cosmetics that contain antioxidants and foods that are antioxidants, maintaining a good lifestyle such as exercise, reducing stress, getting enough sleep, not smoking and drinking alcoholic beverages, etc. The effects of phototherapy can also cause dry skin. Exposure to sunlight and high-intensity ultraviolet radiation, especially at 10:00 to 16:00, should be avoided. The skin cells absorb radiation and produce ROS, which can damage DNA and cell membranes. The process of photodamage also resulted in the destruction of collagen by the enzyme matrix metalloproteinase (MMP) and the accumulation of elastin irregular structure. This interaction produces dry skin, pales, and wrinkles. An example of this is adenosine, a compound that contains a sun protection factor (SPF) 30 when exposed to sunlight. Clothing that covers the skin and caps can also reduce exposure to sunlight [4].

Although currently, several synthetic compounds are useful as anti-aging; they generally have side effects such as allergies, irritation, and photo toxicity, so it is necessary to search for active compounds from natural ingredients that have anti-aging properties. Some antioxidants derived from plants and have been studied as anti-aging skin include aloin, ginseng, curcumin, epicatechin, astaxanthin, resveratrol, magnolol, gallic acid, hydroxyzinc, hydrocortisone, and hydroyxamic acid, etc. [10]. The research for new compounds derived from plants containing phytochemical compounds such as flavonoids, phenolic acids, alkaloids, and terpenes as well as having antioxidant, anti-inflammatory, and anti-aging activities, is currently widely used in the development of cosmetic preparations [11].

The extracellular matrix is the main component in the dermis of the skin, which plays a very important role in the growth and elasticity of the skin. The extracellular matrix contains proteins bound to metalloproteins such as collagen, elastin, and fibrinectin produced by fibroblasts. Collagen is the main protein in the extracellular matrix that is responsible for skin attractiveness. Elastin is an important protein in maintaining skin elasticity in the extracellular matrix. Many other vital organs, including arteries and lungs, also contain high amounts of elastin. Physiologically, organisms contain a certain amount of elastin from early development, which may remain physiologically constant because of the very long half-life and very low turnover. The role of hyaluronic acid and glycosaminoglycans is important in maintaining skin moisture and skin elasticity. The enzymes involved in the breakdown of these substances cause the skin aging process [8, 12].

The development of in vitro methods to test the inhibitory activities of collagenase, elastase, hyaluronidase, and tyrosinase enzymes is a method that can be used in screening tests for anti-aging activities. In vitro assay is a screening test which is a rapid and rational method of reducing the number of in vivo trials and risks associated with human subjects; thus this can reduce research and development costs [13].

**Potentially natural ingredients for anti-aging skin**

From many studies of anti-aging activity tests, extracts and isolates of active components from natural ingredients are a natural indication that natural ingredients contain potential chemical candidates in improving health and inhibiting premature aging [14]. Plant extracts containing phytochemical compounds such as flavonoids, phenolic acids, terpenes, and alkaloids are known to have anti-inflammatory activity and can potentially be used in cosmetic products. The number of pharmaceutical and cosmetic products containing a combination of herbal extracts turned out to have better activity than single extracts [15]. Bravo et al. tested the methanolic extract of *Rubus compactus* and *R. roburicatus*, which have strong activity as inhibitors of enzymes that cause premature aging: elastase, and collagenase [8]. Ethanolic extracts from ripe and unripe fruit, leaves, and roots of *R. coreanus* have been tested for antioxidant, whitening, and anti-wrinkle properties. The ethanol extract of raw fruit shows a high activity as a whitening and anti-winkle agent, so it has the potential to be used as an ingredient in the manufacture of skin care products [16].

The results of a patent search, *R. idaeus* fruit has been patented as an elastase inhibitor by Shioudei Co., [17], *R. fruticosus* leaves have been patented as anti-aging (anti- elastase, anti-collagenase, and anti-tyrosinase) [18]. Antioxidant and enzyme inhibitor activity tests were carried out on several small and colorful fruit plants that live in the Andean mountains, Colombia. The test results showed that generally, unripe fruit had higher antioxidant and enzymatic inhibitor activity than ripe fruit. The fruit extract fraction of *R. fruticosus* also has hyaluronidase inhibitory activity [19].

Several plant extracts have been tested for antioxidant, anticytotoxic, and anti-collagenase activity *in vitro* and show their potential as anti-aging ingredients, namely tangerine peel (Citrus reticulata Blanco) [20], cucumber/Garcinia cambogia [21], essential oil of two varieties *Alpinia zerumbet* (varieties tamarin and shima) [22], white tea leaf (*Camellia sinensis*), thistle portion of *Alce Focus venosus* L., leaves and stems *Galea spuria* L., cabbage rose (*Rosa centifolia* L.), green tea leaves *Camellia sinensis*, Angelica archangelica L. root, *Lilium verum* Hook, *Panax ginseng* L. fruit. [6, 23], the pomace of grape/ *Vitis vinifera* [24], unripe black/buckeye *Carica* [16], Tagetes erecta flower [25], *Rubus compactus* and *Ugni myricoides* fruit [8], unripe *F. communis* [26]. In several studies of fruit with several levels of ripeness, statistically, it was shown that immature fruit had better antioxidant activity and enzyme inhibitory power [8, 16].

Several cosmetic preparations have activity as anti-aging of the skin, for example, a mixture of fruit extracts of *Myrtus communis*, *Panax ginseng*, *Ficus carica*, and *Morus alba* have antioxidant, anti-collagenase activity *in vitro* and anti-wrinkle tests *in vivo* [15].

**Isolate compounds that have activity as an anti-aging skin**

Several biofavored isolates from *Alnus viridis* and *Alnus glutinosa* have strong antioxidant and anti-collagenase activity. The triterpenoid compound betulinic acid isolated from the resin of *Betula nigra* has anti-collagenase activity. Polyphenolic and flavonoid compounds isolated from the leaves of *Desmodium kari* and *Rosmarinus officinalis* have anti-collagenolytic and anti-elastase activity [6]. Polyphenolic catechins and epigallocatechin gallate (EGCG) compounds isolated from green tea (*Camellia sinensis*) have activity as collagenase and elastase inhibitors. Phenolic compounds such as epicatechin, catechin, resveratrol, and procyanidin B2 [24] are also reported to have elastase inhibitory activity. The compound identified as *Zygonolysine* I was isolated from the root extract of *Sanguihsoura officinalis*. This compound was tested to evaluate its free radical scavenging activity, anti-elastase activity, and type I collagen synthesis in normal human fibroblast cells. The results show good results and have potential in anti-aging cosmetic preparations [27]. Cinnamaldehyde compounds from *Cinnamomum verum* have elastase inhibitory activity up to 96.5% [28]. Two triterpenoids derived from unripe fruit of *Rubus fruticosus* showed inhibitory activity against elastase and tyrosinase enzymes *in vitro* and silico [29].

The flavonoid xanthohumol has also been isolated from the *Humulus lupulus* L. plant which has anti-elastase and anti-collagenase activity [30]. Research from Kim et al. [29] showed that of 5 compounds isolated from *Gallusornis hanoiensis* stems, pyrrocyan acid had...
activity as a strong elastase inhibitor. Lee et al. reported that they isolated phenolic compounds in Areca catechu leaf, which have inhibitory activity against porcine pancreatic elastase (PPE), human neutrophil elastase (HNE), and hyaluronidase [31] (fig. 1, table 1).

**Table 1: Compounds that have anti-aging activity**

<table>
<thead>
<tr>
<th>No.</th>
<th>Compounds</th>
<th>Source</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zizyphukoside I</td>
<td><em>Sungursorbo officinalis</em> root</td>
<td>Anti- elastase 5.4% in 667 mg/mL</td>
<td>[27]</td>
</tr>
<tr>
<td>2</td>
<td>Cinamuklevidil</td>
<td><em>Cinnamomum verum</em> Volatile oil</td>
<td>Anti- elastase 96.56%</td>
<td>[20]</td>
</tr>
<tr>
<td>3</td>
<td>Flavonoid xanthohumol</td>
<td><em>Namus lepale</em> L</td>
<td>Anti- elastase IC50 0.0014</td>
<td>[32]</td>
</tr>
<tr>
<td>4</td>
<td>Pinocembrinic acid</td>
<td><em>Collisteron lanceolatar stem</em></td>
<td>Anti- elastase IC50 1.5 mg/mL</td>
<td>[33]</td>
</tr>
<tr>
<td>5</td>
<td>Flavonoid</td>
<td><em>Areca catechu</em> L</td>
<td>Anti- elastase IC50 21.4 mg/mL</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Phenolic</td>
<td><em>Areca catechu</em> L</td>
<td>Anti- elastase IC50 20.2 mg/mL</td>
<td>[31]</td>
</tr>
<tr>
<td>7</td>
<td>Isoflavone</td>
<td><em>Mentha piperita</em> root</td>
<td>Anti- elastase IC50 15.6 mg/mL</td>
<td>[32]</td>
</tr>
<tr>
<td>8</td>
<td>Flavonone, chalcone, flavanol</td>
<td><em>Cinnamomum verum</em> Volatile oil</td>
<td>Anti- elastase IC50 1.3-213.1 μM</td>
<td>[32]</td>
</tr>
<tr>
<td>9</td>
<td>Epi-epicatechin gallic</td>
<td><em>Cinnamomum verum</em> Volatile oil</td>
<td>Anti- elastase IC50 5.5-13.2 μM</td>
<td>[32]</td>
</tr>
<tr>
<td>10</td>
<td>Epi-epicatechin gallic</td>
<td><em>Cinnamomum verum</em> Volatile oil</td>
<td>Anti- elastase IC50 1.3-213.1 μM</td>
<td>[32]</td>
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Kanakirat et al. researched anti-elastase on several flavonoids and obtained the results of activity of quercetin = myricetin = kaempferol = galangin. These studies have revealed that the number and position of free hydroxy groups are important structural features for the compound’s modulatory activities on oxygen-dependent neutrophil functions as oxidative burst. This proves the importance of the catechol group on ring B of flavonoids in anti-elastase activity. The structure of the flavonoid test can be seen in fig. 2 [35].

**Fig. 2: The structure of some flavonoids that have been tested for antielastase [35]**
The results of the research of Kipleli Abikai et al. 2015 showed that the root methanol extract of Rubus sanctus Schreber contains a new compound, quercetin-3-O-β-galactoside, and was named hyperoside. Cinnamaldehyde compounds from Cinnamomum verum have elastase inhibitory activity up to 96.56% [28]. Xanthohumol flavonoid compounds have also been isolated from the Humulus lupulus L. plant, which has anti-elastase and anti-collagenase activities [30]. Research from Kim et al. 2009 showed that of the 5 compounds isolated from Callichiostro lanceolatus stems, pyracenec acid had activity as a strong elastase inhibitor [33].

Isolation of the compound was guided by the elastase enzyme inhibitory activity test from the herb fl. sanctus, namely, the methanol extract of the herb was fractionated using column chromatography with silica gel followed by preparative TLC and structural elucidation resulted in a quercetin-3-O-β-galactoside and named hyperoside [36].

Phytochemical compounds from plants that have potential as anti-aging skin

Plant extracts rich in phytochemical compounds such as flavonoids, phenolic acids, terpenoids, alkaloids, monoterpens, antioxidant, and active anti-inflammatory compounds are also commonly used in the development of topical cosmetic preparations [37]. Several studies have shown that anti-skin aging and antioxidant activity in plants is also related to the plant defense system, consisting of terpenes and polyphenols or phenolic compounds [3, 39] as shown in fig. 3. In vitro studies have shown that phytochemical compounds can reduce oxidation levels and inhibit the work of collagenase, elastase, hydrolase, and tyrosinase enzymes. The strength of the activity of the polyphenol group depends on the position and the phenol group. Otherwise, the contrary research on 20 plants containing high tannin levels showed no correlation with anti-elastase and anti-hyaluronidase activity [38].

Terpenes are known to be metabolites in the face of oxidative stress in plants through the mechanism of reducing free radicals [10]. The in silico test also showed that the aromatic group, which has an orthoblephathate group, is one of the important structures for elastase inhibition [39]. The greater the degree of polymerization of polyphenols, indicating an increase in the antioxidant activities of polyphenols to inhibit the elastase enzyme, this inhibition is reversible and competitive. Docking simulations using molecular dynamics show that the polyphenol tetramer structure has more contact points with amino acids on the active site of the enzyme. The hydrogen-bonding interactions and hydrophobic effects formed by the polyphenol groups and the side chains of the enzyme residues stabilize and support this binding mode. This research is relevant to the study of the antinflammatory effect caused by dietary tannins on digestive enzyme activity, reducing food digestibility and nutrients absorption [40].

In vitro and in vivo testing of several pentasaccharide trimers as inhibitors of human neutrophil elastase (HNE) showed reversible and competitive activity. Further, a molecular docking test was carried out and it was concluded that the carbonyl group at position 28, and the double bond at the appropriate location in the pentasaccharide ring system of the trimers contributed to the binding of HNE [41].

CONCLUSION

In an effort to find natural ingredients both in the form of extracts and isolated compounds with anti-aging properties, in vitro screening tests can be carried out, namely inhibition tests on enzymes that affect premature skin aging such as elastase, collagenase, tyrosinase, and antioxidant. Phytochemical compounds that have activity inhibiting the work of these enzymes include polyphenolic compounds, flavonoids, triterpenoids, and other terpenes. Plants containing this compound have the potential to be used as raw materials in the formulation of anti-aging cosmetics.

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AUTHORS CONTRIBUTIONS

YO: conception and design of the work; FF: drafting the manuscript; VN, HR, and NSSA: participated in intellectual discussions and critical revision of the article. All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this article.

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