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Review

Anti-Aging Properties of Plant Stem Cell Extracts

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Received: 9 August 2018; Accepted: 21 September 2018; Published: 22 September 2018

Abstract: Skin aging is a complex process which involves all the layers of the epidermis and dermis. In order to slow skin aging, methods are researched which would strengthen and protect skin stem cells. Science is in search of the right method to stimulate the proliferation of epidermal stem cells. Plant stem cells show outstanding anti-aging properties, as they can, among other activities, stimulate fibroblasts to synthesise collagen, which, in turn, stimulates skin regeneration. One of the most important agents which give anti-aging properties to plant stem cell extracts is kinetin (6-furfuryladenine). This compound belongs to a cytokine group and is considered to be a strong antioxidant which protects protein and nucleic acids from oxidation and glycoxidation processes. It enables cells to remove the excess of free radicals to protect them from oxidative stress.

Keywords: plants stem cell extract; anti-aging properties; kinetin

1. Introduction

Skin aging is a complex process which involves all the layers of the epidermis and dermis. Internal and external factors influence this process. The most important external factor in skin aging is UV radiation, which causes photoaging of the skin. The free radicals that are formed as a result of the UV radiation cause the degradation of unsaturated lipids of the intercellular cement, gaps in the lipid barrier of the skin (and, as a result, increased TEWL), and changes in the structure of fibrillar proteins–collagen and elastins.

The internal factors that cause changes in the skin structure are, primarily, physiological disorders in the rate of epidermis exfoliation, inhibition of tissue regeneration, and inhibition of tissue growth and differentiation processes. The reduction of the regenerative potential of the skin is the result of, among other factors, lower activity of the stem cells.

There are two mechanisms that limit the proliferation of human cells: replicative aging related to changes in the structure and length of telomeres, and premature aging occurring without visible changes in telomeres. The first of the abovementioned mechanisms characterises cells with a high proliferation potential (e.g., fibroblasts). It is initiated with an ongoing loss of telomeric repeats and is accompanied by the uncapping of the telomere loop structure. It is believed that this phenomenon can be the result of the end-replication problem, i.e., the inability of the DNA polymerase to completely synthesise a daughter strand on the parental lagging strand matrix [1,2]. In addition to the end-replication problem, the progressive destruction of telomeric DNA may occur due to long-term exposure of the cells to stressors, especially oxidative stress. One of the direct consequences of the DNA exposure to reactive oxygen species (ROS) is damage within the particularly sensitive oxidation sequence, which is rich in guanine, at the endings of 3′ telomeres. As a result, replication is immediately interrupted and, in consequence, telomeres are shortened [3].

In order to slow skin aging, methods are being researched which would strengthen and protect skin cells. The aim of modern anti-aging cosmetics is to improve the look of the skin by stimulating and

regenerating natural physiological processes that improve the skin condition and to protect the skin from factors that cause its aging, regardless of its actual age [4]. Therefore, anti-aging cosmetics contain substances that protect the skin from solar radiation (UV filters). The second group of materials found in such cosmetics contains substances which neutralise free radicals: vitamins E and C, coenzyme Q10, carotenoids, or polyphenols and flavonoids found in plant extracts. The substances which regenerate and delay aging of the skin include nucleic acids, protein hydrolysates, algae extracts rich in microelements, EFA plant oils (especially oils from cereal germs, oenothera oil, borage oil), and alpha hydroxy acids (AHA) with keratolytic and softening effects. The recently popular ingredients also include: phytohormones, cytokines, and neuropeptides [5]. In recent years, special attention has been paid to stem cells and their potential in the stimulation process of the proliferation of the epidermis stem cells [2,6,7].

Currently, the European law [8] prohibits, on ethical grounds, the use of substances of human and animal (obtained against their welfare) origin; therefore, the cosmetic industry is interested in plant resources. The protection of human stem cells, stimulation of skin regeneration, and prevention of the skin aging processes are the declared effects of plant stem cells [2,9].

2. The Characteristics of Plant Stem Cells

Stem cells are found in plant and animal organisms. They differ from other cells due to their unusual properties, proliferation ability (continuous multiplication), and differentiation into specialised cells (depending on the organ in which they are present), and they are also responsible for the growth and repair of damaged tissues [6,7,10].

The plant stem cells are found in shoot apical meristems and root lateral meristems. In these places, the cells divide throughout the plant's life, creating new organs. All parts of the plant, including leaves, stems, flowers, and seeds, are formed from the connective tissue cells which are in the apical part of the stem. The plant meristems contain growing tips. The growth process occurs in them through systematic cell division. The plant stem cells that are present in growing tips are characterised with totipotency, i.e., the ability of one cell to divide and produce all differentiated cells in an organism. It allows plants to build new organs throughout their life. For cosmetic purposes, plant stem cells are reproduced in cell culture with a micropropagation method (microreproduction), which involves in vitro cell culture. The first step is the selection of the plant part (fruit, leaf, or root). Next, callus creation is induced by cutting the plant and moving the taken stem cells to agar plates. Cell growth occurs in a liquid environment. Special bioreactors are used in a large-scale cell culture, as they ensure controlled culture conditions. The grown stem cells are exposed to high pressure, and then to cell membrane digestion and the release of its contents to the substrate. In total, 55% of the plant cell volume consists of cell walls and membranes. The rest is cytosol (intracellular fluid), which contains various organelles and consists of 90% water [6,7,11].

The extracts derived from plant stem cells are the source of many active substances that are safe for the human body, because they do not produce the response of the immune system. Their acquisition is environmentally friendly and possible even in the case of hard to reach or endangered plants, without causing interference and disturbance in their natural habitat. The plant stem cells are responsible for many positive cosmetic effects, such as [11,12]:

- extending the life of fibroblasts and stimulating their activity (e.g., *Oryza sativa*, *Gardenia jasminoides*);
- increasing the flexibility of the epidermis (e.g., *Symphytum officinale*, *Capsicum annuum*, *Opuntia* spp.);
- regulating cell division (e.g., *Oryza sativa*, *Lotus japonicus*);
- rebuilding damaged epidermis (e.g., *Panax ginsgen*, *Opuntia* spp.);
- activating DNA repair of the cells, protecting them from oxidative stress (e.g., *Rubus ideaus*, *Lycopersicon esculentum*, e.g., *Citrus limon*);
- protecting against UV radiation (e.g., *Dolichos biflorus*, *Opuntia ficus indica*).

It should be noted, however, that plant stem cells are extremely sensitive to external factors, such as light or temperature, and therefore, in cosmetic products, they are used in the form of extracts soluble in lipids (extracted with oils) and soluble in water (extracted with glycerol), powdered extracts (with maltodextrin), liposomes, nanoemulsions, or suspensions [11–13].

3. Plant Stem Cells with Anti-Aging Effects

The best extracts can be obtained from the stem cells of those plants whose seeds or fruit maintain freshness and reproducibility for a long time. An important factor that should be taken into account during the selection of a plant is its habitat in difficult environmental conditions or its ability to "heal" other plants.

The pioneer in producing plant stem cells for the cosmetic industry is Mibelle AG Biochemistry company (Switzerland), which implemented apple stem cells (PhytoCellTec™ Malus Domestica) in 2008. Liposomes were used as extract carriers. In 2008 [6], the results of an experiment were published in which human fibroblasts were incubated with typical symptoms of aging by damaging the cell DNA in a 2% stem cell extract in order to reverse aging. The obtained results confirmed the effectiveness of improving the lifetime of the umbilical cord blood stem cells and extending the lifetime of the cells isolated from human hair follicles. Moreover, the clinical study, which was carried out on a group of 20 probants who used a cream with a 2% PhytoCellTec™ Malus Domestica active ingredient for four weeks, confirmed the effectiveness of the stem cell extract in reducing wrinkles (crow's feet) on their faces. The wrinkles around the eyes were shallowed by 8% after two weeks, and 15% after four weeks of use. Since then, Mibelle AG Biochemistry has introduced extracts from plant stem cells of *Vitis vinifera* (PhytoCellTec™ Solar Vitis), *Saponaria pumila* (PhytoCellTec™ nunatak®), or *Argania spinosa* (PhytoCellTec™ Argan) on the market in the form of suspensions which also show anti-wrinkle effects and which improve the activity of the epidermis stem cells [12].

Anti-aging properties are also found in glycerin extracts from stem cells acquired from ginger (*Zingiber officinale*) leaf cell extracts, obtained by Naolys company (France) [14]. These properties were confirmed with a clinical study of 22 women. After 28 days of use, the skin structure was improved, pores reduced in size by 50%, and a matting effect (gloss reduction by 15% and sebum reduction by 19%) was observed after just six days of application. The in vitro results showed an increase in the synthesis of elastin and fibres and a reduction of the sebum production rate. In addition, Naolys also offers a glycerin extract from stem cells of *Iris pallida* (All Even Sweet iris), *Olea europea* (All Fiber Booster Olive tree), *Hibiscus rosa* (All Fiber Booster Chinese hibiscus), and *Camellia sinensis* (All Fiber Booster Green tea), which also show anti-aging effects on the skin [12].

There are other companies on the cosmetic market which offer active ingredients in the form of stem cell extracts, e.g.,: Active Concepts LLC (USA), Akott Evolution S.R.L. (Italy), Biocosmethic (France), Infinitec (Spain), Innova BM (Bulgaria), In vitro Plant-tech AB (Sweden), Sederma (Croda Personal Care, United Kingdom), Provital Group (Spain), and Vitalab s.r.l. (Arterra Bioscience s.r.l, Italy) [12].

Moreover, the anti-aging effect of the stem cell extracts is also confirmed in the literature.

Syringa Vulgaris (lilac leaf) stem cell extract, due to its verbascoside content, possesses multi-faceted benefits, and may be used in the treatment of commonly seen inflammatory, acneic, aging, and photodamaged skin conditions [15].

Ginseng callus culture extract owes its anti-aging properties to the presence of useful metabolites, e.g., ginseng saponin and polysaccharide [16].

Tomato stem cell extract, obtained from *Lycopersicon esculentum* cell liquid cultures, can also find applications in anti-aging skin care cosmetic formulations to promote healthy skin. It is a rich source of flavonoids (rutin), phenolic acids (chlorogenic acid, coumaric acid, protocatechuic acid), and beta-carotene. Because of its antioxidant activity, the extract can protect the skin cells from oxidative stress and heavy metal-induced damage [17].

M. Caucanas [18] described a beneficial boosting effect of samphire cell biomass on the kinetics of epidermal permeability barrier repair. The study, supported by the results of Lequeux et al. [19], suggested that both the epidermal cell proliferation and maturation/differentiation were stimulated by *Samphire cell stem cell extracts*.

Another source of effective antioxidants, such as neohesperidin and naringin, is *Citrus aurantium stem cell extract* [20]. Citrustem™ obtained from orange stem cells, launching Provital Stem Cells Collection, shows an anti-aging effect. Under the cell extract treatment, the synthesis of collagen and other key elements of the extracellular matrix grow [21]. A group of 20 women between 41 and 55 years old applied a 3% formula of Citrustem™ twice a day for 56 days against a placebo formula. After this period, they observed, among other benefits, a 17.5% increase in skin elasticity.

Moreover, according to the literature, it was confirmed that the stem cells obtained from *Coffea bengalensis* culture [22] and *Nicotiana sylvestris* [23] stimulate fibroblasts to synthesise collagen which, in turn, stimulates skin regeneration.

4. Antioxidant Activity of Steam Cell Extracts

As it has been mentioned above, free radicals are considered to be the most active compounds in skin aging. They damage DNA and assist in dehydrogenation, hydroxylation, and protein glycation. Radicals also damage the lipids in the *stratum corneum*. Consequently, tissue loses its elasticity and capacity to regulate transepidermal water loss (TEWL) and cell replication becomes less efficient [4,5]. Therefore, antioxidants are important raw materials of anti-ageing cosmetics [24].

The extracts from plant stem cells are an excellent source of known antioxidant compounds, such as polyphenols, phenolic acids, flavonoids, triterpenes, carotenoids, and peptides, which give the anti-aging properties [11,12].

The antioxidant activity of phenolic compounds is mainly due to their redox properties, which can play an important role in adsorbing and neutralizing free radicals, quenching singlet and triplet oxygen, and decomposing peroxides [25]. In the case of flavonoids, antioxidant activity depends on their structure. The configuration, substitution, number of hydroxyl groups, and total number of sugar moieties in flavonoids (flavonoids glycosides) play an important role [26–28]. Several mechanisms of antioxidant activity, such as: (1) radical scavenging; (2) suppression of ROS (Reactive Oxygen Species) formation, either by the inhibition of enzymes or by chelating metal ions (iron, copper, etc.), which are involved in free radical generation; and (3) protection of antioxidant defences, are described in the literature. The hydroxyl groups configuration is the most significant determinant of the scavenging of ROS and RNS (Nitrogen Reactive Species) because they donate hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, stabilizing them and giving rise to a relatively stable flavonoids radical [29–31].

N. Goutzourelas et al. [32] studied the antioxidant effect of a phenolic compound from grape (*Vitis vinifera*) stem extracts on endothelial and muscle cells. They found that the polyphenolic composition of grape stem extracts affects their antioxidant capacity. The treatment with grape stem extracts, at low concentrations, improves the redox status of endothelial and muscle cells. On the basis of the obtained results, the researchers suggested that trans-resveratrol, gallic acid, (+)-catechin, ferulic acid, caffeic acid, quercetin, coumaric acid, and kaempferol could be essential for the antioxidant activity of grape stem extracts. The antioxidant properties of Buddleja Davidii stem cell culture are related to the content of phenylpropanoid glycosides, such as the verbascoside, isoverbascoside, leucosceptoside A, and martinoside [33].

Another rich source of phenylpropanoid compounds, especially isoverbascoside, is *Syringa Vulgaris* leaf cell culture extract [34].

Tito et al. [17] reported that the tomato stem extract is a rich source of the most phenolic acids and flavonoids found in tomato fruits. They realized that the content of rutin, coumaric, protocatechuic, and chlorogenic acids, in the cell extract, was higher than in tomato fruit and that the tomato cell extract showed a higher total antioxidant capacity in comparison with that of the tomato fruit

extract. The high antioxidant activity of a raspberry stem cell extract was reported by Barbulova and co-authors [35]. Among other analyzed polyphenolic components, the most abundant were ferulic acid and quercitin ramnoside.

Antioxidant activity of several plant stem cell extracts was confirmed in the work of Bazylak and Gryn [36]. The total poliphenolic content and scavenging of DPPH radicals were evaluated for stem cell extracts of paper mulberry (*Brussonetia kazinoki*), grape (*Vitis vinifer*), magnolsi (*Magnolia sieboldii*), green tea (*Camelia sinensis)*, white ginseng (*Panax ginsen*), and hydroponically cultivated ginseng. All of the studied extracts showed high antioxidant activity, but the most effective ones were the green tea stem cell extract and white ginseng extract [36].

Kinetin—Powerful Antioxidant

One of the most important agents which give anti-aging properties to plant stem cell extracts is kinetin (6-furfuryladenine) (Figure 1), a cytokine hormone for plant growth. It is one of the purine bases of the nucleic acid and an adenine derivative. Kinetin was isolated for the first time from herring sperm in 1955. In 1996, it was discovered in freshly extracted DNA from human cells, in plant cell extracts, and in human urine [37–40]. Kinetin occurs in nature in the stem cells of many plants, e.g., Australian pine tree (*Casuarina equisetifolia*) or gingergrass (*Cymbopogon martinii* var. *motia*) [39]. Very high concentrations of kinetin were found in stem cells of lemon (*Citrus limon*) [41] and raspberry (*Rubus chamaemorus*) [42].

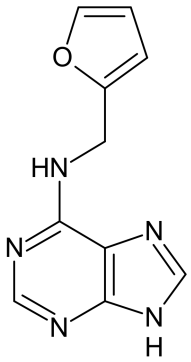

Figure 1. Kinetin Structural Formula [26].

Kinetin is considered to be a strong natural antioxidant which protects protein and nucleic acids from oxidation and glycoxidation processes [43–45]. This compound enables cells to remove the excess of free radicals to protect them from oxidative stress. It works in two ways. It can involve inducing the synthesis of regenerative enzymes, which remove modified bases from the DNA chain and provide protection against free radicals and oxidative stress; or creating complex compounds with copper (II) ions, which activate superoxide dismutase, the key enzyme in the organism's antioxidation barrier [44,45]. Kinetin protects the cell DNA by inhibiting the creation of 8-oxo-dG, an oxidative marker of genetic material damage, which is formed as a result of the Fenton reaction [44].

This natural growth factor is a precise tool for stimulating skin stem cells. According to research, it improves the barrier functions of the spinous layer of the epidermis; stimulates keratinocytes; lowers water loss through the epidermis, which improves its pigmentation; and reduces surface wrinkles [46–51].

According to the literature, the abovementioned cytokine slows down the aging process of the plant's leaf cells [52] and human cells in in vitro cultures [53]. The anti-aging effect of kinetin was also confirmed for the skin endothelium cells. Cytokine activated the cell proliferation, inhibited endothelium cell aging, and stimulated their proliferating and metabolic properties [46].

5. Summary

The topic of stem cells has become very popular in recent years, especially within the cosmetic industry. The extracts obtained from plant stem cells are a source of many active substances, such as polyphenols, phenolic acids, triterpenes, flavonoids, carotenoids, fatty acids, sugars, and peptides, which give the anti-aging properties. They cause, e.g., extension of the life of fibroblasts and stimulation of their regenerative activity. According to the studies, one of the strongest inhibitors of aging processes in human cells is kinetin, a cytokine whose high concentration was found in stem cells of, e.g., citrus fruit and raspberry.

Author Contributions: All the authors contributed to the writing and editing of the article.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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