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Mini-review article

Effect of ginseng and ginsenosides on melanogenesis and their mechanism of action

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ABSTRACT

Abnormal changes in skin color induce significant cosmetic problems and affect quality of life. There are two groups of abnormal change in skin color; hyperpigmentation and hypopigmentation. Hyperpigmentation, darkening skin color by excessive pigmentation, is a major concern for Asian people with yellow–brown skin. A variety of hypopigmenting agents have been used, but treating the hyperpigmented condition is still challenging and the results are often discouraging. *Panax ginseng* has been used traditionally in eastern Asia to treat various diseases, due to its immunomodulatory, neuroprotective, antioxidative, and antitumor activities. Recently, several reports have shown that extract, powder, or some constituents of ginseng could inhibit melanogenesis *in vivo* or *in vitro*. The underlying mechanisms of antimelanogenic properties in ginseng or its components include the direct inhibition of key enzymes of melanogenesis, inhibition of transcription factors or signaling pathways involved in melanogenesis, decreasing production of inducers of melanogenesis, and enhancing production of antimelanogenic factor. Although there still remain some controversial issues surrounding the antimelanogenic activity of ginseng, especially in its effect on production of proinflammatory cytokines and nitric oxide, these recent findings suggest that ginseng and its constituents might be potential candidates for novel skin whitening agents.

1. Introduction

Panax ginseng (ginseng) has been used traditionally in eastern Asia over thousands of years. It has been used orally to treat various diseases including hypertension, diabetes mellitus, liver and kidney dysfunction, mental disorders, and postmenopausal disorders. In addition, topical applications have also been used to heal wounds and reduce skin inflammation [1]. In the past few decades, it has been proved that ginseng extracts actually show a wide range of effects against human diseases. Their potential therapeutic effects have been mainly attributed to its immunomodulatory [2,3], neuroprotective [4,5], antioxidative [6], antitumor [7], and hepatoprotective activities [8].

Ginseng contains a number of active ingredients including ginsenosides, polysaccharides, phytosterols, peptides, polyacetylenes, fatty acids, and polyacetylenic alcohols, which have different effects on carbohydrate and lipid metabolism, cognition, angiogenesis, and the neuroendocrine, immune, cardiovascular, and central nervous systems [9,10]. Among the active constituents of ginseng, ginsenosides are known to be the major biologically active components of ginseng and the most widely studied. Several studies have shown that ginsenosides play important roles in the pharmacological effects of ginseng [11]. So far, over 30 different ginsenosides have been isolated and identified from ginseng [11]. However, ginseng contains other constituents, including ginsenoyne, phenolic compounds, polyacetylenes, sesquiterpenes, methoxypyrazine, alkylpyrazine derivatives, sesquiterpene alcohols, panasinsanols, and β-carboline [12,13]. The biological functions of these compounds are being investigated by a number of researchers.

There are two traditional preparations of ginseng; white ginseng and red ginseng. White ginseng is peeled, dried, ginseng root and red ginseng is produced by steaming fresh ginseng root at 98–100°C for 2–3 h, and then drying until the moisture content is <15% [14]. Red and white ginseng have both been shown to have immunomodulatory [15,16], anti-inflammatory [17], antioxidant [18], and antiatopic activities [19]. Moreover, red ginseng has been reported to have more potent pharmacological activities than white ginseng in some respects [20–22]. The differences in biological activities between red and white ginseng are caused by the

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chemical changes of ginsenosides after the steaming process [23]. Steaming partially converts the original ginsenosides to deglycoslated derivatives [24]. As a result, the species and amounts of ginsenosides are quite different based on the processing method used. Chu et al [25] showed that a total of 53 and 43 compounds were tentatively identified in white ginseng and red ginseng samples, respectively. The featured compounds are mainly malonyl ginsenosides in white ginseng, and decarboxyl products of malginsenosides and the dehydrated compounds from polar ginsenosides were characteristic in red ginseng [25].

It is interesting that ginsenosides show a wide variety of biological activities, although the absorption rates from orally administered intact ginsenosides are very low. In the human intestinal tract, ginsenosides are metabolized by intestinal bacteria and the metabolites are absorbed [26,27]. Thus, the pharmacological actions of these ginsenosides have been closely related to their biotransformation by human intestinal bacteria [28]. In this context, fermentation strategies have been used to improve oral absorption and bioavailability. Several studies showed that the transformation of ginsenosides into deglycosylated ginsenosides is needed to increase ginseng's effectiveness *in vivo* [27].

Abnormal changes in skin color induce significant cosmetic problems with a negative effect on quality of life. There are two groups of pigmentary disorders: disorders of the quantitative and qualitative distribution of normal pigment and the abnormal presence of exogenous or endogenous pigments in the skin. The first group includes hyperpigmentation and hypopigmentation (leukodermia). Hyperpigmentation is darkening of the skin color due to excessive pigmentation. Usually, hyperpigmentation issues are major concerns for people of color [29]. Hyperpigmentation-related diseases include melasma, lentigines, nevus, ephelis, freckles, postinflammatory hyperpigmentation, and age spots [30]. Postinflammatory hyperpigmentation appears in many skin conditions, including acne, eczema, and contact dermatitis. Meanwhile, hypopigmentation is lightening of the skin by insufficient pigmentation [31]. Skin color is determined by various factors including melanin content, oxygenation state of hemoglobin in capillary vessels, carotenoid content, water content, and organization of collagen fibers in the dermis. Among these factors, melanin is the major determinant of skin color [32]. In this context, understanding the mechanisms involved in melanogenesis is of great interest pharmaceutically and cosmetically.

Melanogenesis is a biochemical pathway responsible for melanin synthesis that is controlled by complex regulatory mechanisms [33]. Melanogenesis occurs in melanocytes confined in separate cytoplasmic organelles called melanosomes, which contain key enzymes of melanogenesis. Differences in skin color are related to the size, number, shape, and distribution of melanosomes, whereas melanocyte density typically remains relatively constant [34]. Although tyrosinase is the key regulatory enzyme of melanogenesis, tyrosinase-related protein (TRP)-1, dopachrome tautomerase (DCT/TRP2), and melanosomal matrix proteins (Pmel17, MART-1) carry out important roles in regulating melanogenesis [35]. The genes of tyrosinase, TRP-1, and DCT contain common transcription starting sites, the microphthalmia-associated transcription factor (MITF) binding sites. MITF plays a critical role in the transcriptional regulation of melanogenesis [36]. The intracellular signal transduction pathways of protein kinase C, cyclic AMP (cAMP), and nitrogen oxide are involved in the regulation of melanogenesis [34]. Various endogenous and exogenous factors, such as estrogen and ultraviolet (UV) radiation, affect melanogenesis via signal transduction pathways. These endogenous/exogenous factors exert their actions directly on melanocytes or indirectly via surrounding skin cells [36].

Melanocytes, keratinocytes, dermal fibroblasts, and other skin cells communicate with each other by factors that are secreted and cell–cell contacts [37]. It has been shown that the interactions between keratinocytes and melanocytes are critical in the regulation of melanogenesis [38]. Keratinocytes control melanocyte growth and activity through various soluble factors and cell adhesion molecules [39,40]. In addition, dermal factors have been found to be involved in the regulation of melanogenesis [41].

At the same time, stimulated melanocytes secret a number of signal molecules targeting not only keratinocytes but also skin immune cells [42,43]. Soluble factors released by melanocytes include proinflammatory cytokines and chemokines such as interleukin (IL)-1α/1β, IL-6, IL-8 IL-10, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, catecholamines, eicosanoids, serotonin, α-melanocyte stimulating factor (α-MSH), and nitric oxide (NO) [42,43].

A variety of hypopigmenting agents including hydroquinone, arbutin, tretinoin, kojic acid, azelaic acid, vitamin C, *N*-acetylglucosamine, niacinamide, linoleic acid, ellagic acid, methimazole, dioic acid, soy extract, licorice extract, rucinol, and glycolic acid have been used alone or in combination to treat abnormal hyperpigmentation [29,31]. These agents can interfere with the pigmentation process at several different steps of skin pigmentation. However, the treatment of hyperpigmented conditions still remains challenging and the results are often discouraging. Thus there is a need for novel skin-whitening agents that are highly effective and tolerable.

In this article, we review recent reports investigating the skin-whitening effect of ginseng and its components and the underlying mechanisms of action, and then discuss their potential as candidates for novel skin-whitening agents.

2. Effects of ginseng and its components on melanogenesis

P. ginseng is one of the most widely used medicinal plants in traditional oriental medicine. Over thousands of years, it has been used to improve the overall condition of skin, as well as to treat a wide variety of diseases. However, genuine scientific approaches to clarify the efficacy of ginseng in skin have only been made in recent years. Several reports have shown that ginseng extract, powder, or some other constituents could inhibit melanogenesis *in vitro* and *in vivo*. Table 1 summarizes the direct effects of ginseng and its components on skin color and key enzymes involved in melanogenesis. Song et al reported that red ginseng powder improved melasma in a human clinical trial [44]. They orally administered Korean Red Ginseng powder for 24 weeks to female patients with melasma. After 24 weeks, the melasma area and severity index score decreased and melasma quality of life scale showed improvement in 91% of patients. The mean level of pigmentation and erythema levels also decreased. In addition, 74% of the patients showed some improvement on the patient- and investigator-rated global improvement scales [44].

Most of reports investigating the antimelanogenic effect of ginseng were conducted *in vitro* used purified tyrosinase or melanocyte cell lines. In melan-a cells treated with ethanol extract of ginseng seeds, melanin content and tyrosinase activity was reduced [45]. In addition to the crude extract or powder, several studies tested the effects of specific constituents of ginseng. The phenol compounds inhibited tyrosinase activity while ginsenoside prevents UVB-induced intracellular increase of reactive oxygen species [46–48]. In some reports, ginsenosides alone exerted antimelanogenic effects. Aglycone of ginsenoside Rh4 inhibited melanin synthesis in B16 melanoma cells, possibly by involvement of protein kinase A pathway [49]. Ginsenoside Rh4 is one of the components isolated from Korean Red Ginseng [50]. It significantly