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

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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, 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, inhibition of transcription factors or signaling pathways involved in melanogenesis, decreasing production of inducers of melanogenesis, and enhancing production of antimelanogenic factor. Although there are still remaining 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.
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 secrete 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/IL-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. Glycoside 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

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**Table 1.** Direct effects of ginseng and its components on skin color and key enzymes involved in melanogenesis.

| Component | Effect on Skin Color | Effect on Key Enzymes |
|-----------|---------------------|-----------------------|
| Ginseng extract | Improvement | Inhibition |
| Ginseng powder | Improvement | Inhibition |
| Ginsenoside Rh4 | Inhibition | Inhibition |

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chemical changes of ginsenosides after the steaming process [23]. Steaming partially converts the original ginsenosides to deglycosylated 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 mal-ginsenosides 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 pigmented disorders: disorders of the qualitative and quantitative distribution of normal pigment and the abnormal presence of exogenous or endogenous pigments in the skin. The first group includes hyperpigmentation and hypopigmentation (leukoderma). 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 pharmacologically 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].
reduced melanin content and tyrosinase activity in α-MSH and forskolin-stimulated B16 melanoma cells. It reduced the cAMP level and cAMP response-element binding protein level in B16 melanoma cells, and this might be responsible for the downregulation of MITF and tyrosinase [49]. In addition, ginsenoside Rb1 inhibited melanogenesis through the inhibition of tyrosinase activity in α-MSH-stimulated B16 cells in a dose-dependent manner [51].

The antimalanogenic effect of ginseng does not arise from ginsenosides only. The crude methanol extract of the fresh leaves of *P. ginseng* showed inhibitory activity on mushroom tyrosinase, and p-coumaric acid was characterized as the principal tyrosinase inhibitor in the extract [47]. p-Coumaric acid inhibited melanogenesis in B16F10 melanoma cells stimulated by α-MSH, and was suggested to interfere with melanogenesis by its structural similarity with tyrosine [52]. Interestingly, p-coumaric acid showed weaker inhibition against mushroom tyrosinase but more strongly inhibited human or murine tyrosinase in comparison with kojic acid and arbutin [53]. Enzyme kinetics analysis indicates that p-coumaric acid is a mixed type (for tyrosine) or competitive inhibitor (for DOPA) of human tyrosinase. In addition, p-coumaric acid potently inhibits melanogenesis in human epidermal melanocytes exposed to UVB [53]. Cinnamic acid, one of the major components of *Cinnamomum cassia* Blume, is found in the root and seed of *P. ginseng* [54,55]. Cinnamic acid is reported to have inhibitory activity on mushroom tyrosinase [56,57]. Cinnamic acid significantly reduced melanin production, tyrosinase activity, and tyrosine expression in the melan-a cells [56]. In addition, cinnamic acid showed depigmenting activity on the UBV-tanned skin of brown guinea pigs [57].

It is already known that the pharmacological actions of these ginsenosides have been closely related to their biotransformation by human intestinal bacteria [28]. Although the contents of total ginsenosides in red ginseng and fermented red ginseng using *Lactobacillus brevis* were not significantly different, the ginsenoside metabolite content was higher in fermented red ginseng compared to red ginseng [58]. The tyrosinase inhibitory activity of fermented red ginseng extract was more potent compared with red ginseng extract in a test using mushroom tyrosinase [58].

### Table 1

Direct effects of ginseng and its components on melanogenesis in vivo and in vitro

| Reagent                        | Experimental model                        | Dose              | Effects on melanogenesis                                                                 | Ref. |
|--------------------------------|------------------------------------------|------------------|-----------------------------------------------------------------------------------------|------|
| Powder of KRG                  | Melasma lesion of female patients         | 3 g/d oral, 24 wk | MASI: decreased, MELASQoL: improved Patient- and investigator-rated global improvement scale: improved | [44] |
| Ethanol extract of ginseng seed | Melan-a cells cultured with phorbol-12 myristate 13-acetate | 100 ppm, 3 d     | Tyrosinase activity: decreased Melanin content: decreased                              | [45] |
| Extract of KRG and FKRG        | Mushroom tyrosinase                       | 50μM, 5 d        | Tyrosinase activity: decreased Melanin content: decreased                              | [49] |
| Aglycone of ginsenoside Rh4    | B16 cells stimulated by α-MSH             | 20–50μM, 5 d     | Tyrosinase activity: decreased Melanin content: decreased                              | [46] |
| p-Coumaric acid                | Mushroom tyrosinase                       | 125–500μM, 2 d  | Tyrosinase activity: decreased Melanin content: decreased                              | [51] |
| Ginsenoside Rb1                 | B16 cells stimulated by α-MSH             | 0.1% cream, topical, 8 wk | Luminosity values: increased                                                           | [75] |
| Ginsenoside F1                  | Human skin artificially tanned by UV irradiation |                 |                                                                                       |      |

α-MSH, α-melanocyte stimulating factor; FKRG, fermented Korean Red Ginseng; KRG, Korean Red Ginseng; MASI, melasma area and severity index; MELASQoL, melasma quality of life scale; MITF, microphthalmia-associated transcription factor

antimalanogenic activity via action on the several factors related in melanocyte physiology.

Among a large number of soluble factors produced from melanocytes, keratinocytes, fibroblasts, and immune cells in skin, adrenocorticotropic hormone (ACTH), α-MSH, endothelin-1, prostaglandin E2, prostaglandin F2α, NO, and histamine are well-known stimulators of melanogenesis [37,59–63]. By contrast, the effects of cytokines on melanogenesis are more complicated. IL-1α/β and granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate melanogenesis, while IL-6, TGF-β1, and TNF-α downregulate melanin production [36,64].

GM-CSF is produced and released from UV-irradiated keratinocytes [65]. GM-CSF has been reported to be involved in regulating the proliferation and differentiation of epidermal melanocytes [39,66]. Treatment of melan-a cells with conditioned media from UV-irradiated SP-1 keratinocytes increased melanocyte proliferation, and the proliferative effect of the conditioned media was blocked by anti-GM-CSF antibody treatment [66]. When UV-irradiated SP-1 keratinocytes were treated with red ginseng extract or saponin of red ginseng, the increased melanocyte proliferation by the conditioned media was blocked [67]. In that report, red ginseng extract or saponin of red ginseng treatment decreased the expression of GM-CSF induced by UV-B irradiation in SP-1 keratinocytes [67]. As mentioned above, inflammatory cytokines such as IL-1 and TNF-α take part in the regulation of melanogenesis. Ginseng extracts and ginsenosides have been reported to have anti-inflammatory activities in several different studies. Ginsenosides inhibit different inducer-activated signaling protein kinases and transcription factor nuclear factor (NF)-κB, and then decrease the production of proinflammatory cytokines and mediators of inflammation [68]. Korean Red Ginseng extracts decreased TNF-α and IL-8 production in lipopolysaccharide (LPS)-stimulated HaCaT keratinocytes and show radical scavenging and antioxidant activity in human dermal fibroblasts [69]. These findings suggest that ginseng extracts and ginsenosides might affect melanogenesis through their anti-inflammatory activities.

The effect of ginseng on NO production is still questionable. Several reports showed that ginseng reduces NO production [70–72]. Sun Ginseng, a new processed ginseng prepared by steaming at high temperature, reduced UV-B-induced cell damage and decreased NO production by inhibition of inducible NO synthase mRNA synthesis in HaCaT keratinocytes and human dermal fibroblasts [70]. Red ginseng marc oil inhibited inducible NO synthase and cyclooxygenase-2 via NF-κB and p38 pathways in LPS-stimulated RAW264.7 cells [71]. In addition, ginsenjilinol, a

3. **Effects of ginseng and its components on factors related to melanogenesis**

As reviewed above, crude extract or some components of ginseng and its components showed antimalanogenic activities by direct inhibition on key enzymes of melanogenesis, such as tyrosinase. Moreover, ginseng and its components could exert...
protopanaxatriol-type saponin obtained from the roots of *P. ginseng*, shows inhibitory activity on NO production in LPS-stimulated RAW264.7 cells [72]. By contrast, there are some controversial reports that ginseng extract enhanced NO production or NO signaling [73,74]. Hong et al reported that ginseng extract administration stimulated nongenomic endothelial NO synthase activation and enhanced NO production in spontaneously hypertensive rats [73]. In another report, water extract of Korean Red Ginseng exerted vasoprotective effects through augmentation of NO production by inhibiting arginase [74]. Therefore, the effect of ginseng on melanogenesis via NO signaling remains to be clarified by further study.

Human skin tissue does not consist only of melanocytes, keratinocytes, and fibroblasts. Considerable numbers of immune cells including Langerhans cells, macrophages, mast cells, and T cells are working actively in skin tissue. Because the immunostimulatory activities of many ginsenosides are known, it is not surprising that ginsenosides could enhance the reactivity of skin immune cells. In a recent paper, a cream containing 0.1% ginsenoside F1 (a metabolite of ginsenoside Rg1) showed a significant whitening effect on artificially tanned human skin [75]. However, ginsenoside F1 did not directly inhibit mRNA expression of tyrosinase or DCT in normal human epidermal melanocytes. Instead, ginsenoside F1 enhanced production of IL-13 from human epidermal γδ T cells, and IL-13 significantly reduced the mRNA expression and protein amount of both tyrosinase and DCT resulting in visible brightening of normal human epidermal melanocyte pellets [75]. These results suggest that ginsenosides might be able to regulate melanogenesis via their effect on skin immune cells.

**4. Conclusion**

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 the antimelanogenic effect of ginseng or its components included the direct inhibition of key enzymes of melanogenesis (tyrosinase and DCT), inhibition of transcription factors (MITF, NF-κB) or signaling pathways (protein kinase A pathway and protein kinase C pathway) involved in melanogenesis, decreasing the production of inducers of melanogenesis (cAMP, GM-CSF), and enhancing production of antimelanogenic factor (IL-13). Fig. 1 summarizes the effects of ginseng and its components on melanogenesis. Although issues surrounding the antimelanogenic activity of ginseng still remain controversial, especially in its effect on the production of proinflammatory cytokines and NO, these recent findings suggest that ginseng and its constituents might be potential candidates for novel skin-whitening agents.

**Conflicts of interest**

The author declares no conflicts of interest.

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