J Ginseng Res 45 (2021) 363–370

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: https://www.sciencedirect.com/journal/journal-of-ginseng-research/

Review Article

The regulatory role of Korean ginseng in skin cells

Long You [1], Jae Youl Cho [1,2,*]

[1] Department of Integrative Biotechnology, and Biomedical Institute for Convergence at SKKU (BICS), Sungkyunkwan University, Suwon, Republic of Korea
[2] Department of Biocosmetics, Sungkyunkwan University, Suwon, Republic of Korea

ARTICLE INFO

Article history:
Received 15 June 2020
Received in Revised form
16 August 2020
Accepted 26 August 2020
Available online 1 September 2020

Keywords:
Korean ginseng
Skin health
Keratinocytes
Melanocytes
Fibroblasts

ABSTRACT

As the largest organ in our body, the skin acts as a barrier against external stress and damages. There are various cell types of skin, such as keratinocytes, melanocytes, fibroblasts, and skin stem cells. Korean ginseng, which is one of the biggest distributions of ginseng worldwide, is processed into different products, such as functional food, cosmetics, and medical supplies. This review aims to introduce the functional role of Korean ginseng on different dermal cell types, including the impact of Korean ginseng in anti-photodamaging, anti-inflammatory, anti-oxidative, anti-melanogenic, and wound healing activities, etc. We propose that this information could form the basis of future research of ginseng-derived components in skin health.

1. Introduction

Skin, the organ that we are most familiar with in daily life, is also one of the most complex and largest organs in the body. It comprises at least three main layers: the epidermis, the dermis, and the subcutis [1]. The epidermis is the outermost layer of the skin. It has several small layers and mainly acts as a barrier to prevent damage from substances in the environment. The dermis is a middle layer that contains numerous nerve cells, which enables the ability to feel. The dermis also contains various immune cells. The deepest layer of the skin is subcutis, which is between the skeletal and dermis layers and connects the muscles and bone (see Fig. 1 and Fig. 2).

As the largest organ in the body, the skin has some very distinct functions. First of all, the primary function of the skin is protection [2]. It acts as a robust barrier in defense of injury and infection from adversity in the surrounding environment, such as chemicals, micro-organisms, pressure, radiation, etc. Secondly, the skin has a role in regulation. It is pivotal in adjusting the body temperature via sweat and the production of vitamins. The third functional role of the skin is in sensation. It is well known that nerve cells derived from the skin make up a big extensive network. They have many unique receptors for hot, cold, aches, and so on. These receptors can detect and react against the environment. If nerves are damaged, sensation will be lost in the affected areas, a condition known as neuropathy. Hence, although some skin diseases are not life-threatening in the short-term, they may cause long-term disabilities.

The skin is made up of several different kinds of subsets, which includes keratinocytes, melanocytes, fibroblasts, skin stem cells, and so forth. Keratinocytes account for a high percentage in the epidermis, which constitute around 95% of the outermost layer. Their primary role is to form a barrier against environmental damage from such as UV irradiation, bacteria, and water loss. Melanocytes are located in the bottom layer of the epidermis in most cases. However, as melanin-producing cells, they only comprise around 5-10% of all skin cells in the human body [3]. Because the dominant factor in evaluating skin color is melanin [4], melanocytes have an important role in deciding human skin color and regulating abnormal changes in daily life. The fibroblasts lay on the dermis, which grow under the epidermal layer. The responsibility of fibroblasts is to generate joint tissue, which helps the human skin to recover from normal wounds [5]. In addition, the constant regeneration of the skin itself during a whole lifetime is due to epidermal stem cells, which exist as various types and help the skin to replenish corresponding cell types in repair of wounds and homeostasis [6].

* Corresponding author. Department of Integrative Biotechnology, Sungkyunkwan University, Suwon, Republic of Korea.
E-mail address: jaecho@skku.edu (J.Y. Cho).

https://doi.org/10.1016/j.jgr.2020.08.004
p1226-8453 e2093-4947/$ – see front matter

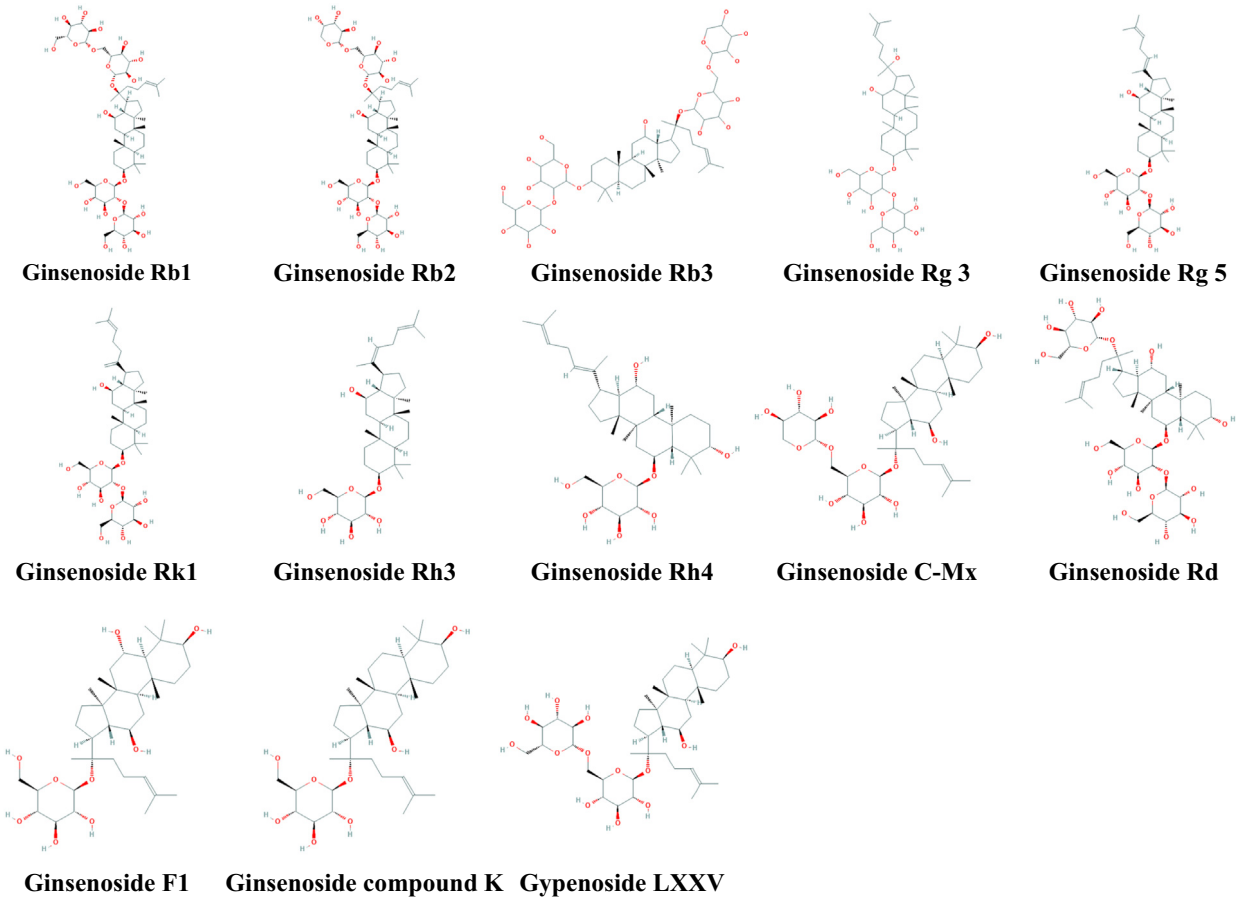

Fig. 1. The structures of ginseng-derived components.

Ginseng, which is a valuable folk medicinal herb, has been used in eastern countries for more than 5,000 years [7]. In fact, ginseng is the root of a plant genus called *Panax*, which means 'treat all' in Greek. Ginseng can be divided into 3 types according to the date from cultivation to harvest: at less than 4 years, ginseng is known as fresh ginseng because it will be consumed in a fresh state; between 4 to 6 years, ginseng is dried directly after peeling and called white ginseng; and if ginseng that has been grown for more than 6 years, it is produced by steaming at a temperature of around 100°C for 2 to 3 hours. Then it is dried until the moisture content less than 15%. After that, this kind of ginseng is called red ginseng [8]. In this article, we will only discuss the Korean ginseng that grows and is produced in Korea and known as Korean ginseng.

Korean ginseng, *Panax ginseng* Meyer, has been studied in several situations in the field of skin health for many years (Table 1). Among these various studies, some functions, such as anti-photoaging, antiwrinkle, and anti-melanogenic, have attracted a great deal of attention. One metabolite of *Panax ginseng* has been reported to inhibit the production of VEGF and TNF-α which is induced by UVB through the NFAT signaling pathway [9] and could have a potential role in protecting skin from UVB-induced photodamage. Ginsenoside Rg3 (S) (Rg3), which is found at a high concentration in red ginseng, also shows significant protection against ultraviolet- (UV) or infrared (IR)-induced skin photoaging [10]. Another study suggests that a mixture of *P. ginseng* and *C. pinnatifida* (GC) has the role of anti-aging by suppressing wrinkle formation and enhancing the moisture in human skin [11].

In this article, we will review several reports that associated with how Korean ginseng works on different kinds of skin cell subsets and regulatory methods. Then, we will discuss the potential application of Korean ginseng.

2. Main body

2.1. The role of Korean ginseng in skin keratinocytes

Keratinocytes comprise over 95% of the cell mass of human epidermis [12,13], which take part in the various stages of differentiation in the epidermis [13]. They are organized into basal, spinous, granular, and cornified layers that correspond to specific stages of differentiation [14,15]. To maintain a mechanical barrier to the outside world, the primary function of keratinocytes is to provide the structural integrity of the epidermis, which establishes the first line of defense against pathogens in the skin [16,17]. Several extracts and metabolites have been isolated from Korean ginseng to study its function. We found some papers that related to the effects of Korean ginseng on keratinocytes and found that these studies mainly focused on the cell death, skin inflammation and oxidative stress.

First, the function of Korean ginseng on cell death will to be discussed. Some papers have reported that the extract from Korean Red Ginseng (KRG), which is made by steaming and drying fresh ginseng, can reduce the expression level of p53 and "growth arrest and DNA damage 45 (GADD45)" induced by peroxynitrite ($ONOO^-$) in HaCaT cells. $ONOO^-$ is a powerful biological oxidant, which can cause DNA damage. KRG can protect cells from $ONOO^-$-induced genotoxicity and repair the DNA damage by increasing cell viability and modulating p53 signaling [18]. KRG

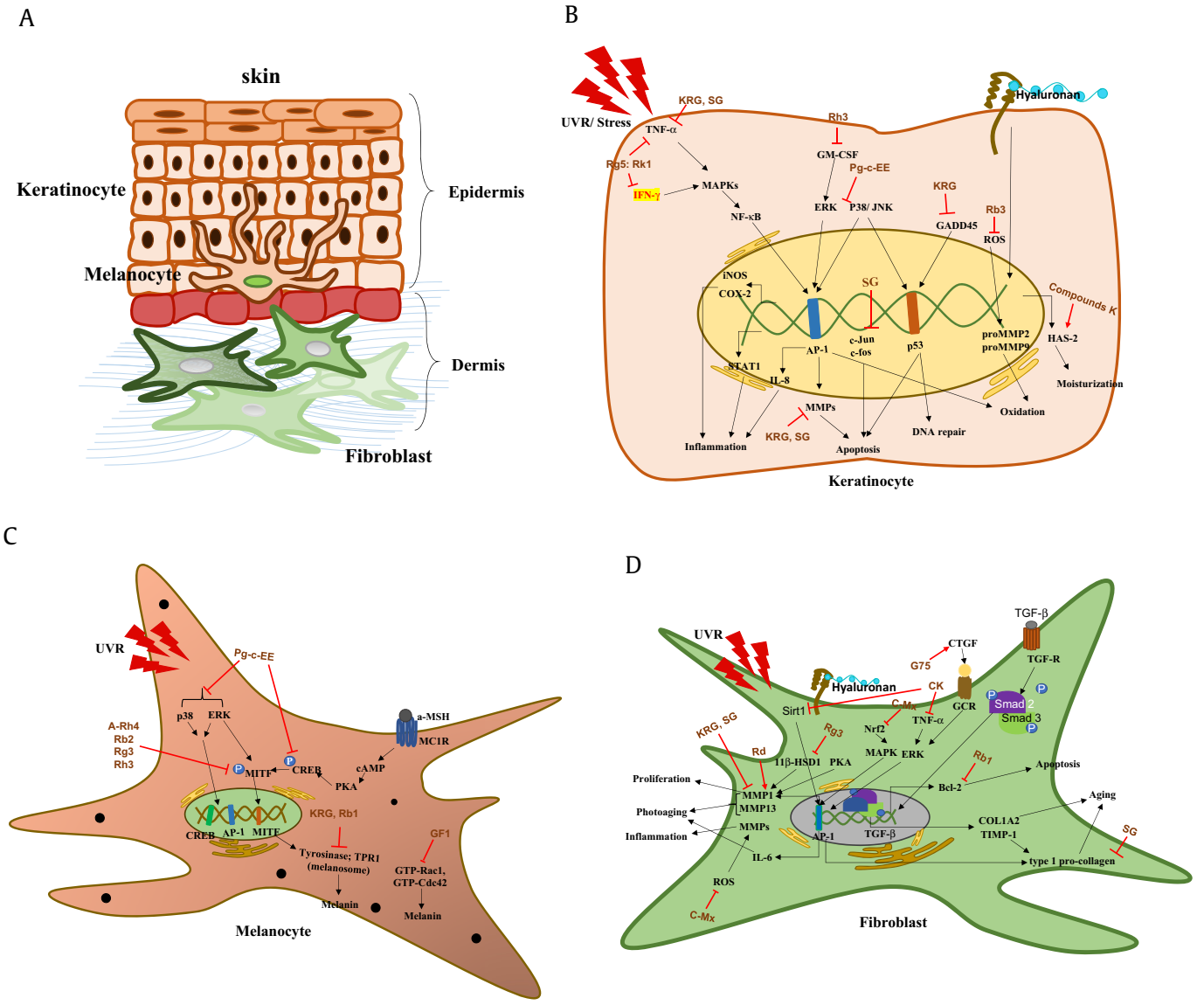

Fig. 2. The role of Korean ginseng in skin keratinocytes, melanocytes and fibroblasts. A. Schematic structure of skin. B, C and D. Functional role of ginseng-derived components in B. keratinocytes, C. melanocytes, and D. fibroblasts.

can also be used to improve the side effects of radiation therapy. Some papers have demonstrated that mucositis is caused by radiation therapy [19]. The reasons that radiation can lead to mucositis are based on loss of epithelial cell renewal, apoptosis, and reactive oxygen species (ROS)-induced ulcer formation [20–22]. Because of this, KRG was used to study the protective effect on irradiated normal human keratinocytes. KRG inhibits HaCaT cells apoptosis and intracellular ROS, which is induced by radiation. Moreover, KRG stabilizes changes in mitochondrial membrane potential (MMP) and reverses the expression of ataxia telangiectasia mutated protein (ATM)-p53 and the c-Jun N-terminal kinase (JNK)-p38 pathway which is significantly increased by irradiation [23]. Another newly processed ginseng, sun ginseng (SG) [24], shows good effects on anti-UVB irradiation. Studies have found that SG has a protective role against UVB-induced cell damage in keratinocytes. It can repair the expression of the anti-apoptotic gene (bcl-2 and bcl-xL) suppressed by UVB in epidermal keratinocyte cells, which has an anti-apoptotic effect in strong UVB irradiation. Whereas, SG also inhibits c-Jun and c-Fos gene expression in a keratinocyte cell line, which was thought to be a potential agent against UVB cell damage [25].

In addition, the effects of Korean ginseng on skin inflammation have been studied. If keratinocytes are stimulated by lipopolysaccharide (LPS), inflammation will be induced, which causes chronic atopic dermatitis (AD). Although acute AD is mainly caused by T helper 2 type (Th2) reaction, chronic phase of AD is a mixed response between Th1 and Th2 reaction [26–28]. Because of this inflammatory response, the expression of tumor necrosis factor-alpha (TNF-α) increases. Guistizieri et al found that TNF-α is the most powerful inducer of interleukin (IL)-8 [29], which leads to a remarkable increase in IL-8. Interestingly, after treating with KRG extracts, LPS-stimulated TNF-α in human keratinocytes is suppressed significantly. Its inhibition also leads to a decrease in IL-8. This finding reveals that KRG extract might be a useful immunosuppressive agent in the treatment of chronic AD [30]. AD is a skin inflammation disease that affects millions of people worldwide. Park et al applied KRG water extract into a 1-chloro-2,4- dinitrobenzene (DNCB)-induced BALB/c mouse model, which has AD-like

Table 1
Pharmacological activities of ginseng-derived components in biological responses of skin cells

Component	Skin Cell Type	Cellular Response	Molecular Target	Mediated Signaling	Reference
KRG	Keratinocytes	DNA damage	GADD45	p53	[18]
		Apoptosis	MMP	ATM/p53, JNK/p38	[23]
		Inflammation	TNF-α, IL-8	MAPKs	[29]
SG		Apoptosis	c-Jun, c-Fos	bxl-2, bcl-XL, AP-1	[25]
		Inflammation	TNF-α, IL-6, and IFN-γ	iNOS, COX-2	
		Aging	MMP-1	Procollagen	[69]
Pg-c-EE		Oxidation	p38, ERK, JNK	AP-1	[50]
Ginsenoside Rg 5: Rk1		Inflammation	TNF-α, IFN-γ	TARC/CCL17	[33]
				NF-κB/p38 MAPK/STAT1	
Ginsenoside Rh3		Inflammation	GM-CSF	ERK	[34]
Ginsenoside Rb3		Oxidation	ROS, proMMP-2, proMMP-9	GSH, SOD	[39]
Compound K		Moisture stress	HAS-2	HA-binding Protein	[40]
KRG	Melanocytes	Melanogenesis	Tyrosinase	Melanin	[47]
Pg-c-EE			AP-1, CREB	p38, ERKs, CREB	[33]
Ginsenoside A-Rh4			MITF	cAMP, PAK	[53]
Ginsenoside Rb1			Tyrosinase	Melanin	[55]
Ginsenoside Rb2			MITF	cAMP	[54]
Ginsenoside Rg3			MITF	ERK, TRP1	[56]
Ginsenoside Rh3			bFGF, MITF	ERK	[61]
Ginsenoside F1			GTP-Rac1, GTP-Cdc42	Rho-family GTPase	[57]
KRG	Fibroblasts	Photoaging	MMP1, MMP13	MAPK/AP-1, NF-kB	[64]
		Aging	COL1A2 promoter, Smad2	COL1A2, type 1 collagen	[70]
SG		Aging	MMP1	TIMP-1, type 1 collagen	[50]
Ginsenoside Rb1		Apoptosis	Bcl-2	-	[63]
Ginsenoside Rd		Proliferation	MMP1	PKA	[71]
Ginsenoside Rg3		Photoaging	11b-HSD1, MMP1, IL-6	-	[10]
Gypenoside LXXV (G75)		Wound healing	CTGF	Glucocorticoid receptor	[73]
Compound K		Aging	MMP1, MMP2	type 1 pro-collagen, sirtuin 1, AP-1	[66]
		Inflammation	MMP1, TNF-α	ERK/AP-1	[68]
Ginsenoside C-Mx		Inflammation	ROS, MMP, IL-6	NF-κB	[67]
			Nrf2	MAPK/AP-1	

lesions [31]. They found that KRG water extract can significantly improve skin conditions, and can also suppress the expression of inflammatory regulators, chemokines, and cytokines by mitogen-activated protein kinase (MAPK) signaling pathways. Oh et al reported that Ginsenoside Re can improve skin barrier function by increasing filaggrin protein and caspase-14 level, which enhanced the cornified cell envelope formation in HaCaT cells [32]. Rg5:Rk1, which is derived from *P. ginseng*, significantly reduces TNF-α/IFN-γ-induced thymus and activation-regulated chemokines (TARC/CCL17) and has potential anti-AD effects through inhibiting NF-κB/p38 MAPK/STAT1 signaling pathway [33]. Not only does KRG work on human keratinocytes but also affect murine SP-1 keratinocytes, which originate from SENCAR mice. The saponin of KRG (SKRG) can inhibit granulocyte macrophage colony-stimulating factor (GM-CSF), which is a proinflammatory cytokine increased by UVB-irradiation. SKRG treatment suppresses UVB-induced phosphorylation of epidermal growth factor receptor (EGFR), then also decreases extracellular signal-regulated kinase (ERK). After testing 15 different ginsenosides, ginsenoside Rh3 was confirmed to be the active saponin that inhibits the expression of GM-CSF [34]. Although ginsenoside Rh3 did not affect the cell viability of SP-1 keratinocytes, it can block GM-CSF production that is induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). In addition, ginsenoside Rh3 can inhibit TPA-induced protein kinase Cδ (PKCδ) and ERK phosphorylation in SP-1 keratinocytes [35]. Lastly, UVB can quickly induce epidermal keratinocytes to generate superoxide radicals, which can convert to other ROS species [36]. UVB-induced ROS production results in the up-regulation of MMP-1 and degradation of collagen. Thus, down-regulation of ROS generation is crucial for preventing skin photoaging [37,38]. Although ginsenoside Rb3, which is a protopanaxadiol-type ginsenoside, cannot affect cell viabilities on HaCaT keratinocytes under UVB irradiation, it can suppress the enhancement of ROS, pro-matrix metalloproteinase-2 (proMMP-2) and pro-matrix metalloproteinase-9 (proMMP-9), which were induced by UVB, and also improve total glutathione (GSH) and superoxide dismutase (SOD) levels which were inhibited by UVB. Ginsenoside Rb3 acts as a potential anti-oxidative agent in human HaCaT keratinocytes subjected to photodamage [39]. As one of the major metabolites of ginsenosides, compound K was estimated by researchers through cDNA microarray analysis. After screening more than 100 transcripts, they found that compound K can enhance the expression of hyaluronan synthase (HAS) 2. Moreover, compound K upregulates the hyaluronan (HA) synthesis by increasing the HAS2 gene *in vitro*. In addition, the aged hairless mouse skin was treated bycompound K. The results demonstrated that compound K can increase the amount of HA content and the thickness of the epidermis. The epidermal thickening may be due to the water accumulation that results from the amassing of HA induced by compound K [40]. This finding indicated that compound K might prevent or improve the deteriorations, such as xerosis, caused by the age-dependent decrease of the HA content in human skin.

2.2. The role of Korean ginseng in skin melanocytes

Skin melanocytes also reside in the basal layer of the epidermis, the same location as keratinocytes. The ratio between melanocytes and keratinocytes is around 1:10 in the epidermal basal layer [41]. The main function of melanocytes is to produce melanin and melanosomes [42], which are related to skin color and skin cell photoprotection. Melanosomes are the cytoplasmic organelles in melanocytes and provide a place for melanogenesis, which is a pathway for synthesizing melanin [43]. Two kinds of melanin can be produced by melanogenesis: pheomelanin and eumelanin. They show the opposite function and a different way of synthesis. Pheomelanin is reddish yellow, which exhibits phototoxic pro-

oxidant property, whereas eumelanin is brownish black that has photoprotective anti-oxidant characteristic [44,45]. However, if the synthesis function becomes disordered, skin color will be abnormal. These two abnormal changes in the skin are hyperpigmentation and hypopigmentation. In hyperpigmentation, skin color is darker than normal because of excess production of melanin [45], and in hypopigmentation, some patches of skin are lighter than others. Both of these are serious skin conditions that affects thousands of people worldwide [46]. For these two kinds of abnormal pigmentation, especially unusual hyperpigmentation is a major issue to be concerned. Korean ginseng has been used as a traditional medicine in treating various diseases, for instance, in immune modulation, antioxidation and anti-tumorigenesis. Therefore, researchers wanted to study whether the extract or some constituents of Korean ginseng could inhibit melanogenesis. In fact, antimelanogenic properties have already been discovered in Korean ginseng.

Kong et al reported that cinnamic acid, which is mainly found in Korean ginseng, can inhibit tyrosinase, that is a pivotal enzyme in the melanogenesis pathway, in Melan-a cells. Because of the potent inhibition of tyrosinase, melanin synthesis is also suppressed. In addition, a hyperpigmentation model was established in brown guinea pig skin by UVB-irradiation. Cinnamic acid was found to remove melanin synthesis remarkably and exhibit good depigmenting activity, which has obvious skin whitening effects [47]. Song et al. found that female patients with melasma who received oral administration of KRG powder, a mixture of ginsenoside and phenolic compounds, for 24 weeks, the area of melasma and severity index was significantly relieved. Moreover, KRG powder exhibited good tolerability in oral administration for most of the patients [48]. Jiang et al reported that the ethyl acetate extract from *P. ginseng*, which contains polyphenolic compounds as the main components, could relieve hyperpigmentation effects by reducing oxidative stress [49]. The ethanol extract of *P. ginseng* berry calyx (Pg-C-EE) can block activator protein 1 (AP1) and cyclic adenosine monophosphate response element-binding (CREB) protein to prevent melanogenesis [50]. KRG extract (KRGE) was applied *in vitro* and *in vivo* to certify that it can relieve melanogenesis by potently suppressing tyrosinase activity and melanin production [51].

Oh et al discovered that UV-irradiation can induce GM-CSF production in SP-1 keratinocytes. GM-CSF can significantly increase the proliferation of melan-a melanocytes. KRGE and SKRG can decrease the expression of GM-CSF and then block the proliferation of melan-a melanocytes, which has a potential role in regulating UV-induced melanocyte proliferation [52]. Jeong et al first reported that ginsenoside compound aglycone of Ph4 (A-Rh4) can directly suppress melanin synthesis in B16 melanoma cells. A-Rh4 can significantly reduce cyclic AMP (cAMP) in B16 melanoma cells by down-regulating microphthalmia-associated transcription factor (MITF) and tyrosinase, which has a potential antimelanogenic effect through the protein kinase A (PKA) pathway [53]. Other studies, including Lee et al, report that ginsenoside Rb2 can reduce melanogenesis in melan-a cells by down-regulating MITF and tyrosinase expression *in vitro*. Furthermore, Rb2 can prevent the inhibition of body pigmentation in a zebrafish model *in vivo* through suppressing tyrosinase activity [54]. Later, Wang et al found ginsenoside Rb1 can significantly inhibit the melanogenesis-stimulating effects of α-melanocyte-stimulating hormone (α-MSH) in B16 melanoma cells. Moreover, ginsenoside Rb1 downregulates tyrosinase activity in B16 melanoma cells in a dose-dependent manner. Both of the results exhibit that ginsenoside Rb1 can suppress melanogenesis in B16 cells via decreasing tyrosinase activity [55]. Interestingly, ginsenoside Rg3 was simultaneously found to have a melanin inhibitory role in both normal human epidermal melanocytes and B16F10 cells [56]. Ginsenoside Rg3 suppresses the melanin biosynthesis resulting from the inhibition of the crucial melanogenesis enzyme, tyrosinase, without affecting cell viability. Moreover, ginsenoside Rg3 potently repressed the expression of tyrosinase-related protein 1 (TRP1) and down-regulated the tyrosinase transcription factor MITF. In addition, ginsenoside Rg3 can enhance the protein level of ERK signaling in a dose-dependent manner. To identify whether ginsenoside Rg3 can suppress melanogenesis through activating ERK pathway, PD98059, which is a specific inhibitor of ERK, was used to treat the B16F10 cells that were stimulated by α-MSH and co-treated with ginsenoside Rg3. Surprisingly, PD98059 attenuated the antimelanogenic effect induced by ginsenoside Rg3 and significantly recovered the tyrosinase activity and melanin content, which suggested that the activation of ERK induced by ginsenoside Rg3 can lead to the reduction of melanin synthesis through restraining MITF and its downstream expression of tyrosinase and TRP1 [56].

Another metabolite of Korean ginseng known as ginsenoside F1, which is a hydrolyzation product of ginsenoside Re and ginsenoside Rg1, showed a more interesting mechanism, although it can decrease the melanin secretion induced by α-MSH in B16F10 melanoma cell culture media, it does not affect cell viability or inhibit intracellular expression levels of melanin and tyrosinase activity [57]. Surprisingly, ginsenoside F1 can change cellular morphology, which includes enlarging cell bodies, and retract dendrites in B16F10 cells. Because of this, pigment granules accumulate in melanocyte cell bodies and the melanosome transfer is remarkably affected, which causes visible pigmentation to reduce significantly. Moreover, dendrite retraction results from the notable weakening of forskolin-induced GTP-Rac1, GTP-Cdc42 and the suppression of the Rho family GTPase by ginsenoside F1 [57]. In other studies, keratinocytes irradiated by UVB can secrete some paracrine factors to indirectly stimulate the proliferation of human melanocytes [58]. Among a variety of factors, basic fibroblast growth factor (bFGF) which is one of the paracrine factors secreted by UVB-exposed keratinocytes, plays an essential role in increasing the proliferation of epidermal melanocytes [59,60]. Lee et al found that bFGF enhances the proliferation of murine melan-a melanocyte by activating ERK. They tested the effects of several ginsenosides and discovered that Rh3 can inhibit ERK phosphorylation, which is induced by bFGF. Moreover, ginsenoside F1 can slightly postpone the maximum phosphorylation of ERK induced by bFGF. However, if they treat Rh3 and ginsenoside F1 simultaneously, the phosphorylation of ERK can be significantly suppressed. Moreover, the combined treatment of Rh3 and ginsenoside F1 can suppress the protein level of MITF induced by bFGF in melan-a cells, that exhibits the antiproliferation effect on bFGF-induced melan-a melanocyte proliferation [61].

2.3. The role of Korean ginseng in skin fibroblasts

Skin fibroblasts are located on the dermis, the inner layer of the skin. They cover the underlying soft tissues and maintain the integrity of connective tissues. A large number of studies have investigated the relationship between Korean ginseng and human dermal fibroblasts. Some functions of dermal fibroblasts are similar to those of skin keratinocytes. The total saponins and ginsenoside Rb1 of KRG have been used both *in vitro* and *in vivo* to assess antiphotoaging effects. They can significantly reduce thickness and wrinkle formation and recover skin elasticity under UVB-irradiation. Total saponins and ginsenoside Rb1 can also rescue the breakage of collagen fibers [62].

Signaling pathways that may associate Korean ginseng with the prevention of UVB photodamage have been discovered. Hwang et al reported that Korean mountain cultivated ginseng that was

extracted by ethanol can inhibit the production of MMP1 and MMP13 which were induced by UVB through activating MAPK/AP-1 and NF-κB signaling pathways [63]. BIOGF1K is an extracted fraction which is rich in compound K [64]. It can prevent fibroblast cells from UVB photodamage through relieving apoptosis. In addition, BIOGF1K reduces the expression of MMP-1 and 2 and remarkably improves the mRNA levels of type 1 procollagen sirtuin 1. BIOGF1K also down-regulates the AP-1 pathway for anti-photoaging activity [65]. Ginsenoside C-Mx relieves UVB-induced skin damage by NF-κB pathways as well [66].

In addition, how the inflammation response induced by UV irradiation in human dermal fibroblasts is an attractive question that is not fully understood. It was reported that compound K can inhibit MMP-1 expression induced by TNF-α via suppressing the ERK/AP-1 pathway but not p38 and the JNK pathway. Compound K down-regulates the phosphorylation of c-Src and epidermal growth factor receptor (EGFR), which are the upstream pathways of ERK to against inflammation. Through this signaling pathway, compound K reduces the degradation of collagen in human dermal fibroblasts [67].

Previously, Lee et al found that SG has a protective role of cell damage from UVB irradiation on keratinocytes. SG also has the same function on human dermal fibroblasts to prevent UVB damage by reducing the mRNA levels of c-Jun and c-Fos. At the same time, SG decreases the production of inflammatory cytokines and recovers the expression of procollagen, which is stimulated and suppressed by UVB in dermal fibroblasts [25]. Moreover, further studies about the anti-aging effects of SG have been published. Song proved that SG can inhibit MMP-1 expression, and dose-dependently enhance the tissue inhibitors of MMP (TIMP)-1. Both the inhibition of MMP-1 and increasing TIMP-1 can significantly increase the production of type I collagen, which shows good anti-aging properties [68]. Other researchers have reported that *P. ginseng* root extract (PGRE) activates the human a2(I) collagen (COL1A2) promoter to enhance the transcription of COL1A2. Through increasing COL1A2, PGRE can increase the production of human collagen. In addition, they also found that PGRE can induce the phosphorylation of Smad2 and then increase the synthesis of type I collagen, which has anti-aging effects [69].

Besides anti-photodamage and anti-aging effects, Korean ginseng also has a good impact on skin regeneration. Kim et al. reported that the ginsenoside Rd can remarkably enhance the proliferation and migration of human dermal fibroblasts. It is also involved in the PKA signaling pathway to reduce MMP-1 and induce type I collagen. Animal wound models were used to prove that ginsenoside Rd has a potent effect on wound healing, which could be a natural medicine in skin regeneration [70]. Another paper by Lee et al confirmed that Korean ginseng can accelerate the proliferation and collagen synthesis of human dermal fibroblasts in wound healing [71]Gypenoside LXXV (G75) was applied *in vivo* to test cutaneous wound healing in fibroblasts. G75 can potently up-regulate the production of connective tissue growth factor through the glucocorticoid receptor pathway [72]. Enzyme-modified ginseng extract and its major compound ginsenoside F2 have a similar mechanism in treating UVB-induced skin damage [68]. Besides UV irradiation, infrared irradiation is also a natural stressor for skin aging and leads to cortisol accumulation. Cortisol is a mammalian stress hormone that is activated by the enzyme 11 beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Therefore, finding an 11β-HSD1 inhibitor is a good way to prevent aging. The KREG that contains ginsenoside Rg3 can inhibit 11β-HSD1 in both human dermal fibroblasts and a normal human 3D skin model and then exhibits good antiphotoaging effects in UV- or IR-exposure [10].

The promotion of skin hydration was studied in human dermal fibroblasts treated with a gintonin-enriched fraction (GEF), which is a novel component of Korean ginseng. Gintonin is also a ligand of G protein-coupled lysophosphatidic acid (LPA) receptors. LPA has been studied in stimulating the proliferation and migration of fibroblasts. GEF together with the LPA receptor activate transient induction of $[Ca^{2+}]_i$ via Ca^{2+} signaling and promote the release of HA, which exhibit beneficial properties in skin protection [73].

2.4. The role of Korean ginseng in skin stem cells

Because the skin is the first barrier against a variety of external stresses and damages, repair and recovery are critical for skin cells. Among different skin cells, skin stem cells are important for cell self-renewal and replenishment. However, there are not many research papers related to the application of skin stem cells. Dermal papilla cells (DPCs) are the mesenchymal cells in the skin. Moreover, they are also thought to be a multipotent stem cell [74]. Park et al reported that fructus *P. ginseng* (FPG) extract can significantly stimulate the proliferation of DPCs through up-regulating the expression of Bcl-2 and down-regulating Bax, which shows an anti-apoptotic effect. In addition, FPG extracts also extend the anagen phase during the hair cycle *in vivo* which is useful for hair regeneration and hair loss [75].

3. Discussion

The history of ginseng can be traced back 4000 years ago. Korea, China, Canada, and the USA account for more than 99% of total ginseng production in the world. Among the world ginseng market, which includes ginseng root and processed products, Korea is the largest distributor in the world [76]. Ginseng distribution has numerous forms, for example, fresh ginseng, dried ginseng, boiled and dried ginseng (Taekuksam), red ginseng and related products. In these processed forms, red ginseng is the most attractive product and accounts for approximately 59% of the Korean ginseng market. Red ginseng is processed into functional food, cosmetics and medical supplies, etc.

In this review, we discussed the function of Korean ginseng in different kinds of dermal cell subsets: keratinocytes, melanocytes, fibroblasts and skin stem cells. In skin keratinocytes, Korean ginseng plays a role in anti-photodamaging, anti-inflammation and antioxidation. Korean ginseng can repair DNA damage and increase cell viability [18,23–25]. In addition, Korean ginseng significantly suppresses LPS-stimulated TNF-α in human keratinocytes and inhibited the expression of inflammatory regulators, chemokines and cytokines to treat atopic dermatitis [29–31]. Moreover, Korean ginseng removed MMP expression and increased collagen synthesis under oxidative stress [37–40]. In skin melanocytes, Korean ginseng mainly relieves hyperpigmentation of the skin by suppressing MITF and its downstream protein tyrosinase [53,55,56]. It can whiten skin and reduce melanin production [47,51]. In addition, Korean ginseng also can block melanocyte proliferation, which is induced by UV irradiation [52,55]. In addition, Korean ginseng has similar functions between dermal fibroblasts and skin keratinocytes. It can reduce photodamage [64,67], rescue the expression of collagen [63,68,70], regenerate skin [69,70] and is associated with wound healing [68,73]. Even though several studies have investigated the function of Korean ginseng on the skin, still very little is known about Korean ginseng. The mechanisms related to how Korean ginseng really works on several skin cell types are unknown. Because of this, we need to study the mechanisms related to Korean ginseng in depth.

Data availability statement

Datasets related to this article can be found at https://www.ncbi.nlm.nih.gov/pubmed, hosted at the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM).

Conflicts of interest

The authors declare that no conflicts of interest exist.

Acknowledgments

This research was funded by the Basic Science Research Program through the National Research Foundation of Korea (NRF), the Ministry of Science and ICT, Republic of Korea (2017R1A6A1A03015642).

References

[1] Gould J. Superpowered skin. Nature 2018;563:S84–5.
[2] Gravitz L. Skin. Nature 2018;563:S83.
[3] Hoerter JD, Bradley P, Casillas A, Chambers D, Denholm C, Johnson K, Weiswasser B. Extrafollicular dermal melanocyte stem cells and melanoma. Stem Cells Int 2012;2012:407079.
[4] Ortonne JP. Normal and abnormal skin color. Ann Dermatol Venereol 2012;139:S125–9.
[5] Nilforoushzadeh MA, Ashtiani HRA, Jaffary F, Jahangiri F, Nikkhah N, Mahmoudbeyk M, Fard M, Ansari Z, Zare S. Dermal fibroblast cells: biology and function in skin regeneration. J Ski Stem Cell 2017;4.
[6] Blanpain C, Fuchs E. Epidermal stem cells of the skin. Annu Rev Cell Dev Biol 2006;22:339–73.
[7] Yun TK. Brief introduction of panax ginseng CA meyer. J Korean Med Sci 2001;16:S3.
[8] Kim K. Effect of ginseng and ginsenosides on melanogenesis and their mechanism of action. J Ginseng Res 2015;39:1–6.
[9] Liu X, Xiao Y, Hwang E, Haeng JJ, Yi T. Antiphotoaging and antimelanogenesis properties of ginsenoside C-Y, a ginsenoside Rb2 metabolite from American ginseng PDD-ginsenoside. Photochem Photobiol 2019;95:1412–23.
[10] Nam J, Min J, Son M, Oh J, Kang S. Ultraviolet-and infrared-induced 11 beta-hydroxysteroid dehydrogenase type 1 activating skin photoaging is inhibited by red ginseng extract containing high concentration of ginsenoside Rg3 (S). Photodermatol Photoimmunol Photomed 2017;33:311–20.
[11] Hwang E, Park S-Y, Yin CS, Kim H-T, Kim YM, Yi TH. Antiaging effects of the mixture of Panax ginseng and Crataegus pinnatifida in human dermal fibroblasts and healthy human skin. J Ginseng Res 2017;41:69–77.
[12] Barker JNWN, Griffiths CEM, Nickoloff BJ, Mitra RS, Dixit VM, Nickoloff BJ. Keratinocytes as initiators of inflammation. Lancet 1991;337:211–4.
[13] Nickoloff BJ, Turka LA. Keratinocytes: key immunocytes of the integument. Am J Pathol 1993;143:325–31.
[14] Johansen C. Generation and culturing of primary human keratinocytes from adult skin. J Vis Exp 2017;2017:1–5.
[15] Fuchs E, Raghavan S. Getting under the skin of epidermal morphogenesis. Nat Rev Genet 2002;3:199–209.
[16] Bos JD, Kapsenberg ML. The skin immune system its cellular constituents and their interactions. Immunol Today 1986;7:235–40.
[17] Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol 2009;9:679–91.
[18] Kim H Do, Ha SE, Kang JR, Park JK. Effect of Korean red ginseng extract on cell death responses in peroxynitrite-treated keratinocytes. J Ginseng Res 2010;34:205–11.
[19] Hillery M, Schwartz RJ. Time-averaged properties of the Jaynes-Cummings model: effects of detuning. Phys Rev A 1991;43:1506–11.
[20] Cummings MM, Cummings Martin M. Interview by ole K. Harlem. Tidsskr Den Nor Laegeforening 1987;107:1151–3.
[21] Buek V. Jaynes-Cummings model with intensity-dependent coupling interacting with Holstein-Primakoff SU(1,1) coherent state. Phys Rev A 1989;39:3196–9.
[22] Shumovsky AS, Kien F Le, Aliskenderov EI. Squeezing in the multiphoton Jaynes-Cummings model. Phys Lett A 1987;124:351–4.
[23] Chang JW, Park KH, Hwang HS, Shin YS, Oh YT, Kim CH. Protective effects of Korean red ginseng against radiation-induced apoptosis in human HaCaT keratinocytes. J Radiat Res 2014;55:245–56.
[24] Kim WY, Kim JM, Han SB, Lee SK, Kim ND, Park MK, Kim CK, Park JH. Steaming of ginseng at high temperature enhances biological activity. J Nat Prod 2000;63:1702–4.
[25] Lee H, Lee JY, Song KC, Kim J, Park JH, Chun KH, Hwang GS. Protective effect of processed Panax ginseng, sun ginseng on UVB-irradiated human skin keratinocyte and human dermal fibroblast. J Ginseng Res 2012;36:68–77.
[26] Homey B, Steinhoff M, Ruzicka T, Leung DYM. Cytokines and chemokines orchestrate atopic skin inflammation. J Allergy Clin Immunol 2006;118:178–89.
[27] Moreno AS, Mcphee R, Arruda LK, Howell MD. Targeting the T helper 2 inflammatory axis in atopic dermatitis. Int Arch Allergy Immunol 2016;171:71–80.
[28] Böhm I, Bauer R. Th1-Zellen, Th2-Zellen und atopische Dermatitis. Hautarzt 1997;48:223–7.
[29] Giustizieri ML, Mascia F, Frezzolini A, De Pità O, Chinni LM, Giannetti A, Girolomoni G, Pastore S. Keratinocytes from patients with atopic dermatitis and psoriasis show a distinct chemokine production profile in response to T cell-derived cytokines. J Allergy Clin Immunol 2001;107:871–7.
[30] Hong C-E, Lyu S-Y. Anti-inflammatory and anti-oxidative effects of Korean red ginseng extract in human keratinocytes. Immune Netw 2011;11:42.
[31] Park JH, Ahn EK, Ko HJ, Lee JY, Hwang SM, Ko SM, Oh JS. Korean red ginseng water extract alleviates atopic dermatitis-like inflammatory responses by negative regulation of mitogen-activated protein kinase signaling pathway in vivo. Biomed Pharmacother 2019;117:109066.
[32] Oh Y, Lim HW, Kim K, Lim CJ. Ginsenoside Re improves skin barrier function in HaCaT keratinocytes under normal growth conditions. Biosci Biotechnol Biochem 2016;80:2165–7.
[33] Ahn S, Siddiqi MH, Aceituno VC, Simu SY, Zhang J, Jimenez Perez ZE, Kim Y-J, Yang D-C. Ginsenoside Rg5:Rk1 attenuates TNF-α/IFN-γ-induced production of thymus- and activation-regulated chemokine (TARC/CCL17) and LPS-induced NO production via downregulation of NF-κB/p38 MAPK/STAT1 signaling in human keratinocytes and macrophages. Vitr Cell Dev Biol - Anim 2016;52:287–95.
[34] Chung I, Lee J, Park YS, Lim Y, Chang DH, Park J, Hwang JS. Inhibitory mechanism of Korean red ginseng on GM-CSF expression in UVB-irradiated keratinocytes. J Ginseng Res 2015;39:322–30.
[35] Park YS, Lee JE, Park J Il, Myung C hwan, Lim YH, Park CK, Hwang JS. Inhibitory mechanism of ginsenoside Rh3 on granulocyte–macrophage colony-stimulating factor expression in UV-B–irradiated murine SP-1 keratinocytes. J Ginseng Res 2020;44:274–81.
[36] Aitken GR, Henderson JR, Chang SC, McNeil CJ, Birch-Machin MA. Direct monitoring of UV-induced free radical generation in HaCaT keratinocytes. Clin Exp Dermatol 2007;32:722–7.
[37] Kim MS, Oh GH, Kim MJ, Hwang JK. Fucosterol inhibits matrix metalloproteinase expression and promotes type-1 procollagen production in UVB-induced HaCaT cells. Photochem Photobiol 2013;89:911–8.
[38] Chae S, Piao MJ, Kang KA, Zhang R, Kim KC, Youn UJ, Nam K-W, Lee JH, Hyun JW. Inhibition of matrix metalloproteinase-1 induced by oxidative stress in human keratinocytes by mangiferin isolated from Anemarrhena asphodeloides. Biosci Biotechnol Biochem 2011;75:2321–5.
[39] Oh SJ, Oh Y, Ryu IW, Kim K, Lim CJ. Protective properties of ginsenoside Rb3 against UV-B radiation-induced oxidative stress in HaCaT keratinocytes. Biosci Biotechnol Biochem 2016;80:95–103.
[40] Kim S, Kang BY, Cho SY, Sung DS, Chang HK, Yeom MH, Kim DH, Sim YC, Lee YS. Compound K induces expression of hyaluronan synthase 2 gene in transformed human keratinocytes and increases hyaluronan in hairless mouse skin. Biochem Biophys Res Commun 2004;316:348–55.
[41] Cichorek M, Wachulska M, Stasiewicz A, Tymińska A. Skin melanocytes: biology and development. Postep Dermatologii I Alergol 2013;30:30–41.
[42] Seiji M, Fitzpatrick TB. The reciprocal relationship between melanization and tyrosinase activity in melanosomes (melanin granules). J Biochem 1961;49:700–6.
[43] Simon JD, Peles D, Wakamatsu K, Ito S. Current challenges in understanding melanogenesis: bridging chemistry, biological control, morphology, and function. Pigment Cell Melanoma Res 2009;22:563–79.
[44] Riley PA. Melanin. Int J Biochem Cell Biol 1997;29:1235–9.
[45] Costin G-E, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. FASEB J 2007;21:976–94.
[46] Lee A-Y, Noh M. The regulation of epidermal melanogenesis via cAMP and/or PKC signaling pathways: insights for the development of hypopigmenting agents. Arch Pharm Res 2013;36:792–801.
[47] Kong YH, Jo YO, Cho C-W, Son D, Park S, Rho J, Choi SY. Inhibitory effects of cinnamic acid on melanin biosynthesis in skin. Biol Pharm Bull 2008;31:946–8.
[48] Song M, Mun JH, Ko HC, Kim BS, Kim MB. Korean red ginseng powder in the treatment of melasma: an uncontrolled observational study. J Ginseng Res 2011;35:170175.
[49] Jiang R, Xu X-H, Wang K, Yang X-Z, Bi Y-F, Yan Y, Liu J-Z, Chen X-N, Wang Z-Z, Guo X-L, et al. Ethyl acetate extract from Panax ginseng C.A. Meyer and its main constituents inhibit alpha-melanocyte-stimulating hormone-induced melanogenesis by suppressing oxidative stress in B16 mouse melanoma cells. J Ethnopharmacol 2017;208:149–56.
[50] Lee J-O, Kim E, Kim JH, Hong YH, Kim HG, Jeong D, Kim J, Kim SH, Park C, Seo DB, et al. Antimelanogenesis and skin-protective activities of Panax ginseng calyx ethanol extract. J Ginseng Res 2018;42:389–99.
[51] Saba E, Kim S-H, Lee YY, Park C-K, Oh J-W, Kim T-H, Kim H-K, Roh S-S, Rhee MH. Korean Red Ginseng extract ameliorates melanogenesis in humans and induces antiphotoaging effects in ultraviolet B–irradiated hairless mice. J Ginseng Res 2019.
[52] Oh CT, Park J Il, Jung YR, Joo YA, Shin DH, Cho HJ, Ahn SM, Lim YH, Park CK, Hwang JS. Inhibitory effect of Korean Red Ginseng on melanocyte

proliferation and its possible implication in GM-CSF mediated signaling. J Ginseng Res 2013;37:389–400.
[53] Jeong Y-M, Oh WK, Tran TL, Kim W-K, Sung SH, Bae K, Lee S, Sung JH. Aglycone of Rh4 inhibits melanin synthesis in B16 melanoma cells: possible involvement of the protein kinase A pathway. Biosci Biotechnol Biochem 2013;77:119–25.
[54] Lee DY, Jeong YT, Jeong SC, Lee MK, Min JW, Lee JW, Kim GS, Lee SE, Ahn YS, Kang HC, et al. Melanin biosynthesis inhibition effects of ginsenoside Rb2 isolated from panax ginseng berry. J Microbiol Biotechnol 2015;25:2011–5.
[55] Wang L, Lu A-P, Yu Z-L, Wong RNS, Bian Z-X, Kwok H-H, Yue PYK, Zhou LM, Chen H, Xu M, et al. The melanogenesis-inhibitory effect and the percutaneous formulation of ginsenoside Rb1. AAPS PharmSciTech 2014;15:1252–62.
[56] Lee SJ, Lee WJ, Chang SE, Lee G-Y. Antimelanogenic effect of ginsenoside Rg3 through extracellular signal-regulated kinase-mediated inhibition of microphthalmia-associated transcription factor. J Ginseng Res 2015;39:238–42.
[57] Kim JH, Baek EJ, Lee EJ, Yeom MH, Park JS, Lee KW, Kang NJ. Ginsenoside F1 attenuates hyperpigmentation in B16F10 melanoma cells by inducing dendrite retraction and activating Rho signalling. Exp Dermatol 2015;24:150–2.
[58] Imokawa G. Autocrine and paracrine regulation of melanocytes in human skin and in pigmentary disorders. Pigment Cell Res 2004;17:96–110.
[59] Yoshida A, Anand-Apte B, Zetter BR. Differential endothelial migration and proliferation to basic fibroblast growth factor and vascular endothelial growth factor. Growth Factors 1996;13:57–64.
[60] Hirobe T, Shinpo T, Higuchi K, Sano T. Life cycle of human melanocytes is regulated by endothelin-1 and stem cell factor in synergy with cyclic AMP and basic fibroblast growth factor. J Dermatol Sci 2010;57:123–31.
[61] Lee JE, Park J Il, Myung CH, Hwang JS. Inhibitory effects of ginsenosides on basic fibroblast growth factor-induced melanocyte proliferation. J Ginseng Res 2017;41:268–76.
[62] Kim YG, Sumiyoshi M, Sakanaka M, Kimura Y. Effects of ginseng saponins isolated from red ginseng on ultraviolet B-induced skin aging in hairless mice. Eur J Pharmacol 2009;602:148–56.
[63] Hwang YP, Choi JH, Kim HG, Choi JM, Hwang SK, Chung YC, Jeong HG. Cultivated ginseng suppresses ultraviolet B-induced collagenase activation via mitogen-activated protein kinases and nuclear factor κB/activator protein-1-dependent signaling in human dermal fibroblasts. Nutr Res 2012;32:428–38.
[64] Hossen MJ, Hong YD, Baek KS, Yoo S, Hong YH, Kim JH, Lee JO, Kim D, Park J, Cho JY. In vitro antioxidative and anti-inflammatory effects of the compound K-rich fraction BIOGF1K, prepared from Panax ginseng. J Ginseng Res 2017;41:43–51.
[65] Hong YH, Kim D, Nam G, Yoo S, Han SY, Jeong SG, Kim E, Jeong D, Yoon K, Kim S, et al. Photoaging protective effects of BIOGF1K, a compound-K-rich fraction prepared from Panax ginseng. J Ginseng Res 2018;42:81–9.
[66] Liu X-Y, Hwang E, Park B, Ngo HTT, Xiao Y-K, Yi T-H. Ginsenoside C-mx isolated from notoginseng stem-leaf ginsenosides attenuates ultraviolet B-mediated photoaging in human dermal fibroblasts. Photochem Photobiol 2018;94:1040–8.
[67] Hwang E, Lee TH, Park S-Y, Yi TH, Kim SY. Enzyme-modified Panax ginseng inhibits UVB-induced skin aging through the regulation of procollagen type I and MMP-1 expression. Food Funct 2014;5:265–74.
[68] Song KC, Chang T-S, Lee H, Kim J, Park JH, Hwang GS. Processed Panax ginseng, sun ginseng increases type I collagen by regulating MMP-1 and TIMP-1 expression in human dermal fibroblasts. J Ginseng Res 2012;36:61.
[69] Lee J, Jung E, Lee J, Huh S, Kim J, Park M, Park M, So J, Ham Y, Jung K, Hyun CG, et al. Panax ginseng induces human Type I collagen synthesis through activation of Smad signaling. J Ethnopharmacol 2007;109:29–34.
[70] Kim WK, Song SY, Oh WK, Kaewsuwan S, Tran TL, Kim WS, Sung JH. Wound-healing effect of ginsenoside Rd from leaves of Panax ginseng via cyclic AMP-dependent protein kinase pathway. Eur J Pharmacol 2013;702:285–93.
[71] Lee GY, Park KG, Namgoong S, Han SK, Jeong SH, Dhong ES, Kim WK. Effects of Panax ginseng extract on human dermal fibroblast proliferation and collagen synthesis. Int Wound J 2016;13:42–6.
[72] Park S, Ko E, Lee JH, Song Y, Cui C-H, Hou J, Jeon BM, Kim HS, Kim SC. Gypenoside LXXV promotes cutaneous wound healing in vivo by enhancing connective tissue growth factor levels via the glucocorticoid receptor pathway. Molecules 2019;24.
[73] Lee R, Lee N-E, Hwang H, Rhim H, Cho I-H, Nah S-Y. Ginseng gintonin enhances hyaluronic acid and collagen release from human dermal fibroblasts through lysophosphatidic acid receptor interaction. Molecules 2019;24.
[74] Driskell RR, Clavel C, Rendl M, Watt FM. Hair follicle dermal papilla cells at a glance. J Cell Sci 2011;124:1179–82.
[75] Park S, Shin WS, Ho J. Fructus panax ginseng extract promotes hair regeneration in C57BL/6 mice. J Ethnopharmacol 2011;138:340–4.
[76] Baeg IH, So SH. The world ginseng market and the ginseng (Korea). J Ginseng Res 2013;37:1–7.