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Review Article

Ginseng and ginseng byproducts for skincare and skin health

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ABSTRACT

Ginseng is a traditional herbal medicine with a long history of use for the prevention and/or treatment of various diseases. Ginseng is used worldwide as a functional food to maintain human health. In addition, ginseng has been used as a raw ingredient in cosmetics with various applications, ranging from skin toning to anti-aging. Some cosmetic products contain ginseng extracts from Korea and other countries, as it is thought that ginseng can also exert beneficial effects on human skin. However, it remains unclear which ginseng component(s) could be the main active compound that directly contributes to skin health and/or prevents skin aging. It is also important to understand the mechanisms by which the ginseng component(s) exert their effects on the skin and skin health. This review describes recent *in vitro* and *in vivo* studies involving ginseng extracts, ginseng ingredients, and ginseng byproducts for skincare and skin health and discusses emerging evidence that ginsenosides, gintonin, and ginseng byproducts could be novel candidates for skincare and skin health applications ranging from anti-aging to the treatment of skin diseases such as atopic dermatitis and hypertrophic scars and keloids. The mechanisms underlying the beneficial effects of ginseng components and byproducts on skin health are discussed. In addition, this review shows how ginseng components, such as gintonin, a newly identified ginseng component, might contribute to skin health and skin disease when used as a supplementary ingredient in cosmetics and further proposes a novel combination in cosmetic products containing both ginsenosides and gintonin.

1. Introduction

Skin is the soft and flexible outer covering over the body and is the largest organ in the human body [1,2]. Skin comprises water, protein, fats, and minerals and has three main functions: protection, regulation, and sensation [1,2]. The skin acts as the first line of defense, protecting the body from germs, and plays a crucial role in regulating body temperature against external environmental changes [1,2]. Nerves in the skin enable tactile perception of various stimuli, such as heat, cold, and various other sensations. The skin consists of three layers: epidermis, dermis, and hypodermis [1]. Owing to its extensive surface area, the skin is also easily exposed to and is vulnerable to damage by a range of external factors, such as ultraviolet (UV) radiation, which may lead to burns, wounds, dehydration, skin aging, melanin deposition, microbial invasion, skin barrier abnormalities, and skin-related diseases such as cancer [3]. Hence, several cosmetics and skincare methods have been developed to treat skin problems and promote skin health to enhance appearance [3].

However, human use of cosmetics has a very long history. The earliest archaeological evidence of cosmetics suggests that it was used by ancient Egyptians and the Sumerians around 3500 BC [4]. Subsequently, evidence has emerged that cosmetics were used in ancient Greece and Romania [4]. Since ancient times, cosmetics used by humans have mainly been applied to the face, scalp, and other head parts.

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Currently, cosmetics are composed of a mixture of chemicals derived from natural or synthetic sources [5]. Cosmetic products are designed for various purposes, such as personal care, hair care, skincare, and skin health. People use cosmetics to "beautify the human body to make it look more attractive, eliminate other odors, or change the appearance." In addition, "cosmetics are used to maintain and promote the health of skin and prevention of hair" [6]. Recent cosmetics have functionality and are applied to a person's face, hair, or other body parts to slow or suppress skin aging [6]. Currently, cosmetics can be classified into several categories, including general, functional, and medicinal cosmetics, depending on the area of use, purpose of use, or components and properties [7]. Cosmeceuticals are new medicines for beauty [7].

The history of the use of ginseng as a tonic for maintaining a healthy body and sound mind goes as far back in time as that of the use of cosmetics [4,8]. Currently, ginseng is globally used as a functional food to maintain human health. Ginseng contains three major bioactive components: ginsenosides, ginseng polysaccharides, and gintonin. Ginseng also contains other minor components, such as polyphenols. More than 30 ginsenosides are divided into protopanaxadiol (PPD), protopanaxatriol (PPT), and oleanolic acid types, which mainly differ in the composition of carbohydrate portions or side chains [8]. The main biological actions of ginsenosides are non-receptor-mediated anti--oxidative stress and anti-inflammatory effects [9]. Ginseng polysaccharides, including acidic polysaccharides, exhibit immune-boosting effects [10]. Gintonin has recently been isolated from ginseng and is a newly reported component of ginseng [11,12]. Gintonin is a type of glycolipoprotein complex that is different from ginseng ginsenosides and polysaccharides in its physicochemical properties [11,12]. The main active ingredients of gintonin are lysophosphatidic acids (LPAs), which are ligands for G protein-coupled LPA receptors, and their activation has been reported to have diverse biological effects, including those on the nervous and non-nervous systems [11]. LPA precursors, such as lysophospholipids (*i.e.*, lysophosphatidylcholine, lysophosphatidylethanolamine, and lysophosphatidylinositol), phospholipids (*i.e.*, phosphatidic acid and phosphatidylcholine), and free fatty acids (such as linoleic acid and palmitic acid), also exist in the gintonin-enriched fraction [11,12].

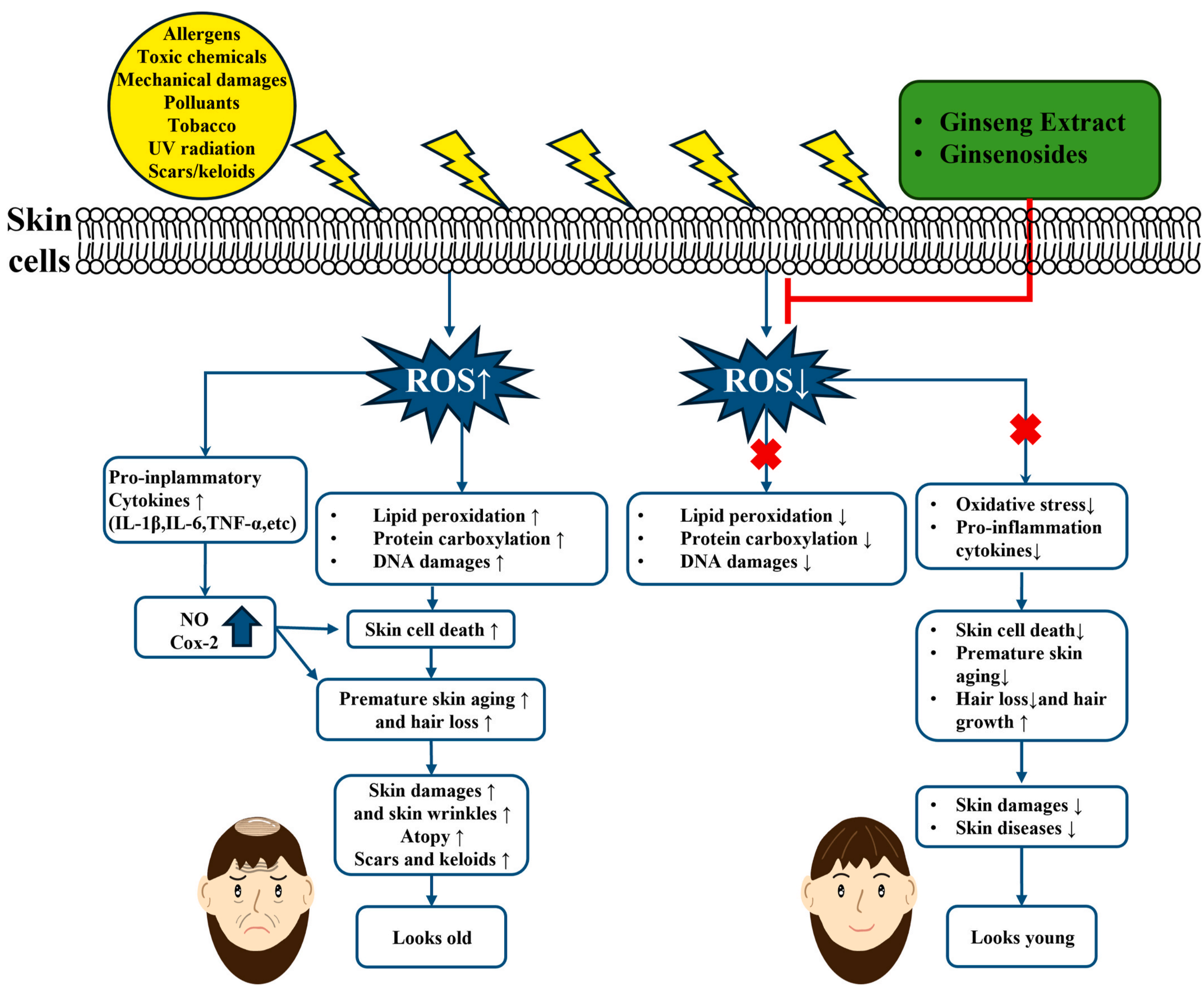

Fig. 1. Ginseng extract- and ginsenoside-induced anti-oxidative stress and anti-inflammatory effects for skin cell protection. The protective effects of ginseng extract and ginsenosides on skin cells (i.e., human dermal fibroblasts, keratocytes, and melanocytes) are because of their anti-oxidative activity against diverse exterior factors ranging from allergens to UV radiation. Their anti-oxidative stress activities are further coupled with their anti-inflammatory effects via non-receptor–mediated pathways in various skin cells. Thus, ginseng extract- and ginsenosides-induced anti-oxidative and anti-inflammatory effects finally contribute to skincare and skin health.

In addition to its use in functional foods, recent trends show that ginseng or ginseng byproducts are also being used as ingredients in cosmetic products for various purposes, ranging from skin toners to anti-skin aging and treatment of skin diseases [13,14]. Therefore, as ginseng has been proven to have beneficial effects on human skin and skin health, in addition to its beneficial effects on human health, some cosmetic products manufactured worldwide currently contain ginseng extract. However, relatively little is known about which component(s) in ginseng and their by-products contribute to skin healthcare. In this review, we first discuss the main causes and factors that induce skin aging and damages. Next, we show that ginseng extract, ginseng components, and ginseng byproducts, which are derived from a natural source called ginseng, can be used as cosmetic ingredients. Finally, the mode of action is discussed.

2. The main causes of skin aging and damage

Several causes of accelerated skin aging, including UV radiation, air pollution, smoking, stress, nutritional deficiency, and sleep deprivation [15] (Fig. 1). UV radiation is one of the main causes of skin aging and damage, and this process is termed photoaging, which is extrinsic aging; photoaging is caused by exposure to UV radiation during outdoor activities [16]. Exposure to UV radiation directly decreases skin thickness and elasticity. The histological changes occurring in skin owing to UV exposure are damage to collagen fibers and deformation of elastin fibers, leading to skin aging. Other important factors affecting skin aging caused by UV exposure are reactive oxygen species (ROS), free radicals, and skin inflammation, which are abnormally induced by UV radiation. ROS are also produced during oxidative phosphorylation in the mitochondria of normal skin cells; however, they are mainly produced by exposure to UV radiation [17]. The mechanisms by which UV radiation induces skin aging are as follows: 1) ROS generated by exposure to UV radiation causes peroxidation of the lipids present in the membranes of skin cells, thereby damaging the cell membrane and causing oxidative stress. 2) UV radiation also damages intracellular organelles, such as mitochondria, nuclear DNA, and proteins that perform various functions. 3) UV radiation induces inflammatory responses in skin cells (Fig. 1). When the skin is affected by wounds or diseases, such as atopy, an inflammatory response occurs in the tissue [18]. Consequently, the skin barrier is destroyed, exposing the tissue to external infections. As a result, inflammatory responses occur or the wound does not heal well [18]. During inflammation, the immune inflammatory factors TNF-α, IL-1, IL-4, etc are produced in large quantities, delaying normal skin recovery.

Normal skin cells restore normal functions through the activity of the endogenous antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx), which remove ROS, or free radicals [19,20]. However, under conditions such as disease or other stresses (i.e., when normal antioxidant enzymes are depleted or malfunction owing to stress, drinking, or smoking), the skin loses its ability to recover, and skin aging occurs more quickly when exposed to UV radiation [21]. The use of cosmetics containing UV sunscreen is a way to protect skin from damage owing to extrinsic factors such as air pollution and UV radiation. As mentioned earlier, ginseng might be useful for skin care and/or skin health, as it contains various bioactive ingredients that may not only delay natural skin aging but also protect against skin damage induced by extrinsic sources such as UV radiation. The following section discusses in detail the roles of ginseng components in skin care and skin health.

3. Effects of ginseng ingredients: results from *in vitro* and *in vivo* studies

3.1. The use of ginseng total extract in skin-related cells

Ginseng extract has been used as a raw ingredient in cosmetics since the 1980s. It is currently one of the most widely used raw plant materials in cosmetics [22]. The ginseng root extract has been used as a raw material in cosmetics because of its anti-skin aging, skin-whitening, anti-wrinkle, and moisturizing effects [23]. Ginseng extract has been reported to increase anti-oxidative enzyme activity and inhibit ROS formation in skin cells [24]. These dual actions of ginseng extract not only increase collagen content and reduce skin wrinkles but also protect keratinocytes and dermal fibroblasts from damage caused by UV radiation and inhibit melanin production to achieve whitening effects [24]. In addition to skin, ginseng extract can induce the differentiation of dermal papilla cells, which are also thought to be skin stem cells and suppress apoptosis, thereby stimulating skin renewal on the cellular level [25]. Ginseng extract also prolongs the anagen phase of the hair cycle, which is useful for hair regeneration and prevention of hair loss [26]. Ginseng extract also facilitated *in vitro* wound healing [27] (Fig. 1).

3.2. The use of ginsenosides in skin-related cells and in vivo studies

Many ginsenosides have been identified until now [28]. At the cellular level, ginsenosides, such as compound K and ginsenosides Rb1, Rb2, Rg1, Rg3, and F1, show various anti–skin aging–related activities such as collagen synthesis, anti-senescence, UV-induced anti-aging, and anti-melanogenesis [29–34]. Ginsenosides protect skin cells from photoaging induced by UV radiation exposure [33]. In an *in vivo* study using mice, ginsenoside Rk3 inhibited the free radical–induced destruction of collagen in skin tissue and reduced skin damage caused by exposure to UV radiation [35]. Additionally, when hairless mice were treated with the ginseng saponin fraction and ginsenoside Rb1 while simultaneously being exposed to UV radiation over 12 weeks, treatment with both components showed recovery of skin thickness under UV radiation and improved elasticity [36]. Histological observations showed that epidermal thickness and extracellular matrix decreased, which suppressed skin cell aging caused by UV exposure and improved skin elasticity and wrinkles [35,36]. Ginsenosides have also been reported to facilitate wound healing in other *in vitro* and *in vivo* studies [37,38] (Fig. 1 and Table 1).

Table 1
Ginseng ingredients that contribute to beneficial effects on skin cells *in vitro* and in *in vivo* models of skincare and skin health.

Ginseng components	*In vitro* and *in vivo* effects on skin cells and skin	References
Ginsenosides	Inhibition of melanogenesis in skin cells Increase of collagen and hyaluronic acid release in skin cells Alleviation of UV radiation–induced skin cell damage and anti-photoaging *In vitro* and *in vivo* wound healing facilitation Promotion of *in vivo* hair growth Improvement of atopic dermatitis Hypertrophic scars and keloids	[27,31,34,35,37,38,39,40,41,42–47]
Gintonin	Increases in collagen and hyaluronic acid releases in skin cells Anti-aging effects against UV radiation–induced skin cell aging *In vivo* wound healing facilitation Promotion of *in vivo* hair growth Improvement of atopic dermatitis symptoms	[48–51,52]
Korean red ginseng marc polysaccharides	Improvement of atopic dermatitis symptoms	[53]

Skin cells include human dermal fibroblasts, keratocytes, and melanocytes.

3.3. The use of gintonin in hair- and skin-related cells and in animal studies

Gintonin is a newly identified component of ginseng, and its active ingredients are LPAs, which are pleiotropic growth factors that stimulate skin cell proliferation, survival, and migration [54]. The *in vitro* and *in vivo* effects of gintonin on skin cells and wound healing were investigated [48]. *In vitro* studies using human dermal fibroblast cells performed by Lee et al. (2019) showed that gintonin first induced a $[Ca^{2+}]_i$ transient, which in turn stimulated cell proliferation, an effect that was not observed with other ginseng components, such as ginsenosides and ginseng polysaccharides. Interestingly, gintonin-induced skin cell proliferation and migration were achieved via the LPA1/3 receptor signaling pathway, as an LPA1/3 receptor antagonist blocked the effects of ginseng in hair- and skin-related cells [48,49]. In addition, gintonin stimulates the release of hyaluronic acid and collagen from fibroblasts, which are key elements for skin moisture and elasticity. In further studies using human dermal keratinocytes, Choi et al. (2021) and Won et al. (2023) showed that gintonin facilitated *in vitro* wound healing by stimulating cell migration. In an *in vivo* study, topical gintonin application or administration at the wound site promoted hair growth and facilitated tail wound healing progression, respectively [50,51]. They also showed the *in vitro* and *in vivo* hair growth promotion and wound healing effects of gintonin, respectively [50,51,53,55] (Fig. 2 and Tables 1 and 2).

3.4. The use of ginseng polysaccharides and ginseng oil in skin-related cells and in animal studies

Compared to reports on the use of ginsenosides to promote skin health, reports using ginseng polysaccharides and ginseng oil on skin care and/or skin health are few. Lee et al. (2021) showed that treatment of red ginseng-derived acidic polysaccharides (RGAP) to sebocytes and outer root sheath (ORS) cells, which were pretreated with lipopolysaccharides (LPS), increased the expression of inflammatory cytokines like interleukin (IL)-1β, IL-6, IL-8, and TNF-α, toll-like receptor 2, p-c-Jun, and p-JNK [61]. In addition, RGAP increased the expression of LL37 (cathelicidin) in LPS-treated sebocytes and ORS cells and the production of sebum in LPS-treated sebocytes. In an *in vivo* study, RGAP promoted the increased expression of inflammatory biomarkers in *Cutibacterium acnes*-associated inflammatory nodules in mice [61].

Jung et al. (2021) showed that Korean red ginseng oil treatment of LPS-pretreated sebocytes and ORS cells increased gene and protein expression of inflammatory cytokines, including IL-1β, IL-6, IL-8, and tumor necrosis factor-α [62]. Red ginseng oil not only increased the protein expression of p-c-Jun and p-JNK in LPS-treated sebocytes and ORS cells but also increased the gene expression of TLR2 in LPS-treated sebocytes [62]. Similar to the effect exerted by RGAP [61], Korean red ginseng oil also increased the expression of LL-37 in LPS-treated sebocytes and ORS cells and increased the production of sebum in LPS-treated sebocytes. Interestingly, both RGAP and red ginseng oil may act as aggravating factors in inflammatory situations [61,62]. However, these two reports are limited to acne vulgaris, a kind of skin disease.

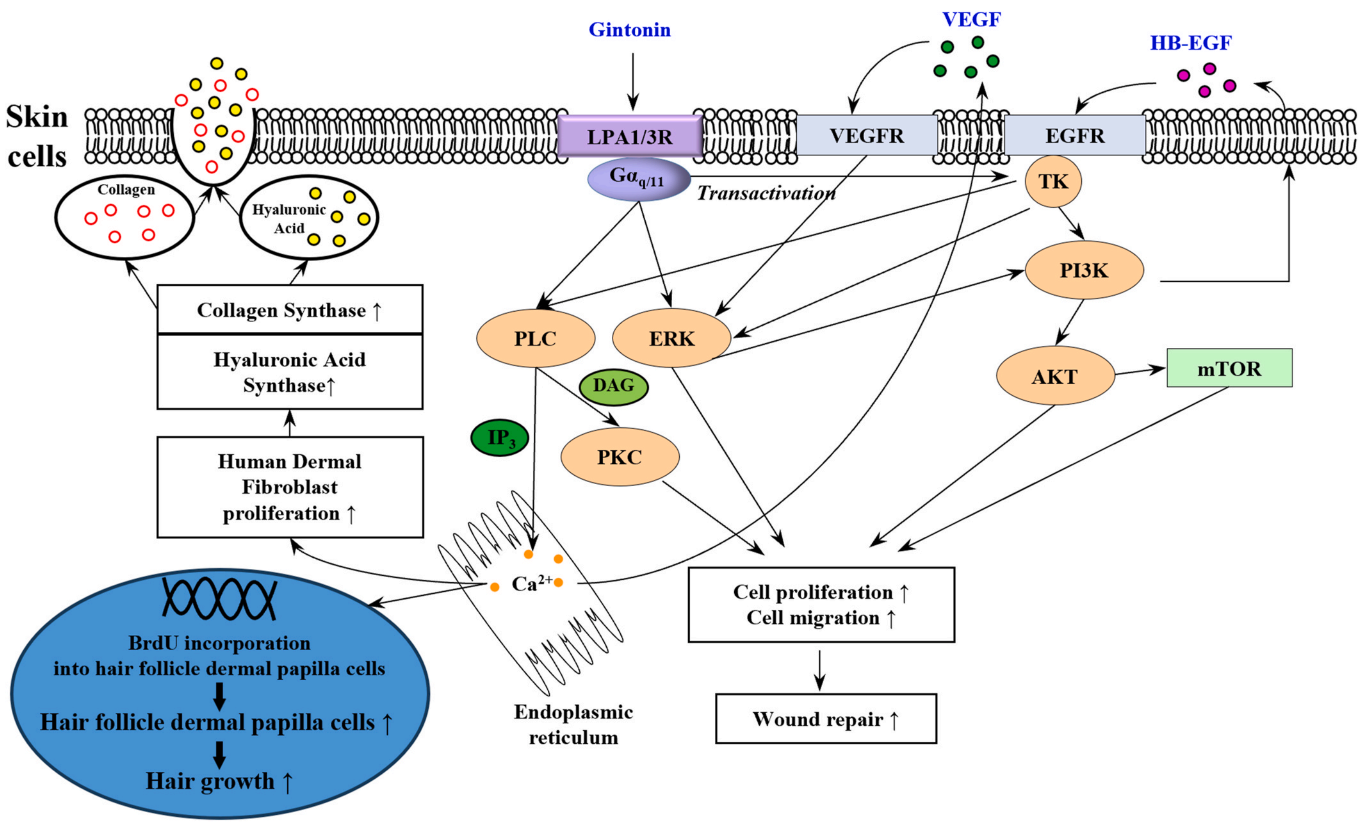

Fig. 2. Gintonin-mediated signaling pathways for skin cell protection, wound healing, and promoting hair growth. In contrast to ginseng extract and ginsenosides, gintonin-mediated skincare and skin health is primarily mediated via LPA1/3 receptors in skin cells. Thus, activation of LPA1/3 receptors by gintonin are coupled to the induction of a $[Ca^{2+}]_i$ transient via a membrane signaling transduction pathway. Gintonin-induced transient elevation of intracellular Ca^{2+}, a second messenger, is linked to diverse skin cellular effects from cell proliferation to VEGF and Hb-EGF release. Other detailed signaling pathways of gintonin for skincare and skin health are also described. Activation of LPA receptors by gintonin is also coupled to transactivation of EGF receptor and release of Hb-EGF, which are also known as important growth factors for skincare and skin health. Gintonin-mediated EGF transactivation–related effects were not observed in ginsenosides and ginseng polysaccharides.

Table 2
Comparison of mode of action of ginseng ingredients for skincare and skin health.

Ginseng components	Mode of actions in skin cells	Skin cell membrane receptors	References
Ginsenosides	Anti-oxidative stress effects Anti-inflammatory effects Increases of collagen and hyaluronic acid release and synthesis Decrease of tyrosinase activity Decrease of hypertrophic scars-related factor expressions	Non-receptor mediation	[39,56–59,42–47]
Gintonin	Increases of skin cell proliferation of fibroblast and keratocytes via $[Ca^{2+}]_i$ transient Induction of $[Ca^{2+}]_i$ transient for collagen and hyaluronic acid release and hair growth Transactivation of EGF receptor via c-Src pathway Stimulation of VEGF and HB-EGF release in skin cells Inhibition of autotaxin activity	LPA1/3 receptor subtypes	[48–51,52]
Ginseng polysaccharides	Anti-oxidative stress effects Anti-inflammatory effects	Non-receptor mediation	[60]

Further studies are required to confirm whether both RGAP and red ginseng oil exhibit the same increase in inflammatory cytokines in other skin-related cells in the absence or presence of LPS.

4. Effects of ginseng byproducts: results from *in vitro* and *in vivo* studies

4.1. Ginseng byproducts and cosmetics

Ginseng is a perennial plant and is usually cultivated for 4–6 years before harvest. Whole ginseng consists of flowers, fruits, leaves, stalks, and roots [63]. Traditionally, ginseng root is mainly used as an herbal medicine, and it has recently been used in functional foods, whereas other parts of ginseng are usually discarded [64]. Korean red ginseng root, prepared from fresh ginseng, is currently a major ginseng product for human use in the Korean ginseng industry. Korean red ginseng (KRG) roots are usually subjected to hot water extraction to obtain Korean red ginseng products with yields of 50–60 % KRG [64]. The remaining 50-40 % of the hot water extract products are usually discarded. Korean red ginseng marc (KRGM) is another ginseng byproduct [64]. In addition, at least there are four ginseng byproducts such as flower buds, ginseng berries (fruit), ginseng leaves, and ginseng stalks, which also contain diverse ginsenosides [65]. Particularly, although several thousand tons of KRGM are produced every year in Korea, it is not well utilized in the Korean ginseng industry, and ginseng byproducts have not been actively recycled or upcycled in the ginseng industry despite the Ministry of Food and Drug Safety allowing the use of KRGM as a food additive or a raw material for cosmetics [64].

Recently, some ginseng byproducts have been used as raw materials in cosmetics, with two notable examples. First, ginseng fruits harvested when they are in full bloom are mainly used as raw materials for cosmetics [66]. As ginseng fruits can be harvested only during a specific season, such as summer, and the quantity of ginseng fruits is small, the production of cosmetics using ginseng fruits is not high. Consequently, products containing ginseng fruit extracts are relatively expensive and have a short sales period. The other is KRGM, which is abundantly obtained after red ginseng root extraction and is used as an ingredient in cosmetic products; when not used for cosmetic products, KRGM is discarded as compost or used as animal feed [64]. KRGM is used as a cosmetic ingredient in two forms. One form is where red ginseng oil is obtained through supercritical carbon dioxide extraction of the material left over after red ginseng extraction; however, the yield of red ginseng marc-derived oil is very low [67]. Red ginseng oil, thus obtained from KRGM, is used as a raw material in cosmetics [67]. The other is red ginseng marc, used directly as a cosmetic ingredient [64]. The *in vitro* and *in vivo* studies mentioned in the subsequent sections have shown that ginseng berry and red ginseng marc extracts can be useful as raw materials for cosmetics owing to their antioxidant and anti-inflammatory effects.

4.2. The use of ginseng fruit (berry) marc in in vitro studies involving skin-related cells

Kim (2021) investigated whether ginseng fruit marc extract could be used as a raw material in cosmetics used for skin care [66]. Kim (2021) prepared an ethanol extract of ginseng fruit marc using 70 % ethanol, determined the total polyphenol and flavonoid content of the extract, and examined several parameters such as antioxidant properties, anti-inflammatory effects, and the cell survival and migration rate of keratinocytes. Kim (2021) found that after ethanol extraction, ginseng berries contained large amounts of total polyphenols and flavonoids. Kim (2021) also showed using the MTT assay that the ethanol extract of ginseng fruit marc had high cell viability and was relatively non-toxic, as the cell survival rate was over 90 % at concentrations of 0.25 and 0.5 mg/mL [66]. The antioxidant effect, determined by estimating the radical scavenging activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, was also high and had a dose-dependent effect, confirming that ginseng fruit marc extract did not exhibit cytotoxicity through antioxidant effects with polyphenols and flavonoids.

In vitro wound healing assays using keratocytes performed by Kim (2021) showed that a higher concentration of the ginseng berry marc extract (2.5, 5, and 10 mg/mL) resulted in a higher rate of healing, showing the potential of the extract in promoting skin regeneration. Kim (2021) thus confirmed that the ginseng berry marc ethanol extract has low *in vitro* toxicity and facilitates wound healing because it contains high amounts of polyphenols and flavonoids that are necessary for skin cell protection. Additional follow-up investigations, including applications to human skin, might open up the possibility of the application of ginseng berry marc as an effective raw material for the manufacture of cosmetics for skin care and skin health.

4.3. The use of the KRGM extract in in vitro studies involving skin-related cells

Lee et al. (2016) prepared extracts from KRGM powder using three different solvents: H_2O, 30 % ethanol, and 30 % 1,3-butylene glycol [68]. They first checked cell viability by treating B16F10 cells with each of the three extracts; the H_2O and 30 % 1,3-butylene glycol extracts did not show substantial cytotoxicity, except at high concentrations; however, the ethanol extract showed cytotoxicity only at low concentrations. Thus, the ethanol extract of KRGM exhibited cytotoxicity and showed that the components extracted from KRGM could vary depending on the solvent used. They also examined the free radical–scavenging activities using DPPH and superoxide dismutase (SOD). The DPPH scavenging activities were as follows: ethanol extract (33.2 %) > 1,3-butylene glycol (26.3 %) > water extract (22.6 %). The results of this study showed that the ethanol extract of KRGM had higher antioxidant activity than the other solvent extracts. Thus, the 1,3-butylene glycol extract and ethanol extracts of KRGM were shown to have high free radical–scavenging activities [68].

Next, to use the KRGM extract for cosmetic purposes, they examined the ability of each extract to inhibit elastase activity as an anti-wrinkle effect. Interestingly, they found that the order of inhibition of elastase activity was water extract (55.7 %) > 1,3-buthylene glycol extract (35.3 %) > ethanol extract (4.72 %) when used at the same concentrations. Thus, the dried water extract of red ginseng showed the highest effectiveness in suppressing skin wrinkles. Lee et al. (2016) showed differences in the cytotoxicity, free radical scavenging capacity, and wrinkle improvement efficacy between different red ginseng extracts, which vary depending on the extraction solvent. They concluded that differential preparations of the KRGM extract could be used as cosmetic raw materials.

4.4. The use of KRGM gintonin in in vitro and in vivo studies

Recently, Lee et al. (2023) isolated gintonin with a high yield from KRGM and named KRGM gintonin. KRGM gintonin also contains high amounts of LPA $C_{18:2}$, lysophosphatidylcholine (LPC), and phosphatidylcholine (PC) [64]. Lee et al. (2023) first investigated the anti--skin–aging effects of KRGM gintonin under UV exposure in human dermal fibroblasts (HDFs). KRGM gintonin induced the $[Ca^{2+}]_i$ transient via LPA1/3 receptors and increased cell viability/proliferation under UV exposure [64]. KRGM gintonin attenuated UV-induced cell senescence by inhibiting cellular β-galactosidase overexpression and facilitating wound healing. These results suggest that KRGM gintonin can be used as an ingredient in cosmetics to prevent UV radiation–induced skin aging (Fig. 3).

4.5. KRGM-derived polysaccharides in in vitro and in vivo studies

In addition to ginseng berry marc, KRGM extract, and KRGM gintonin, ginseng polysaccharides have been isolated from KRGM. Kim et al. (2019) prepared KRGM polysaccharides by applying an enzyme-linked high-pressure process [60]. KRGM polysaccharides show anti-aging and anti-atopic dermatitis (AD) efficacy [60]. In acute oral toxicity and skin irritation tests, KRGM polysaccharides showed very low toxicity. KRGM acidic polysaccharides inhibited UV-induced matrix metalloproteinase-1 (MMP-1) protein expression through activator protein-1 (AP-1), a major transcription factor for MMP-1. KRGM polysaccharides also attenuated *Dermatophagoides farinae* crude extract (DFE)–induced atopic dermatitis-like symptoms as assessed by skin lesion analyses, dermatitis score, and skin thickness [60]. These results show that KRGM polysaccharides as well as KRGM extract and KRGM gintonin have the potential to be used as cosmeceutical ingredients for skin health (Fig. 3).

5. The modes of action of ginseng in skincare

The multiple modes of action for skin health by ginseng extracts, their components, and byproducts are described in the following section (Table 2).

5.1. Endogenous collagen, elastin, hyaluronic acid and keratin formation, and growth factor release and whitening effects by reducing melanin formation

Hyaluronic acid is required to maintain skin moisture; the skin becomes dry in the absence of sufficient levels of hyaluronic acid [69]. Collagen and elastin are also required to maintain skin elasticity [70]. Keratin is an intermediate filament protein in epithelial cell cytoskeletal components that provides a physical barrier, mechanical stability, and protection from cell stress [71]. Ginseng extract and ginseng components such as ginsenoside Rb1 and gintonin stimulate the release of hyaluronic acid, collagen, and other skin health-related components in cells that consist of skin [31,48,72]. Thus, the direct effects of ginseng extract, ginsenoside Rb1, and gintonin on endogenous skin components may help to maintain healthy skin. Ginseng extract or ginsenoside Rb1-induced inhibition of melanin formation in skin cells also exhibited

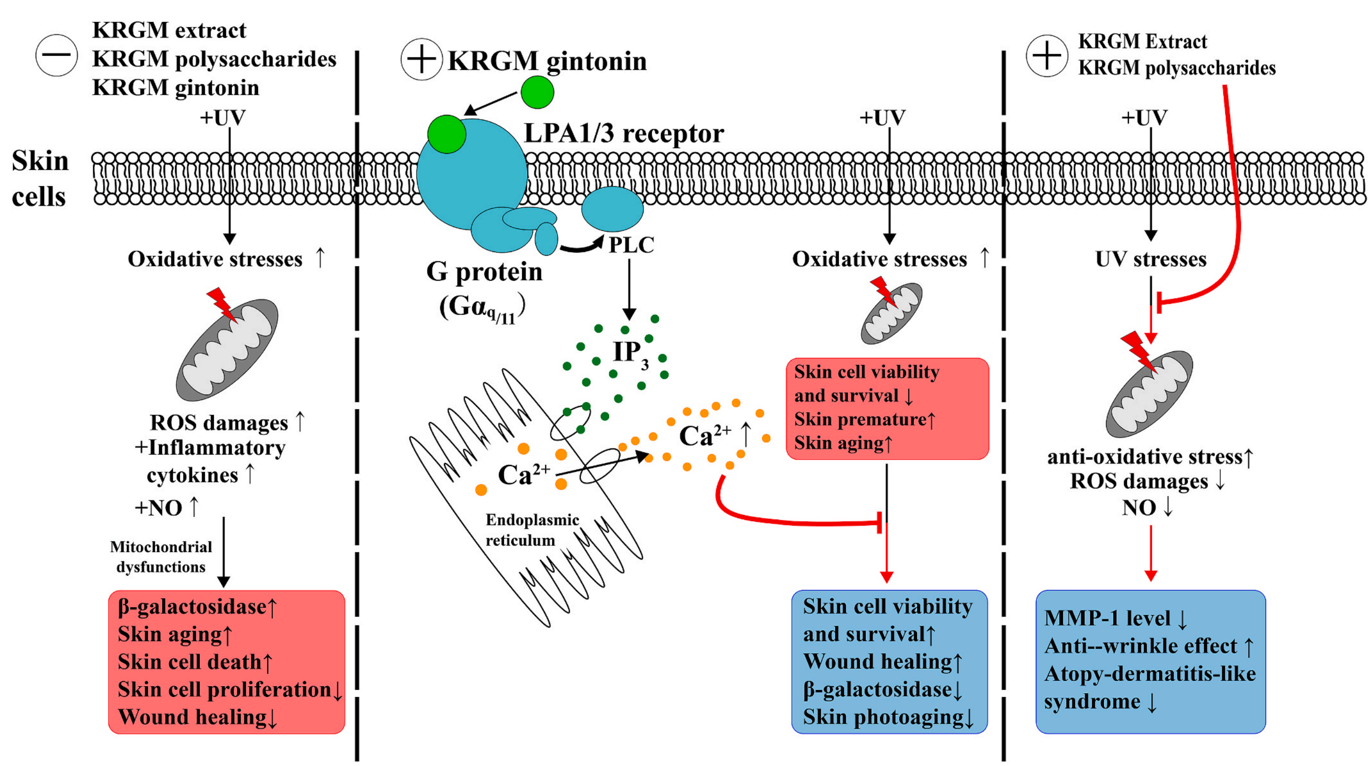

Fig. 3. Roles of ginseng byproducts, such as Korean red ginseng marc extract, Korean red ginseng marc polysaccharides, and Korean red ginseng marc gintonin, in skincare and skin health. In addition to ginseng extract, ginsenosides, and gintonin, recent studies showed that components derived from ginseng are also useful for skincare and skin health, as illustrated here, as they exhibit anti-skin aging effects, facilitate wound healing, and possess anti-wrinkling properties to the same extent as ginseng extract and ginsenosides. The detailed actions of ginseng components from Korean red ginseng marc are described.

whitening effects on the skin [73] (Figs. 1 and 2).

5.2. Anti-oxidative stress and anti-inflammatory effects on skin cells

Ginseng extracts and their components, such as ginsenosides and gintonin, exhibit anti-oxidative stress and anti-inflammatory effects on both the nervous and non-nervous systems, including skin cells and tissues [39,56]. Regarding anti-oxidative stress effects, *in vitro* and/or *in vivo* studies have shown that treatment with ginseng extract, ginsenosides, and gintonin inhibits ROS formation and lipid peroxidation and increases the formation of endogenous antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and an antioxidant, glutathione [57,58]. In addition, *in vitro* and *in vivo* studies have shown that ginseng extract, ginsenosides, and gintonin also have anti-inflammatory effects. Thus, treatment of ginseng extract or ginsenosides inhibits inflammation-related procytokines and cytokine production such as IL-1β, IL-6, IL-8, and TNF-α in nervous and non-nervous systems [59]. Therefore, the administration of ginseng extract, ginsenosides, and gintonin might help repair damage sustained by the skin owing to external oxidative stress and inflammation induced by various sources, such as UV radiation (Fig. 1).

5.3. Anti-photoaging effects

A small amount of UV radiation is well known to be essential for good health because it produces vitamin D from the cholesterol in the skin [74]. Vitamin D promotes bone formation and strengthens the musculoskeletal system [75]. However, the acute effects of large amounts of UV radiation include DNA damage, sunburns, phototoxic and photoallergic reactions, and suppression of the immune system [76]. Photoaging caused by a heavy dose of UV radiation is one of the reasons for premature skin aging [77]. Prolonged UV overexposure ultimately causes an increase in the expression of β-galactosidase, which is a biomarker for skin aging [64]. In addition, UV radiation damages skin cell fibers, which are called elastin [78]. When these fibers break down, the skin begins to sag, stretch, and lose its ability to regain its original shape after stretching [79]. The skin also bruises and tears more easily, and it takes longer to heal [79]. The long-term effects of UV radiation exposure on the skin and lips include cutaneous melanoma, a life-threatening malignant skin cancer, and other types of skin cancers [80].

At least three distinct mechanisms exist by which ginseng extract, ginsenosides, and gintonin protect skin cells or skin in *in vitro* or *in vivo* studies, respectively, against UV radiation–induced skin damage [29–34] (Figs. 1–3). First, ginseng extract reduces skin cell damage caused by UV exposure. This is achieved by increasing the viability of keratocytes and fibroblasts by reducing lactate dehydrogenase release and increasing the expression of anti-apoptotic genes such as BCL-2 and BCL-XL [81]. The second is the anti-inflammatory effect of ginseng components, as described above. Ginseng components reduce NO production and decrease cyclooxygenase-2 (COX-2) and TNF-α transcription, indicating that ginseng components inhibit UV exposure–induced inflammation [81,82]. The third mechanism is anti-oxidant effects. Ginseng components, such as ginsenoside Rc, prevent UV-induced increases in ROS production and pro-MMP-2 and -9 levels in human keratinocytes [82]. In addition, treatment with ginsenoside Rc results in increased glutathione content and enhanced SOD activity following exposure to UVB radiation [82]. Furthermore, ginsenoside Rc treatment enhances caspase-14 activity and counteracts the UV-induced downregulation of filaggrin expression [82]. However, no significant difference was observed between ginsenoside Rc-treated skin and normal skin in terms of keratinocyte viability, regardless of exposure to UV radiation. This study suggests that ginsenoside Rc may exert anti-photoaging and barrier function–protective effects in keratinocytes, thus protecting the skin against photo-oxidative stress induced by exposure to UV radiation [82]. In addition, ginseng extract may exhibit anti-aging properties by inducing procollagen gene expression and inhibiting matrix metalloprotease-1 gene expression caused by UV exposure [82]. These results showed that the anti-wrinkle effect of Korean red ginseng involved the inhibition of collagen degradation rather than increased collagen synthesis under UV exposure. Thus, ginseng extract-, ginsenosides-, and gintonin-induced alleviation of UV-induced skin cell damage via anti-oxidative and anti-inflammatory effects might be a result of the inhibition of overexpression of β-galactosidase, a photoaging marker, which was increased by UV exposure.

5.4. Roles of growth factors in skin health: LPA and LPA receptors, EGF receptor transactivation, and VEGF release

LPA is one of blood-borne lysophospholipids with diverse biological activities, including stimulation of cell growth, cell survival through the prevention of apoptosis, modulation of cell shape through regulation of the actin cytoskeleton, and cell migration [10]. LPA is a lipid-derived growth factor [11]. LPA receptors are first derived from the endothelial cell differentiation gene (Edg family) in blood vessels and are activated by LPA for blood vessel development and vascular maturation [12]. In addition to their angiogenic actions, LPA and its cognate receptors are involved in multiple physiological processes in the skin. LPA and LPA receptors not only regulate skin function but also play important roles in hair follicle development and skin wound healing in humans [83]. Gintonin, an exogenous LPA receptor ligand, stimulates skin cell proliferation and migration, increases collagen and hyaluronic acid synthesis, facilitates hair growth, and promotes *in vitro* and *in vivo* wound healing [48,49].

EGF has multiple functions in skin cells. EGF is a mitogenic growth factor, especially in skin epithelial cells [53], and is now considered an important candidate molecule for skin regeneration. Many kinds of cosmetics contain EGF as an ingredient [40]. Thus, EGF plays a pivotal role in wound healing and maintaining tissue homeostasis by regulating epidermal cell survival, proliferation, migration, and promotion of blood vessel formation [53]. In vitro studies have shown that EGF promotes the migration and contractility of aged fibroblasts and increases the synthesis of both hyaluronic acid and collagen [84]. Although ginseng components such as ginsenosides and ginseng polysaccharides have no effect on EGF release and EGF receptor regulation, gintonin, via LPA1/3 receptor subtypes, transactivates the EGF receptor through the c-Src pathway, resulting in increased EGF receptor phosphorylation and stimulation of cell migration [55]. Interestingly, gintonin also stimulates the release of heparin-binding EGF-like peptide (HB-EGF), an autocrine and paracrine keratinocyte growth factor that binds to EGF receptors and stimulates keratinocyte cell growth and migration [51]. Thus, gintonin might play a dual role in skin health–related EGF receptor activation; one is the direct transactivation of the EGF receptor through LPA receptor regulation; the other is the release of HB-EGF, a member of the EGF family, to facilitate skin wound healing through EGF receptor activation [51] (Fig. 2).

Another factor regulated by ginseng extract and its components, such as ginsenosides and gintonin, is VEGF, which is closely related to new blood vessel formation [85]. Angiogenesis is a prominent feature of wound healing processes [85]. VEGF plays a role in several aspects of the wound repair process [85]. Although several different mediators regulate angiogenesis, VEGF is believed to be one of the most important pro-angiogenic mediators during wound healing [86]. Multiple cellular sources likely contribute to the increase in VEGF levels after skin injury [86]. VEGF, which is normally expressed at low levels by epidermal keratinocytes, is upregulated in these cells in injured skin [87]. Studies in human wounds and animal models have indicated that VEGF is produced by keratinocytes early in the wound-healing process [88]. Therefore, promoting VEGF activity may promote skin regeneration by enhancing blood vessel formation and tissue wound recovery. Ginsenosides Rb1, Rg1, and other ginsenosides stimulate the release of VEGF from blood vessel endothelial and skin cells [89]. Gintonin also stimulates VEGF release from neuronal cells such as astrocytes, blood vessel endothelial cells, and skin cells [90]. Gintonin-mediated VEGF release in skin cells via LPA1/3 receptors activates VEGF-related downstream signaling pathways to facilitate the progress of wound healing [90]. Thus, gintonin-mediated skincare might involve growth factors and both EGF/EGF receptor and VEGF/VEGF receptor signaling pathways via LPA receptor regulation (Fig. 2).

6. Effects of ginseng extract and ginseng ingredients in skin diseases

Ginseng extracts and their components also alleviate some skin diseases as described in below section (Table 1).

6.1. Roles of ginseng extract and ginseng ingredients in the treatment of atopic dermatitis

Atopic dermatitis (AD) is a chronic, pruritic, and inflammatory skin disorder [91] and is considered a representative skin disorder, especially in children; however, the causes of AD are not yet clear [91]. Atopic skin lesions are usually associated with severe rashes, edema, hemorrhage, and desquamation [91]. In addition, histopathological examination of atopic skin lesions shows epidermal thickening and infiltration of inflammatory cells, such as eosinophils and mast cells [92]. Ginseng extracts and ginseng components, such as ginsenosides and gintonin, have been tested for the amelioration of the symptoms of 2,4-dinitrofluorobenzene (DNFB)-induced AD in an NC/Nga mouse model [93].

It was reported that oral administration or topical application of ginseng extract or ginsenosides attenuated AD-like skin lesions and scratching behavior [94]. Both decreased not only the mRNA expression of inflammation-related cytokines such as IL-1β, IL-4, IL-6, IL-8, and IL-10 and TNF-α but also that of serum IgE and IFN-γ in mice [59,95]. In addition, both treatments decreased the DNFB-induced MAPKs activity. Histologically, both inhibited dermatitis lesions such as hypertrophy, hyperkeratosis, and infiltration of inflammatory cells into the epidermis and dermis [41]. Thus, ginseng extract- and ginsenoside-induced alleviation of AD may be owing to anti-inflammatory effects, as observed in other skincare effects, although little is known about the other molecular mechanisms underlying the anti-AD effects of ginseng extract and ginsenosides.

Recent studies have shown that gintonin-mediated anti-metastasis and antitumor activities are achieved via its inhibitory effects on autotaxin (ATX) activity [96]. Interestingly, recent evidence has also shown that ATX activity and levels are significantly elevated in human patients with AD compared to those in normal subjects, which indicates that ATX may be involved in human atopy [97,98]. As described above, gintonin exerts anti-inflammatory effects via the inhibition of proinflammatory cytokine production by immune cells, in addition to the strong inhibition of ATX activity. Lee et al. (2017) showed that oral administration of gintonin to mice with DNFB-induced atopy for 2 weeks reduced ear swelling and the atopy skin index to a greater extent compared to treatment with saline alone. Oral administration of gintonin also reduced the serum levels of IgE, histamine, IL-4, and INF-γ [52]. Histological examination also showed that the oral administration of gintonin attenuated skin inflammation and significantly reduced eosinophil and mast cell infiltration [52]. Moreover, oral administration of gintonin not only decreased serum ATX levels but also reduced serum ATX activity. Overall, the anti-AD effects of ginseng extract and ingredients might be attributed to anti-inflammatory activity and inhibition of serum ATX activity in an AD animal model.

6.2. In vitro and in vivo effects of ginsenosides on formations of skin hypertrophic scars and keloids

Hypertrophic scars and keloids occur as results of excessive scar formations [42]. Keloids grow beyond the original wound and are unlikely to regress, which is not observed in hypertrophic scars. These scars decrease the quality of life of patients greatly, due to the pain, itching, contracture, cosmetic problems, and so on, depending on the location of the scars [42]. Although the exact pathogenesis of hypertrophic scar and keloid formations is unknown [42], the pathogenesis is hypothesized to involve fibroblast dysregulation of the normal healing process resulting in excessive production of collagen and extracellular matrix proteins (MMPs). Growth factors and cytokines are also altered in keloid scars, with increased amounts of TNF-α, interferon-β and interleukin 6. Thus, NF-κB, TGF-β1, IL-6 and MMP-2, which are an important role in keloid formation pathogenesis [43]. Recent studies showed that ginsenosides have beneficial effects by inhibiting hypertrophic scars and keloids formation at cellular levels and rabbit model. For example, ginsenoside Rb1 (0.56 mg intradermal injection after rabbit ear wound) was also effective to reduce scar elevation index via inhibitions of the mRNA expression and immunohistochemical reactivity of scar related factors such as MMP2, tissue-inhibitor of metalloproteinase 1, α-smooth muscle actin, and TGF-β1 in rabbit model [44]. Similarly, treatments of 20(*R*)- and 20(*S*)-ginsenoside Rg3 (50 and 100 μg/ml for 3 days) significantly inhibited cell proliferation, collagen synthesis, vascularization and extracellular matrix (ECM) deposition through TGF-β/Smad and Erk signaling pathways in human hypertrophic scar-derived fibroblast and keloid-derived fibroblast, respectively [45,46]. In addition, 20(*S*)-ginsenoside Rg3 reduced hypertrophic scar formations via the inhibition of collagen accumulations and down-regulations of VEGF expression in rabbit model (topical application with 4 mg/ml) [47]. These reports show a possibility that ginsenosides can be used for attenuations or preventions of abnormal skin scar and keloid formations, if the effects of ginsenosides are proved after clinical tests.

7. Conclusion

Recent *in vitro* and *in vivo* studies, as described above, suggest that ginseng ingredients can be used in functional and medicinal cosmetics because they exhibit anti–skin aging and anti-wrinkle effects, facilitate wound healing and whitening, stimulate hair growth, and even inhibit hypertrophic scars and keloids [28,42–47] (Table 1). Developing target-oriented functional or medical cosmetics with enhanced levels of ginseng ingredients matching those in functional foods containing ginseng may be necessary. However, it might not be easy to enhance ginseng ingredients in cosmetics, as ginseng root itself is an expensive herb, and individual ginsenosides are even more expensive. An alternative for lowering the cost of ginseng ingredients is to utilize ginseng byproducts produced during the cultivation and processing of red ginseng products. This could be a way to upcycle ginseng byproducts and increase their added value [99].

In addition, if different ginseng components or fractions are combined as cosmetic ingredients, they can complement each other, leading to additive or synergistic effects for skincare and skin health. For example, although target membrane receptors for ginsenosides do not exist, they have been proven to exert beneficial effects through non-receptor-mediated mechanisms, such as non-specific antioxidative and anti-inflammatory effects within the skin system [100]. In contrast, ginseng-derived gintonin or KRGM gintonin-containing LPAs have a high affinity for membrane LPA receptor subtypes in skin cells and exert specific cascade effects through these receptors using $[Ca^{2+}]_i$ transients [64]. Thus, by adding both ginsenosides and gintonin, the non-receptor-mediated anti-oxidative stress effects and anti-inflammatory effects, respectively, can be combined in a single cosmetics product, as the effects of gintonin, which are achieved through LPA receptor regulation, distinguish it from those of ginsenosides and ginseng polysaccharides.

In conclusion, ginseng is a traditional herbal medicine used to improve physical and mental health in Asian and Western countries. Recently, ginseng utilization has rapidly expanded into cosmetic fields for skincare and skin health for various purposes, including whitening and hair growth, as appearance is as important as the body in the current times of increased life expectancy. Finally, in the future, a strategy involving the combination of individual ginseng ingredients from simple ginseng extracts using ginseng byproducts might be needed to develop specific skin target–oriented functional and/or medicinal cosmetics.

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