Arch Dermatol Res (2015) 307:397–403
DOI 10.1007/s00403-015-1569-8

REVIEW

Ginsenosides and their metabolites: a review of their pharmacological activities in the skin

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Received: 26 October 2014 / Revised: 17 March 2015 / Accepted: 29 April 2015 / Published online: 30 May 2015

Abstract Ginsenosides are representative pharmaceutical compounds found in various forms in *Panax ginseng*, a traditional medicinal plant. They are converted to their metabolites Rg2, Rg3, compound K, and others by human intestinal microflora following ingestion. Numerous studies have demonstrated beneficial effects of ginsenosides against aberrant molecular processes responsible for cancer, metabolic diseases and neurodegenerative diseases. Recently, antiaging effects of ginsenosides in human skin have been reported from clinical trial and in vitro model data. Ginsenosides have hence been proposed as promising natural cosmeceutical agents. In this review, we will critically review the known biological effects of several ginsenosides (Rb1, Rg3, Rd and compound K), such as anti-inflammatory and anticancer activities, which arise from the modulation of diverse molecular pathways. The application potential of ginsenosides as cosmeceutical ingredients will also be reviewed.

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Keywords Ginsenoside metabolites · Rb1 · Rd · Rg3 · Compound K

Introduction

Ginseng refers to the root and rhizome of *Panax ginseng* (*P. ginseng*) and is a representative medicinal herb belonging to the *Araliaceae* family. There are seven major species of ginseng distributed throughout East Asia, Central Asia, and North America [2]. The name ginseng comes from the Chinese word '*jen-shen*' (man-herb), while the name *Panax* originates from Greek roots meaning "cure-all". Indeed, *P. ginseng* has been widely used as a traditional herbal medicine for more than 2000 years. Among the *P. ginseng* species, Asian ginseng (*P. ginseng* C. A. Meyer) is the most widely used and studied, and is believed to exhibit properties that promote longevity and improve overall health. Indeed, recent accumulative data have demonstrated that *P. ginseng* and its constituents exert protective effects against chronic diseases such as cancer [9], circulatory diseases [13, 66], and metabolic syndrome [21, 42].

There are many bioactive constituents in *P. ginseng*, of which ginsenosides are the principle compounds responsible for its biological activity [2]. Many researchers have thus sought to unravel the underlying molecular mechanisms responsible for the purported beneficial effects of ginsenosides on human health [30, 36, 43, 44]. Thirty-one ginsenosides have been identified to date, with some novel ginsenosides recently reported. Based on their structure, ginsenosides are classified into two groups: protopanaxadiols (PPDs) and protopanaxatriols (PPTs) [11, 57]. PPDs include the compounds Rb1, Rb2, Rc and Rd, while PPTs include Rg1, Re, Rf and Rg2. Although the base scaffold is

similar between the two groups, their pharmacological effects are markedly different.

Recently, with increasing reports on their beneficial effects on skin health, ginsenosides have drawn attention as potential cosmeceutical agents. In terms of skin cosmetology, ginsenosides are one of the safest and most potent natural antiaging agents for skin, and have been used for 1000 years. Several works of traditional literature have mentioned the skin protective and improving effects of ginsenosides [14, 17, 34, 37]. Indeed, some studies have reported beneficial effects such as antiwrinkle formation and protection against excessive sun exposure using in vitro [6, 14] and in vivo models [37, 56, 64].

However, despite the long history of *P. ginseng* use, the underlying molecular mechanisms responsible for the pharmacological activity of *P. ginseng* components, especially their cosmeceutical activities, are poorly understood. Hence, a better understanding of the bioactive properties and underlying mechanisms of the individual ginsenosides is necessary to unveil their potential application as cosmeceutical agents.

Major ginsenosides: background

Rb1 is one of the major ginsenoside components and is present at concentrations of approximately 0.4–0.5 % in ginseng extracts. A previous study has reported that Rb1 is the major ginsenoside, constituting more than 80 % of the total ginsenosides present in *P. ginseng* [51]. Rb1 content in ginseng extract varies depending on the manufacturing and processing procedures. Rb1 is readily transformed to its metabolites in the human body, and under acidic conditions is converted to Rg3 in the gut [16]. In the human intestine, various microorganisms contribute to the metabolism of Rb1 [35, 38, 53, 58], with ginsenoside Rd and compound K arising as the major metabolites (Fig. 1) [35, 38, 53]. This microorganism decomposed to small size ginsenoside in the human intestinal organ (Fig. 1). Due to the pharmacological activities of Rb1 and compound K, many researchers have sought to develop and accelerate the enzymatic biotransformation of Rb1 [7, 18, 25, 55].

Rg3 is another major PPD ginsenoside and is exclusively found in red ginseng, and is also bioconverted from Rb1 by human intestinal microflora. After administration of 400 mg/kg of fermented red ginseng extract in rats, 41.7 μg min/ml of Rg3 was detected in the plasma [4]. Due to the pharmacological activity of Rg3, many researchers have tried to enhance its production by mimicking biotransformation processes [10, 54, 55]. For example, Yang et al. [55] demonstrated the use of recombinant *β*-glucosidase from *Microbacterium esteraromaticum* to facilitate the biotransformation of Rb1 to Rg3.

Although Rd is only present in trace quantities, it is one of the most potent ingredients in *P. ginseng* [36, 43, 49]. In 2000, Kim et al. [3] isolated three human intestinal bacterial strains: *Eubacterium* sp., *Streptococcus* sp. and *Bifidobacterium* sp., which contribute to ginsenoside Rd production via their metabolic activity. Furthermore in previous study, nearly 1 μM of Rd was detected in rat plasma, after 8 h of *Panax notoginseng* (16 ml/kg) oral administration [46]. Many researchers have attempted to produce ginsenoside Rd from Rb1, Rb2 and Rc by hydrolyzing and removing a sugar moiety to establish a more economically feasible method of production [20, 33, 48, 68].

Compound K [20-*O*-*β*-D-glucopyranosyl-20(*S*)-protopanaxadiol] is a ginseng saponin metabolite which is produced by intestinal bacteria. 0.9 μg/ml and 0.2 μg/ml of compound K was detected in human blood and urine, respectively, after 150 mg/kg day [67]. The production mechanisms of compound K were first identified by Kobashi's group [1] in 1998, who reported that compound K is detected after oral administration of Rb1 by hydrolyzing bacteria such as *Eubacterium* sp. A-44. Indeed, it has been reported that increased plasma concentrations of

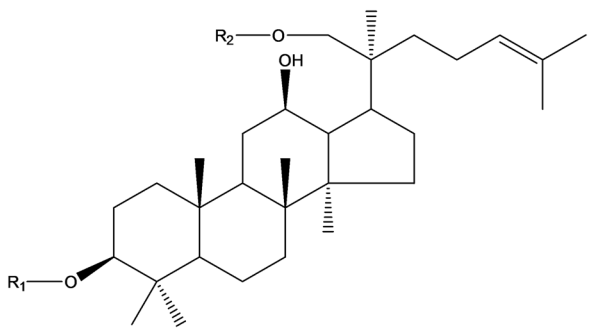

Fig. 1 Chemical structure of ginsenosides

Ginsenoside	Structure formula	Empirical formula
Rb1	R1 : Glc-Glc R2 : Glc-Glc	$C_{54}H_{92}O_{23}$
Rg3	R1 : Glc-Glc R2 : H	$C_{48}H_{82}O_{18}$
Rd	R1 : Glc-Glc R2 : Glc	$C_{42}H_{72}O_{13}$
Compound K	R1 : H R2 : Glc-Glc	$C_{36}H_{62}O_{8}$

compound K arise after oral administration of fermented Korean red ginseng extract in healthy Korean subjects [32].

Biological activities

A number of studies have investigated the biological activities of Rb1 in skin tissue (Table 1). Wound healing promotion is a well-known physiological property of Rb1, and acceleration of the wound healing process occurs via the modulation of various cellular signaling factors such as monocyte chemoattractant protein-1 and hypoxia-inducible factor-1α [27, 37]. In 2006, Sakanaka's group demonstrated the burn wound healing action of Rb1 using in vivo and in vitro models, and suggested that the underlying mechanism of Rb1 relies on the induction of vascular endothelial growth factor (VEGF) and interleukin-1β expression. Notably, the doses of Rb1 used in the study were relatively low, between 0.1 and 10 fg/g in ointment in the study [37]. Furthermore, some studies have demonstrated the skin protective effects of Rb1 against ultraviolet (UV) exposure. UV is a leading cause of skin diseases, including skin aging and cancer. Cai's group [5] reported a reduction in UV-induced apoptosis of HaCaT cells after Rb1 treatment. While DNA mutation by UV irradiation normally results in apoptosis, Rb1 treatment resulted in a suppression of UV-induced apoptosis. It was suggested that the anti-apoptotic effects of Rb1 on UV-treated cells is due to the induction of the body's DNA repair system, most likely through nucleotide excision repair (NER). Meanwhile, the antiaging effects of Korean red ginseng in skin were demonstrated using replica analysis in a mouse model [26]. In this study, the animal diet was supplemented with 2.5 % red ginseng extract, which reduced wrinkle formation induced by UVB. Simultaneously, decreased matrix metalloproteinase-1 (MMP-1) expression and increased type I procollagen levels were observed in the group supplemented with 2.5 % red ginseng, which may have contributed to the antiwrinkle formation effect. Interestingly, Rb1 is the most abundant compound in Korean red ginseng, at 43.5 mg/g of extract [26].

Accumulating evidence in the literature is unraveling the various biological effects of Rb1 in skin. Nevertheless, the direct molecular mechanisms and targets have not been clearly elucidated. It is therefore necessary for future studies to clarify such unknown mechanisms.

It has been well documented that Rg3 exerts a protective effect against cancer [15, 41, 68], neurotoxicity [24], and metabolic disease [21, 42, 50] (Table 1). In regard to its anticancer properties, an increase in cancer cell apoptosis is a major outcome [22, 41, 52]. In a previous study, ginsenoside Rg3 induced the intrinsic apoptotic pathway in hepatocellular carcinoma (HCC) cells by altering apoptosis-related gene expression. In addition, it was observed

Table 1 Phramacological activities of ginsenosides and their molecular mechanisms in the skin

Ginsenoside	Pharmacological activities on the skin	Molecular targets/mechanisms	References
Rb1	Wound healing	Stimulate of VEGF production via HIF-1α expression	[37]
	Antiwrinkle formation	Increase of type I collagen expression through PPARδ	[26, 39]
		Decrease of mRNA or protein level of MMP-1	
	Photoprotection	Inhibit UV-induced DNA damage by inducing NER complex, such as XPC and ERCC1	[5, 65]
		Down-regulate the expression of p16, p21 and p53	
	Hair loss prevention	Induction of p63 expression	[44]
Rd	Immune-suppression	Reduce the CD4(+) and CD8(+) T cells	[64]
	Hair loss prevention	Induction of p63 expression	[44]
	Wound healing	Increase of intracellular cAMP levels and phosphorylated CEBP expression in nucleus	[36]
Rg3	Antitumor	Reduce TPA-induced activation of NF-κB and ERK	[8, 28, 61]
		Down-regulation of NF-κB and AP-1 transcription factors	
	Anti-scar formation	Decrease of VEGF and collage Type I	[12, 60]
Compound K	Antiwrinkle formation	Up-regulate production of type I collagen	[17]
	Photoprotection	Increase the expression of NER complex, such as XPC and ERCC1	[6]
	Skin hydration	Induce HAS1 upregulation and HA production	[34]
	Anti-atopic dermatitis	Reduce MDC level in serum, eosinophils' infiltration and mast cells in skin, and cytokine production in splenocytes	[31]

that ginsenoside Rg3 not only inhibits HCC tumor growth and pathology in an animal model, but also improves overall survival [22]. Mitochondrial-mediated apoptosis pathways have also been suggested as another mechanism of action for ginsenoside Rg3 [52], which increases cellular reactive oxygen species (ROS) production and subsequent accumulation of cytochrome C in the cytosol. Recently, the anti-photoaging activity of ginsenoside Rg3 was reported [45]. In this previous study, ginsenoside Rg3 reduced the major phenomenon of photoaging, oxidative stress and MMP-2 activity.

The neuroprotective effects of ginsenoside Rg3 have been investigated [24] by focusing on its anti-inflammatory effects. Ginsenoside Rg3 suppresses cytokine expression in Aβ42-treated BV-2 cells and blocks the nuclear factor (NF)-κB signaling pathway. Antiobesity and antidiabetic effects of ginsenoside Rg3 have been demonstrated in several models [21, 42, 50]. In 2009, Hwang et al. [21] described the antiobesity activity of ginsenoside Rg3 by demonstrating its effect on the regulation of AMP-activated protein kinases and the peroxisome proliferator-activated receptor (PPAR)-γ in 3T3-L1 cells. In addition, the antidiabetic effect of ginsenoside Rg3 has been suggested [42], as increasing glucose transport by upregulating glucose transporter 4 mRNA expression.

Taken together, these results show that although ginsenoside Rg3 exhibits a variety of biological effects against chronic diseases such as cancer, obesity and diabetes, its direct targets have not been identified. It is therefore necessary to elucidate the direct molecular target(s) of Rg3.

The best-described biological activity of ginsenoside Rd is related to neurogenesis [47, 62], neuroprotective [43] and anti-ischemic effects [19, 49] (Table 1). In 2012, Zhao's group conducted a clinical study to elucidate the effect of ginsenoside Rd on acute ischemic stroke in 390 patients. The trial group received a 14-day intravenous infusion of ginsenoside Rd. Notably, the ginsenoside Rd group showed significant improvement across the overall distribution of scores compared to placebo, and there were significant differences between the two groups [49]. After 2 years, this study group has unraveled the underlying mechanism of ginsenoside Rd on anti-ischemic activity [19] using the Sprague–Dawley rat model. Ginsenoside Rd significantly reduced apoptosis-inducing factor release and NF-κB p65 subunit accumulation. These effects have also proposed to be responsible for the anti-inflammatory activity of ginsenoside Rd [30], and were observed not only in LPS-induced RAW264.7 cells, but also in LPS-administered ICR cells in a mouse model. In the LPS-induced group, aberrantly increased nitric oxide and prostaglandin E2 levels were detected, while ginsenoside Rd treatment reduced these markers. Furthermore, the down-regulation of inducible nitric oxide synthase, cyclooxygenase-2 and NF-κB was suggested to be the underlying mechanism of ginsenoside Rd [30].

The cosmeceutical activities of ginsenoside Rd have not been clearly elucidated in comparison to other protopanaxadiol compounds. However, the potential applications for ginsenoside Rd in cosmeceuticals have been suggested in several previous papers [36, 44, 64]. Sung et al. [36] demonstrated the wound healing effect of ginsenoside Rd using keratinocyte progenitor cells and human dermal fibroblasts, which was later confirmed by a laser burn wound model. In addition, this group proposed that the cyclic AMP-dependent protein kinase pathway is associated with ginsenoside Rd-regulated wound healing. Interestingly, increased type I collagen and reduced MMP-1 expression were detected in ginsenoside Rd-treated cells [36]. Given the importance of type I collagen and MMP-1 in wrinkle formation, this result underlines the potential of Rd as a promising anti-photoaging agent. The prevention of hair loss by ginsenoside Rd has also been demonstrated using the shaved skin of B57CL/6 mice. After treatment with ginsenoside Rd on the skin, cell genesis in different phases of adult hair follicles was investigated. The results indicated that ginsenoside Rd promotes hair growth via cell growth acceleration, with the underlying mechanism of ginsenoside Rd proposed to be the induction of p63 expression in hair follicles [44].

As described above, the various biological activities of ginsenoside have been demonstrated using in vitro and in vivo models, as well as clinical studies. Although the cosmeceutical effects of ginsenoside Rd remain poorly understood in comparison to the other ginsenosides, its potential for application is becoming increasingly clear. Further studies on the effects of this compound are necessary.

Recently, compound K has received increasing attention due to its pharmacological activity (Table 1). Indeed, various studies have outlined its biological activity and underlying mechanisms of action [16, 28, 59, 65]. The anticancer activity of compound K has been studied for several decades [29, 63, 69]. In a colon cancer model, compound K induced both apoptotic and autophagic pathways via ROS generation and c-Jun NH2-terminal kinase activation [29]. Wang et al. [63] revealed that compound K increases apoptosis in bladder cancer T24 cells via ROS generation and p38MAPK activation. The compound also inhibits the growth of acute myeloid leukemia cells via suppression of DNA synthesis and cell cycle arrest [9].

Above all, compound K has been regarded as a promising new cosmeceutical agent, due to its biological activities in the skin [6, 17, 34, 56]. The improved anti-aging potential and safety of fermented red ginseng (FRG) compared to red ginseng (RG) is notable, because

compound K is a major metabolite of FRG [40]. In a previous study, although the total ginsenoside content was similar between FRG and RG extracts, the ginsenoside metabolite content was higher in FRG (14914.3 μg/ml) than RG (5697.9 μg/ml). Furthermore, FRG extract caused not only tyrosinase inhibition and increased elastase activity, but also decreased the effect of skin irritation [40]. In 2011, Liu et al. [17] demonstrated that compound K inhibits UVA-induced type I procollagen degradation and MMP-1 activation. After UV irradiation of skin, increased MMP-1 breakdown of collagen matrix in the dermis resulted in the formation of wrinkles [14]. Thus, compound K has been proposed as an anti-photoaging cosmetic ingredient.

Additionally, the anti-apoptotic effect of compound K has been investigated in a UV-exposed human keratinocyte model [6]. Hyaluronic acid synthase (HAS) produces hyaluronic acid (HA), which acts to retain a large amount of water in the skin [59]. Increased HAS2 and HA expression was detected after compound K treatment in HaCaT cells and hairless mouse skin, respectively. This study group recommended the possibility of compound K in therapeutic applications. Although, the pharmacological activities of compound K have been well established using various experimental models, further clinical trials are required to expand its potential applications.

Summary

Although *P. ginseng* has been widely used as a medicinal plant, the underlying mechanisms and direct targets of its constituent compounds remain to be fully understood. Among the various ginsenosides, Rd and compound K, in particular, have received increased attention for their natural antiaging effects in skin. Numerous studies have demonstrated that these ginsenosides act as regulators of intracellular signaling pathways. Ginsenoside Rd exhibits wound healing effects in keratinocyte and fibroblast models by regulating cAMP-dependent protein kinase pathways [36]. Furthermore, our group has confirmed that compound K induces HA expression by activating Src/ERK and Akt signaling pathways in HaCaT cells (unpublished data). However, in comparison to the number of studies on other mechanisms of ginsenosides such as for cancer and obesity [27, 29, 38, 41], research on the antiaging effects in skin remains relatively sparse.

Due to the fact that ginsenoside is primarily administered orally, it is necessary to understand the metabolic pathways and bioavailability of ginsenosides in the human body. Indeed, after administration of 20(*S*)-protopanaxadiol in rats, the 23 metabolites were characterized in plasma, bile, urine and feces. The metabolites of 20(*S*)-protopanaxadiol are produced by demethylation, dehydration, dehydrogenation, oxidation, deoxidation and glucuronidation [23]. Most ginsenosides are converted to their metabolites in the gastrointestinal tract. Many studies have reported similar or superior effects of metabolites in comparison to their parent ginsenosides [6, 34, 69]. Further studies and deeper insights into the interactions between ginsenoside compounds and their metabolites with cellular targets will facilitate the development of novel medicinal and cosmeceutical products.

Acknowledgments This work was supported by the Leap Research Program Grant (2010-0029233) of the National Research Foundation, Ministry of Science, ICT and Future Planning, Republic of Korea.

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