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The functional evolution of Korea ginseng: black ginseng

Myoungsook Lee[1*]

Abstract

Korea ginseng (*Panax ginseng* C.A. Meyer) has been used in traditional medicinal foods for more than 2000 years. Because of the growing interest in personalized healthcare to prevent diseases, white ginseng (WG) is technically evolving into highly qualified products with reinforced specific functionalities of ginsenosides, such as red ginseng (RG) or black ginseng (BG). Using the PubMed research engine, we found 225 BG-related published papers from 1995 to 2024. The most common papers ($n=46$) were related to processing technologies, such as ginsenoside transformation, manufacturing processes and product evaluation. Reviewing papers on the functionality of BG with in vitro and in vivo models, they usually cover the basic mechanism of functionality, such as antioxidant ($n=38$), antitumor ($n=28$), menopausal ($n=26$), anti-inflammatory ($n=24$) and immune ($n=20$) mechanisms. There are insufficient studies that are directly related to diseases such as obesity, diabetes mellitus, hypertension and liver disease; moreover, a significant randomized controlled trials study of BG was not found. In this study, we reviewed the research trends on the technologies and functionalities of BG in Korea and forecasted the potential of BG as a new material for healthcare in the industry.

Keywords Korea black ginseng, Systematic review, Anti-oxidant, Anti-obesity, Anti-inflammation, Chemoprevention

Introduction

Korea ginseng (*Panax ginseng* C.A. Meyer) has been used in traditional herbal medicine for more than 2000 years [1]. Since Korea ginseng contains more than 34 various ginsenosides unlike Chinese and American ginseng, it is used as a therapeutic herbal medicines worldwide because of its beneficial effects on cardiovascular, metabolic and immune functions [2–7]. Because of the growing interest in personalized health to prevent diseases, white ginseng (WG) is continuously evolving into highly qualified products with specific type of ginsenosides having different functionalities, such as red ginseng (RG) and black ginseng (BG). Compared to WG, which is simply dried fresh ginseng without steaming, RG and BG are made by the repetition of steaming and drying fresh ginseng. As the number of cycles, the steaming/drying process increased, the color changed from red brown (RG) to black (BG) [8].

The functional effects of WG (high-Rb1, Rg1, Rc and Rb2), RG (high-Rb1, Rc, Rg1, Rb2) and BG (high-Rk1, Rg3 and Rg5) are well known. Although total proto-ginsenosides are lower in BG (0.14%) than in WG (3.95%) and RG (2.92%), a new type of BG that has a unique ginsenoside profile, and non-ginsenosides, such as polysaccharides, amino acids, polyphenols, flavonoids, vitamins and trace elements, was identified [9]. Compared to WG and RG, BG has been shown to have positive pharmacological activities in antioxidant, anticancer, cholinesterase inhibition, antidiabetes, antiaging and hyperlipidemic effects, but its ability to enhance immunity and protect the liver is more predominant in RG than in BG [10, 11]. At present, various ginsenosides are significantly

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improved by the enzyme treatment or biotransformation by the gut microbiota, which increases the absorption rate or pharmacological effects to regulate multiple mechanisms in the human body [12]. However, metabolic evidence for the functionality of BG has not been clearly elucidated by clinical trials.

BG, as a functional food of medicine and nutritional supplement, has come to the market in various products, such as candy, cookie, drink, porridge and soup. With the safety of mass-producing specific ginsenosides or mixing other ingredients, the new customized BG products have been developed in the industry as functional health foods or medicines characterized by good nutrition, flavor and texture [13]. Currently, the size of the global ginseng market is $2.5 billion, and the medicinal properties and efficacy of ginseng have gradually been scientifically proven [14]. However, for the products of BG with specific ginsenosides to succeed in the industrial market, first, methodology of processing and manufacturing should be improved. Standardization of the methodology is needed because specific ginsenosides are produced differently according to different methods [15]. Second, more meaningful biomarkers should be developed because the same biomarker is sometimes used as a marker for multiple diseases. Third, safety issues and difficulties in mass production for minor ginsenosides should be solved by high-tech technologies [16]. In this study, we reviewed the research trends on the technologies and functionalities of BG in Korea and forecasted the potential of BG as a new material for healthcare in the industry.

Research methods and data collection

Through the PubMed research engine, 225 published reports of BG during 1995–2024 were found. Most of papers were related to processing technologies ($n=46$) including ginsenoside transformation and manufacturing processes. The functionality reports of BG include characteristics that are often described in terms of basic mechanisms to prevent diseases, such as antioxidants ($n=38$), menopause ($n=26$), anti-inflammatory ($n=24$) and immunity ($n=20$) rather than reports directly related to diseases such as diabetes mellitus (DM; $n=11$), obesity (n=7), hypertension ($n=3$) and non-alcoholic fatty liver disease (NAFLD; $n=1$). [Fig. 1] Therefore, we focused on basic mechanisms to prevent diseases, such as antioxidant and inflammatory effects, cancer, obesity, circulation and antiaging (senescence).

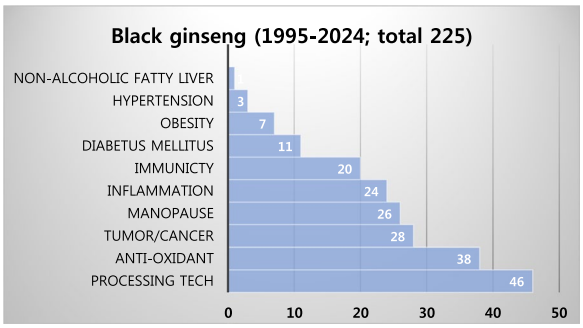


Fig. 1 Various functionality of BG identified by published paper during 1995–2024 (PubMed search engine)

Key findings and discussion

Ginsenosides of the BG process

BG is a relatively new product in Korea, and its black color is imparted via a "kujeungkupo" process which includes 9 cycles of steaming and drying [15, 17]. Ban et al. determined the optimum conditions, such as steaming at 113.04 °C for 18 h and drying at 100 °C for 8.03 h, although Rg3 levels and phytochemicals (polyphenols) increased as the temperature/time for steaming/drying increased [17]. Carcinogens have also increased at higher temperatures and longer times; therefore, many methodologies have been developed because of their effectiveness and efficiency in obtaining valuable target materials. The specific ginsenosides present in the BG were analyzed by HPLC (Waters Alliance 2695, Milford, MA, USA), and the end-products from 1 to 9 cycles of steaming at 95–100 °C for 1.5 h and drying at 48 °C for 2 h are shown in Fig. 2. Although the standard preparation steps of BG have not been established, two ways to prepare BG including "repeated steaming/drying" and "fermentation" are organized by researchers.

During the steaming process, ginsenosides transform into specific ginsenosides by hydrolysis, dehydration and isomerization at C-3, C-6 or C-20, and reducing sugars, acidic polysaccharides and phenolic compounds increase [18]. Compared to the WG and RG, this steaming process results in BG containing relatively less polar ginsenosides such as 20(S)-protopanaxadiols (PPD) series (Rb1, Rb2, Rc, Rd) and 20(S)-protopanaxatriols (PPT) series (Re, Rg1), which feature a very simple pattern with Rg3, Rh1 and Rk1 accounting for approximately 80%. Ginsenosides in the BG, such as Rg1, Rg3, Rh1, Rh2, Rb1, Rb2, Rb3, Re, Rf, Rc, F1, F2 and CK, were identified [8, 19, 20]. Structures of PPD/PPT and dehydro-PPD/-PPT are shown in Fig. 3 [21]. BG in water and ethanol extracts has higher levels of ginsenosides Rh1, Rg2 and Rb1 than RG, and the levels of these three ginsenosides are greater in ethanol extracts than in water extracts [20]. Park et al. reported that there were no differences in the contents of ginsenosides after 5 or 9 steaming/drying cycles. Similarly, Rh1, Rg3 and Rk1 increased after 3 steaming cycles. The content of Rg3 in BG was 8.20 mg/g, approximately 18 times greater than that (0.46 mg/g in RG). In addition, the ratio

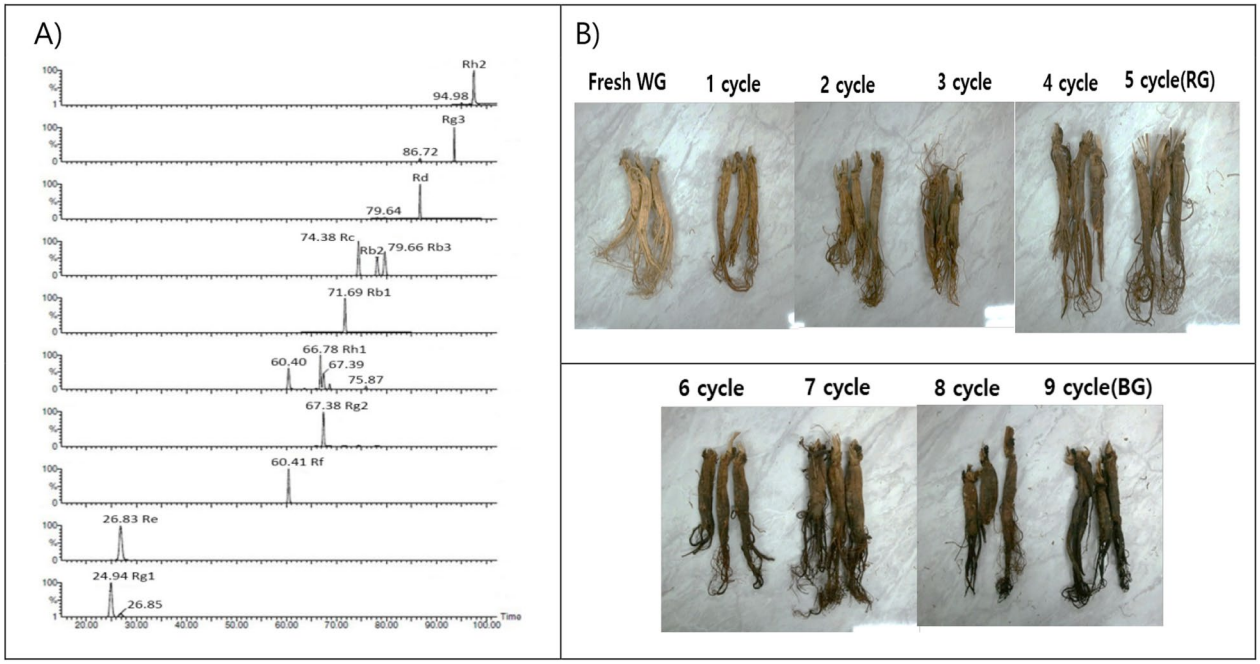
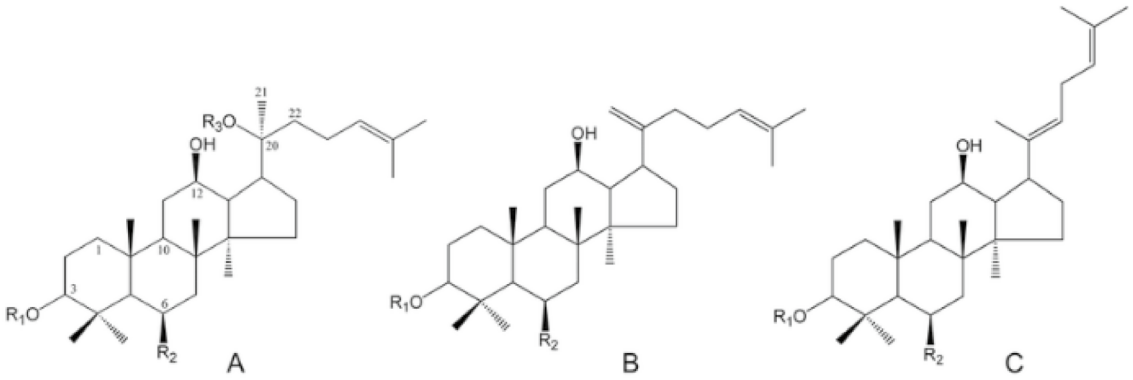


Fig. 2 Standard of ginsenosides, Rh2, Rg3, Rd, Rb3, Rb1, Rh1, Rg2, Rf, Re, Rg1 was detected by HPLC (**A**; Ref [19]) and the end-products from WG to BG during the 9 cycles of steaming at 95–100 °C for 1.5 h and drying at 48 °C for 2 h (**B**)

of PPD and PPT increased from 1.9 to 8.4 as the number of steaming cycles increased [8]. Interestingly, to maximize the absorption rate or diversify the pharmacological effects of ginsenosides, technique involving enzyme treatment or biotransformations has been developed. Most major ginsenosides of PPD or PPT were converted to low molecular weight (MW) by the gut microbiota during the deglycosylation, oxygenation and hydrolysis processes. PPD series (Rb1, Rb2, Re) were changed to CK by *Bacteroides, Bifidobacterium, Eubacterium, Fusobacterium* and *Provotella oris*, but PPT series were converted to Rh1, Re and Rh1 by *Bacteroides, Eubacterium* and *Fusobacterium* [22, 23]. The high activity of β-glucosidase from *Lactobacillus* and *Leuconostoc* significantly increased ginsenoside transformation from high to low MW [24].

In the conventional method of steaming, the ginsenosides available for significant activity are insufficient, and the carcinogen benzopyrene is also generated at high temperature; thus, a fermentation process for BG has been developed. [25]. JM An and SM Lee developed a simple method of steaming from 9 to 2 cycles to increase the content of irradiated phonon and ginsenosides [26]. After the 1st and 2nd steaming steps, the fermentation step in which *Saccharomyces cerevisiae* was placed in the extract was subjected to enzyme processing with α-amylase and cellulase. The levels of Rb1, Rb2, Rc, Re, Rg1, Rg3 and Rh1 and the levels of irradiated phonon were 8–12 times or 6 times greater than those of the conventional method, respectively. Moreover, the fermentation, coating and ultraviolet irradiation stages are advantageous for preventing benzopyrene from being detected [27]. Ginseng is typically processed within one week of harvesting; however, a method for storing at low temperature to prevent spoilage has been developed to improve its safety by limiting benzopyrene production during processing. Fermentation at different times and temperatures can increase Rg3 (25–26%) and Rh2 (threefold) and results in a unique aroma [28–31]. Immersion in citrate or sodium citrate with fermentation promoted the production of the rare ginsenosides Rg3, Rg5 and Rk1 [32, 33]. Daedong Korea Ginseng Co. Ltd. developed fermentation technologies for mass-producing rare ginsenosides Rg3, Rk1, Rg5 Rf, Rg2, Rb3, Rd and Rh2 using yeast fermentation. [34.] In particular, fermented BG concentrate extracted from buckwheat sprouts, dried figs and fingerling mushrooms received good scores in the sensory evaluation of consumers' aroma and taste. The total phenol content and antioxidant activity of functional BG increase as the oriental medicine technique of BG is steamed or immersed in makgeolli which is a traditional Korean liquor made by adding yeast to rice or wheat [35]. In another experiment, raw sun-dried ginseng was fermented from fruit and vegetables and then steamed and dried [33]. Han et al. also obtained Rh2-rich BG (0.21%) by fermentation of fruits and vegetables [29].



Ginsenosides	R1(C3)	R2(C6)	R3(C20)	Structure
PPD				
Rb1	GlC(1-2)Glc	H	GlC(1-6)Glc	A
Rb2	GlC(1-2)Glc	H	Arap(1-6)Glc	A
Rc	GlC(1-2)Glc	H	Araf(1-6) Glc	A
Rd	GlC(1-2)Glc	H	Glc	A
F	Glc	H	Glc	A
Rg3	GlC(1-2)Glc	H	H	A
CK	H	H	Glc	A
Rh2	Glc	H	H	A
PPT				
Re	H	GlC(2-1)Rha	Glc	A
Rf	H	GlC(2-1)Glc	H	A
Rg1	H	Glc	Glc	A
Rg2	H	GlC(2-1)Rha	H	A
F1	H	H	Glc	A
Rh1	H	GLC	H	A
DHPPD				
Rk1	GlC(1-2)Glc	H	H	B
Rk3	H	Glc	H	B
Rg5	GlC(1-2)Glc	H	H	C
DHPPT				
Rh4	H	Glc	H	C

Fig. 3 Chemical structures of **A**, **B** and **C** types of ginsenosides. PPD: protopanaxadiol, PPT: protopanaxatriol, DHPPD: dehydroprotopanaxadiol, DHPPT: dehydroprotopanaxatriol, Glc: β-D-glucopyranosyl. Arap:α-L-arabinopyranosyl, Araf:α-L-arabinofuranosyl and Rha:α-L-rhamnopyranosyl

According to patent (KR100529475B1), the total saponin concentration of BG was greater in roots (85.4 mg/g) rich in Rg3(11.99 mg/g) than in the body(66.5 mg/g) [36]. In addition, Rd-enriched BG was developed by hydrolyzing starch and the PPD ginsenoside into Rd (1.00–7.00 mg/g) which has a high sugar content of 5.00–7.00 Brix [37]. It is

necessary to select a suitable starter or catalyst, and there are very strict requirements for time, temperature and humidity during fermentation to enhance the quality of BG. Efficient starters can shorten the fermentation time, and the best fermentation temperature, which depends on the selected starter, is 30–65 °C, and the fermentation humidity is 50–80%. However, the fermentation technologies explored for BG and their optimized parameters are still not unified; therefore, scientific and standard fermentation methods need to be further studied.

Initially, the BG manufacturing process involved the simple process of separating and recombining saponins from different part (head, body, root, leaf, etc.) to obtain specific active ingredient [38]. Gradually, various food technologies such as fermentation and enzyme methods are being used for diversification depending on the purpose of developing, strengthening or increasing the amounts of active ingredients. (Table 1) If the products of RG or BG with specific ginsenosides are popular on the markets, first, the methodology of processing and manufacturing should be standardized because specific ginsenosides are produced differently according to different methods [15]. Second, safety issues and difficulties in mass production for minor ginsenosides should be solved. In the future, high-quality technology for RG or BG production as future products will be needed for healthcare purposes.

Functionality of the BG

Antioxidant effect

Oxidative stress involves elevated intracellular levels of reactive oxygen species (ROS), to maintain cellular homeostasis and support physiological functions. The excessive release of ROS can result in the development of antioxidant defense systems such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx). However, insufficient ROS scavengers are correlated with ATP-depleted cell damage, chronic inflammation and apoptosis-induced cell death [4].

Repeated heat processing causes the releasing phenolic compounds and Maillard reaction products, which enhances the anti-inflammatory and free radical scavenging activity of BG compared with WG or RG [39]. Fermented ginseng, which also contains many less polar ginsenosides, was reported to have a detoxifying effect against H_2O_2-induced hepatotoxicity in HepG2 cells [40] Choudhry et al. reported that CK, Rg-3 and Rg-5-enriched BG exhibited significantly greater antioxidant activity and total phytochemicals (flavonoid and polyphenol) than WG and RG. BG inhibited apoptosis and therefore protected cells from H_2O_2-induced AML-12 hepatocyte damage, probably through ROS scavenging [41]. Many pharmacological studies have shown that the compounds K(CK)-rich Rg-3 and Rg-5 have several health-promoting effects, such as anti-inflammatory, antitumor and antioxidant potential [42]. BG extract decreased ROS and NO production and reduced iNOS expression levels in vitro and in vivo in zebrafish embryos due to Rb1, Rg3 and Rk1 on endoplasmic reticulum stress [43]. The main PPT types in BG, such as Rg4, Rg6, Rh4, Rg2, have been reported to exhibit various biological activities including antiseptic, antidiabetic, wound-healing, immune-stimulating and antioxidation. RGX365, rare PPT-enriched BG, such as Rg2, Rg4, Rh1, Rh4, suppressed inflammatory gene iNOS via the inhibition of p-STAT-1 and NF-kB. Therefore, BG has both antioxidant and anti-inflammatory effects [44].

In high-fat/high-fructose-induced non-alcoholic fatty liver disease (NAFLD) mice**,** Rg3 and Rk1-rich BG significantly reduced lipogenic gene expression, ROS and plasma aminotransferase (AST/ALT) but increased antioxidant enzymes activities (catalase, and superoxide dismutase) as well as that of HepG2 cells [45]. Rg5-rich BG, a rare ginsenoside, has been reported to alleviate acetaminophen-induced hepatotoxicity due to its antioxidant, antiapoptotic and anti-inflammatory effects [46]. Fetal alcohol syndrome is caused by excessive ethanol consumption during pregnancy. In a whole embryo culture study, BG protected ethanol-exposed embryotoxicity through pre-/post-natal growth retardation, central nervous system dysfunction, behavioral abnormalities and facial dysmorphology [47]. BG has antioxidant effect on metabolites of oxidative stress produced by ethanol, such as ROS superoxide, hydrogen peroxide and hydroxyl anion. A major rare saponin from BG, Rk1, has antioxidant and antiapoptotic effects on cisplatin-induced nephrotoxicity in HEK-293 human embryonic kidney cells [48]. **C**isplatin has been proven to be useful for the clinical treatment of malignant tumors, but its' clinical application is limited because of the side effects of cisplatin on nephrotoxicity. Rk1-rich BG suppressed oxidative stress by increasing nuclear factor erythroid 2-related factor 2 and heme oxygenase-1 and cisplatin-elevated Bax, cleaved caspase-3/-9 and increased Bcl-2 were reversed. Rg3 (20 mg/kg/d) has therapeutic properties in $AlCl_3$ (64 mg/kg/d for 120 days)-induced oxidative stress in rat bone disorders like osteoporosis. It decreased ROS and MDA, while GPx and SOD activities were increased. Moreover, Rg3 facilitates bone formation by increasing Ca, P, type I collagens, osteocalcin, bone alkaline phosphatase activity [49].

Compared to WG and RG, BG showed antioxidant effects; however, this variant was inferior to RG in enhancing immunity, relieving fatigue, alleviating depression/anxiety, decreasing body fat and reducing blood pressure.

Table 1 National patents to develop the methods of BG process

#of patents (Date)	Assignee	Title	Contents
KR100496418B1 (2005-06-28)	PanaxKorea Co, Ltd	Manufacturing method of black rootlets of ginseng	Processing the root portion of the ginseng having the highest content of saponin
KR100529475B1 (2005-11-21)	HJ Kim	Making method of BG	Use 4 years BG, root (85.4 mg/g) > body (66.5 mg/g), Rg(11.88 mg/g) and Rg3 (11.99 mg/g) in roots ▲
KR100543862B1 (2006-01-23)	HEUKSAM KOREA CO.,LTD	A black ginseng having excel content of active ingredient and the concentrate of BG	With rootlets, contents(mg/g) were for Rg3(9.0 ~ 15.0), Rb1(1.5 -5.0), Rb2(1.0- 4.0), Rc(1.0- 4.0), Rd(1.0- 6.0), Re(0.2–1.5), Rf(0.6-1.5), Rh1(1.0–1.2), Compound K(0.05- 0.1)
KR100692294B1 (2007-03-12)	CJ Park	Manufacturing method of BG extracts having chemopreventive effect about large intestine cancer	The steaming and aging process 7 times and dried to a moisture 14% or less
KR100753771B1 (2007-08-31)	JW Lee	The manufacturing process of the BG and BG concentrate	Develop total saponins (mg/g) of 80–300 with 25 steps and produce high Rg3, Rg2, Rd, Rf, Rh1, etc
KR100729214B1 (2007-06-19)	Korea Bio Red Ginseng Co.,Ltd	Making manufacture of BG	High-crude saponin (57.03 mg/g) and Rg3 (163.1 mg/100 g)
KR20080106077A (2008-12-04)	YJ Park	A method for preparing novel black-red ginseng and the extract there from and the composition comprising the same	Anticancer ginsenosides with Rg2, Rg3, Rh1, Rh2, Rk1, Rg5 and less benzopyrene
KR100910585B1 (2009-08-03)	BOMUN PHARMACY & FOOD. CO., LTD	Fermented BG and the method of preparing it	Fermentation technique was developed by mature process with low temperature High Rh2 (19.8 times), Rg3(21.3 times) and essential amino acids
KR101064719B1 (2011-09-15)	JM An	Manufacturing method of BG comprising step to coat	Rb1, Rb2, Rc, Re, Rg1, Rg3, Rh1 and irradiated phonon ▲ No benzopyrene
KR101058875B1 (2011-08-23)	JM An	BG manufacturing method	
KR101152827B1 (2012-06-12)	JM An	Manufacturing method of BG comprising step irradiating ultraviolet rays	
WO2012074159A1(2012-5-7)	JM An and SM Lee	Black ginseng production and method	Fermentation with *S. cerevisiae* and enzyme methods with α-amylase and cellulase
KR101776288B1 (2017-09-11)	Danurim Inc	BG liquor using decocting BG and the manufacturing method thereof	Using rootlets, develop BG liquor with high Eg2, Rg3 and amino acids High scores of sensory evaluation
EP2203151B1 (2017-04-19)	Amorepacific Corporation	Use of melanin biosynthesis inhibitors from ginseng for skin whitening	High-ginsenoside F1 from tails and leaves
KR101982680B1 (2019-05-27)	Geumsan Dukwon Co. Ltd	BG-enriched ginsenoside Rd	Developed Rd-enriched BG (1–7 mg/g) with a-amylase (*B. licheniformi*) cellulase (*T. reesei*), glucoamylase (*A. niger*) and increased sugar content (5–7 Brix)
KR102209028B1 (2021-01-28)	SS Joo	Pharmaceutical composition for preventing or treating of neurodegenerative diseases comprising fermented steam-dried ginseng berry	Expression of acetylcholine, inhibition of amyloid-beta accumulation in dementia-animal model

Table 1 (continued)

#of patents (Date)	Assignee	Title	Contents
KR102366845B1 (2022-02-24)	Daedong Korea Ginseng Co.Ltd	Method for producing BG concentrate with enhanced specific ginsenoside content using yeast fermentation	Using yeast fermentation, high-Rg3, Rk1, Rg5, Rf, Rg2, Rb3, Rd, Rh2 contents Good scores in consumers' sensory evaluation of aroma and taste
KR102503431B1 (2023-02-27)	Ginseng by Pharm Co.Ltd	Composition for preventing, improving or treating coronavirus infection containing BG as an active ingredient	Prevention of COVID-18 virus infection with enzyme processing

Anti-inflammatory effect

Inflammation is the immune response to infection with harmful substances, such as bacteria or viruses, and immune cells detect them and secrete numerous inflammatory mediators [50]. Psychological stress reactions, such as increased heart rate and body temperature, and increased antioxidative, apoptotic and inflammatory metabolism, lead to stress responses. The stress responses change the expression of various genes related to the metabolism and can eventually contribute to various diseases. Therefore, the excessive release of ROS during stress can result in the development of chronic inflammation. ROS in the intestines activate the JNK associated with NF-κB signals, resulting in damage to the intestinal barrier. In addition, ROS activates NF-κB directly through the others, TNF-α, interleukin (IL-)-1β and IL-6 [51].

Ginseng is known to act as an immune modulator that maintains homeostasis and enhances resistance to illness. Rb1 had a 15%-27% neuroprotective effect on activation of microglia in the penumbra via downregulation of IL-6 NF-κB expression in rats with cerebral ischemia [52]. Song et al. reported that treatments with JP5 (RG extract with high Rg5/Rg3) and BG1 (BG extract with Rk1/Rg3) inhibited the expression of inflammatory proteins, such as p-NF-κB and TNF-α, a key inflammatory signaling factor, in both heat-stressed liver and HepG2 human hepatocellular carcinoma cells [53]. In a RCT, the administration of 1.5 g RG three times daily for 12 weeks did not significantly affect inflammatory markers, including hs-CRP, in metabolic syndrome participants [54]. Rb1, Rg3 and Rk1-rich BG extracts also recovered NAFLD-induced shortened villi, inflammatory immune cell infiltration, upregulated IL-6 and binding immunoglobulin expression in NAFLD mouse model [43]. Lee et al. also reported Rg5-enriched BG have greater anti-inflammatory and antinociceptive effects on LPS-induced RAW 264.7 cells than do Rg1 and Rb1-enrich RGs [55]. BG better inhibits the pro-inflammatory mediators, iNOS and COX-2 and the pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α. Korean BG has potent anti-inflammatory and antioxidant activities by reducing ROS, TNF-a, IL-6 and MCP-1 in cigarette/lipopolysaccharides-exposed animals and PMA-stimulated human airway epithelial NCI-H292 cells [56]. However, Park et al. reported no significant differences in the levels of biomarkers associated with inflammation, glucose metabolism and lipid metabolism in the head, face and body temperatures of humans treated with BG extracts (KGR-BG1;1500 mg) [57].

Atopic dermatitis (AD) is a chronic inflammatory skin disease with chronic recurrent outcomes characterized by itching, dryness, eczematous lesions and keratin. In particular, the frequency of AD occurrence has increased among young people including 10–20% of children and elderly people, and AD is recognized as a social problem beyond being a medical problem [58]. Although the pathogenesis of AD has not yet been completely elucidated, it is an immunological change caused by an imbalance between Th1 and Th2 cells, resulting in the secretion of the inflammatory cytokines IL-4, IL-6, IL-8, IL-13, MCP-1, IgE and tumor growth factor-β (TGF-β) [59]. However, the inhibitory effects of BG extract (radix/leaf) on IL-6, IL-8 and MCP-1 secretion by *Dermatophagoides pteronissinus*-induced human leukemia THP-1 and MCP-1 cells are highly significant [60].

During the COVID-19 pandemic, researchers used medications to block cytokines storm syndrome (CSS) including IL6, IL-8, IL2 and TNF-α, which are deadly complications of COVID-19 like respiratory failure. *Panax ginseng* is suggested as a therapeutic agent to prevent CSS due to its ability to block IL-6 pathway [61]. It is important that Korean ginseng has potential effect of CSS; therefore, the effects of BG on COVID-19 should be studied in the future.

Chemopreventive effects

The oral toxicity of BG extract was evaluated for its cytotoxic and pharmacological activities in six cancer cell lines derived from human carcinomas of different origins. BG was shown to elicit cytotoxic activity against several cancer cell lines, such as A-431(skin), (fibrosarcoma), MCF-1 (breast cancer), A549(lung), NCI-N87 (stomach), HepG2 (liver), Capan-1(pancreas), HT-1080 HT-29(colon) [62, 63]. Compared to 20(S)-Rg3, low-dose BG extract has greater effects on cell viability, and Rg5 is the main effector of the cytotoxic activity of BGE. Flavored BG with high Rg5 inhibited the growth of tumors in H_{22} tumor-bearing mice in a dose-dependent manner at doses of 250, 500 and 1000 mg/kg, improved immune function and induced tumor cell apoptosis [64]. BG significantly decreased the solid cancer masses in xenograft mouse models. Rg3 significantly inhibited the metastasis of SKOV-3 ovarian cancer cells or SKOV-3 tumor-bearing mice. The inhibitory effect of Rg3 is partially due to the inhibition of tumor-induced angiogenesis and a decrease in invasive ability and MMP-9 expression [65]. Compared to WG, Rg3, Rh1 and Rh2-rich BG (800 ug/ml) have antitumor effects on colon 26-M3.1 carcinoma cells and anti-inflammatory effects, such as a reduction in TNF-a expression in LPS-activated macrophages [66]. Rg3 and CK, 20-O-β-(D-glucopyranosyl)-20(S)-PPD, major ginseng metabolites deglycosylated by the human gut microbiome, or bioconversion from Rb1 by *Leuconostoc citreum* LH1 of Kimchi, showed significant antiangiogenic effects on many cancer cell lines,

including pulmonary, gastric and ovarian cancer cells [67]. CK exerts anticancer effects via multiple molecular mechanisms, including the inhibition of proliferation, invasion and migration, the induction of apoptosis and autophagy, and antiangiogenic effects in vitro and in vivo in models of 10 types of cancer [68]. CK is involved in apoptosis signaling via P38 MAPK/AMPK-mTOR/JNK pathway, autophage via the PisK-Akt-mTOR pathway and migration inhibition via ERK-MMP9/MMP2 pathway. Therefore, the antiangiogenic effects of CK might have therapeutic potential for controlling the growth and invasiveness of different cancers.

Minor ginsenosides, Rh2, Rh1, a PPD/PPT aglycone, reduced the proliferation of various cultured cancer cells and induced apoptosis by altering membrane integrity, while Rg3 has also been shown to possess antitumor properties [69, 70]. Rh2 in the BG inhibited the proliferation of human tumor cell lines, such as B16 (mice melanoma), HeLa(cervical), SK-HEP1 (hepatocellular) and PC-3 (prostate), with P53-dependent FAS expression-related apoptosis via downstream caspase-8/9 activation by mitochondrial cytochrome C release [71]. 2-Deoxy-Rh2 exhibits remarkable anticancer effects on various human cancer cells by suppressing glucose uptake and mitochondrial respiration [72]. While Rg3, CK and Rh2-high BG have been shown to have both chemopreventive and antiangiogenic effects, the Korea Company Ginseng Science developed antitumor BG product, and Rg3 was approved as a new drug adjuvant for cancer patients in China [73, 74]. At present, validation of the safety of daily administration is very important. BG extract was added to SD rats at 0–2000 mg/kg for 28 days, and NOAEL of BG extract (2000 mg/kg) was used as the essential safety information for human consumption. [62, 75]

Antiobesity effects

Obesity, as a disease and actively researched prevention and treatment, can greatly increase the risk of developing diabetes, high blood pressure, hyperlipidemia, coronary artery disease, stroke, arthritis, etc. If obesity is left untreated, it can result in astronomical socio-economic costs. According to the Health Functional Foods Act, there are 25 body fat reduction functional ingredients approved by the Ministry of Food and Drug Safety in Korea. We would like to forecast the potential of BG as a material to increase added value as a research object for pharmacological substances.

After high-fat diet-induced obesity (DIO) in beagle dogs, 12 weeks of BG and silkworm administration reduced plasma TG and TC, and nine genes (NUGGC, EFR3B, RTP4, ACAN, HOXC4, IL17RB, SOX13, SLC18A2 and SOX4) associated with obesity were differentially expressed in the BG [76]. This study revealed that obesity-related differentially expressed genes could be important candidates involved in the mechanism of the antiobesity effects. Rg3 significantly suppressed lipid accumulation, a marker of adipogenesis and the mRNA level of aP2 which plays an important role in adipocyte differentiation, in a time- or dose-dependent manner in 3T3-L1 [77]. When the extract of Rg3-enriched BG (100 mg/kg/d) from 5-year-old fresh ginseng was administered daily for 3 weeks, BG persistently suppressed weigh gain, the weight of both epididymal and abdominal fat and plasma TG compared to WG and RG [78]. Rg3 dose-dependently inhibited the expressions of adipogenic markers such as fatty acid synthase (FAS), peroxisome proliferator-activated receptor gamma (PPAR-γ) and CCAAT/enhancer binding protein alpha (C/EBP-α) in 3T3-L1 cells. However, Rg3 (0.1 mg Rg3/kg diet, 8 weeks) did not significantly affect body weight gain and fat pads [79]. Therefore, Rg3 has shown potential for use in reducing fat accumulation.

Rh1 (20 mg/kg) suppressed the protein expression of PPAR-γ, C/EBP-α, FAS and aP2 in 3T3-L1 cells and decreased body weight gain, and epididymal fat and plasma TG levels as well as F4/80, CD68, TNF-α, IL-6 and IL-1β in DIO mice [80]. Both of the BG in the water and ethanol extracts had higher levels of Rh1, Rg2 and Rb1, and the levels of the three ginsenosides were greater in the ethanol extracts than in the water extracts [20]. BG with ethanol extracts significantly regulated phosphorylation of adipogenetic factors, such as PPAR-γ, C/EBPα and AMPK in 3T3-L1 cells, and promoted secretion of anti-inflammatory cytokine, such as IL-10 and decreased MCP-1 infiltration in 3T3-L1 cocultured with RAW264.7 cells [20]. They also found that BG in ethanol extracts extended the doubling time of stem cells from subcutaneous fat in mice. BG with high Rb1 promotes browning by inducing uncoupling protein 1 (UCP1) expression in 3T3-L1 cells and primary white adipocytes [81]. Rb1 suppressed the expression of adipogenic genes such as C/EBPα and sterol regulatory element-binding transcription factor-1c, but enhanced the expression of specific markers of browning, such as PR domain containing 16 (PRDM16), PPAR-γ coactivator-1 alpha (PGC-1α) and UCP1.

In the DIO model, the gene expression levels of TNF-α, IL-6 and MCP-1 in the subcutaneous abdominal adipose tissue of mice significantly increased with aging [82]. Immune cells such as macrophages and T cells can infiltrate adipose tissue and are responsible for the inflammatory cytokine production [83]. Rh1, Rg2 and Rb1-rich BG from ethanol extracts reduced the ratio of M1(MCP-1)/M2(IL-10) macrophages produced by adipose tissues [20]. Upregulated inflammatory cytokines and macrophage-specific genes precede a dramatic increase in

circulating-insulin levels in DIO; therefore, rosiglitazone can downregulate macrophage-induced genes [84]. The inflammatory state is the main sources of pro-inflammatory cytokines in adipose tissue. It is believed that a new obesity research model related to relationships between obesity and inflammation or the immune system is needed to develop new BG products with specific ginsenosides.

Ginseng extracts or Rb1 has been proven to reduce BMI and lipid accumulation by decreasing the ratio of *Firmicutes* to *Bacteroidetes*, because *Bacteroides, Parabacteroides* and *Lactobacillus* probiotics are upregulated to reduce the abundance of bacteria that can induce obesity [85]. HFD consumption increased the abundances of microbiota, such as *Firmicutes, Deferribactes* and *Tenericutes,* but reduced the abundances of *Proteobacteria, Verrucomicrobia and Bacteroidetes.* RG increased *Proteobacteria* and *Verrucomicrobia* reduced by HFD, decreased *Firmicutes,* and *Tenericutes,* which were increased by HFD [86]. The presence or absence of saponins in ginseng may have different effects on the gut microbiota composition under a HFD. The gut microbiota may be a potential target for ginseng to prevent or treat metabolic diseases; however, the interaction between ginsenosides and the microbiota has not been clearly explored, particularly for BG.

Circulation improvement (glucose and lipid metabolism)

In oriental medicine, ginseng, a pharmaceutical raw material, has been used to treat diabetes and complex diseases for a long time. Since antidiabetic functionality of various ginsenosides in ginseng has been reviewed, Seo et al. reported that the specific ginsenosides have antidiabetic effects via different mechanisms, and these effects do not depend on the type of WG, RG or BG [87]. Moreover, not only saponins but also non-saponins (glycans, glycopeptide, etc.) can improve blood glucose and insulin resistance. In terms of insulin secretion or sensitivity, Rg3, Rb1, Rg1, Rg5 and CK reduce apoptosis by decreasing caspase-3 and Fas, and activating insulin secretion with increasing AMPK in Rattus beta cells [88]. CK increased insulin secretion in HIT-T15 cells**,** a beta cell line and mouse insulinoma MIN6 pancreatic β-cells [89, 90]. In STZ-induced diabetic mice, 200 mg/kg of BG reduced hyperglycemia and increased the insulin/glucose ratio by improving β-cell function [91]. The inhibition of β-cell apoptosis by BG in the pancreas was associated with suppression of the cytokine-induced NFκB signals. Moreover, these antidiabetic effects of BG were more potent than those of RG [92].

Previous studies have reported that Rb1, Rb2, Re, Rg1 and Rg2 are effective in gluconeogenesis, and that Rb1, Rc, Rg3, Re, Rh2 and CK affect glucose uptake in adipose or muscle tissues [87]. BG significantly reduced fasting blood glucose because it enhanced enzyme activity related to glycolysis, the HMT shunt and the degradation of fatty acids. Kang et al. reported that the mechanisms of BG ethanol extract may be associated with suppressing gluconeogenesis by AMPK activation and affecting glucose uptake in lever tissues via the glucose transporter (GLUT) upregulation [92]. BG delays diabetes-associated muscle atrophy by activating mTOR. The major bioactive compounds including Rg1, Rg3(S), Rg3(R), Rg5, Rk1 and Rh4 were evaluated for their effects on glucose uptake in C2C12 myotubes, and Rh4 significantly ($p < 0.05$) increased glucose uptake with increasing GLUT-1/-4 [93]. BG also depressed pyruvate carboxykinase and glucose 6-phosphatase during gluconeogenesis, and glycogen phosphorylase on glycogenolysis. However, BG increased the expression of the genes, such as GLUT-1, GLUT-4 and acyl-CoA oxidase, carnitine palmitoyl transferase 1a and medium chain acyl-CoA dehydrogenase for beta oxidation [93]. In Zhu's study, the levels of serum FBS, insulin, creatinine, urea and UA in Rg5-treated diabetic nephropathy mice were significantly reduced, while the renal histopathology was markably improved [94]. The BG with high Rg5 significantly reduced ROS production, expressions of oxidative stress markers, Nox4 and TXNIP, in the kidney. Rg5 inhibited the expression of the NLRP3 inflammasome (NLRP3, ASC and Caspase-1) and the inflammatory cytokines (IL-1β and IL-18), but the expression of NF-kB and the p-p38 MAPK were decreased with Rg5. According to cohort research on diabetic nephropathy, among diabetic nephropathy who received Rg3-rich RG ($n = 107$) for a long time (1986–1995), approximately 7% of patients received hemodialysis, which was lower than the general proportion of 30% [95].

Ethanol-extracted BG has been shown to have both hypoglycemic and hypolipidemic effects on type 2 diabetic db/db mice. Rh4, Rg5 and Rk1-enriched BG regulated glucose and lipid metabolism as evidenced by a reduction in hepatic steatosis caused by a reduction in insulin resistance and ROS in liver. BG also decreased adipogenesis by decreasing both PPAR-γ in adipocytes and GLUT-4/-2 in liver and muscle [11]. Saba et al. reported that BG extracts efficiently reduced serum lipids, total cholesterol (TC) and low-density lipoprotein (LDL) levels, in high-cholesterol diet-fed SD rats [96]. The expression of key genes involved in liver lipogenesis, such as acetyl-CoA acetyltransferase-2, 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase and sterol regulatory element-binding protein 2, was increased. BG extract reduced the accumulation of fat in adipose tissues and inhibited the neutral fat content in liver cells [96]. According to the reports that WG (6 g/d for 8 wks) has

hypolipidemic effects by improving serum lipid profiles and lipid peroxidation in humans, a similar effect of BG will be expected in humans [97]. In DOX-induced heart failure animal model, BG (total saponin; 30, 60, 120 mg/kg) could dose dependently regulated autophagy and apoptosis in cardiomyocytes by upregulating the expression of proteins involved in autophagy signaling pathways, such as p-Akt/Akt and p-mTOR/mTOR [98]. As a result of the pharmacological action of Rg3 in BG, an inhibitory effect on blood coagulation and antithrombotic efficacy was observed in both in vitro and in vivo experiments. In addition, antihypertensive effect of BG, medicinal food, was verified in hypertensive model [99]. In RCT for metabolic syndrome patients ($n=62$), RG (3 g/d for 4wks) decreased blood pressure and increased mitochondrial function [100]. In mild-hypertensive patients who exhibited pre-hypertension (120/80–139/89 mmHg) and stage I hypertension (140/90–159/99 mmHg), Korean ginseng and Chinese ginseng had greater antihypertensive effect than American ginseng at the same doses of 4.5 g/d for 4 weeks [101].

Antiaging

Recent advances have been made on the antiaging mechanism of BG, but it is inadequate. The major mechanism by which BG is associated with aging is limited to oxidative stress through the scavenging of ROS; therefore, we focused on the antiskin-aging properties and neuroprotective effects of BG in the brain.

Aged skin is caused by UV light, ROS, environmental pollution and various pathogenic conditions such as aging and cancer. These conditions impaired the skin structure by increasing melanogenesis (tyrosinase) and ROS-induced inflammation (mitogen-activated protein kinase; MAPKs signals) and degrading collagen and elastin (collagenase/elastase) as an antiwrinkle effect [31, 102].

BG inhibited the production of matrix metalloproteinase (MMP)-1/-13 by regulating MAPKs and NF-kβ pathways in human fibroblasts [28]. Without cytotoxicity, fermentation of BG with *Saccharomyces cerevisiae* significantly increased the expression level of type I procollagen, an antiwrinkle marker, in HS68 human fibroblast [103]. In a clinical study ($n=23$), fermented BG-induced type I collagen synthesis and inhibition of MMP-1 activity. It also reduces melanogenesis by inhibiting tyrosinase and reducing the oxidation of DOPA, leading to skin whitening [31]. Using C2C12 myoblasts, Lee et al. reported that BG (20 ug/ml) enhanced myoblast differentiation and myotube growth via Akt/mTOR/p70S6K activation [102]. The fermentation of BG with *Aspergillus niger* strain KHNT-1 had antiskin aging properties, such as antimelanogenic, antiwrinkle and antioxidant activities. It also inhibited tyrosinase and melanin production in B16F10 murine melanoma cells [104, 105]. This fermented BG stimulated antiwrinkle effects in UVB-irradiated human dermal fibroblasts by inhibiting elastase and MMP-1/-9 activation, and increasing antioxidant activity in H_2O_2-induced HaCat human epidermal keratinocytes [104]. Fermented RG made from *L. brevis was* also used as an ingredient in cosmetic products. Since the contents of ginsenosides did not differ much between RG and BG, the antiaging potential of fermented RG or BG was evaluated based on differences in the concentrations of non-ginsenosides such as polyphenols and flavonoids. However, many studies have been shown that the contents of ginsenoside metabolites, such as CK, Rh1, F2 and Rg2, and tyrosinase and elastase inhibitory activities are greater in fermented RG [106, 107]. Interestingly, the fermentation process had better antimelanogenic, antiwrinkle, skin irritation and allergen, and antioxidant effects than those of non-fermented ginseng [108].

Neurodegenerative diseases associated with aging are characterized by severe damage to the cholinergic system; therefore, neurotrophic factors play crucial roles in the growth and differentiation of neurons such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) [108]. In an aged mice (18 months), BG (200 mg/Kg/d for 16wks) protected against DNA damage in the brain via significant expression of choline acetyltransferase, vesicular acetylcholine transporter, growth-associated protein 43, synaptosomal-associated protein 25, NGF and BDNF as well as RG [109]. Rg3-rich BG (30 mg/kg/d) in 10-month-old model reduced TG, TC, FBS and ROS levels, and increased antioxidant activity, choline acyltransferase and acetylcholine (ACh) transporters. The effects of the BG extract were greater than those of WG and RG extracts [110]. Alzheimer's disease is a brain disorder characterized by a progressive decline in cognitive functions and the degeneration of cholinergic neurons in the central nervous system. BG roots with high levels of RK3, Rh4 and 20(S)/(R)-Rg3 delayed dementia by increasing brain ACh as cholinesterases inhibitors and reducing oxidative damage in the brain [111]. These results suggest that BG may suppress cognitive decline with aging via the regulation of antioxidant systems. Rh1-enriched BG-induced neuroprotective effects by activating the phosphoinositide 3-kinase or Akt signaling pathway in amyloid-β-induced neuroblastoma cells [28]. Saba et al. found that BG-enriched Chong-Myung-Tang, which is widely used in Korea as a memory, improves agent in high-school students and improves memory capacity by Morris Water Maze test in rats. The molecular mechanism of action may involve the suppression of oxidative and inflammatory stress (COX-2, lL-1β) related to MAPK- NF-kB pathway. This result can

Table 2 Functional effects of BG in vitro, in vivo and human studies

Function	Model	Treatments (Dose/Period)	Target/Mechanisms	References
Antioxidant	Whole embryo culture	BG EtOH (1, 10, 100ug/ml;2 days)	mRNA antioxidant enzymes (GPx) ▲	[46]
	PERK & XBP1 KO MEF cells	BG Ext with high Rb1, Rg3 & Rk1 (0, 10, 50, 100, 200 ug/ml)	H_2O_2-induced ROS, NO, INOS ▼	[43]
	Zebrafish	BG (0, 1, 10, 50, 100, 200 μg/mL)	H_2O_2-induced ROS, ▼	[43]
	NAFLD mice	Rb1, Rg3 and Rk1-rich-BG (0.5,1, 2%)	ER stress markers ▼ Glutathione, catalase ▲	[44]
	H_2O_2--induced AML-12 hepatocytes	Rg3/CpK/Rg5-rich BG	BG enhanced antioxidant activity with ROS scavenging compared to WG and RG, and inhibited apoptosis	[41]
	Chemical assay	RK3, Rh4, 20(S)/(R)-Rg3 rich BG (0-10 mg/ml)	DPPH scavenging activity ▲	[112]
	Human embryonic kidney (HEK)-293 cells	Rk1-rich BG	GSH, lipid peroxidation (MDA) ▼ Nrf2, HO-1 ▲ Bax, cleaved caspase-3/caspase-9 ▼	[47]
	Hepatotoxic mice	Rg5 (10 or 20 mg/kg, 7 days)	With 4-HNE/CYP2E1 expression, oxidants removed in acetaminophen (APAP)-induced hepatotoxic mice (COX-2/iNOS)▲ Bax, cleaved caspase-3/caspase-9 ▼	[44]
	AlCl3 Induced Osteoporosis rat	Rg3-rich BG	ROS, MDA ▼ GPx and SOD activities ▲ Bone formation▲ (with Ca, P, type I collagens, osteocalcin, bone alkaline phosphatase)	[48]
Anti-inflammation	LPS-induced RAW 264.7	High-Rg1/Rb1-RG and high-Rg5 -BG	BG decreases iNOS & COX-2 and pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α	[54]
	CS/LPS-exposed animals	BG Ext (20,50, 100 mg/Kg)	Smoking-induced inflammation markers (TNF-α, IL-6, MCP-1, elastase, TAK-1) ROS ▼	[55]
	NAFLD mice	Rb1, Rg3 and Rk1-rich-BG (0.5,1, 2%)	IL-6, CCAAT/CHOP, binding immunoglobulin protein (BiP) ▲	[43]
	SD-rats with heat stress	JP5(100,300 mg/Kg)/BG1(100,300 mg/Kg)	ROS and catalase, GR, GPx, SOD2 감소 JNK-MAPK signals (Caspase1, BCl2) ▼ p-NF-κB/TNF-α and NLRP3 inflammasome ▼	[52]
	Heat-stressed HepG2 cells	Rg5/Rk1 (1,25,50ug/ml)		
	Human (n = 180)	BG Ext (KGR-BG1 1500 mg 6 wks)	No significant differences were observed in the head, face and body temperature No changes on inflammation, glucose metabolism and lipid metabolism	[56]

Table 2 (continued)

Function	Model	Treatments (Dose/Period)	Target/Mechanisms	References
	Human leukemia THP-1 (monocytic) and EoL-1 (eosinophilic)	BG extract (radix/leaf)	IL-6, IL-8 and MCP-1 secretion ▼ in *D. pteronissinus*-induced THP-1 and EoL-1 cells Effective in atopic dermatitis	[58]
Chemo-prevention	6 human cancer cell lines	Rg5 &Rg3-rich BG	BG was higher cytotoxicity than RG in all six cell lines higher efficacy in Rg5 than Rg3	[61]
	Ovarian cancer cells (SKOV-3) bearing mice	Rg3 (0.3–3.0 mg/kg) IP injection (tumor-bearing mice)	Tumor-induced angiogenesis ▼ (by reduction of MMP-9 expression_	[65]
	Colon26-M 3.1 cells/macrophages	WG (2000ug/ml) Rg3, Rh1 and Rh2-rich BG (800ug/ml)	Antitumor & anti-inflammatory effects (TNF-α, IL-1β and IL-6) ▲	[66]
	10 types of cancer; in vitro & in vivo	CK	Apoptosis, autophagy, antiangiogenesis ▲ in 10 types of cancer such as lung, liver, breast, colorectal, brain, leukemia, bladder, nasopharyngeal, ovarian and renal cancer	[67]
	A375-S2 human melanoma cells	Rh2	Cell growth▼ G-Rh2-induced apoptosis is partially dependent on caspase-8 and caspase-3 pathway	[68]
	Leukemia cells (THP-1)	Rh1/Rh2 vs Rg3	PPD/PPT aglycone (Rh1/Rh2) increases apoptosis with releasing LDH, not in Reg3	[69]
	14 cancer cell lines (Hela cervical)	Rh2	Caspase-8 and caspase-9 ▲ Death receptors Fas and TNFR1 ▲ P53-dependent Fas involved in apoptosis process via capase-8/-9 activation	[70]
	Human MCF-7 breast cancer cells	2-Deoxy-Rh2 (LC_{50}; 32.6uM) vs 20(S)Rh2 (IC_{50}; 45.22uM)	Deoxy-Rh2 Apoptosis, ROS production ▲ - Glucose uptake & intracellular ATP production, cellular O2 consumption ▼	[71]
	SD rats	Rg5 and 20(S)-Rg3-rich BG 28 days	Set up NOAEL of BG extract 2000 mg/Kg	[72]
Anti obesity	3T3-L1	Rg-rich BG (30, 50, 100 uM)	PPAR-γ, CEBPa, FAS, FABP4, perilipin▼	[78]
	DIO-beagle dogs	HF + BG (12 Ws)	Nine obesity genes (NUGGC, EFR3B, RTP4, ACAN, HOXC4, IL17RB, SOX13, SLC18A2 and SOX4) ▼ Gut microbiome regulation	[75]
	Rats	Rg3-rich BG (100 mg/Kg/d for 3wks)	Weight gain, epididymal/abdominal fats and plasma TG▼ More effective than WG & RG	[77]
	3T3-L1 & High fat diet-induced obesity (DIO) rats	Rh1(20 mg/kg)	PPAR-γ, C/EBP-α, FAS and aP2▼ Weight gain, epididymal/abdominal fats and plasma TG▼ F4/80, CD68, TNF-α, IL-6 and IL-1β▼	[79]
	3T3-L1	Rb1-rich BG	Adipogenic genes (C/EBPα, SREBP-1c) ▼ Browning markers (PRDM16, PGC-1α, & UCP1) ▲	[80]

Table 2 (continued)

Function	Model	Treatments (Dose/Period)	Target/Mechanisms	References
	3T3-L1/RAW 264.7 or Stem cells	Rh1, Rg2 and Rb1-rich BG EtOH	PPAR-γ, C/EBPα and pAMPK regulation IL-10 ▲ MCP-1 ▼ Doubling time of stem cells in subcutaneous fat ▲ Ratio of M1/M2 macrophages ▼	[20]
Circulation (glucose & lipid metabolism)	Rattus beta cells	Rg3, Rb1, Rg1, Rg5 and CK	Activation insulin secretion with increasing AMPK	[87]
	HIT-T15, & MIN6 cells	CK	Activation insulin secretion in a beta cell line and Mouse Insulinoma MIN6 pancreatic β-cell	[88, 89]
	db/db mice	BG EtOH GBG05-FF(300, 900 mg/Kg for 4 wks)	Plasma lipids ▼ Glucose homeostasis & glucose uptake ▲ HbA1c ▼ Lipid accumulation/liver damage ▼ p-AMPK (liver), GLUT2(liver), GLUT4 (muscle) ▲	[91]
	C2C12 myotubes	BG EtOH GBG05-FF	Increased glucose uptake via AMPK, Sirt1 and PI3-K pathway	[92]
	STZ-induced diabetic mice	BG EtOH GBG05-FF	PEPCK, G6Pase, LG, GS expression ▼ GLUT1, GLUT4, ACO CPT1a MCAD ▲	[92]
	STZ-induced insulin-deficient diabetic mice	BG-High Rg5 & CKs(200 mg/kg)	Hyperglycemia ▼ Insulin/glucose ratio and β-cell function by NFkB suppression ▲ Better than RG for antidiabetic effect	[90]
	High fat/STZ-induced diabetic nephropathy mice	BG-High Rg5 (30, 60 mg/kg/d)	Rg5 is a potential compound to prevent or control diabetic renal injury Biomarkers for insulin resistance, oxidative stress, renal histopathology and inflammation ▼	[93]
	Type 2 db/db mice	BG-High Rh4, Rg5 and Rk1 (100,900 mg/kg BW)	Antihyperglycemic & hypolipidemic effects Insulin resistance, ROS, adipogenesis, GLUT-4 &-2 ▼	[95]
	Heart failure rats	BG saponins (30, 60, 120 mg/Kg BW)	p-Akt/Akt & p-mTOR/mTOR ▲ Beclin1, p62 & LCII/LC3I ▼	[97]
	High-cholesterol diet SD rats	BG EtOH(200 mg/kg)	TC and LDL levels ▼ Lipogenesis genes; CoA acetyltransferase, HMG-CoA reductase, SREBP2 ▼	[97]
Anti aging	C2C12 myoblasts	BG (0.1, 1, 10,20 ug/ml)	Akt/mTOR/p70S6K activation. ▲ Myoblast differentiation and myotube hypertrophy	[103]
	B16F10, HaCa, HDF cells	Fermented BG by *Aspergillus niger* KHNT-1	Antimelanogenesis in B16F10 murine melanoma cells ▲ Elastase in human dermal fibroblast (HDF) cells ▼ Antioxidation in H_2O_2-induced HaCat human epidermal keratinocyte cells ▲	[104]

Table 2 (continued)

Function	Model	Treatments (Dose/Period)	Target/Mechanisms	References
	Human subjects ($n=23$)	1% BG cream formulation (2/day for 8 ws)	Antiwrinkle and skin-whitening ▲ Same effects on human CCD-986sk and mouse B16F1 cells Collagenase/matrix metalloproteinase -1 (MMP-1) ▲	[27]
	18-month aged mice	BG (200 mg/Kg/d for 16 wks)	DNA damage in brain ▼ Choline acetyltransferase, acetylcholine transporter, growth-associated protein 43, synaptosomal-associated protein 25, NGF and BDNF expression ▲	[28]
	10-month aged mice	BG-Low(10 g/kg) or BG-High (30 g/Kg)	Cognitive decline by aging ▼ Antioxidant system ▲	[112]
	Chemical assay	RK3, Rh4, 20(S)/(R)-Rg3 rich BG (0-10 mg/ml)	Aetylcholinesteras (AChE) and butyrylcholinesterase (BChE) ▼	[111]
	Rat and BV2 microglial cells	BG-enriched CMT	DNA damage in brain ▼ Improved the learning behavior▲ Oxidative and inflammatory stress (COX-2, IL-1β) related to MAPK- NF-kB pathway. ▼	[112]

▲, Increase; ▼, Decrease

be used as a reference for future neurobehavioral studies [112]. Even though the effect of 14 plants (including Korean ginseng) on the modulation of the hypothalamic–pituitary–adrenal axis has been unclear in human studies, it is essential to continuously explore the antiaging mechanism of effective BG ingredients from the molecular levels with advanced technologies and develop its efficacy in the industries [113].

Conclusions and implications

BG extract, which maximizes various active ingredients including ginsenosides, has been reformulated to suit consumer use, such as powders, concentrates, sticks and slices. Recently, various functional ingredients have been mixed based on the unique aroma and taste of BG to increase its added value. I believe that the process of developing high-tech based high-quality products such as functional foods for healthcare is an evolutionary process to dominate the ginseng industrialization market.

It is known that strengthened ginsenosides produced by the BG manufacturing process have diverse functionalities (Table 2). Rg5 is known to have antianxiety, brain function improvement, antidiabetes mellitus and antihepatitis effects, and Rg3 is known to have anticancer, antioxidation, platelet aggregation inhibitory effects. Rb1 is known to have central nervous system inhibition and liver function protection effects, and Rb2 is known to have antidiabetic, antiarteriosclerosis and hepatocyte proliferation effects. Rg2 is known to inhibit platelet aggregation and improve memory loss, and Rh1 is known to have hepatoprotective, antitumor and platelet aggregation inhibitory effects.

Unfortunately, we could not review the multiple effects of ginsenosides in BG in increasing specific functionalities. It was difficult to present scientific evidence for the functional effects of BG due to the lack of RCT studies or research results that were insignificant even if there were RCT studies. However, I would like to make some suggestions based on the results of the review. For the products of BG with specific ginsenosides to succeed in the industrial market, first, the government should support BG's RCT research to ensure that it is competitive in the market as a scientifically based product. Second, the standardization of processing methodology for ginsenoside extraction and development of biomarkers for specific disease should be improved. Third, safety issues and difficulties in mass production for minor ginsenosides should be solved. In the future, the high-quality technology development for future products will be needed for healthcare purposes.

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