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Ginseng Berry, a Promising Anti-Aging Strategy: Recent Opinions on the Biological Effects of a Traditional Korean Ingredient

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Abstract

A recent effort in the development of new medications and immune modulatory agents is to search for candidates among natural products because they have relatively low toxicities in clinical applications. Ginseng root has been used as a traditional medicine in Korea, Japan and China and has demonstrated efficacy against various human diseases, such as cancer, viral infectious diseases, diabetes, and atherosclerosis. Recent observations and clinical studies have elevated the interest in the potential health effects of the ginseng berry, an association that appears to be due to the phytochemical content of this fruit. The ginseng berry has various bioactivities, such as anti-diabetic, anti-cancer, anti-inflammation, anti-oxidation, anti-neuro degeneration, and enhancement of sexual function bioactivities. Moreover, the effective anti-aging component of the ginseng berry, syringaresinol, has the ability to stimulate longevity via gene activation. Further molecular and clinical studies are necessary to elucidate the numerous bioactive substances in the ginseng berry that contribute to public health.

Keywords: Ginseng Berry; Ginsenoside Re; Syringaresinol; Panax Ginseng; Bioactive; Phyto Chemical

Introduction: Ginseng and the Ginseng berry

Ginseng (*Panax ginseng*) is a popular herbal medicine that has been used in Asia for 5,000 years [1]. Ginseng is classified as fresh, white, or red ginseng, depending on the processing method. As a traditional herb, red ginseng is known as an adaptogen that restores and improves normal well-being. The use of this herbal plant has been widespread throughout the world because of its therapeutic effects. The well-known biochemical and pharmacological effects include anti-cancer [2], anti-fatigue [3], and anti-diabetic effects [4], along with promoting the synthesis of DNA, RNA and proteins [5]. The herb is used as a tea, an extract, or raw directly from powdered root [6]. The representative bioactive compounds are widely considered to begin senosides, which are ginseng-specific saponins [7]. Currently, more than 100 naturally occurring saponins of various types and products of enzymatic conversion have been isolated from the roots, stems, leaves, flowers, berries, and seeds of ginseng. The different parts of ginseng contain distinct ginsenoside profiles, and thus, different parts probably possess different pharmacological effects [8].

Recently, many health reports have recommended an increase in fruit intake as part of a healthy dietary pattern [9,10]. These reports allow for various forms of fruit, including fresh, frozen, and dried, as well as juices, and recommend fruits such as oranges, apples, bananas, grapes, raisins, and berries. Whereas berries are known as a good source of potassium or fiber, recent studies suggest that berry fruits are a rich source of many phytochemicals that have a broad spectrum of bioactivity and a positive impact on general health. Several berry fruits, including blackberries, blueberries, cranberries, raspberries, and strawberries, have recently received attention as a result of their effects *in vitro* and their associations with lowered risks for some chronic diseases, which were found in recent observational research [11,12]. As a perennial herb, ginseng develops flowers and fruits that bloom in its third and fourth year. Unlike the widely used ginseng root, the ginseng berry is preserved for planting and has not been used by general populations. A recent study reported that the ginseng leaf and berry have higher levels of ginsenosides than ginseng root, and their pharmacological activities have also been reported [13]. In this review, we will summarize the research on the role of dietary ginseng berries in delaying aging, as well as evidence suggesting positive biological effects to prevent age-related diseases.

Ginseng Berry Bioactive Content and Composition

The bioactive components of ginseng are triterpene glycosides or saponins, which are commonly regarded as ginsenosides.

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It has been reported that ginsenosides are the most effective agents in ginseng in the treatment and prevention of cancer and the regulation of blood glucose and blood pressure [14]. Ginsenosides are divided into three major groups based on the triterpene aglycones panaxadiol, panaxytriol, and olenolic acid derivatives [15]. Other chemical compounds from *Panax ginseng* include alkenes, alkynes, sterols, fatty acids, mono-triterpenes, phenyl propanoids, kairomones, carbohydrates (sugars and polysaccharides), amines, flavonoids, organic acids and vitamins. In addition to amino acids, nucleic acids, various enzymes and inorganic compounds are obtained from ginseng [16]. More than 60 different types of ginsenoside have been identified that are contained in the plant roots, leaves and fruits [17,18]. Because different parts of the plant contain distinct ginsenoside content, the pharmacological activity of the various parts of the plant may be different. Recent studies have demonstrated that the ginseng berry has a different ginsenoside profile and higher ginsenoside content than the root [19]. Interestingly, among the ginsenosides, ginseng berry extract contains high levels of ginsenoside Re, amounting to almost more than 30-40 times that of ginseng root, indicating that the ginseng berry may be a superior form to ginseng root extract for ingesting a large amount of ginsenoside Re [20]. In addition, ginseng berry extract contains larger amounts of vitamin E, vitamin K, folic acid, and potassium than the raw materials (i.e., skin, flesh, juice) of ginseng. Currently, ginseng berry extract is being evaluated in clinical and preclinical trials because its components are more efficacious as compared to ginseng root extract.

Chemistry and Pharmacological Effects of Ginsenoside Re

Ginsenosides are glycosides that contain an aglycone with a dammarane (except Ro). They are divided into two groups based on the type of aglycone: the proto panax adiol ginsenoside group and the proto panaxa triolginsenoside group. Ginsenosides possess different chemical structures due to variations in the type of sugar moiety and the number and site of attachment. Ginsenoside Re belongs to the proto panaxatriol group and is a major component in ginseng leaf and berry, occurring in much higher quantities than in root [13]. Previous studies have shown that ginsenoside Re exhibits multiple pharmacological activities via different mechanisms both *in vivo* and *in vitro*. First, ginsenoside Re has anti-inflammatory effects, and it ameliorates inflammation by inhibiting macrophage activation [21,22] and regulating auto phagy [23]. Ginsenoside also has anti-diabetic activities. Ginsenoside Re reverses insulin resistance in the muscles of high-fat-diet-fed rats [24], and this effect is most likely due to the inhibition of NFκB [25]. Moreover, ginsenoside Re lowers blood glucose and lipid levels [26,27], as well as exhibits an anti-diabetic effect in ob/ob mice [28]. It also reduces the oxidative stress level in pancreatic beta-cells and diabetic rats [29,30] and, interestingly, attenuates diabetes-associated cognitive deficits in rats [31]. Several studies have suggested that ginsenoside Re has protective effects and beneficial functions on the cardiovascular system, such as contractive and electromechanical alternans [32-35], anti-arrhythmic effects [33,36] nit-ischemic activity [37-39], angio genic regeneration [40,41], and electrophysiological activities of cardiac cells [42-45]. Ginsenoside Re also exhibits neuro protective effects, and the beneficial effects of ginsenoside Re on Alzheimer's disease [46-48], Parkinson's disease [49], and depression [50] have been reported. The neuro protection of ginsenoside Re is mediated by an anti oxidative effect [38,51], the regulation of inflammatory mediators [52], and nitric oxide signaling [53]. Some reports have proposed that ginsenoside Re can promote sperm capacitation [54] and motility [55] and also has an estrogenic effect [56]. Ginsenoside Re has demonstrated angio genic effects in *in vitro* [41,57] and *in vivo* [40,41] models. The multitude of pharmacological activities of ginsenoside Re can be obtained by dietary ingestion of the ginseng berry. Oral ingestion of ginseng berry extract results in significantly higher absorption (0.33-0.75%) compared to the low oral bioavailability of ginsenoside Re from ginseng root (0.19-0.28%) [20]. In herbal or alternative medicine, a whole herbal extract might be advantageous compared to isolated natural ingredients.

Ginseng Berry: Preventive and Therapeutic Roles

Because the ginseng berry has more abundant ginsenoside content than the root parts [58] (Table 1), the ginseng berry not only exhibits ginseng root-like effects but also has many other specific biological activities. Moreover, in addition to ginsenoside Re, the ginseng berry contains other bioactive components that can be efficiently absorbed from dietary ginseng berry extract [20] .Here, we review the pharmacological activities of a whole extract of the ginseng berry as well as evidence suggesting the potential of a novel anti-aging compound.

Anti-Diabetic Activity

Ginseng has received increasing attention as a complementary and alternative medicine for the treatment of diabetes. Ginseng extract treatment has been reported to have hypoglycemic effects in animal models of type 1 and 2 diabetes [4, 59]. A previous study reported that ginseng berry extract exhibited greater hypoglycemic activity as compared to the same dosage of a root extract [60]. And the consumption of ginseng berry extract increased insulin secretion and ameliorated hyperglycemia in diabetic mice [61,62]. The anti-diabetic effects of the ginseng berry that have been discussed focus on effective components [63], reduced blood glucose levels [64-67] and administration [68,69]. A recent study revealed that ginseng berry extract improved insulin sensitivity in aged mice by increasing protein levels of tyrosine phosphorylated insulin receptor substrate-1 and insulin resistance-related protein AKT [70]. According to these results, the ginseng berry may ameliorate age-related metabolic disorders, such as diabetes.

Anti-Cancer Activity

The reports from early studies demonstrated that ginseng has strong immune-stimulatory properties, such as macrophage and dendritic cell activation, proliferation, and viability of spleen cells [71,72]. Recent studies have reported that the ginseng berry also exhibits anti-cancer activity in *in vitro* [2, 73-77] and *in vivo* [2, 78,79], as well as the ability to attenuate chemotherapy-induced

side effects [80,81]; these effects result from the promotion of dendrite cell maturation. Interestingly, the ginseng berry induced a higher degree of co-stimulatory molecule up regulation than the root extract at the same concentrations [82]. These studies indicate that the ginseng berry is an intense tumor therapeutic vaccine adjuvant that can be used in investigations and clinical research.

Anti-Inflammation and Anti-Oxidative Activity

Recent studies have reported that anti-inflammatory compounds prevent the progression of atherosclerosis without altering the blood lipid profiles in hyper lipidemic mice [83,84], indicating that anti-inflammatory compounds may be used as therapeutic agents for the treatment of inflammatory diseases. The ginseng berry has been shown to suppress reactive oxygen species production [85,86], NF-κB activation [19] and inflammatory gene expression [87] *in vitro* and *in vivo*. The ginseng berry suppressed atherosclerotic lesion development by inhibiting NF-κB-mediated atherogenic inflammatory gene expression through the induction of antioxidant enzymes without lowering serum lipid levels in a hyper lipidemic mouse model [19]. Moreover, chronic pretreatment with ginseng berry attenuated oxidative stress in cardio myocytes [88] and up regulated human umbilical vein endothelial cell proliferation and migration [89]. These studies provide insight into the therapeutic potential of the ginseng berry for the treatment of oxidative stress and inflammation-related diseases.

Anti-Sexual Dysfunction

Sexual dysfunction has a severe impact on the quality of life of affected individuals. Previous studies reported that more than half of the male population has some degree of erectile dysfunction [90] and one-third of the global male population, across all ages, has some degree of premature ejaculation [91]. To treat these symptoms, PDE5 inhibitors and selective serotonin reuptake inhibitors are used; however, these drugs can produce negative side effects, including headache, gastrointestinal disorder, muscle pain and blurred vision and may have dangerous interactions with other medications [92,93]. To avoid the risks of side effects, people often turn to dietary ingredients, such as ginseng. Ginsenosides have been shown to enhance nitric oxide production by inducing nitric oxide synthase activity [94,95]. Recently, ginsenoside Rg1, which is abundantly present in the ginseng berry, was also shown to improve male copulation behavior via the nitric oxide/cGMP pathway [96]. Clinical observation of patients after 8 week oral treatment indicated that ginseng berry improved all domains of sexual function including erectile dysfunction and premature ejaculation [97]. The ginseng berry had a greater relaxation effect on rabbit corpus cavernosum smooth muscle than did ginseng root extract and increased intra cavernosal pressure in a rat model in both a dose- and duration-dependent manner. This relaxing effect might be mediated by nitric oxide production [98]. According to these studies, the ginseng berry can be used as an alternative medicine for men with sexual dysfunction.

Anti-neuro Degeneration Activity

Continued research indicates the occurrence of neuronal and behavioral deficits during aging, even in the absence of neurodegenerative diseases such as Alzheimer's diseases and Parkinson's diseases. There has been a growing interest in a number of pharmacological approaches to help slow the rate of both cognitive and functional declines associated with aging. Recently, several dietary supplements with either straw berry or blue berry extracts have been reported to reduce some neurological deficits in animal models of aging [99,100]. Fruits are beneficial in both forestalling and reversing the deleterious effects of aging on neuronal communication and behavior [101]. Some of the actions reported to be elicited by ginseng include an ability to induce effects within the central nervous system that control functions related to stamina, fatigue, physical stress, and the functions of memory, learning, and behavior [102]. A number of different cognitive tests have indicated that ginseng exerts potential positive effects on memory and learning performance in a variety of animal species [103-105]. In addition, herbal mixtures that contain ginseng have been proven to improve cognitive performance [106]. The neuro active effects of free amino acids in ginseng seed and berries have also been proposed [107]. It has been suggested that one potential mechanism by which the ginseng berry improves various neurological functions is via an interaction with the cholinergic and serotoninergic neurotransmitter systems. The suggestion of this pathway is supported by reports that have shown that selective damage to serotonergic neurons affects certain aspects of memory functions, specifically, spatial working memory [108,109]. Moreover, one of the behavioral paradigms found to be improved by ginseng and ginseng berry supplementation was that of electroconvulsive shock, which is known to modulate the cholinergic neurotransmitter system, especially within brain areas, such as the hippocampus [110-112]. It has also been proposed that ginseng and the ginseng berry enhance the components of cholinergic systems, such as choline acetyl transferase, which is also thought to be important in the formation of memory [113-115]. Although there have been a number of studies emphasizing the potential helpful effects of ginseng on cognitive performance in animal models, few epidemiological reports have been performed. In fact, a comprehensive investigation of the literature found few studies exploring the effects of ginseng on human cognitive performance, in which significant improvement in mental arithmetic and abstraction tests were reported [116-118].

Exploring other Bioactive Constituents in the Ginseng Berry and Syringaresinol

Because of its numerous potent biological activities, there have been many efforts to discover other useful components in the ginseng berry besides ginsenoside. The ginseng berry has many unique bioactive constituents compared to the generally used ginseng root. Through various assays [13,119-122], a new triterpenoid saponin, isoginsenoside-Rh3 [123], alkaloid ginsenine [124] and a dammarane-type triterpene ketone, panaxadione

[125,126], were isolated. Interestingly, ginsenoside-free molecules promote ethanol metabolism [127]. Recently, a lignin compound, syringaresinol(4,4'-(1S,3aR,4S,6aR)-tetrahydro-1H,3H-furo[3,4-c]furan-a,4-diylbis(2,6-dimethoxyphenol)), was isolated from panax ginseng pulp and found to activate SIRT1 gene expression, leading to delayed cellular senescence and improved endothelial cell function in endothelial cells [128]. Syringaresinol treatment induced the binding of FOXO3 to the *SIRT1* promoter in a sequence-specific manner, leading to the induction of *SIRT1* expression. Syringaresinol exists either exclusively as one enantiomer or as enantiomeric mixtures in plant foods. Recent studies revealed that (+)-syringaresinol, but not (-)-syringaresinol, up regulates *SIRT1* gene expression; thus, the ginseng berry, with a predominantly high content of (+)-syringaresinol, exhibits higher activity in inducing *SIRT1* gene expression. Syringaresinol has enantio selective effects upon biological activity [129]. Syringaresinol also has protective effects against hypoxia/re oxygenation-induced injury. Syringaresinol caused the destabilization of hypoxia-inducible factor 1 following hypoxia/re oxygenation and then protected cellular damage and death in a FOXO3-dependent mechanism [130]. These findings strongly suggest that the ginseng berry has potential as an effective anti-aging reagent.

Concluding Remarks

The ginseng berry is a rich source of dietary bioactivities and has various biological activities in addition to that of the ginseng root. It possesses higher ginsenoside content than its root, which has been traditionally used in herbal medicine for many human diseases and age-related attenuates. In this study, we reviewed the biological and pharmacological activities of the ginseng berry, including anti-diabetic, anti-cancer, anti-inflammation, anti-neuro degeneration, and also sexual function effects. In addition, an anti-aging component of the ginseng berry, syringaresinol, has the potential for activating the longevity genes *sirt1* and *foxo*. According to numerous reports, the ginseng berry has the potential to be widely used as an anti-aging reagent for many age-related human diseases and to increase vitality. Basic research has suggested a number of potential mechanisms of action for ginseng berry bioactive substances, although further molecular research is necessary. Furthermore, the optimal dose of ginseng berry bioactive substances has not been determined for urinary tractor cardiovascular health. Another major deficiency concerning the evaluation of existing clinical reports is the lack of quantification of ginseng berry bioactive substances or assessment of their concentration in blood or urine. There is potent experimental evidence that ginseng berry bioactive substances have favorable effects on blood glucose metabolism, blood pressure, oxidative stress, inflammation, cancer, and endothelial function. As noted, the average daily fruit consumption is substantially less than what is recommended. In part, encouraging consumption of a greater proportion of plant foods, including fruit, to achieve a healthy dietary pattern will help to attain the recommended dietary intake of micronutrients. Although reference intake values have yet to be developed for phytochemicals, there is a growing consensus that their bioactivities importantly contribute to promoting public health and reducing the risk of chronic diseases. Berry fruit, including the ginseng berry, represents an especially rich source of many phenolic acids and flavonoids that have been associated with these benefits. Additional research that clarifies specific dietary guidance with regard to the type of berry should help elevate our intake of these bioactive moieties.

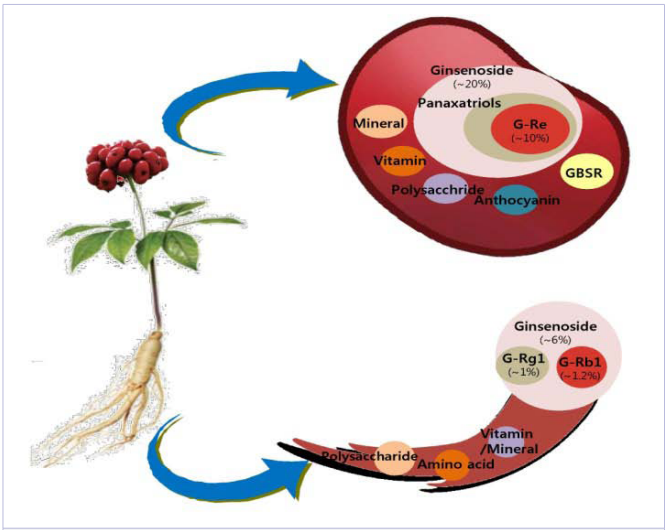

Figure 1: The different constitutions and contents of ginseng berry- and root. Ginseng berry comprises approximately 20% ginsenoside compared to 6% ginsenoside of root part. Especially, ginseng berry has more than 30 to 40 times amount of ginsenoside Re than root (0.1%) whereas root contains 1% of ginsenoside Rg1 and Rb1. Moreover ginseng berry contains 2-3 times content of crude saponin and 20-30 times of ginsenoside than root part. In addition, ginseng berry contains many of vitamins, minerals, and polyphenols as well.

Table 1: Amount and contents of ginsenoside in ginseng berry, leaf and root part.

Part	Ginsenoside (mg/g)							
	PPD				PPT			PPT/PPD
	Rb1	Rb2	Rc	Rd	Re	Rg1	Rg2	
Berry	8	20	21	18	100	19	9	1.9
Leaf	5	3	2	4	42	8	4	3.8
Root	9	3	10	3	4	5	1	0.4

Ginsenoside contents and amount of ginseng berry, leaf and root [58]. PPD: protopanaxadiol; PPT: protopanaxatriol.

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