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Review Article

Brain plasticity and ginseng

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A B S T R A C T

Brain plasticity refers to the brain's ability to modify its structure, accompanied by its functional changes. It is influenced by learning, experiences, and dietary factors, even in later life. Accumulated researches have indicated that ginseng may protect the brain and enhance its function in pathological conditions. There is a compelling need for a more comprehensive understanding of ginseng's role in the physiological condition because many individuals without specific diseases seek to improve their health by incorporating ginseng into their routines. This review aims to deepen our understanding of how ginseng affects brain plasticity of people undergoing normal aging process. We provided a summary of studies that reported the impact of ginseng on brain plasticity and related factors in human clinical studies. Furthermore, we explored researches focused on the molecular mechanisms underpinning the influence of ginseng on brain plasticity and factors contributing to brain plasticity. Evidences indicate that ginseng has the potential to enhance brain plasticity in the context of normal aging by mediating both central and peripheral systems, thereby expecting to improve age-related declines in brain function. Moreover, given modern western diet can damage neuroplasticity in the long term, ginseng can be a beneficial supplement for better brain health.

1. Introduction

Brain plasticity (neuroplasticity) refers to the property of the brain to structurally change in response to internal and external stimuli, leading to alterations in brain function and playing a crucial role in the proper functioning of higher-order brain functions such as cognitive processes, emotional regulation, and social functions [1–3]. Brain plasticity in the human is not limited in early developmental stages. Even in adulthood, certain periods of training such as juggling can induce changes in gray and white matter [4,5]. This suggests the existence of potential to alleviate age-related cognitive decline in later years. Brain plasticity involves not only changes in synaptic connections but also myelin changes, alterations in secretion factors and synaptic pruning by microglia, and neurotransmitter removal by astrocytes, highlighting the intricate interaction between neurons and glial cells in shaping brain plasticity [6].

Various systems within the body also influence brain plasticity. The brain expresses receptors for hormones related to metabolism and is highly sensitive to glucose metabolism, which plays a crucial role in the molecular mechanisms of brain plasticity [7–9]. Continuous exposure to stress can affect brain plasticity. Under chronic stress, cortisol can be released chronically, exposing brain cells to high cortisol level, resulting in reduction of sizes of hippocampus and prefrontal cortex, which can be observed in major depressions [10]. Furthermore, the tone of the sympathetic nervous system and blood pressure are associated with neuroplasticity in regions like the hypothalamus, midbrain, pons, medulla, and spinal cord [11]. Increased oxidative stress is related to damage to memory and synaptic plasticity, and its reduction can reverse memory and synaptic plasticity impairment in rodent models [12]. Gut microbiota influences the gut-brain axis, affecting neuroplasticity and inducing changes in brain function [13].

Traditionally ginseng has been cultivated for health purposes mainly in Asia. Ginseng includes *Panax ginseng Meyer* (Korea ginseng), *Panax quinquefolius* L. (American ginseng), *Panax notoginseng Burk* (Tienchi seng), *Panax Japonicus C.A. Meyer* (Japanese ginseng) [14]. The roots of Korean ginseng have been used and studied the most, and are divided into fresh ginseng, white ginseng, and red ginseng based on water content and processing methods. Fresh ginseng easily undergoes changes at room temperature, so it is processed into red ginseng, which undergoes steaming and drying processes, or white ginseng, which

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undergoes a simple drying process. Generally, red ginseng is known to have higher biological effects and fewer side effects compared to fresh ginseng or white ginseng [15]. During the steaming process of red ginseng production, many ginsenosides are transformed. Red ginseng contains ginsenosides such as Rg2, Rg6, F4, 20(E)-F4, Rh1, Rh4, Rk3, Rg3, Rg5, Rz1, Rk1, Rg9, Rg10, which are converted from major ginsenosides such as Rb1, Rb2, Rc, Rd, Rg1, and Re in fresh ginseng [16–18]. When comparing the concentrations of ginsenosides in fresh ginseng, red ginseng, and red ginseng extract, it is observed that the concentration sequence for many, but not all, ginsenosides follows the order: fresh ginseng < red ginseng < red ginseng extract. For example, the concentration of Rb1 is lowest in fresh ginseng (2.02 mg/g), intermediate in red ginseng (5.8 mg/g), and highest in red ginseng extract (6.43 mg/g) [15]. The steaming of ginseng at high temperature not only converts the components of ginsenosides, and concentrates the density but also enhances biological activity such as endothelium-dependent relaxation and radical-scavenging activity [17].

Numerous researches have investigated the effects of ginseng components on brain function, and several studies have shown their permeability across the blood-brain barrier (BBB) and the underlying mechanisms. For instance, ginsenoside Rb1 has shown to utilize the glucose transporter 1 for transport across the BBB [19]. Moreover, the brain uptake of ginsenosides Rg1, Re, Rd and Rb1 has been found to be enhanced through the A1 adenosine receptor (A1R) signaling pathway induced by extract of *Ginkgo biloba* leaves, indicating the ability of those ginsenosides to cross the BBB [20]. Additionally, following intravenous administration of fluorescent-labeled gintonin, a ginseng-derived G-protein-coupled lysophosphatidic acid (LPA) receptor ligand, its presence was observed in endothelial cells, neurons and glial cells in the brain [21]. Furthermore, after oral administration of ginseng total saponins to mice, Rg1 was found to be the most prominent in the brain using high-performance liquid chromatography-mass spectrometry (MS)/MS, while immunofluorescence studies showed ginsenosides were widely distributed among vascular endothelial cells, astrocytes and a few neurons [22]. In the study of pharmacokinetics of Re in the brain, after subcutaneous administration of a single dose of Re (12.5, 25, or 50 mg/kg), it was detected in the cerebrospinal fluid (CSF). The peak concentration (C_{max}) was observed at 60 min for all doses. Re was not detectable after 240 min in the dialysates of the 12.5 mg/kg group [23]. This suggests that Re enters the blood-cerebrospinal fluid barriers within a 1-h time window and is metabolized within few hours in the CSF.

Ginseng may act on neuroplasticities and higher-order brain functions through changing neurons, glial cells, peripheral hormone secretion, and gut bacterial compositions (Fig. 1). Ginseng has been studied a lot as a medicinal herb, but especially in Asia, healthy people who are not in pathological conditions take it to improve their physical and brain functions, or to prevent aging-related functional declines. Therefore, it is necessary to understand how ginseng use affects health of people in the normal aging process. In this review, we focus on the following aspects of ginseng extracts and its fractions, rather than single compounds: (1) how ginseng affects higher-order brain functions and factors associated with brain plasticity in clinical studies conducted on individuals in the

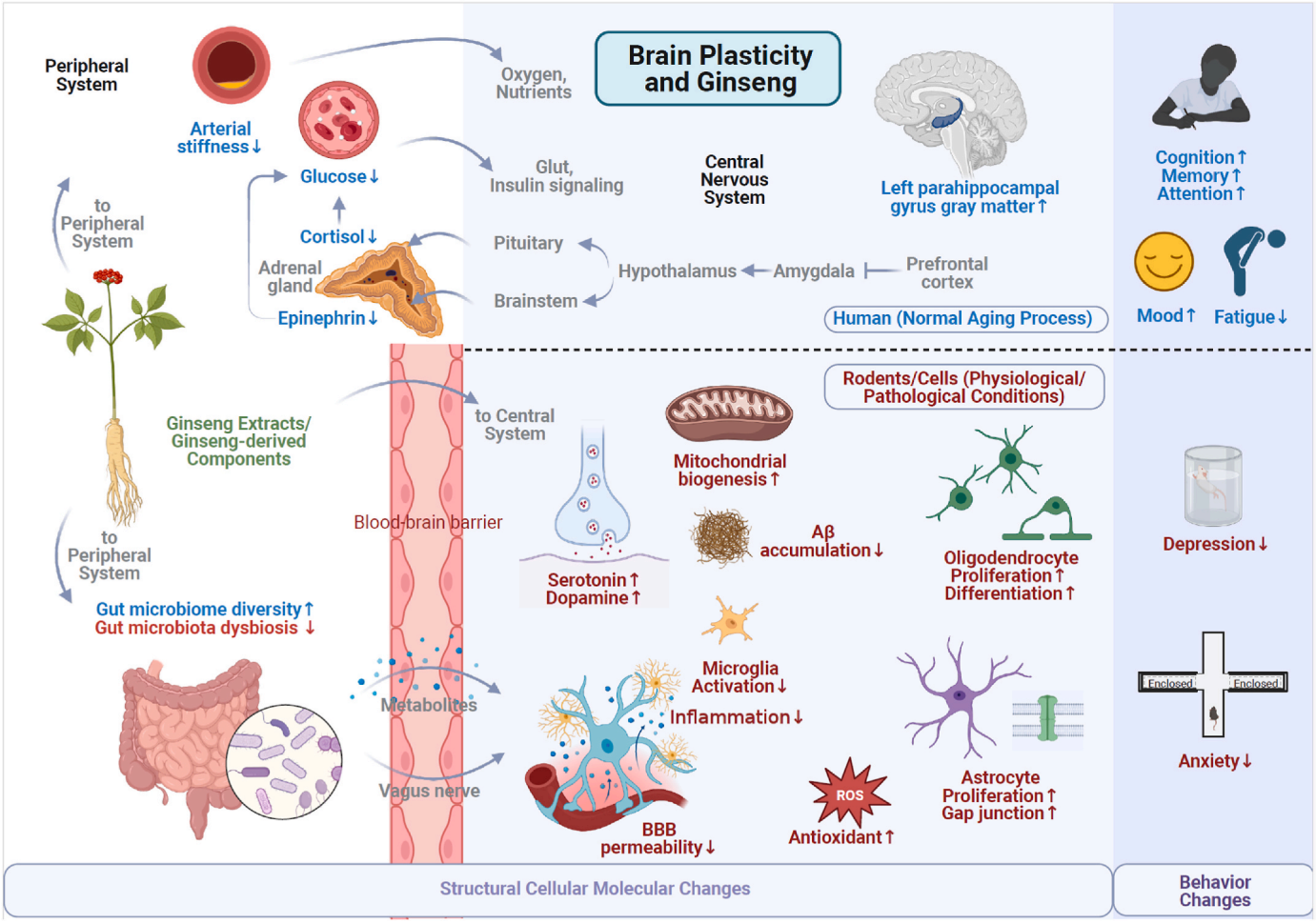

Fig. 1. Scheme of the effects of ginseng on brain plasticity. Intake of ginseng extract or ginseng-derived components affects brain plasticity through modulating central and peripheral systems. The words marked in blue represent the clinical research results of individuals in the normal aging process (Table 1), those in red indicate findings from rodent or cell experiments under physiological or pathological conditions (Table 2). Created with BioRender.com.

normal aging process; (2) the mechanisms by which ginseng acts on brain plasticity based on animal and cell experiments. In the latter, studies published within the last 3 years were mainly included in this review.

2. The impact of ginseng on human brain plasticity during normal aging process

To understand how ginseng relates to brain plasticity in people in the normal aging process, we have summarized clinical studies to date that have conducted experiments and observations on the effects of ginseng on factors related to brain plasticity or brain function in people under normal aging process (Table 1). In the course of normal aging, globally over 850 million perimenopausal women aged 40–60 years old undergoes a complexity of neurological symptoms such as depression and cognitive dysfunction that may persist into postmenopause with an increased risk of neurodegenerative diseases such as alzheimer's disease (AD) and multiple sclerosis after menopause [24]. With this in mind, the percentage of female is included in Table 1.

2.1. Cognition and brain structure

Brain plasticity can occur across entire lifespan, including later life [25]. Changes in cognitive function involve neuroplasticity. Normal aging process accompanies shrinkage of the brain which involves a partial functional decline in several domains of cognition such as memory, verbal fluency, visuospatial ability, executive function and attention [26]. High-fat/high-sugar diets, to which people are prone to be exposed in the modern society, damage neuroplasticity, leading to memory and learning deficits [27]. According to reports, ginseng use improves cognitive function suggesting the potential of ginseng in preventing or reversing the adverse effects of normal aging or those prevalent unhealthy diets on neuroplasticity. In the studies that investigated changes in cognitive functions resulting from ginseng intake in people undergoing the normal aging process, cognitive improvements were reported in both young [28–33] and middle-aged adults [34–37] with either *Panax quinquefolius* [30,31,34,35] or *Panax ginseng* [28,29,32,33,36,37]. Cognitive function, as measured by several parameters, changed after 8-week [32,36], 6-week [37], 2-week [31], 8-day [29] and even after a single administration [28,30,31,33–35].

In a randomized double-blind cross-over design (N = 20, 75 % female, mean age = 21.2), healthy young adults who were single-administered with 400 mg of *Panax ginseng* (G115) exhibited significant improvements in memory performance, the speed of performing memory task, and accuracy of attention task [28]. In another study with similar design for healthy young adults (N = 27, 37 % female, mean age = 21.9), reduction of single dose to 200 mg *Panax ginseng* improved the performance of a mental arithmetic task [33]. When the intake was extended to 8 days (N = 30, 50 % female, mean age = 22.9), the improvement in the mental arithmetic task was replicated in young adults [29]. These results indicate that ginseng intake, whether in acute or long-term doses, can be beneficial for improving the working memory of young adults.

Two double-blind placebo-controlled trials investigating cognitive function in middle-aged adults were conducted using Korean Red Ginseng (KRG) from *Panax ginseng*. In the first study (N = 51, 76 % female, mean age = 39.6), healthy middle-aged adults who consumed 1 g of KRG per day for eight weeks exhibited an increase in gray matter volume of the left parahippocampal gyrus, along with improvements in combined cognitive functions (including executive function, attention, and memory) [36]. Given the crucial role of the parahippocampal gyrus in memory encoding and retrieval, the increase in its volume can be seen as structurally supporting the enhancement in its function. In another study (N = 62, 57 % female, mean age = 40.4), middle-aged individuals with high stress levels who consumed 2 g of KRG per day for six weeks reported tendency of improvements in cognition [37].

Additionally, studies on patients with AD have reported improvements in cognitive function with ginseng intake. In a randomized open-label study involving AD patients (N = 61, 61 % female, mean age = 66.8), participants were followed for two years while taking 0, 4.5, or 9 g of KRG per day (divided into 2–3 doses per day). Cognitive function was measured every 12 weeks using the AD Assessment Scale (ADAS) and Mini Mental Status Examination (MMSE). At 24 weeks, the KRG-treated groups showed significant improvement, and this improvement was sustained over the two-year follow-up [38]. Another randomized trial examined the effect of *Panax ginseng* on cognitive performance in AD patients (N = 97, 66 % female, mean age = 66.2). The group that consumed *Panax ginseng* powder for 12 weeks (4.5 g/day) showed significant improvement in cognitive function, as measured by ADAS and MMSE, compared to the control group. However, cognitive function declined again when ginseng intake was discontinued, returning to the control level [39].

Panax quinquefolius has also shown beneficial effects on cognitive function in both single-dose and long-term use. In a randomized double-blind, placebo-controlled, cross-over design study (N = 32, 50 % female, mean age = 22.5), young adults who consumed *Panax quinquefolius* (Cereboost) as a single dose exhibited improvements in choice reaction time accuracy, immediate word recall, numeric working memory speed, and alphabetic working memory speed, indicating enhanced cognitive function [30]. Another study demonstrated that single-dose consumption of *Panax quinquefolius* improved working memory and attention in young adults (N = 61, 75% female, mean age = 20.6) [31]. In addition to single-dose consumption, this study also conducted a two-week consumption study (200 mg Cereboost/day), which similarly resulted in enhanced cognitive function. Similar to *Panax ginseng*, *Panax quinquefolius* has shown its potential to enhance cognitive function not only in young adults but also in middle-aged individuals. Middle-aged healthy adults who consumed a single dose of *Panax quinquefolius* (200 mg) experienced an increase in working memory and spatial working memory (N = 52, 59 % female, mean age = 51.6) [35], as well as a reduction in prefrontal steady state visually evoked potentials latency, indicating an increase in the recruitment of prefrontal brain regions during spatial working memory processing (N = 20, 35 % female, mean age = 53.9) [34].

The brain with relatively lower antioxidant activity compared to other organs consumes a substantial amount of oxygen due to its high energy demand, resulting in its increased susceptibility to oxidative stress. Many studies report that oxidative stress is associated with age-related cognitive decline [40]. Ginseng, when administered orally in mouse models, exhibits antioxidant effects within the brain and enhances learning and memory [41]. Improved cognitive function in humans following ginseng consumption [28–31,33–37] may also be related to ginseng's antioxidant effects [42–47], resulting in enhanced cellular function. Six studies have reported the antioxidant effects of ginseng in individuals undergoing normal aging process, including menopausal women. These studies utilized fermented *Panax ginseng* [42], *Panax ginseng* [43], KRG [44–46], and *Panax quinquefolius* [47] and involved healthy adults in early middle age [42,43,47,48] and late middle age [45,46]. These studies varied in duration from 2 to 12 weeks [42,43,45,46], including a single-dose study [47]. In a randomized placebo-controlled clinical trial (N = 81, 74 % female, mean age = 40.4), middle-aged healthy adults who consumed 1 or 2 g of *Panax ginseng* daily for four weeks showed significant reductions in serum reactive oxygen species (ROS) and malondialdehyde levels in both dose groups. Additionally, the 2 g dose group exhibited a significant increase in total glutathione content and glutathione reductase activity [43]. In another randomized controlled trial, healthy adults with daily KRG consumption at doses of 3 g (low) or 6 g (high) for eight weeks showed an increase in plasma superoxide dismutase (SOD) and a reduction in low-density lipoprotein (LDL) oxidation in both doses. In the high-dose group, glutathione peroxidase and catalase activities were increased [44]. In another study targeting menopausal women (N = 71, mean age

Table 1
Effects of ginseng on brain plasticity (-contributing factors) under normal (aging) conditions in humans.

Brain Plasticity/ Contributing factors	Design	Participants	Female %	Age	Type of ginseng	Dosage	Duration	Outcomes	Ref
Cognition	A randomised double-blind, placebo-controlled, balanced, cross-over design	Healthy young adults (N = 20)	75	21.2	*Panax ginseng* (G115)	400 mg/ day	A single dose	• Cognitive drug research battery test: Immediate word recall ↑ at 4, 6h; Digit vigilance false alarms ↓ at 2.5, 4h; Choice reaction time accuracy ↑ at 1, 2.5h; Spatial memory RT↓ at 2.5h; Numeric working memory ↓ at 2.5h, 6h; Delayed word recall accuracy ↑ at 2.5, 6h; Word recognition RT ↓ at 2.5, 4h	[28]
Cognition, Mood	A randomised double-blind, placebo-controlled, balanced, cross-over design	Healthy young adults (N = 30)	50	22.9	*Panax ginseng* (G115)	200, 400 mg/day	8 days	• Subjective mood (=calmness): ↑at 2.5, 4h (day 1) in both doses; ↑ at 1, 4h (day 8) in 200 mg • Three-back task response time: ↓at 2.5h (day 1, 8) in 400 mg (=↑mental arithmetic) • Three-back task sensitivity index: ↑at 1, 2.5, 4h (day 1, 8) in 400 mg	[29]
Cognition, Mood	A randomised, double-blind, placebo-controlled, cross-over design	Healthy young adults (N = 32)	50	22.5	*Panax quinquefolius* (Cereboost)	100, 200, 400 mg/ day	A single dose	• Cognitive functions: Choice reaction time accuracy↑, immediate word recall↑, corsi block score↑ in all doses; Numeric working memory speed↑ in 200 mg/day; Alphabetic working memory speed↑ in 100, 400 mg/ day • Mood: Calm↑ in 100 mg/day	[30]
Cognition, Mood, Fatigue	A randomised, double-blind, placebo controlled, balanced, cross-over design	Healthy young adults (N = 58(A), 59 (B))	75	20.6	*Panax quinquefolius* (Cereboost)	200 mg/ day	A. A single dose B. 2weeks	A. • Visit 1 (=experimental day 1): ANT (executive function and attention) accuracy↑ at 4, 6h; ANT RT ↓ at 2h • Visit 2 (=experimental day 14): ANT accuracy↑ at 2, 4, 6h; ANT RT ↓ at 2, 4, 6h; corsi blocks accuracy (visuo-spatial working memory)↑ at 4h; switching task RT ↓ (executive function↑) at 2h B. Rapid visual information processing↑ (sustained attention); ANT accuracy↑; self-assurance↑; mental fatigue↓	[31]
Mental health	A randomized, double-blind, placebo-controlled trial	Healthy young adults (N = 29 at 4 weeks; N = 24 at 8 weeks)	57	21.6	*Panax ginseng*	200 mg/ day	8 weeks	Social functioning↑; mental component summary↑ at 4 weeks, but not at 8 weeks	[32]
Cognition, Fatigue	A randomised double-blind, placebo-controlled, balanced, cross-over design	Healthy young adults (N = 27)	37	21.9	*Panax ginseng* (G115)	200 mg/ day	A single dose	Among 1st~6th consecutive cognitive demand battery tests (each taking 10min: Serial 3s/ Serial 7s/RVIP/Mental fatigue rating) after 30min of post-administration, • Performance of a mental arithmetic task↑: RVIP RT↑ at 4th; RVIP false alarms ↓ at 6th; Serial 3s total responses ↑ at 3,4,6th • Mental fatigue ↓ at 5, 6th test.	[33]
Cognition	A randomised double-blind, placebo-controlled, balanced, cross-over design	Middle-aged adults (N = 20)	35	53.9	*Panax quinquefolius* (Cereboost)	200 mg/ day	A single dose	Prefrontal steady state visually evoked potentials latency ↓	[34]
Cognition	A double-blind, placebo-controlled, balanced, crossover design	Healthy middle-age adults (N = 52)	59	51.6	*Panax quinquefolius*	200 mg/ day	A single dose	Spatial working memory↑ at 3h	[35]
Cognition, Brain structure	A randomized, double-blind, placebo-controlled trial	Healthy adults (N = 37)	76	39.6	KRG	1 g/day	8 weeks	Gray matter volume of the left parahippocampal gyrus↑; Combined cognitive function (Executive function, Attention, Memory)↑	[36]

(*continued on next page*)

Table 1 (*continued*)

Brain Plasticity/ Contributing factors	Design	Participants	Female %	Age	Type of ginseng	Dosage	Duration	Outcomes	Ref
Cognition, SNS	A double-blind, placebo-controlled trial	Adults with high stress (N = 55)	57	40.4	*Panax ginseng* (KRG: LAX-101)	2 g/day	6 weeks	Epinephrin↓; Visually controlled continuous performance correct response time ↓ (=Cognition↑)	[37]
Antioxidant	A randomized, placebo-controlled clinical trial	Healthy adults (N = 82)	74	40.4	*Panax ginseng*	1, 2 g/day	4 weeks	• Serum ROS↓, MDA↓ in both doses. • Total glutathione ↑, glutathione reductase ↑ in high dose.	[43]
Antioxidant	A randomized, double-blind, placebo-controlled trial	Healthy adults (N = 57)	60	36.2	KRG	3, 6 g/day	8 weeks	• Plasma SOD activity↑in both doses • GPx, catalase activities↑in high dose • 8-*epi*-prostaglandin $F_{2\alpha}$, LDL oxidation↓ in both doses	[44]
Antioxidant, Fatigue	A double-blinded, placebo-controlled clinical trial	Postmenopausal women (N = 63)	100	59.2	KRG	2 g/day	8 weeks	Mitochondria DNA copy number↑; total antioxidant status ↑; fatigue↓	[45]
Antioxidant	A randomized, double-blind, placebo-controlled trial	Postmenopausal women (N = 71)	100	54.1	KRG	3 g/day	12 weeks	Serum SOD activity↑	[46]
Antioxidant	A randomized controlled clinical trial	Healthy adults (N = 14)	57	34.1	*Panax quinquefolius*	A cup of infusions	A single dose	Comet score ↓on blood samples after ultraviolet B irradiation	[47]
Sleep	A randomised, double-blind, placebo controlled trial	Healthy young men (N = 16)	0	20.7	Fermented ginseng (*Panax ginseng*)	1845 mg/ day	8 days	Improved the first-night effect (=Improved reductions in total sleep time and sleep efficiencies and increases in number of wake after sleep onset on the first night of testing); Subjective sleep quality ↑	[58]
Fatigue	A randomized, double-blind, placebo-controlled trial	Healthy adults (N = 47)	77	61.1	Enzyme-modified KRG	2 g/day	4 weeks	Visual Analogue Fatigue Scale↓	[55]
HPA	A randomized, double-blind, placebo-controlled trial	Healthy men with stress (N = 87)	0	48.7	KRG	2 g/day	8 weeks	ΔCortisol ↓	[60]
HPA, Antioxidant	A double-blinded, placebo-controlled, counterbalanced within-group study	Healthy adults (N = 19)	52	39.9	Fermented *panax ginseng* (GINST15)	160, 960 mg/day	14 days	[Women] Stress-inducible dose-dependent cortisol ↓ at 0, 30, 60 min after intense exercise stress in both doses [Men] Stress-inducible dose-dependent cortisol ↓ at 0, 30, 60 min in high dose. [Women, Men] Total glutathione concentrations ↑ at 0, 30, 60 min; SOD concentrations ↑ at 0, 30 min in high dose	[42]
Glycemic control	A randomized, double-blind, and placebo-controlled clinical trial	Adults (N = 63)	42	52.3	*Panax ginseng* berry	1 g/day	12 weeks	Postprandial incremental glucose ↓at 60 min post-oral glucose tolerance test	[62]
Glycemic control	A double-blind, placebo-controlled randomized design	Non-diabetic men (N = 52)	0	25.7	*Panax notoginseng*	3 g/day	3 day	Postprandial plasma glucose ↓at 30 min post-oral glucose tolerance test	[63]
Glycemic control	A randomized, double-blind, placebo-controlled, multiple crossover design	Healthy adults (N = 13)	54	28.0	KRG	3 g/day	A single dose	Postprandial glucose ↓ at 45, 60, 90, 120 min post-oral glucose tolerance test	[64]
Glycemic control	A placebo-controlled, crossover	Non-diabetic adults (N = 10)	40	41.0	*Panax quinquefolius*	3, 6, 9 g/ day	A single dose	Postprandial incremental glucose↓ at 30, 45, and 60min in all doses; ↓ at 90 min in 3, 9 g.	[65]
Vascular health	A randomized, placebo-controlled, double-blind clinical trial	Postmenopausal women (N = 63)	100	54.0	KRG	3 g/day	12 weeks	Kupperman index↓; menopause rating scale↓; total cholesterol↓; LDL↓; hs-CRP↓; carotid intima-media thickness↓	[48]
Vascular health	An acute randomized, controlled, double blind, crossover trial	Healthy fasted adults (N = 17)	47	30.0	KRG	3 g/day	A single dose	Augmentation index (=arterial stiffness)↓	[67]
Vascular health	A double-blind, randomized, crossover design	Healthy adults (N = 23)	61	25.0	Rg3-enriched KRG	400 mg/ day	A single dose	Augmentation index (=arterial stiffness)↓; central and brachial mean arterial pressure↓; central systolic and diastolic blood pressure↓; brachial systolic and diastolic blood pressure↓ at 3 h	[68]
Gut microbiome	A clinical trial	Adults (N = 53)	71	48.4	KRG	3 g/day	24 weeks	Gut microbial richness ↑	[71]

*In Ref. [37], subjects are people who received following scores: stress response inventory≥81 points; Beck Depression Inventory≥10 points.
**Female% indicates female percentage among total participants.
***Abbreviations: KRG, Korean Red Ginseng; RT, Reaction Time; ANT, Attention Network Test; RVIP, Rapid Visual Information Processing; ROS, Reactive Oxygen Species; MDA, Malondialdehyde; SOD, Superoxide Dismutase; GPx, Glutathione Peroxidase; LDL, Low-density Lipoprotein; CRP, C-reactive protein.

= 54.1), KRG intake at 3 g daily for 12 weeks increased serum SOD activity [46]. *Panax quinquefolius* also exhibited antioxidant effects when blood samples collected after a single administration were exposed to ultraviolet B irradiation. This resulted in a reduced Comet score, indicating enhanced cellular DNA protection against oxidative stress (N = 14, 57 % female, mean age = 34.1) [47]. All these research findings support that ginseng contributes to the enhancement of memory, attention, and executive functions, thus benefiting cognitive function in adulthood.

2.2. Mood and fatigue

Ginseng appears to have an influence on neuroplasticity related to mood regulation in healthy individuals [29–31]. There are four studies investigating mood in healthy individuals, with a focus on young adults. These studies involve a single-dose [30], 8-day [29], and 2-week [31] consumption, utilizing both *Panax ginseng* [29] and *Panax quinquefolius* [30,31]. Ginseng consumption enhanced subjective mood, increasing calmness [29,30], and boosted self-assurance aspects of mood [31].

Fatigue is a cognitive and physical experience which accompanies neuroplasticity in the brain [49,50]. Cognitive fatigue is associated with reduced motivation and increased mental effort [51], while physical fatigue is related to elevated perceived energy deprivation [52]. In a study which examined the relationship between perceived state fatigue and brain structural connectivity in healthy older adults, higher connectivity in the surface area within the striatal-frontal-parietal networks was associated with lower levels of fatigue (both cognitive and physical) [49]. Moreover, fatigue is linked to higher inflammation, suggesting that reducing inflammation may help to reduce fatigue [53,54]. In healthy young and older adults, a single dose [200 mg *Panax ginseng* (G115), mean age = 21.9] [33], two weeks [200 mg/day *Panax quinquefolius* (Cereboost), mean age = 20.6] [31], and four weeks (2 g/day Enzyme-modified KRG, mean age = 61.1) [55] of ginseng consumption all reduced the feeling of general fatigue, which was measured by visual analogue fatigue scale. In a randomized controlled trial targeting menopausal women (N = 63, mean age = 59.2), daily KRG consumption of 2 g for eight weeks increased total antioxidant status and mitochondrial DNA copy numbers measured in peripheral blood, and reduced clinical symptoms of fatigue, as measured by the fatigue severity scale which measures both cognitive and physical fatigue [45]. Given the anti-inflammatory properties of ginseng [56] and inflammation's effects on fatigue [54], ginseng may impact brain plasticity related to fatigue by the anti-inflammatory features of ginseng as well as anti-oxidation.

In addition to this, ginseng has also been reported to have an impact on sociality, mental health, and sleep in healthy individuals. Changes in social interactions such as social isolation can alter brain connectivity [57]. In a randomized double-blind placebo-controlled trial (N = 30, 57 % female, mean age = 21.6), young adults who consumed 200 mg of *Panax ginseng* daily for 8 weeks, improvements were observed in social functioning and mental health [32]. Furthermore, 8 days of ginseng consumption improved the subjective quality of sleep [58]. These evidences indicate that ginseng may be involved in brain plasticity related with mood, fatigue, and mental health.

2.3. Hypothalamus-pituitary-adrenal gland axis and sympathetic nervous system

Ginseng has shown the effect of alleviating symptoms in rodents subjected to chronic mild stress [59], and it has been reported to improve mental health also in healthy humans [32]. In a normal state, the prefrontal cortex inhibits the amygdala, while in a chronically stressed state, the amygdala becomes overactive, leading to over-activation of the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), increasing the peripheral levels of cortisol and epinephrine, respectively. Daily consumption of 2 g of KRG for 6 weeks reduced blood epinephrine levels in middle-aged individuals with high stress and depression [37]. In a randomized double-blind placebo-controlled study targeting healthy middle-aged men (N = 87, mean age = 48.7), daily consumption of 2 g of KRG for 8 weeks resulted in reduced cortisol secretion compared to the placebo group [60]. In a double-blind placebo-controlled, counterbalanced within-group study targeting healthy adults (N = 19, 52% female, mean age = 39.9), middle-aged individuals who consumed 160 or 960 mg of GINST15 (an enzyme-fermented *Panax ginseng*) daily for 14 days showed a cortisol level reduction in response to exercise stress dependent on the ginseng dose [42]. These results suggest that ginseng reduces the body's physiological stress response, potentially by influencing partial neural circuits involving the prefrontal cortex-amygdala-HPA axis. In addition, ginseng administration also appears to help to recover the autonomic nervous system, potentially by modulating circuits of the prefrontal cortex-amygdala-hypothalamus-brainstem-SNS.

2.4. Glycemic control, vascular health, and gut microbiomes

There are other factors such as glycemic control, vascular health, and gut microbiomes that affect brain plasticity. Hormone receptors related to metabolism are expressed in various regions of the brain and contribute to brain plasticity. In particular, hormones and peptides associated with glucose homeostasis play a vital role in neuroplasticity in the hippocampus, forming the basis for learning and memory [7,9]. Glucose metabolism in the brain is considered to be critical for its function and it has been shown over decades that hypometabolism is detected in the neurodegenerative diseases such as AD [61]. Ginseng seems to improve the glucose metabolism processes, and in relation to ginseng and blood glucose, four clinical studies have been reported in healthy young and middle-aged adults [62–65]. No study has specifically analyzed the effects of ginseng on glycemic control in women alone, but it may offer potential neurological benefits for them. During the menopausal transition, when the levels of estrogen, a crucial regulator of energy metabolism in the brain, decline, a hypometabolic state can lead to neurological dysfunction. This might be potentially alleviated by ginseng, given its effects on glycemic control. Given the above-mentioned end products of the HPA axis and SNS (i.e., cortisol and epinephrine) also increase blood glucose level, the reduction of blood glucose levels by ginseng may be at least partially contributed to by the reduced activation of the HPA axis and SNS.

Studies about the arterial stiffness and brain integrity suggest that the corpus callosum, the internal capsule, and the corona radiata may be the most susceptible parts to microvascular damage, which appears to be associated with cognitive performance [66]. In addition, structural changes in gray matter are also associated with arterial stiffness [66]. Ginseng might indirectly influence neural plasticity by possibly improving vascular health, although more research is needed to confirm this. In double-blind crossover design studies targeting healthy young adults, a single administration of KRG 3 g significantly reduced arterial stiffness compared to the control group (N = 17, 47 % female, mean age = 30) [67], and a single administration of RG3-enriched KRG 400 mg reduced arterial stiffness, arterial pressure, central/brachial systolic and diastolic blood pressure (N = 23, 61 % female, mean age = 25) [68]. In a randomized placebo-controlled double-blind trial involving postmenopausal women (N = 63, mean age = 54), daily KRG administration of 3 g for 12 weeks reduced carotid intima-media thickness, and total

cholesterol, LDL, and menopausal symptoms [48].

Gut microbiome communicate bi-directionally with the brain through the 'gut-brain axis,' influencing neuroplasticity [13]. Ginseng has been reported to impact gut bacteria and alter cognitive function in animals [69,70]. One clinical study related to ginseng consumption and gut microbiome composition has been reported in healthy adults. In this clinical study (N = 53, 71 % female, mean age = 48.4), individuals who consumed 3 g of KRG daily for 24 weeks exhibited an increase in gut microbial richness [71].

As above, the effects of ginseng consumption on neural plasticity and the factors which are associated with neural plasticity were investigated in clinical studies (Table 1). In the following section, how ginseng affects

Table 2
Effects of ginseng or its derived components on the contributing factors for brain plasticity under physiological/pathological conditions in animal/cell models.

Brain Plasticity/ Contributing factors	Related Higher-order Functions	(Potential) Target Cells	In vivo (species)/In vitro	Model	Type of ginseng	Outcomes	Ref
Mitochondria	N.A.	Neuron	In vitro	Primary cortical neurons	Total ginsenosides	Mitochondrial respiration capacity ↑, ATP production↑, mitochondrial biosynthesis↑	[78]
Serotonin, GABA, BDNF	Anxiety	Neuron	Mice	Immobilization stress	KRG	Anxiety-like behaviors↓/Tryptophan hydroxylase, GAD67, $GABA_A$ receptor ↑in the cortex/BDNF ↑ in HP	[73]
Serotonin, Dopamine, BDNF, Antioxidant	Depression	Neuron	Rats	UCMS	KRG	Normalized UCMS-induced depression-related behaviors./Reduced serum corticosterone./A decrease in serotonin and dopamine turnover in PFC and HP./ Increased protein expressions of BDNF, pNrf2, Keap1, pAKT in PFC	[74]
Serotonin	Depression	Neuron	Rats	SPS	KRG	Depression-like behaviors↓/serotonin ↑in HP, mPFC.	[75]
NMDAR	Anxiety, Sociality	Neuron	Mice	CSDS	KRG	Anxiety-like behaviors↓/social avoidance↓/ Recovered CSDS-induced NR1, NR2A, NR2B protein overexpression in HP	[76]
BDNF	Cognition, Memory	N.A.	Rats	SPS	KRG	SPS-induced cognitive and spatial memory deficits↓/NF-kB activated Inflammation↓, BDNF mRNA↑, synaptic protein PSD-95↑ in HP	[56]
Antioxidant	Learning, Memory	Neuron	Mice	Scopolamine-induced hypomnesic mouse model	Enzymatically hydrolyzed KRG	Learning and memory deficits↓/ Hippocampal damage↓/Nrf2↑, and its downstream antioxidant enzymes NQO1 and HO1 ↑in HP/[In vitro] In hippocampal neurons, attenuation of glutamate-induced cytotoxicity by ROS reduction.	[41]
Proliferation, Differentiation	N.A.	OL	Mice	In vivo (male C57BL/6), In vitro (Primary OPC cultures)	Saponin, Non-saponin, Rb1	Non-saponin: OPC proliferation ↑/Saponin, Rb1: oligodendrocyte differentiation↑	[79]
Proliferation	N.A.	OL	In vitro	In vitro (Primary OPC cultures)	Gintonin	OPC proliferation↑	[80]
Myelin	N.A.	OL	Mice	Cuprizone model, In vitro (Primary OPC cultures)	KRG	Increased myelin gene expression.	[81]
Mitochondria, Proliferation	N.A.	Astrocyte	Mice	In vivo (male C57BL/6), In vitro (primary human brain astrocytes)	KRG	Number of astrocytes↑, Mitochondrial biogenesis↑	[83]
Gap junction	Depression	Astrocyte	Rats	Chronic restraint stress	KRG	Depressive symptoms↓, Cx43↑ in PFC, astrocytes number↑, astrocyte gap junction function ↑	[84]
Inflammation	Memory	Microglia	Mice	In vivo (Scopolamine-induced impairment), In vitro (BV2 cell line)	Black ginseng-enriched Chong-Myung-Tang	Memory ↑/Suppressed NO production, proinflammatory cytokine expression (iNOS, COX2, IL1b), NFkB pathway, MAPK pathway in BV2 cells.	[85]
Myelin, Inflammation	Anxiety, Motor function	Microglia, OL	Mice	Cuprizone model	KRG	Activation of resident microglia ↓/demyelination↓, OL degeneration↓	[82]
Serotonine, Gut-Brain Axis, Inflammation	Anxiety, Depression	Neuron, Blood, Gut microbiota	Mice	Transplanting the feces of patients with ulcerative colitis and depression	Fermented red ginseng	Anxiety and depression-like behaviors↓/ hippocampal, hypothalamic IL-6↓/blood corticosterone↓/hippocampal BDNF + NeuN + cell↑/hypothalamic dopamine, serotonine↑/colonic inflammation↓/gut dysbiosis↓	[86]
Gut-Brain Axis, BBB	Cognition	Gut microbiota	Mice	Tg2576 (AD model)	KRG	Improved the cognitive behavior/Aβ accumulation↓/Iba-1 ↑/Claudin-5 ↑ (= BBB permeability↓)/Increased gut *Lactobacillus* species↑	[69]
Gut-Brain Axis	Anxiety	Gut microbiota	Mice	Irritable bowel syndrome	KRG	Visceral pain↓/anxiety-like behavior↓/ beneficial microbes (*Lactobacillus johnsonii, Lactobacillus reuteri, and Parabacteroides goldsteinii*)↑/IL-1β↓ in the gut	[70]

*Abbreviations: N.A., Not Available; KRG, Korean Red Ginseng; HP, Hippocampus; UCMS, Unpredictable Chronic Mild Stress; PFC, Prefrontal Cortex; mPFC, medial PFC; NR, NMDA Receptor; CSDS, Chronic Social Defeat Stress; SPS, Single Prolonged Stress; ROS, Reactive Oxygen Species; OPC, Oligodendrocyte Precursor Cell; OL, Oligodendrocyte; NO, Nitric Oxide; AD, Alzheimer's Disease.

neural plasticity in cellular and molecular levels are explored through animal and cell experiments.

3. Ginseng's molecular mechanisms in brain plasticity

Brain plasticity involves various peripheral and central changes [6,72]. In Table 2, recent literatures published within the past three years that can help to understand the molecular mechanisms through which ginseng acts in brain plasticity are summarized. Ginseng has influenced brain plasticity by affecting various cells within the central nervous system, including neurons [41,56,73–78], oligodendrocytes [79–82], astrocytes [83,84], microglia [82,85], and peripheral systems such as gut microbiota [69,70,86]. In terms of molecular level, the effects of ginseng have been observed in the altered levels of neurotransmitters (such as serotonin [73–75,86], dopamine [74,86], and gamma-aminobutyric acid (GABA) [73]), N-methyl-D-aspartate receptor (NMDAR) subunits [76], synaptic proteins [56], and Brain-Derived Neurotrophic Factor (BDNF) [56,73,74]. It has induced anti-oxidation [41,74] and anti-inflammation [56,70,85], increased mitochondrial function and biogenesis [78,83], enhanced the functions of astrocyte gap junctions [84], and the BBB [69]. Moreover, ginseng was involved in cell proliferation and differentiation [79,80,83,84]. Through these complex cellular and molecular mechanisms, ginseng has promoted brain plasticity and enhanced brain functions, including reductions in anxiety [70,73,76,86] and depression [75,84,86], and improvements in cognition [56], learning [41], memory [41,56,85], and sociality [76].

3.1. Neurons

Mitochondria are crucial in synaptic plasticity because they provide energy for synaptic transmission and can buffer calcium [87]. Many researches have shown that the mitochondria is a major target of Rb1, exhibiting the effects of Rb1 on mitochondrial regulations such as mitochondrial energy metabolism, mitochondrial fission and fusion and reactive oxygen species release [88]. Other ginsenosides and the metabolites such as Rg1, Rg3, Rg5, Rb2, Rd, Re, CK, F1, F2 have also been reported to function in mitochondria via multiple mechanisms [89]. Treatment of primary cortical neurons with total ginsenosides, which are major active components of *Panax ginseng*, has been shown to increase mitochondrial respiration capacity, adenosine triphosphate (ATP) production, and mitochondrial biosynthesis [78]. This suggests that the uptake of ginseng components by brain cells can facilitate an environment that supports synaptic plasticity which requires a significant amount of energy.

Ginseng seems to be involved in creating an environment that affects the synthesis, turnover of neurotransmitters, receptors, and synaptic proteins. The consumptions of KRG support the enhancement of serotonin levels in the brain across three different rodent models. Specifically, KRG intake increased the expression of the enzyme tryptophan hydroxylase, which is involved in serotonin synthesis, in the mouse cortex under immobilization stress [73]. It also elevated serotonin levels in the hippocampus and medial prefrontal cortex (mPFC) of rats subjected to single prolonged stress (SPS, post-traumatic stress disorder model) [75] and reduced serotonin turnover in the PFC and hippocampus of rats exposed to unpredictable chronic mild stress (UCMS, a depression model) [74]. The treatment of Rg1, the abundant constituent of *Panax ginseng Mayer*, increased the activity of serotonergic neurons in the dorsal raphe nucleus of male rats, suggesting its modulation of serotonergic systems [90]. Similarly, another ginsenoside Rb3 also significantly increased the level of 5-hydroxytrylamine (5-HT) which were reduced by the stress exposure in the prefrontal cortex and amygdala [91].

Furthermore, KRG consumption reduced dopamine turnover in the PFC and hippocampus of rats under UCMS conditions [74], and increased GAD67, which is essential for GABA neurotransmission, and elevated the levels of $GABA_A$ receptors in the mouse cortex under the immobilized stress [73]. It also enhanced synaptic protein PSD-95 in the rat hippocampus under SPS conditions [56] and recovered the overexpressed level of NMDAR subunit protein induced by chronic social defeat stress in the mouse hippocampus [76]. In the UCMS rat model, Rb1 treatment significantly up-regulated 5-HT, 5-hydroxyindoleacetic acid (a metabolite of 5-HT), norepinephrine and dopamine levels in the brain, exhibiting that the antidepressant-like effects of Rb1 are mainly mediated by changes in central neurotransmitters of serotonergic, noradrenergic and dopaminergic systems [92]. In a study of microdialysis conducted on adult male rats, Re dose-dependently increased dopamine and acetylcholine in the hippocampus and mPFC [23]. Ginsenosides Rb1, Rg5, and Rk1 have reported to upregulate the expersssions of GABA receptors [93–95]. Recent studies have shown that ginsenosides regulate miRNA in neuronal cells [96–99]. Considering the potential of these ginseng components to regulate miRNA, they may possibly enhance the expression of neurotransmitters by inhibiting miRNA that suppresses tryptophan hydroxylase, dopamine, and GAD67 expression, although more research will be needed for a better understanding of the mechanisms involved. Interestingly, serotonin has been found to enhance mitochondrial biogenesis [100], as serotonin receptor type 3 and 4 localize to the mitochondrial membrane and modulate mitochondrial functions [101]. This suggests that the effects of KRG on mitochondria [78] may be partially attributable to the elevated serotonin levels induced by KRG [73–75].

BDNF is significantly related to neuroplastic changes, and disruptions in this signaling are associated with psychiatric disorders. Specifically, BDNF is transported and secreted in both pre and post-synapses. It binds to tropomycin receptor kinase B (TrkB) receptors located on both pre and post-synapses, activating the PI3K/mTOR, MAPK, and PLC-γ pathways. In post-synapses, it can activate postsynaptic translation, including BDNF, and induce synaptic plasticity. In pre-synaptic terminals, the activation of these pathways through BDNF binding-induced TrkB activation can also increase neurotransmitter release [102]. In rodent stress models (immobilization stress, UCMS, SPS), the consumption of KRG induced increased expression of BDNF in the hippocampus and PFC [56,73,74]. In UCMS models involving consumption of *Panax ginseng*-containing compounds [103] or Rb1 [104], BDNF-TrkB downstream signaling in the hippocampus [103,104] or PFC [104] is activated, followed by increasing pAKT/AKT, pERK/ERK, pCREB/CREB, and thereby activating PI3K and MAPK signaling, promoting transcriptional activation, and enhancing synaptic plasticity [103]. Recent research suggests that Rb1 affects BDNF through miR134, influencing synaptic plasticity in the hippocampus [96]. In addition to Rb1, many other ginsenosides also have been reported to activate CREB/BDNF signaling through several pathways to enhance synaptic plasticity. The expression of the BDNF receptor TrkB is promoted by Rd, Rb1, PF11, and Rg1. Among its downstreams, Rg1 increases the expression of MEK1/2, while Rd facilitates PI3K expression. Moreover, Rg1 stimulates PKA, CAMPKII, ERK, and CREB. Additionally, Rd, Rb1, Rg1, Rg3, Rg5, F1, and PF11 increase the levels of both CREB and BDNF [105]. As BDNF signaling is important in synaptic plasticity, ginseng consumption may exhibit its bioactivity in synaptic plasticity through this signaling.

The brain is an organ that highly demands energy, consuming approximately 20% of the body's basal oxygen consumption [106]. However, despite this, the brain has a modest antioxidant defense, therefore is vulnerable to oxidative stress [107]. In rodent stress models, the intake of KRG activates the nuclear factor erythroid 2-related factor 2 (NRF2)-mediated antioxidant defense system in the PFC [74] and the hippocampus [41], protecting brain cells from oxidative stress [41,74]. Most of ginsenosides including Rg1, Rb1, Rh1, Rd, Rg3, Rk1, Re, CK, and Rg5 exhibit antioxidant stress effects [108]. According to ginseng research in neuronal cells, Rb1 increases the expression of miR-130b-5p, thereby inhibiting neuronal apoptosis and anti-inflammatory factors [109], while Rg1 decreases the expression of miR-144, thereby preserving the expression of Nrf2 [97]. These results suggest that the neuroprotective effects of ginseng are contributed to by the modulation of

anti-oxidative factor expression mediated by miRNA.

3.2. Oligodendrocytes, astrocytes, and microglia

Brain plasticity involves not only synaptic plasticity but also myelin plasticity. Oligodendrocytes are glial cells which form myelin structure. Experience-dependent neural activation can regulate myelination and alter the myelin structure [110]. Myelin adjusts the speed of action potential conduction, thereby modulating the efficiency of information exchange and playing a crucial role in neuronal plasticity [6]. Such myelin plasticity influences motor learning [111], sociability [112], and more. In primary oligodendrocyte precursor cell (OPC) culture, gintonin, a fraction of ginseng [80], and the non-saponin fraction [79] promote OPC proliferation, while saponin fractions, especially Rb1, promote oligodendrocyte differentiation and myelin formation [79]. In an in vivo cuprizone demyelination model, administrations of KRG, Rb1 or Rg1 promoted the recovery of myelin or oligodendrocyte numbers [81,82,113]. Furthermore, in a chronic PD mouse model, Rg1 exhibited a protective role against lipid peroxidation stress in oligodendrocytes, protecting myelin sheaths and mature oligodendrocytes [114]. Although more research is needed, KRG may contribute to brain plasticity not only through synaptic plasticity but also myelin regulations.

Astrocytes located at synapses can be involved in both short- and long-term plasticity [6]. Furthermore, astrocytes, just like neurons, possess a substantial number of mitochondria [115], allowing them to regulate local levels of ions, glutamate, and fatty acids, control inflammatory signals, and promote mitophagy by taking up damaged mitochondria released from neurons [116]. Additionally, mitochondrial transfer from astrocytes to neurons has been observed in vitro and in vivo after stroke [117]. Mice that consumed KRG for three days exhibited an increase in astrocyte numbers in the subventricular zone, and KRG treatment also increased astrocyte numbers in primary human brain astrocytes [83]. Furthermore, KRG treatment to astrocytes increased mitochondrial biogenesis [83]. In another study, KRG consumption in depression model rats increased astrocyte numbers and enhanced astrocyte gap junction function [84]. One of major ginsenosides, Rg1 improves the function of astrocyte gap junction in the PFC and hippocampus of the depressed rats [118,119], while another major ginsenoside Rb1 facilitates transfer of astrocytic mitochondria to neurons against ischemic stroke [120]. KRG may contribute to overall brain plasticity through securing astrocytes which function in synaptic plasticity by increasing the number of astrocytes and through increasing mitochondrial supply to neurons by increasing mitochondrial production in astrocytes.

Pro-inflammatory cytokines have a negative impact on neuroplasticity, potentially via a reduced expression and function of BDNF [121]. Ginseng seems to function in suppressing inflammation in the central nervous system. When a compound rich in black ginseng was applied to microglial BV2 cells in vitro, it led to the suppression of nitric oxide (NO) production, expression of proinflammatory cytokines (iNOS, COX2, IL1β), and the NF-κB pathway [85]. Additionally, in a cuprizone model mice, KRG consumption decreased resident microglial activation and anxiety-like behavior, while it improved motor function, coordination, and balance [82]. Several ginsenosides including Rg3 [122], Re [123], Rh1 [124], Rg1 [125], Rb1 [126], Re [127] have been reported to suppress microglia activation, reducing inflammation. Ginseng and its components may suppress microglial activation and reduce brain inflammation, thus having a positive impact on brain plasticity.

3.3. Gut microbiome

Gut microbes can influence brain plasticity through various pathways. Gut microbes can change the production of certain molecules that can affect neurotransmitter production in the brain (e.g., Tryptophan → serotonin). Short-chain fatty acids (SCFA), a byproduct of dietary fiber fermentation, can enter the brain and regulate microglia maturation and function or participate in epigenetic chromatin remodeling in various brain cells, thus influencing neuroplasticity [128]. In multiple mouse models, ginseng has consistently improved gut microbiota dysbiosis. Specifically, administering fermented red ginseng via oral gavage to mice transplanted with feces of patients with ulcerative colitis and depression improved gut dysbiosis and reduced colon inflammation. In the brain, it decreased hippocampal and hypothalamic IL-6, increased $BDNF^{+}NeuN^{+}$ cells in the hippocampus, elevated hypothalamic dopamine and serotonin levels, and reduced anxiety and depression-like behaviors [86]. In another study, KRG administration to Tg2576 (AD model mice) altered the gut microbiota diversity, increasing *Lactobacillus* species. Moreover it decreased blood-brain barrier permeability, microglial activation, Aβ accumulation in the brain, and increased cognitive function [69]. In irritable bowel syndrome model mice, KRG consumption also increased beneficial bacteria, including *Lactobacillus johnsonii*, *Lactobacillus reuteri*, and *Parabacteroides goldsteiniirk*, while reducing the level of gut inflammatory cytokine (IL-1β). It also decreased visceral pain and anxiety-like behavior [70]. Gut microbes can influence brain plasticity and function through neuroactive metabolites, vagus nerve activation, and immune systems. Accumulated evidences suggest that ginseng has a beneficial impact on brain plasticity and function through mechanisms including changes in the composition of these gut microbes.

3.4. Targets of ginseng in the brain

Ginseng is a complex compound containing various components, thus its beneficial effects on the brain may be derived from the synergy of ginseng components targeting multiple molecules. One systems pharmacology study identified nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3 (NLRP3) as a shared target of major ginsenosides to achieve cumulative bioactivity [129]. NLRP3-inflammasome activation has been also known as a molecular target of various ginseng saponins: Rg3, Rd, Rg1, 25-OCH3-PPD, CK, Rh1, CS IVa, and PF11 [130]. As NLRP3 inflammasome is a major contributor to the development of neuroinflammation, its modulation by ginseng suggest ginseng's therapeutic effects on neurodegenerative diseases [131]. Moreover, in the brain, ginsenosides have been found to provide neuroprotective effects related to mitochondria in neurodegenerative models. For examples, Rg3 modulates ATP and the electron transport chain, while Rg1 or Re change Bax/Bcl2 and CytoC levels in mitochondria in the AD model [89]. Whether they are direct or secondary effects of ginseng components remains elusive. In hepatic cells, some ginsenosides (i.e., Rc, Rd, Re, Rg2, Rh1, Rh2, PPD, PPT, F11, TG) bind to the aryl hydrocarbon receptor (AHR), thus are regarded as AHR agonists [132]. It is interesting to know whether their interactions exist in the brain or not.

While specific receptors for ginsenosides have remained elusive in the brain, another ginseng-derived component gintonin, a LPA-ginseng protein complex, can selectively activate LPA receptors, which are abundantly expressed in the brain, to target various cellular effects including cell proliferation or survival, cell migration, and morphological changes [133]. Gintonin administration to Aβ transgenic AD mice reduces amyloid plaque deposition and prevent long-term memory impairment [134].

Molecular-level changes in both the central and peripheral systems, induced by ginseng consumption, have a complex impact on brain plasticity, resulting in alterations in individual behavior. In mouse stress models, KRG consumption reduces anxiety [73,76] and depression [75], while it enhances memory, learning, cognition [41,56], and social behavior [76]. In this manner, ginseng consumption significantly induces changes in brain cells, structures and function.

4. Conclusion

In this review, the impact of ginseng on brain plasticity and the

related factors in humans undergoing the normal aging process shows its effects on cognition, mood, fatigue, physiological stress responses, glucose metabolism, vascular health, and gut microbiota composition. Through cellular and animal studies examining the mechanisms, ginseng was found to not only influence neurons through modulating neurotransmitters, synaptic proteins, neurotrophic factors, anti-oxidation, but also play a significant role in the functionality of glial cells such as astrocytes, oligodendrocytes, and microglia. Ginseng also impacts the composition of gut microbiota, changing gut-brain interactions, contributing to neuroplasticity. Additionally, ginseng contribute to modulate mitochondrial synthesis, cell proliferation, differentiation, and inflammation in brain cells. The cellular molecular-level changes, followed by structural changes induced by ginseng translate into enhancements in higher brain functions, such as cognition, memory, learning, and social behavior, and improvements in emotional well-being, reducing anxiety and depression.

Ginseng influences brain plasticity by acting on brain cells, affecting synaptic plasticity and myelin modulations. It also exerts its influence on various systems in the body, including the endocrine system, blood glucose regulation, the gut-brain axis, and more. Ginseng consumption may contribute to brain plasticity through the following potential peripheral pathways: changes in metabolites, cytokines, and afferent vagus nerve by promoting beneficial bacteria; alterations in brain cell responses through blood glucose-dependent glucose transporter and insulin signaling; increase in blood flow to the brain through the reduction of arterial stiffness; and reduction in neurotoxicity by decreased cortisol exposure to brain cells. Ginseng consumption is also expected to contribute to brain plasticity within the brain through the following potential mechanisms: increase in serotonin, dopamine, BDNF, antioxidants and anti-inflammatory processes, and mitochondrial biosynthesis in neurons; decrease in inflammatory signaling in microglia; increase in the proliferation, mitochondrial biosynthesis, and gap junction function in astrocytes; increase in proliferation, differentiation and myelination in oligodendrocyte-lineage cells. Through these molecular mechanisms, ginseng consumption improves following multiple brain functions associated with brain plasticity: improvements in cognition, learning, memory, and attention; reductions in fatigue, anxiety, and depression (Fig. 1).

Ginseng can have beneficial effects on brain plasticity, contributing to the followings: 1. It can help prevent brain function decline in individuals during the normal aging process. 2. It may protect against the risk of neuroplasticity damage induced by dietary factors, such as a western-style diet, highly processed foods, and exposure to toxic substances from environmental pollution. Future research is anticipated to investigate how long-term ginseng consumption can enhance brain function during the normal aging process and how it can prevent or reverse neuroplasticity damage resulting from external factors such as an unhealthy diet or environmental pollution.

Declaration of competing interest

None.

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