Special Article

NUTRITION REVIEWS

Effects and mechanisms of ginseng and ginsenosides on cognition

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Reviewed here is the existing evidence for the effects of ginseng extracts and isolated ginsenosides relevant to cognition in humans. Clinical studies in healthy volunteers and in patients with neurological disease or deficit, evidence from preclinical models of cognition, and pharmacokinetic data are considered. Conditions under which disease modification may indirectly benefit cognition but may not translate to cognitive benefits in healthy subjects are discussed. The number of chronic studies of ginseng effects in healthy individuals is limited, and the results from acute studies are inconsistent, making overall assessment of ginseng's efficacy as a cognitive enhancer premature. However, mechanistic results are encouraging; in particular, the ginsenosides Rg_3, Rh_1, Rh_2, Rb_1, Rd, Rg_2, and Rb_3, along with the aglycones protopanaxadiol and protopanaxatriol, warrant further attention. Compound K has a promising pharmacokinetic profile and can affect neurotransmission and neuroprotection. Properly conducted trials using standardized tests in healthy individuals reflecting the target population for ginseng supplementation are required to address inconsistencies in results from acute studies. The evidence summarized here suggests ginseng has potential, but unproven, benefits on cognition.

INTRODUCTION

Ginseng is the most widely consumed herbal nutritional product in the world.[1] According to the most recent data available, ginseng had a total world export value in 2010 of over US$350 million, which was expected to rise to more than US$400 million in 2012.[2] Ginseng is a root used in medicinal food recipes, particularly soups and stews; it is also added to confectionary and drinks for its reputed medicinal and performance-enhancing properties. The extract of the root is a highly regarded Asian herbal medicine, and ancient, prime specimens of wild-harvested ginseng root have been sold at auction for record prices: a 325-year-old plant was sold in August 2012 for US$1.57 million, while a 115-year-old piece of ginseng brought approximately US$1 million.[3] Such prices can be commanded because of ginseng's reputation as a panacea promoting longevity; as a rejuvenative herb; as an adaptogen for stress, weakness, and fatigue, both mental and physical; and as supportive treatment for many other ailments, including diabetes, cardiovascular disease, and inflammatory disorders.[4] The modern evidence base for the use of ginseng in these settings, however, is less clear. In this review, the results from studies of the effects of ginseng extracts and isolated ginsenosides on cognitive function in humans, which include clinical studies in healthy volunteers as well as in patients with neurological disease or deficit, are appraised. Evidence from studies in animal and cellular models of cognitive correlates or neuropathology is also examined in order to identify legitimate cognitive benefits, along with possible mechanisms of action, of ginseng or ginsenosides.

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Key words: attention, cognition, ginseng, ginsenoside, memory

doi:10.1111/nure.12099

Overview of the botany and chemistry of ginseng and ginsenosides

"Ginseng" refers to plants of the genus *Panax*, which includes at least 11 species. The species most commonly used in herbal medicine is *Panax ginseng* C.A. Mey. (Asian or Korean ginseng),[5,6] with *Panax quinquefolius* L. (American ginseng)[7,8] also widely used. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Siberian ginseng), also used for medicinal purposes, belongs to the same family (Araliaceae) and has related – but different – saponin constituents. Extracts from ginseng are complex mixtures of multiple components. The triterpene saponins (the ginsenosides) are considered the main phytochemical constituents that contribute to the purported cognitive effects of ginseng[5,7,9,10] (see Figure 1). Ginsenosides found in *P. ginseng* and *P. quinquefolius* have a dammarane ring-based structure[11,12] and can also be found in extracts of *Panax notoginseng*[13] (notoginseng) and *Panax vietnamensis* Ha & Grushv.[14] (Vietnamese ginseng). Other members of the genus, such as *Panax japonicus* (T.Nees) C.A. Mey.[15] (Japanese ginseng), contain predominantly oleanonane saponins, although dammarane derivatives have also been isolated from *P. japonicus* and *Panax pseudoginseng* Wall. (Himalayan ginseng). This review focuses on the ginsenosides found in *P. ginseng* and *P. quinquefolius*, which have been the most extensively investigated.

Some ginsenosides are common to both *P. ginseng* and *P. quinquefolius*; however, some compounds are unique to each species. Further compounds are produced by processing methods used in traditional Chinese medicine (TCM). Steaming and fermenting structurally transform some ginsenosides and alter the composition of extracts. White ginseng is produced by drying fresh ginseng in sunlight, whereas red ginseng, the type most widely used in TCM, results from steaming fresh ginseng at 95–100°C for 2–3 hours prior to drying. Nine cycles of steaming at 98°C produces black ginseng, which is used much less frequently.[16] A relatively new type of processed ginseng, sun ginseng, is produced using a high temperature (100–120°C for 2 h).[17,18] Ginseng can also be fermented. A variety of methods are employed,[19–21] using conventional fermentation organisms such as *Lactobacillus* and *Aspergillus* as well as with other fungal species used in TCM, e.g., *Ganoderma lucidum*[22] and *Phellinus linteus*.[23] Red ginseng is the type most commonly fermented, resulting in "fermented red ginseng." Such processing further changes the composition of extracts, but these procedures are varied and complex, and the changes in ginsenoside profiles are not well documented. It is clear, however, that red, black, white, and sun ginseng preparations each contain different profiles of ginsenosides, which are present in different ratios to both the parent extract and to related compounds that are not detectable in the unprocessed material.[16,18,21,24] The pharmacological effects of various powdered ginseng preparations, standardized ginseng extracts, and isolated ginsenosides have been studied in a range of cell-based, animal, and clinical trials relevant to numerous conditions and pathological states. In the case of cognition, however, variations in study methodologies and in the content of ginsenoside administered restrict the direct comparison of results between studies, hamper attempts to define the effects of individual ginsenosides,[25,26] and highlight the importance of investigating extracts of biologically relevant (i.e., bioactive and bioavailable) ginsenosides.

Ginsenosides fall into two major subtypes: those derived from protopanaxadiol (PPD), which include Rb_{1-3}, Rc, and Rd, and those derived from protopanaxatriol (PPT), which include Re, Rf, and Rg_1[5,7] (see Figure 1). These ginsenosides occur in different proportions in *P. ginseng* and *P. quinquefolius*,[11] although Rb_1 and Rg_1 are the most abundant in both species (Table 1). Rf is unique to *P. ginseng*, and pseudoginsenoside F11 is unique to *P. quinquefolius*.[9] The steaming and fermenting of ginseng alters the ratios of constituent ginsenosides and thus gives red ginseng a distinct phytochemical and pharmacological profile.[7] An extensive list of ginsenosides is provided by Qi et al.,[9] Xie et al.,[13] and several monographs.[5–8]

Pharmacokinetic studies of ginsenoside metabolites

The half-life of many ginsenosides in pharmacokinetic studies is short (range, 0.2–18 h), and bioavailability is low (summarized by Qi et al.[9]). Along with the limited amounts of minor ginsenosides in ginseng extracts, this suggests that metabolites of the most abundant ginsenosides account primarily, or at least partially, for the functional effects reported.[27,28] Studies conducted in in vitro models of hepatic enzymes and intestinal bacterial metabolism and in animal models of administration and absorption suggest metabolic pathways for several major ginsenosides.[27–31] Metabolites of PPD ginsenosides include compound K, Rg_3, Rh_2, and Rh_2's aglycone, while PPT-type metabolites include Rh_1 and PPT. Metabolites resulting from plant as well as from human metabolism display pharmacological activity (see Table 2), suggesting that some ginsenosides present in herbal extracts can behave as prodrugs. A limited number of pharmacokinetic studies in humans have been performed, but only those that examined ginsenoside metabolism in plasma and urine after administration of ginseng or ginsenosides are discussed below.

A pilot study of standardized *P. ginseng* extract (G115) administered (700 mg p.o.) to 2 healthy subjects

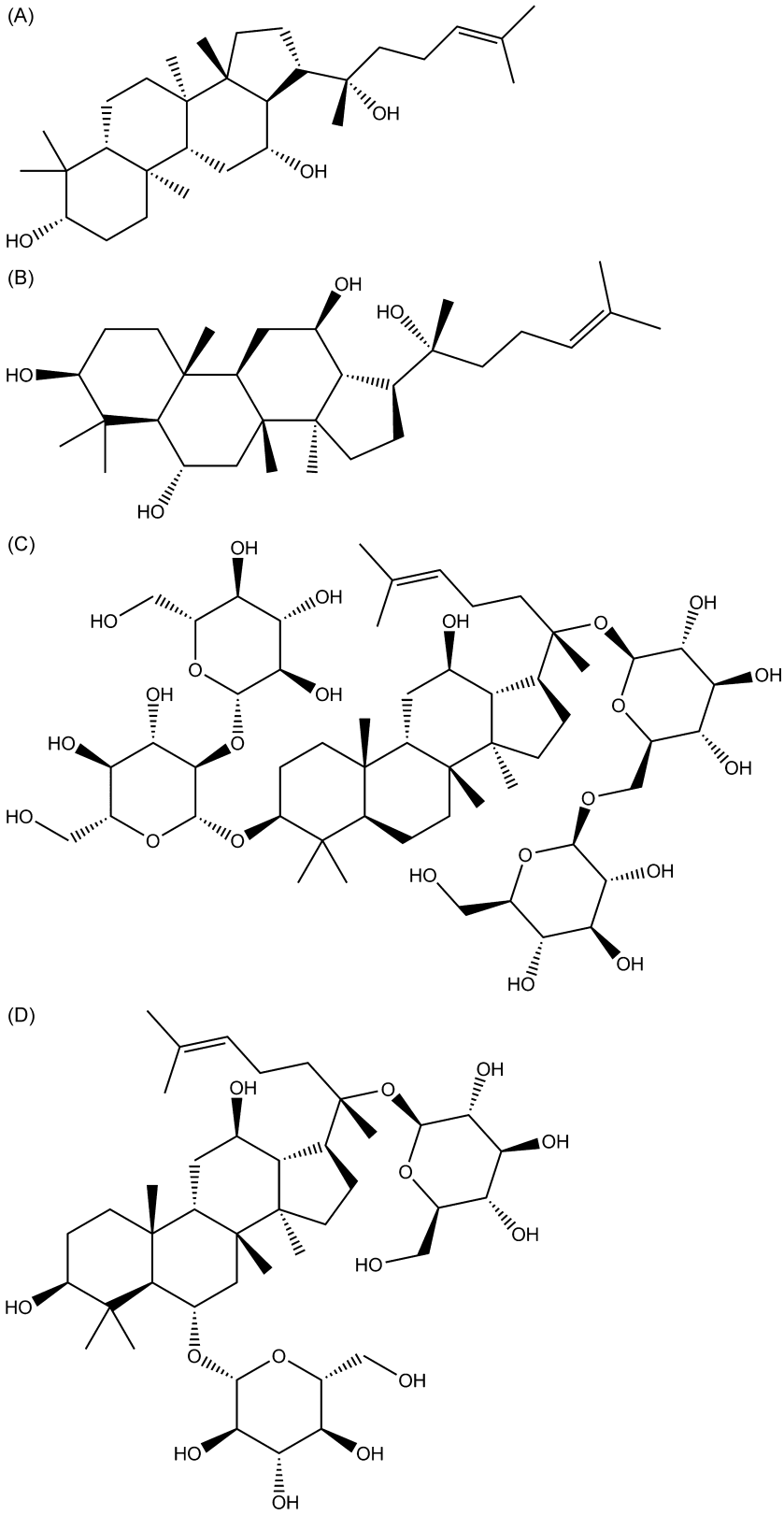

Figure 1 **Dammarane ginsenoside structures of the aglycone parent compounds PPD (A) and PPT (B) and their PPD- and PPT-type derivatives Rb_1 (C) and Rg_1 (D).**

Table 1 **The major ginsenosides from *P. ginseng* and *P. quinquefolius* extracts, along with their effects on the CNS.**

Compound	Occurrence[a]	CNS effects reported in published studies	No. of hits (no. remaining after filtering for CNS relevance)
Rb_1	*P. ginseng* ++ *P. quinquefolius* ++++	Neuroprotective; improved spatial memory and reduced memory impairment in animal models; neurotrophic[79,88,98,133–138]	529 (94)
Rb_2	*P. ginseng* + *P. quinquefolius* (tr)	Anticholinergic activity in rat cortical cultures[139]	162 (8)
Rb_3	*P. ginseng* (tr) *P. quinquefolius* (tr)	Neuroprotective in various models of disease and hypoxia/ischemia (see also Table 2)[140–142]	63 (9)
Rc	*P. ginseng* + *P. quinquefolius* +	Neuroprotective in a model of Huntington's disease[143]	199 (14)
Rd	*P. ginseng* + *P. quinquefolius* ++	Neuroprotective in models of ischemia, neurotoxicity, and excitotoxicity[87,99,144–148]	287 (32)
Re	*P. ginseng* +++ *P. quinquefolius* ++	Neuroprotective in Parkinson's disease and a model of ischemia; induced cognitive improvement in a model of diabetes[149–152]	429 (28)
Rf	*P. ginseng* +	Antinociceptive in mouse models[153,154]	100 (12)
Rg_1	*P. ginseng* +++ *P. quinquefolius* +	Neuroprotective in models of Alzheimer's disease and amyloidogenesis; improved memory and reduced memory impairment in animal models[88,95,110,111,155–159]	537 (120)
Rg_2	*P. ginseng* (tr) *P. quinquefolius* (tr)	Reduced memory impairment in a dementia model; exhibited effects on serotonin and nicotinic receptors[160–162]	89 (6)
F11	*P. quinquefolius* +	Reduced memory impairment in an injury model; neuroprotective in mouse models[89,163,164]	22 (4)
Ro	*P. ginseng* ++ *P. quinquefolius* +	Not available	45 (2)

Abbreviations: CNS, central nervous system.
[a] Occurence stratified according to relative abundance in *P. quinquefolius* and *P. ginseng*.[7]

found that Rb_1, compound K, and Rh_1 and/or F_1 (indistinguishable via mass spectrometry) reach systemic circulation and are detectable in plasma between 1 and 12 hours after dosing and in urine between 3 and 24 hours after dosing.[32] Lee et al.[33] administered *P. ginseng* powder (12 g p.o.) to 34 healthy subjects and identified compound K in plasma 4 hours after administration, reaching a C_{max} of 27.89 ± 24.46 ng/mL at $T_{max} = 10.76 \pm 2.07$ hours. In a

Table 2 **Key ginsenoside metabolites and their proposed pharmacological activities.**

Metabolite[a]	Proposed CNS effects shown in published studies	No. of hits (no. remaining after filtering for CNS relevance)
Compound K	Neuroprotective and antineuroinflammatory; antidepressant in a mouse model; facilitated GABA release in hippocampus[100,165–168]	103 (13)
F1	Not available	35 (3)
PPD	Inhibited Na^+ channel function; antidepressant in a mouse model[169–171]	219 (22)
PPT	Improved memory in mice[90]	164 (17)
Rb_3	Neuroprotective in models of ischemia and Huntington's disease; inhibited NMDA receptor activity and was anticonvulsant in seizure models; antidepressant in animal models[115,142,143,172]	63 (9)
Rg_3	Neuroprotective and antineuroinflammatory in cell and animal models; inhibited $K^+/Na^+/Ca^{2+}$ channel function in multiple cell types[101,137,173–187]	247 (36)
Rh_1	Improved memory in mice, antineuroinflammatory[90,188]	87 (8)
Rh_2	Inhibited Na^+ channel function, inhibited NMDA receptor activity, neuroprotective and antineuroinflammatory in cell and animal models[91,102,169,177,189,190]	159 (17)

Abbreviations: CNS, central nervous system; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-$_D$-aspartic acid.
[a] In addition to these compounds, some ginsenosides found in plant extracts – Rb_1, Rd, and Rg_2 – have also been identified as metabolites of other ginsenosides, as shown in Table 1.

study in which fermented or unfermented *P. ginseng* (3 g p.o.) was administered to 24 healthy volunteers, significant levels of compound K were present in the fermented product prior to administration and in plasma after ingestion (C_{max} = 325 ± 91.97 ng/mL, T_{max} = 3.29 ± 1.0 h, for fermented *P. ginseng*, and C_{max} = 13.88 ± 7.24 ng/mL, T_{max} = 12.04 ± 4.96 h for nonfermented *P. ginseng*).[34] No values for other ginsenoside metabolites were reported. Another study investigating the administration of *P. quinquefolius* powder (10 g p.o.) to 6 healthy volunteers identified Rb_1, Rd, Rg_2, and compound K in plasma 2–12 hours after administration,[35] with only compound K and Rb_1 present in all samples. A decrease in levels of Rb_1 and an increase in compound K over time were also observed, consistent with reports that intestinal bacteria can metabolize Rb_1 to compound K. However, since the last measurement of compound K was taken at 12 hours, the C_{max} of this metabolite was not determined. The Rb_1 concentration in plasma peaked at 4 hours, when C_{max} = 19.90 ± 5.43 ng/mL.

Ginsenoside Re (200 mg p.o.) was administered to 10 healthy volunteers and produced a limited number of probable metabolites in plasma and urine – identified as Re, Rg_1, F_1, Rh_1, and PPT – when assayed 3–12 hours after administration, although no Rg_2 was detected.[36] Pharmacokinetic data were provided only for Re (C_{max} = 0.939 ± 0.549 ng/mL, T_{max} = 1.19 ± 0.44 h, $T_{1/2}$ = 1.82 ± 0.75 h). In another study, Rd (10 mg i.v.) was administered to 10 healthy volunteers and plasma levels monitored up to 96 hours after administration[37]; C_{max} was 2,841.18 ± 473.03 ng/mL, T_{max} 0.50 ± 0.0 hours, and $T_{1/2}$ 19.29 ± 3.44 hours. Finally, the pharmacokinetics of PPD (25 mg p.o.) were studied by Zhang et al.,[38] who found C_{max} = 7.24 ± 3.30 ng/mL, T_{max} = 1.28 ± 0.49 hours, and $T_{1/2}$ = 4.77 ± 2.05 hours.

When attempting to compare the results of studies that do not report specific plasma levels with those of studies that have specifically investigated pharmacokinetic parameters, it worth noting that differences exist between the doses used. Here, doses used in studies examining the clinical effects of standardized extracts were in the range of 100–600 mg (see Results), while the pharmacokinetic study of G115 standardized extract used 700 mg. In the case of powdered ginseng, clinical studies used 4.5–9 g, while pharmacokinetic studies used 3–12 g. Ginsenosides used in pharmacokinetic studies (Re, Rd, and PPD) were in the dose range of 10–200 mg. In all these studies, compounds were administered orally (with the exception of Rd, administered i.v.), and, while some differences exist, doses used in clinical and pharmacological studies were of the same order of magnitude. A key point is that appropriate sampling during studies of ginseng effects is essential in order to determine the likely active components underlying the reported effects.

These pharmacokinetic studies confirm in vitro results suggesting that compound K is a major metabolite of the ginsenosides present in *P. ginseng* and *P. quinquefolius* extracts. Many of these studies, however, do not provide pharmacokinetic analyses for all the metabolites identified. Additionally, since intravenous injection is not the normal route of administration for ginseng supplements, the study of a single injection of Rd[37] is not representative because gastrointestinal metabolism was bypassed. Further studies are needed to properly elucidate the complex pharmacokinetic profiles of ginsenosides at doses relevant to commonly consumed ginseng supplements.

CURRENT RESEARCH ON GINSENG AND COGNITIVE FUNCTION

Cognition and correlates of cognitive function

A wide range of clinical and preclinical (animal cell culture models) studies have assessed the effects of ginseng extracts and ginsenosides on parameters considered relevant to memory, attention, and other features of cognitive function. Detailed descriptions of all relevant measures used in clinical studies exceed the scope of this review but are provided in PASSCLAIM, which examines methodologies used to investigate the effects of food on mental function,[39] and, likewise, in the European Food Safety Authority Scientific Committee's guidelines on the use botanicals.[40] Finally, a valuable review by Macready et al.[41] provides informative discussion on the use of cognitive tests and methodologies in repeat-dose randomized controlled trials of micronutrients. In addition, issues relevant to studies of the acute effects of micronutrients are highlighted.

Cognition refers to processes involved in mental function that enable acquisition, processing, and storage of information and facilitate the use of information for decision-making processes, problem solving, and communication. Cognition can be divided into functional domains comprising hierarchical components. While many sources identify memory, executive function, psychomotor function, attention, and intelligence as high-level cognitive components,[25,41–44] no consensus on a single model of the components of human cognition has been reached. Thus, cognitive test batteries and assessments used by different studies draw on different models and target multiple cognitive elements.[45–47] This review does not attempt to examine models for categorizing cognition in detail, but some contextual definition of the cognitive foci relevant to ginseng effects is warranted. Here, the following key terms are used: *memory* – the storage of information that can be categorized on the

basis of the duration (short or long term) or the type of process involved; *working memory* – the system for temporarily holding and manipulating sensory information, requiring control through executive functions; and *attention* – the processes of selective focusing on task(s) or aspects of the environment.

Batteries of tests developed for use in human clinical trials of cognitive functions include assessment of memory and attention through a range of tests that differ between each battery. While each test is specific, the variation in available tests means that direct comparison between them presents a fundamental problem when attempting to draw overarching conclusions from cognitive trials.[25,41] Many tests are not "task pure"; for example, a test aiming to measure variables of attention can also place a significant load on the participant's working memory. This applies to tests of cognitive function in animals, too, such as the Morris water maze in rodents (described in the section on animal studies), which assesses spatial memory and learning. In addition, results from studies of healthy subjects can be difficult to compare with results from studies that incorporate pathophysiological factors (e.g., animal models of disease or studies in patients with neurological or cognitive dysfunction). The literature reveals interesting geographical differences in the types of studies conducted with ginseng: in the West, where ginseng is used predominantly as a general health supplement, research has tended to focus on effects in healthy volunteers, while in Asia, studies are typically conducted in patients with cognitive impairment or neurological dysfunction, reflecting the role of ginseng in traditional medicine in that part of the world. Ginseng is a component of traditional Korean and TCM preparations (e.g., Shengmai san injections[48] and Sanchi preparations of notoginseng[49]) used in the treatment of cardiovascular and neurological conditions. Studies of the effects of ginseng on neurological deficits, e.g., dementia, Alzheimer's disease, and mild cognitive impairment, may not directly assess cognitive function, although clinical assessments such as dementia scores can provide relevant information or include a cognitive component.[50–52] Therefore, while studies assessing the effects of ginseng and ginsenoside on neurological deficits should not be discounted, such findings should be interpreted carefully for their relevance to healthy populations.

Ginsenosides and human cognition

Studies of the effects of ginsenosides on cognition in healthy human volunteers are limited, and their comparison is hampered by the heterogeneity of participant groups, outcome measures, and study methodologies.[41] The most recent Cochrane review, *Ginseng for Cognition*, describes some of these issues in detail and has reviewed double- and single-blind randomized placebo-controlled trials that assessed the effects of ginseng on cognitive function.[25] It concluded there is indeed evidence for a beneficial effect of treatment with ginseng extracts on cognitive function, although the effects on components of cognition have not been consistently observed between studies. Larger trials using consistent testing methodologies are required to fully assess the acute and chronic effects of ginseng on cognitive function in healthy adults, confirming a previous systematic review.[53] Published critical reviews have also examined the effect of ginseng on Alzheimer's patients and their quality of life,[51,54,55] including outcomes affecting cognitive function. Although noting positive outcomes in individual study measures, these reviews also concluded there was insufficient evidence to support ginseng as an effective treatment.

Literature search methodology

PubMed searches with Boolean search terms that combined identifiers of ginseng and its components with key words relating to cognition and associated neurobiological pathways were used. Search results are summarized in Tables 1, 2, and 3 (detailed in the subheaded Results sections), and search terms are shown below.

Table 1: (ginsenoside OR ginseng) AND [compound] followed by (ginsenoside OR ginseng) AND (brain OR neuron OR memory OR attention) AND [compound]).

Table 2: (ginsenoside OR ginseng) AND [compound] followed by (ginsenoside OR ginseng) AND (brain OR neuron OR memory OR attention) AND [compound]).

Table 3: (ginsenoside OR ginseng) AND [target] followed by (ginsenoside OR ginseng) AND (brain OR neuron OR memory OR attention) AND [target]).

Identification of metabolites: (ginseng OR ginsenoside) AND (pharmacokinetic* OR ADME OR DMPK) AND human. The initial pool of studies retrieved was manually filtered for relevance to cognition.

Studies of cognitive effects in healthy individuals and neurological diseases:

1. (ginsenoside OR ginseng OR G115 OR Ginsana OR Cereboost OR HT1001) AND (memory OR cognitive OR cognition OR learning OR attention OR neurocognitive) AND (clinical OR trial OR clinical study).
2. (ginsenoside OR ginseng) AND (mild cognitive impairment OR dementia OR Parkinson* OR Alzheimer* OR Huntington* OR neurodegeneration) AND (clinical OR trial OR clinical study).

Results retrieved were manually filtered for relevance. From an initial pool of 93 publications, the following were excluded immediately: reviews, studies of pharmacokinetics only, studies not involving any aspect

Table 3 **Potential mechanisms and key molecular targets for ginseng and ginsenoside effects in the CNS.**

Target pathway	Relevance	Ginsenosides	No. of hits (no. remaining after filtering for CNS relevance)
Nitric oxide synthesis and signaling pathway	Nitric oxide is a second messenger and key mediator in inflammation, with roles in neurogenesis and neuronal cell survival signaling; linked to CREB activation	Extract,[165] Rd,[87,191] Rg_3,[192,193] Rh_1,[188] Rh_2,[194] compound K,[100,195] PPT[196]	198 (31)
Antioxidant enzymes	Enzymes regulating production of antioxidant molecules and removal of oxidation are important to inflammation and cell damage and death	Extract,[83] Rd,[148] Re,[149] Rg_3[101,197]	575 (94)
NMDA-type glutamate receptors	Major excitatory receptor involved in neurotransmission across the CNS in plasticity, memory, and neurotoxic cell death	Rb_3,[142] Rd,[144] Rg_1,[198] Rg_3,[181,199] Rh_2[189]	28 (28)
GABA receptors	Major inhibitory receptor involved in neurotransmission across the CNS; vital in plasticity and regulation of neuronal excitability	Rb_3,[140] Rc,[200] compound K[168]	20 (20)
Acetylcholine and its receptors	Acetylcholine neurotransmitter, acetylcholine esterase, and metabotropic and ionotropic receptors are key in formation of memory and sustained attention	Extract,[94,139] Rb_1,[88,201] Rg_2,[162,202] Rg_3[203]	29 (29)
Serotonin receptors	Metabotropic and ionotropic receptors important in mood, anxiety, sleep, and appetite	Rb_1,[167] Rg_2,[161] Rg_3,[204,205] compound K[203]	15 (15)
Na^+ channels	Voltage-sensitive ion channels responsible for the upstroke of neuronal action potentials	Extract,[206] Rg_3,[184,185,207] Rh_2 and PPD[169]	9 (9)
Ca^{2+} channels	Voltage-sensitive ion channels with roles in initiation of action potentials and second messenger signaling pathways, including apoptotic pathways	Extract,[208] Rb_1,[209,210] Rg_1,[198] Rg_3, Rh_2 and compound K[211]	86 (22)
cAMP/PKA/CREB pathways	cAMP second messenger signaling pathways lead to activation of PKA, which mediates signals regulating neurotransmission and – via transcription factors such as CREB – regulates genes involved in neuronal development, plasticity, and survival	Extract,[212] Rb_1,[213] Rg_1,[136] Rh_1,[188] Rg_3 and Rh_2[177]	56 (20)
PI3K/Akt (PKB) pathways	Production of phosphoinositide second messengers by PI3K is key in cell survival and proliferation signaling via link to mTOR pathway (upstream)	Rb_1,[133] Rg_1[214]	73 (10)
MAP kinase pathways	MAP kinases are implicated in a wide range of signaling pathways, particularly those regulating gene expression and cell survival and proliferation	Rg1,[214] compound K,[100] Rh1[188]	116 (21)
PKC pathways	PKC signaling is involved in cell proliferation and plasticity and in gene regulation. Downstream of M1 metabotropic cholinergic receptors, subtypes of serotoninergic receptors, and modulation of ion channels	Extract,[215] Rg1[214]	16 (2)
c-Fos pathways	c-Fos transcription factor acts downstream of PKA and PKC and plays a role in cell plasticity and in formation and consolidation of long-term memory	Extract[216,217]	28 (11)

Abbreviations: cAMP, cyclic adenosine monophosphate; CNS, central nervous system; CREB, cAMP response element-binding protein; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PI3K, phosphatidylinositide 3-kinase; mTOR, mammalian target of rapamycin; MAP, mitogen-activated protein (kinase).

of neurological or brain function, and animal studies. A total of 31 papers involving the clinical study of healthy volunteers or patients with neurological deficits were identified for further investigation. Of these 31 papers, studies in which the species of ginseng used was not stated were excluded.

Animal models of normal cognition, aging, and neuronal injury: (ginseng OR ginsenosides) AND (learning OR memory OR attention OR cognition OR cognitive) AND (rodent OR rat OR mouse OR mice). The initial pool of studies was manually filtered for relevance to cognition.

RESULTS

Cognitive effects in individuals with and without neurological disease

In the studies deemed suitable for further analysis, 15 used extracts of *P. ginseng*, either alone or in combination with another ingredient, such that the effect of *P. ginseng* alone was measured.[50,52,56–67] Of these, 12 studies directly measured components of cognition or neurological function. Nine studies were conducted in healthy volunteers, 1 study examined patients with noninsulin-dependent diabetes,[66] and 2 studies examined the effects of *P. ginseng* on clinical symptoms and cognition in Alzheimer's disease patients.[50,52] Of the 9 studies assessing the effects of *P. ginseng* on cognition in healthy volunteers, 7 investigated acute ingestion of a single dose,[57,59–62,65,67] and 1 subchronic study[63] measured the acute effects after a single dose and compared the results with those obtained over a period of 8 days. Only 1 study assessed chronic effects over a 12-week treatment period,[56] highlighting a lack of chronic data available for *P. ginseng*. All studies used orally administered products.

In the 7 studies of acute treatment with *P. ginseng*,[57,59–62,65,67] the mean participant age was 18–25 years, reflecting the demographic of Western consumers most likely to use supplements such as ginseng.[68] Acute studies usually used a commercially available cognitive test platform, but tests were occasionally tailored for specific purposes, and sometimes additional tests were used. In all acute studies, some effect of treatment was noted on at least one cognitive test or factor, e.g., quality of memory, secondary memory, or speed of attention, and in some cases improvements in self-rated mood were also noted.

However, no single aspect of cognition was consistently improved in all studies. The doses used in acute treatment studies ranged from 200 mg to 600 mg of ginseng extract, administered as a single dose. Other factors, such as overnight fasting and measurement time after dose, varied as well. The single subchronic study[63] used single daily oral doses of 200 mg or 400 mg for 8 consecutive days and noted acute improvements in arithmetic tests at certain time points for the 400 mg dose. However, 200 mg produced an acute negative effect on the arithmetic test, and no evidence of cumulative benefits from repeated ingestion was found for either dose.

In the multiple-treatment study conducted by D'Angelo et al.,[56] a significant improvement was seen only for mental arithmetic after 12 weeks of administration of *P. ginseng* (G115; 100 mg b.i.d., p.o.).[56] In the two studies of the effect of repeated administration of *P. ginseng* to Alzheimer's disease patients (in addition to existing treatments), Heo et al.[50] administered 4.5 g and 9 g of ginseng extract daily p.o. for Disease Assessment Scale (ADAS). Heo et al.[50] also used the Clinical Dementia Rating (CDR). In both studies, patients were selected on the basis of age (Heo et al.,[50] aged over 50 years; Lee et al.,[52] aged 47–83 years) and whether they met clinical criteria for probable Alzheimer's disease. Improvements in the cognitive function of patients, as measured by ADAS (cognitive) and MMSE scores, were observed after 12 weeks of treatment, but Lee et al.[52] observed that the improved cognitive assessments reverted back to control levels after treatment ceased. Heo et al.[50] also reported improvements in the CDR for treated patients. Both studies reported no significant changes in ADAS noncognitive scores, the component of the ADAS that assesses neuropsychiatric rather than cognitive symptoms. In the single study of diabetic patients,[66] 8 weeks of treatment with *P. ginseng* (100 or 200 mg p.o daily) improved self-rated mood, well-being, and psychomotor performance but not the digit span test of memory. While these studies provide encouraging evidence for an effect of *P. ginseng* on cognition, the data are not yet conclusive.

A single acute study tested *P. quinquefolius* in healthy volunteers,[69] and another study investigated *P. quinquefolius* in patients with schizophrenia,[70] treated for 4 weeks with a standardized extract. In the acute study in healthy young volunteers, a single oral dose of 100 mg, 200 mg, or 400 mg of Cereboost (a standardized extract of *P. quinquefolius* produced by Naturex, Avignon, France), significantly improved working memory at all doses, with the lowest dose also improving reaction time and mood. In a chronic study, schizophrenia patients given 100 mg daily p.o. of the standardized extract HT1001 demonstrated improvements in visual working memory and in some clinical symptoms versus those given placebo. Since symptoms of schizophrenia include memory deficits,[71,72] particularly working memory, this study's finding could be of relevance to ginseng effects on cognitive performance in the general population. These studies provide preliminary evidence of a possible effect of *P. quinquefolius* on memory. Another study investigated 200 mg of *P. notoginseng* extract given orally 3 times daily.[49] Although a different species was used, the results are relevant because the extract contained Rg_1 (50%) and Re (6%), which are also found in *P. ginseng* and *P. quinquefolius*. In this trial, ischemic stroke patients aged 18–75 years and diagnosed with ischemic stroke in the anterior cerebral circulation were treated either with aspirin and *P. notoginseng* extract or aspirin and placebo for 28 days before follow-up at 90 days. A significantly greater degree of improvement in neurological deficit, measured by the European Stroke Score, and in ability to carry out activities of daily living, measured by the Barthel index, was observed in the treated group, thus suggesting a potential neuroprotective effect. However, no further details were given about other interventions patients were undergoing, and no direct effect of cognitive function was measured.

No studies using isolated ginsenosides in healthy volunteers have been conducted, which may be due to the limited commercial availability of these compounds. Two relevant clinical trials of isolated Rd in ischemic stroke, however, were identified.[73,74] In both studies, 10 mg or 20 mg of Rd was administered (i.v.) daily for 14 days, and neurological changes were noted using the National Institutes of Health Stroke Scale scores on day 15. No direct measure of cognitive function was used, but the functional improvements seen provide further circumstantial information about the potential effects of ginsenosides on the central nervous system (CNS).

Ginseng is often used in combination with other botanical ingredients, e.g., *Ginkgo biloba* extracts, and while the results of studies showing improvements in cognition are encouraging, they cannot be attributed to ginseng or ginsenosides alone.

The results of the available clinical trials and nonclinical studies taken together are suggestive of an effect of ginseng on cognition, particularly memory, attention, and mood, but there are no chronic studies investigating the effects of ginseng on cognition. In the acute studies published, there is considerable methodological inconsistency, which makes it difficult to evaluate ginseng-specific effects on cognition and to elucidate the mechanism(s) of action contributing to such effects. Clinical trials of ginseng in other physiological or pathological conditions have provided information on the safety and tolerability of ginseng, along with clues to its mode(s) of action. However, caution is required when extrapolating the results of MMSE, ADAS, CDR, and other tests in patients suffering neurological deficit. Inter-

estingly, these studies suggest indirect effects of ginseng on cognition: the effects of ginseng on cerebrovascular function, blood glucose, or inflammatory mediators, for example, could have a profound impact on the CNS. Meanwhile, the majority of currently available mechanistic data have come from experiments in animal models and require further translational work before human-specific conclusions can be drawn.

Animal models of cognition and neurological disease

Clinical trials assessing the effects of ginseng on cognition are limited, but numerous studies using animal models have attempted to identify whether ginseng and ginsenosides affect the CNS and, if so, which aspects of normal brain function and pathology are influenced. Such studies generally take the form of a range of behavioral tests in unimpaired animals or in animals expressing a specific condition (e.g., aging) or feature of neuropathology (e.g., Alzheimer's disease), but equivalents to clinical assessment can also be used, such as assessment of the severity of physiological symptoms. Behavioral models in rodents to investigate learning, memory, and attention are well established, and although there are limitations to the predictive value of these tests,[75] they are an important component of the study of cognition in normal and pathological states. These tests are designed to investigate individual aspects of cognition. There are also a range of established genetic and chemically induced models of neurological diseases affecting cognition,[76] including genetic models of Alzheimer's disease, chemically induced models of neurotoxicity and neurodegeneration, and physically induced models of neurological injury and ischemia.[77] The evidence of cognitive effects of ginseng and ginsenosides, and possible mechanisms of action, in studies involving these models is summarized below. The wide range of administration routes used in animal models (i.e., oral, intravenous, intracerebroventricular, intragastric, and intraperitoneal), however, must be considered. Intraperitoneal injection was the most common route used in the studies examined here, a route that bypasses first-pass metabolism and for which no comparable studies of ginsenosides in humans exist. Additionally, doses calculated in milligrams/kilograms are not easily compared with doses used in human studies in the absence of accompanying measures, e.g., plasma concentrations, particularly given the substantial differences between rodent and human metabolism.

Animal models of normal cognition, aging, and neuronal injury

Studies in an array of models have suggested an effect of ginseng extracts or isolated ginsenosides on cognition in rodents, either directly, by investigating normal memory function, or indirectly, by examining the improvement of experimentally induced deficits. The majority combined a disease or injury model with behavioral and/or biochemical assays in an attempt to derive the underlying mechanisms that support the claimed effects on human cognition. There are few mechanistic studies on unimpaired functions under normal physiological conditions, but several studies investigated the cognitive effects of ginsenosides in models of ethanol-, morphine-, or scopolamine-induced memory impairment and models of anxiety, depression, and aging. The most widely used test in such studies was the Morris water maze test of spatial learning and memory specific for hippocampal functions, in which animals are placed in a pool of water and must find a hidden platform to escape from swimming. The time taken to find the platform on successive trials decreases as an animal learns and remembers the location of the platform in the pool. Other frequently used tests include the open field locomotor activity test, which examines motor activity and may sometimes also be used to assess anxiety, passive-avoidance tests, in which animals learn to avoid an unpleasant stimulus, and contextual fear conditioning tests of associative memory. A complete description of all tests is outside the scope of this review, but a summary of descriptions is provided by Bryan et al.[78]

When studying normal memory function in rats, Liu et al.[79] observed an improvement in spatial cognitive performance in the Morris water maze and an increase in hippocampal neuronal survival, but not proliferation, following oral administration of ginsenoside Rg_1. Qiao et al.[80] also noted increased survival of neurones, but without increased proliferation, in the hippocampus and improved learning in a contextual fear conditioning model when *P. ginseng* extract was administered orally to rats for 5 days. In another study,[81] intraperitoneal administration of ginsenosides Rg_1 and Rb_1 increased levels of the synaptic marker synaptophysin and improved performance in the Morris water maze but did not alter electrophysiological parameters measured in brain slices from treated animals. Studies of age-related memory impairment have also focused on the effects of ginsenosides on hippocampal neurones. In three studies,[82–84] a range of ginsenoside doses (p.o.) improved cognitive performance in the Morris water maze test without affecting locomotor activity. An increase in synaptic-plasticity-related proteins in the hippocampus in two different models of age-related memory impairment was also noted in these studies. In two of these studies,[85,86] beneficial modulation of redox status was also identified. The ginsenoside Rd, administered intraperitoneally at a range of doses, has been shown to enhance the activity of antioxidant enzymes in aged mice and in a rat model of transient focal ischemia.[87]

Restoration of impairment using chemical models of memory deficit was used as an outcome measure in several studies. Scopolamine is a muscarinic acetylcholine receptor antagonist that causes memory impairment through blockade of cholinergic neurotransmission and is widely used to induce memory impairment in rodents. Extracts of *P. ginseng* and *P. quinquefolius*, isolated ginsenosides, and ginsenoside metabolites (i.p and p.o.) at a range of doses have all demonstrated effects in improving impairment in this model,[88–94] most commonly using the Morris water maze and passive avoidance learning tests. Direct effects on cholinergic neurotransmission were proposed as the mechanism of action, i.e., a reduction in acetylcholinesterase activity[88] or a decrease in loss of cholinergic synapses in the hippocampus.[94] Acetylcholine is a crucial neuromodulator of learning, memory, and attention across mammalian species, which makes it an attractive target, but it is not known whether such effects are direct or represent an indirect functional potentiation. Ginsenosides (i.p and p.o.) at a range of doses have also been shown to improve memory and learning impairment in models using morphine or ethanol to create deficits[95–97]; taken together, these data suggest there may be multiple targets for the effects of ginsenosides on learning and memory.

Animal models of neuroprotection and neurodegeneration

The beneficial effects of ginseng and ginsenosides observed in models of neurological disease can broadly be described as neuroprotective in models of ischemia, stroke, seizure, toxicity, and inflammation, and as preventative of neurodegeneration in models of dementia and neurodegenerative diseases. These studies may not assess effects on cognitive components directly but indicate potential mechanisms for effects of ginsenoside on cognition.

A loss or reduction in blood flow in the brain, due to trauma, stroke, or arterial occlusion, can lead to ischemia/reperfusion damage and a loss of neuronal cells and neurological function. Isolated ginsenosides, ginseng extracts, and ginsenoside metabolites (i.p., i.v., and p.o.) at a range of doses have been reported to reduce infarct volume, improve cognitive and neurological function, ameliorate functional deficits, and decrease inflammatory markers in animal models of ischemic damage,[98–108] including middle cerebral artery occlusion and stroke-prone rodent models. Mechanisms proposed include the promotion of neurogenesis in the hippocampus, anti-inflammatory mechanisms, and antioxidant activity. Ginsenosides administered intraperitoneally at a range of doses have also demonstrated anti-inflammatory effects in models of sepsis[100] and Alzheimer's disease[109] as well as in a variety of in vitro tests. Effects in models of Alzheimer's disease and dementia are of particular interest, given their association with cognitive deficits. Ginseng and ginsenosides have demonstrated beneficial effects in models of age-related dementia, e.g., isolated ginsenosides administered orally in the senescence-accelerated mouse model.[82,110]

Behavioral and neuropathological improvements have also been observed following treatment with ginsenosides (p.o. and i.p.), including the metabolite compound K, in models of amyloid precursor protein overexpression[111] and Aβ-peptide injection.[109,112] Mechanisms are again thought to be via anti-inflammatory effects and neurogenesis. This has parallels with other models of neurodegenerative diseases, including Huntington's disease, Parkinson's disease, and neuroinflammatory disorders, and indeed, beneficial effects on behavior have been noted in models of Parkinson's disease that investigated treatment with ginseng extract (p.o.) and ginsenosides (i.p.).[113,114] In addition to demonstrating activity in degenerative conditions characterized by inflammatory loss of neurones, isolated ginsenosides (i.p.) have also been reported to exert neuroprotective and anticonvulsant effects in models of pentylenetetrazole-(PTZ), kainic acid-, and pilocarpine-induced seizure in rats.[115,116] Cell loss in these models is due primarily to glutamate-mediated excitotoxic cell death, and a number of cellular studies have identified glutamate receptors as potential targets for ginsenosides and their metabolites in models of both epileptiform activity and normal neuronal processes that affect cognition.

Non-CNS effects of ginseng and ginsenosides relevant to cognition

Many proposed beneficial effects of ginseng are now being studied in clinical trials and animal models. Besides affecting the CNS directly, ginseng may possess properties that confer cognitive benefits. For example, antioxidant and anti-inflammatory effects, effects on the circulatory system, or effects that ameliorate ischemic damage will also indirectly affect the CNS. Ginsenosides may also affect blood glucose regulation, and although evidence of the effects of ginseng on glucoregulation is not definitive and is sometimes contradictory,[61,62,69,117–120] a recent systematic review concluded that *P. ginseng* shows promising results for improving glucose metabolism.[121] While mechanisms of glucose facilitation of cognitive performance, particularly memory, are still equivocal, a number of reviews suggest that changes in glucoregulation can influence cognitive function.[122–125] Therefore, modulation of glucose regulation or metabolism might represent one of the possible mechanisms of cognitive effects produced by ginseng.

Mechanisms of ginsenoside actions

The animal, biochemical, molecular, and cellular studies of ginsenosides provide information about the potential mode of action of ginsenosides on cognition, but the mechanisms involved have not yet been definitively identified. Table 3 collates information from preclinical studies investigating mechanistic targets known to be involved in cognitive processes. Of key interest are those involved in glutamatergic and acetylcholine (cholinergic) neurotransmission. Glutamate is the major excitatory neurotransmitter throughout the CNS, and ionotropic glutamate receptor functioning is a key component of neuronal plasticity and memory.[126] Acetylcholine (cholinergic) receptors have been implicated as modulators in memory[127,128] (particularly muscarinic) and attention (nicotinic) and as drug targets in a variety of neurological diseases, including dementia[129] and schizophrenia.[130] Other important targets involve the regulation of the expression of genes involved in memory formation and neuronal plasticity. While the pertinence of different cellular correlates of higher cognitive function remains widely debated, long-term synaptic plasticity (e.g., long-term potentiation and long-term depression) in neurons is the best established and most widely used correlate,[131,132] and previous studies suggest neuronal survival pathways are important for improving cognition. These pathways of survival and plasticity intersect. Consequently, targets such as protein kinases A and C and the transcription factor c-Fos are linked to increased neuronal activity, neuronal cell survival, and neuronal plasticity. Receptors for excitatory and inhibitory neurotransmitters may also have cognitive effects via mechanisms other than direct effects on plasticity, memory, and attention. Glutamate receptors are particularly implicated in excitotoxicity and are involved in inflammatory and neurodegenerative neurotoxicity and calcium-regulated signaling. Indeed, any effect of ginsenosides on neurotransmitter release or receptors could potentially be a target for influencing cognition.

CONCLUSION

Despite the long history of the use of ginseng, the abundance of research reports, and the esteem in which this herb is held, there is a lack of chronic studies investigating the effects of ginseng in healthy individuals, and the results of acute studies are inconsistent, making an overall clinical assessment of the efficacy of ginseng in enhancing cognitive function premature at this time. In pathological states such as Alzheimer's disease and ischemic stroke, a beneficial effect may be achieved through a disease-modifying pathway that indirectly affects cognition – for example, by reducing amyloidogenesis, inflammation, or neurotoxicity – and so may not translate to cognitive benefits in healthy subjects. Larger randomized controlled trials in healthy individuals are required to obtain more conclusive findings in these areas and to determine the target population for ginseng supplements. To address issues of consistency in the data from acute studies, standard batteries of tests to characterize extracts of ginseng should be used, as suggested in reviews of other phytochemicals.[41,43]

The mechanisms of action of ginseng and ginsenosides on cognition, proposed thus far by animal and cell-based studies, remain to be definitively established, and it is crucial to consider pharmacokinetic information in identifying any active compound. Although a particular ginsenoside found in an extract may demonstrate an effect when applied directly to neurones, if it has low bioavailability and does not cross the blood–brain barrier, the finding is not applicable to a clinical situation. Despite these concerns, mechanistic data in the literature are encouraging; in particular, the ginsenosides Rg_3, Rh_1, Rh_2, Rb_1, Rd, Rg_2, and Rb_3 and the aglycones PPD and PPT are worthy of further attention. Compound K has a promising pharmacokinetic profile and has shown effects on neurotransmission and neuroprotection in previous studies. As indicated by the evidence summarized in this review, ginseng has potentially beneficial effects on human cognition, but further research is required to establish whether it can be definitively regarded as a cognitive enhancer.

Acknowledgments

Funding. Imogen Smith is supported by a research grant provided to Benjamin J Whalley and Elizabeth M Williamson from GSK Nutrition.

Declaration of interest. Sophie Putnam and Jonathan Farrimond are employees of GSK Nutrition.

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