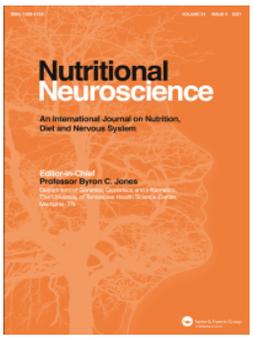
Effects of American ginseng (Panax quinquefolius) extract on human neurocognitive function: a review

Bell, L. ORCID: https://orcid.org/0000-0003-0677-021X, Fanca-Berthon, P., Le Cozannet, R., Ferguson, D., Scholey, A. and Williams, C. ORCID: https://orcid.org/0000-0003-4452-671X (2025) Effects of American ginseng (Panax quinquefolius) extract on human neurocognitive function: a review. Nutritional Neuroscience. ISSN 1476-8305 doi: 10.1080/1028415X.2025.2555921 Available at https://centaur.reading.ac.uk/124800/



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Effects of American ginseng *(Panax quinquefolius)* extract on human neurocognitive function: a review

Lynne Bell [a], Pascale Fança-Berthon [b], Romain Le Cozannet [b], David Ferguson [e], Andrew Scholey [c,d] and Claire Williams [a]

[a]School of Psychology & Clinical Language Sciences, University of Reading, Reading, UK; [b]Givaudan France Naturals, Avignon, France; [c]Nutrition Dietetics and Food, School of Clinical Sciences, Monash University, Melbourne, Australia; [d]Centre for Human Psychopharmacology, Swinburne University, Hawthorn, Australia; [e]College of Education, Michigan State University, Ann Arbor, MI, USA

ABSTRACT

Compared with *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng) has received relatively little research attention. Nevertheless, across several clinical trials a common finding is that *P. quinquefolius* extracts improve aspects of mood, mental fatigue, and cognitive function. This review details the findings from double-blind, randomized, controlled clinical trials which included assessment of cognitive performance, fatigue, or mood, individually or in combination. Limited fatigue benefits were observed in cancer patients at high doses (2000mg). The most notable effects at lower doses (100mg-400 mg) included enhancement of attentional and working memory performance in healthy adults and in Schizophrenia patients. Several studies also highlighted potential mechanisms underlying the cognitive effects of *P. quinquefolius*. These include increased activation of frontoparietal neural circuits and, in the context of the gut-brain axis, alterations of the human gut microbiome composition. The effects are also consistent with cholinergic modulation. Such effects suggest that *P. quinquefolius* extract may have benefits to everyday cognitive function.

KEYWORDS

Nootropic; *Panax quinquefolius*; American ginseng; attention; working memory; fatigue; neuroimaging; microbiome;

Introduction

Species of ginseng have a longstanding reputation for their physical and neurocognitive health benefits. The ginseng family has over 10 species with *Panax ginseng C. A. Meyer* (Asian ginseng) and *Panax quinquefolius L.* (American ginseng) being the most investigated in clinical trials. Interestingly, traditional Chinese medicine differentiates the behavioural effects of these two common species of ginseng. In brief, *Panax ginseng* is described as warming or stimulating and invigorates 'Yang' whereas *Panax quinquefolius* is described as cooling or calming and nourishes 'Yin'[1]. In terms of behavioural effects, this might translate differently. For example, there is evidence of invigorating properties of *P. ginseng* such as published benefits to exercise performance [2]. *P. quinquefolius* is reported to have a balancing effect on the central nervous system [3] and gut [4] which may impact mental health and cognition. Notably, the composition of the two ginseng species does differ, suggesting that different physiological and neurocognitive effects are at least plausible. For example, there are differences in relative abundance and composition of the ginseng-specific ginsenosides which are widely considered to contribute significantly to the physiological effects of the plant [5]. Specifically, ginsenosides Rb1 (1.51%), Re (0.89%), and Rd (0.77%) levels in *P. quinquefolius* are approximately 3-, 6-, and 5-times higher, respectively, than in *P. ginseng* [6]. These account for more than 70% of the total ginsenosides in *P. quinquefolius* which also has a higher Rb1: total ginsenoside ratio than *P. ginseng* [6]. Compositional differences between *P.ginseng* and *P. quinquefolius* are highlighted in Table 1.

To date, numerous ginseng studies have been published. Overall, the quality of this research has been mixed, although recent trials have been reported to be more robust [7]. Most of the research into the effects of ginseng on cognitive and mood outcomes has focused on *P. ginseng* and in particular, extract

CONTACT Claire Williams claire.williams@rdg.ac.uk School of Psychology & Clinical Language Sciences, University of Reading, Reading, RG6 6ES, UK

Table 1. Summary of compositional differences between *P. ginseng* root and *P. quinquefolius* root [6].

Root extract compositions	*P. ginseng*	*P.quinquefolius*
Total Ginsenosides	Up to12%	Up to 15%
Rb1	~0.47%	~1.51%
Re	~0.15%	~0.89%
Rd	~0.15%	~0.77%
Rg1	~0.17%	~0.80%

G115 (standardised as 4% ginsenosides). Previous reviews of preclinical studies and human randomised controlled trials (RCTs) [5, 8, 9] suggest that optimal doses (ranging from 200mg-400 mg daily or one-off doses of 200mg-960 mg [8]) of *P. ginseng* may elicit benefits to mental fatigue, episodic memory, and learning, but findings remain inconclusive. Literature on the cognitive and mood benefits of *P. quinquefolius* has only begun to emerge more recently and is reviewed here.

Like *P. ginseng*, *P. quinquefolius*, has been reported to possess a wide range of activities including effects on the central nervous system (CNS) [5, 10, 11]. To date several RCTs have examined the potential for *P. quinquefolius* to affect cognitive performance, mental fatigue, and mood [12-20], as identified by a search of google scholar, pub med, and web of science using keywords related to American ginseng / *Panax quinquefolius,* cognition, mood, and mental fatigue.

Studies have investigated the benefits of several different *P. quinquefolius* extracts. These include standardized proprietary extracts such as HT1001 (containing Rb1, Rb2, Rc, Rd, Re, and Rg1 (total ginsenosides of 13-20%)) [15], CVT-E002 (containing 20% ginsenosides) [19], Cereboost® (total ginsenosides of 10-12%, with Rb1 standardised 4-7%) [12-14, 18], Euquinax® (5% total ginsenosides) [20]. Some studies also commissioned the production of bespoke supplements containing 3-5% ginsenosides derived from Wisconsin ginseng [16, 17].

In addition to RCTs, one open label study by Sutherland et al. [21] assessed the potential learning and memory benefits of HT1001, in healthy volunteers. Neuropsychological assessments were conducted using the Clinical Memory Scale (CMS), with parallel forms for baseline and post-treatment assessments. A young adult sample (aged 20-24, n = 10) and a middle-aged sample (aged 45-65, n = 10) completed the CMS at baseline and again after 14 days' exposure to 200 mg HT1001 daily. Primary analyses revealed a significant improvement in the CMS Memory Quotient (MQ) following supplementation compared to baseline. Young adults performed better than middle aged adults, but there was no interaction between time and age group. Secondary analyses indicated benefits for both groups on free recall of word lists, cued recall of word pairs, and recognition of figures. Benefits to free recall of pictures were observed in young adults only. The results suggest that memory, as measured with the CMS-MQ, was significantly improved with open-label HT1001. However, a limitation of this study was the lack of placebo control and therefore RCT evidence must also be considered to confirm the effects of *P. quinquefolius* extract.

Panax quinquefolius and cognitive function, mental fatigue, and mood

The following section summarises the RCTs which have focused on the effects of *P. quinquefolius* extract on either cognitive function, mental fatigue, or mood, or a combination. A summary of design and findings for each study is presented in Table 2. Four RCTs have systematically evaluated the potential cognitive and mood effects of *P. quinquefolius* in healthy adults, all using the Cereboost® extract. The first of these was conducted by Scholey et al. [12]. Compared with placebo, administration of the *P. quinquefolius* extract was associated with significant dose – and time-related improvements in cognitive function. Specifically, young-adult participants (mean age 25.2 years, n = 32) received 100, 200 and 400 mg doses and a matching placebo on separate visits and undertook a comprehensive computerized battery of cognitive tests at 1, 3, and 6 h post-dose time points. Several Working Memory tasks were improved by *P. quinquefolius* versus placebo. Corsi Block span (a measure of spatial working memory) was improved by all doses at all time points. Alphabetic Working Memory was improved at all time points by 100 and 400 mg doses (but not 200 mg). Numeric Working Memory speed was improved at all time points by 200 mg only. Choice Reaction Time Accuracy was improved at all time points by 100 mg and at 1 h by 400 mg and at 6 h by 200 mg. The only affected mood item was calmness which was improved at 3 and 6 h by the 100 mg dose. The study

Table 2. Overview of clinical studies into the neurocognitive effects of *P. quinquefolius* extract.

References	Design	Population	Extract type & Dose(s)	Measures	Results
Scholey *et al.* [12]	Rnd, PC, DB, X *Acute* (1, 3, 6 h post-dose) 7-day washout	Healthy young adults (16M, 16F) Age = 25.2±5.0	Cereboost® 100 mg, 200 mg, 400 mg (single doses)	Behavioural outcomes: COMPASS cognitive test battery assessing attention; working memory; secondary memory. Mood measures. Underlying mechanisms: Blood glucose.	Choice Reaction Time accuracy (Attention) ↑ 1-h, 3-h, 6-h 100 mg ↑ 6-h 200 mg ↑ 1-h 400 mg Corsi blocks (Spatial working memory) ↑ 1-h, 3-h, 6-h 100 mg ↑ 1-h, 3-h, 6-h 200 mg ↑1-h, 3-h, 6-h 400 mg Numeric Working Memory Speed ↑ 1-h, 3-h, 6-h 200 mg (faster) Alphabetic Working Memory speed ↑ 1-h, 3-h, 6-h 100 mg (faster) ↑1-h, 3-h, 6-h 400 mg (faster) Immediate Word Recall (Secondary memory) ↑ 1-h, 3-h, 6-h 200 mg Calm (Mood) Blood glucose NS ↑ 1-h, 6-h 100 mg
Ossoukhova *et al.* [13]	Rnd, PC, DB, X *Acute* (1, 3, 6 h post-dose) 7-day washout	Healthy middle-aged adults (22M, 32F) Age = 51.6±6.5	Cereboost® 200 mg (single dose)	Behavioural outcomes: COMPASS and CDR cognitive test battery assessing attention; working memory; spatial working memory; secondary memory. Mood measures. Underlying mechanisms: Blood glucose.	Working Memory Factor ↑ 3-h Spatial Working Memory ↑ 3-h Attention, Secondary memory, Mood, Blood glucose NS
White *et al.* [18]	Rnd, PC, DB, X *Acute* (6 h post-dose) 7-day washout	Healthy middle-aged adults (13M, 7F) Age= 53.9±5.5	Cereboost® 200 mg (single dose)	Behavioural outcomes: Cognitive test battery assessing working memory; attention; spatial working memory. Underlying mechanisms: SSVEP monitoring.	SSVEP ↑ SSVEP latency (reduction) during spatial working memory AX-Continuous Performance Task (Attention, Working memory), Spatial Working Memory NS
Bell *et al.* [14]	Rnd, PC, DB, P *Acute* (2, 4, 6 h post-dose) *Chronic* (2 weeks)	Healthy young adults (15M, 44F) Treatment group: Age 20.6±2.4 Placebo group: Age 20.5±2.7	Cereboost® 200 mg (daily)	Behavioural outcomes: Computerised test battery assessing attention; working memory; executive function; secondary memory. Mood and fatigue measures. Underlying mechanisms: *In vitro* gut microbiota.	Modified ANT (Attention, Executive function) ↑ accuracy at 4-h, 6-h ↑ accuracy incongruent ↑ RT at 2-h (faster) Working memory, Secondary memory, Mood NS RVIP (Attention) ↑ accuracy (fewer commision errors) Modified ANT (Attention, Executive function) ↑ accuracy Mood ↑ Mental fatigue (less fatigue) ↑ Fatigue (PANAS-X, less fatigue)

(*Continued*)

Table 2. Continued.

References	Design	Population	Extract type & Dose(s)	Measures	Results
					↑ Self-assurance (PANAS-X) Gut microbiota ↑ *In vitro* gut microbiota and SCFA Working memory, Secondary memory NS Modified ANT (Attention, Executive function) ↑ Accuracy 2-h, 4-h, 6-h ↑ RT 2-h, 4-h, 6-h (faster) Secondary memory, Mood NS
	Acute-on-chronic (2, 4, 6 h post-dose on day 14)				
Chen & Hui [15]	Rnd, PC, DB, P *Chronic* (4 weeks)	Schizophrenia patients (51M, 13F) Treatment group: Age 43.1±8.5 Placebo group: Age 43.7±7.8	HT1001 200mg (daily)	Behavioural outcomes: Computerised test battery assessing; visual working memory; verbal working memory	Visual pattern test (Visual working memory) ↑ Accuracy Number-letter span test (Verbal working memory) → Accuracy
Kim *et al.* [19]	Rnd, PC, DB, X *Chronic* (6 weeks) 2-week washout	Multiple sclerosis patients (3M, 44F) Age= 46.5±10.4	CVT-E002 400mg (daily)	Behavioural outcomes: Computerised test battery assessing; working memory; executive function; secondary memory. Mood and fatigue measures.	Fatigue NS Mood & Cognitive test measures Not reported
Barton *et al.* [16]	Rnd, PC, DB, P *Chronic* (8weeks)	Cancer patients (96M, 186F) Age= 60±12	Wisconsin ginseng 750mg, 1000mg, 2000mg (daily)	Behavioural outcomes: Mood, fatigue, and sleep measures	Mood, Fatigue, Sleep NS
Barton *et al.* [17]	Rnd, PC, DB, P *Chronic* (8weeks)	Cancer patients (75M, 266F) Treatment group: Age 55.3±12.7 Placebo group: Age 55.9±11.8	Wisconsin ginseng 2000mg (daily)	Behavioural outcomes: Fatigue	MFSI (Fatigue) ↑ Fatigue (less fatigue) POMS (Fatigue) ↑ Fatigue (less fatigue)
Guglielmo *et al.* [20]	Rnd, PC, DB, P *Chronic* (8weeks)	Cancer patients (22M, 10F) Age= 56.5 (range 34-79)	Euquinax® 1000mg (daily)	Behavioural outcomes: Fatigue	Fatigue NS

Rnd = randomized; PC = placebo-controlled; DB = double-blind; X = crossover; *P* = parallel; M = male; F = female; ANT = Attention Network Task; RVI*P* = Rapid Visual Information Processing Task; PANAS-X = Positive and Negative Affect Schedule – expanded; MFIS = Modified Fatigue Impact Scale; MFSI = Multidimensional Fatigue Symptom Inventory; POMS = Profile of Mood States; SSV*EP* = Steady State Visually Evoked Potentials. ↑ = improved compared to placebo (i.e. increased accuracy, reduced error, faster speed, better positive mood, reduced negative mood). → = maintenance of performance compared to placebo performance drop. NS = No significant difference between treatment and placebo.

also included physiological measurement of glucose-regulation, however no differences in blood glucose were observed following ginseng compared to placebo.

Cognitive effects were further explored in a subsequent RCT by Ossoukhova et al. [13] focusing on Working Memory effects, this time in a middle-aged group (aged 40-60, n = 54). This study evaluated the effects of 200 mg *P. quinquefolius* extract on Working Memory (the primary variable). Participants were tested at baseline, then at 1 h, 3 h, and 6 h following placebo and *P. quinquefolius* extract, on separate visits. Again, working memory was differentially improved, this time at 3 h post administration by the active treatment. This effect was evident in a Working Memory 'factor' combining two working memory tasks – spatial working memory and numerical working memory, but was also evident in the Spatial Working Memory task when analysed on its own. As with Scholey et al. [12], this study also included blood glucose measurement but again observed no effect of treatment on blood glucose levels.

White at al. [18] investigated the benefits of an acute 200 mg dose of *P. quinquefolius* versus a placebo on attention and working memory while simultaneously recording brain activity via Steady State Visually Evoked Potentials (SSVEPs), again in healthy middle-aged adults aged 40–60 years. Interestingly, no significant benefits to cognitive function were observed, although significantly decreased SSVEP latency was observed in prefrontal regions during a spatial working memory task. The authors suggest this may be indicative of increased recruitment of prefrontal brain regions during working memory processing. However, the study may have been slightly underpowered as the sample size was small (n = 20) and represented a sub-sample of the Ossoukhova et al. [13] study, where improvements to working memory performance were observed in the full sample.

A more recent study by Bell et al. [14] investigated acute, chronic, and acute-on-chronic benefits of *P. quinquefolius* extract on mood, mental fatigue, and cognition in healthy young adults (mean age 20.6 years, n = 59). Immediately following a 200 mg dose, improvements were observed for a measure of attention during the 6-hour post-dose period. Specifically, accuracy was better for the *P. quinquefolius* group compared with placebo group on cognitively demanding, incongruent trials during an Attention Network Task (ANT). There was also some evidence of a benefit to ANT reaction time. Following two weeks daily supplementation, the benefits to ANT performance were maintained. In addition, working memory benefits were observed on a rapid visual information processing task (RVIP), through a reduction in commission errors (false positives) in the *P. quinquefolius* group compared to placebo group. Mood benefits also became apparent after continued daily supplementation, with participants in the *P. quinquefolius* group self-reporting lower levels of mental fatigue and increased self-assurance compared to the placebo group. Interestingly, the acute-on-chronic investigation revealed a strengthening of the acute benefits observed at the beginning of the study, with ANT benefits observed at a greater number of post-dose time points than observed initially, while additional benefits also emerged for switching ability on a switching task (TST) and working memory accuracy on a Corsi Blocks task. A concurrent, *in vitro* investigation of the effects of the same dose of *P. quinquefolius* extract on gut microbiota, over a similar chronic timeframe, observed increases in beneficial gut microbiota (Akkermansia muciniphila and Lactobacillus) and associated short chain fatty acids (SCFAs; acetate, propionate, and butyrate) in a simulation of the human colon, thereby providing evidence of a possible mechanism of action via the gut-brain axis.

While the above studies have concentrated on healthy populations, a further section of the literature has investigated the impact of *P. quinquefolius* in populations with pathologies that may impact cognitive functioning, including schizophrenia and multiple sclerosis. Chen and Hui [15] investigated four weeks supplementation with *P. quinquefolius* extract HT1001 at a daily dose of 200 mg. Schizophrenia patients (mean age 43.4 years, n = 64) completed cognitive testing at baseline and after the period of supplementation. The cognitive test battery included verbal and spatial working memory tasks from the Wechsler Adult Intelligence Scale – 3rd Edition. Scores on a visual pattern test were observed to improve significantly in the *P. quinquefolius* condition but not in the placebo condition. Scores on a letter-number span test were maintained in the *P. quinquefolius* condition but decreased in the placebo condition. While these findings tentatively suggest a benefit to both visual and verbal working memory in schizophrenia patients, it should be noted that placebo group and *P. quinquefolius* group outcomes were not directly compared at the post-intervention time point, suggesting that final outcomes did not differ significantly between the two groups.

Kim et al. [19] similarly investigated six weeks supplementation with 400 mg daily doses of extract CVT-E002, this time in multiple sclerosis patients (mean age 46.5 years, n = 47). Measures of mood (Becks

Depression Inventory (BDI) & Perceived Stress Scale (PSS)), cognition (Paced Auditory Serial Addition Test (PASAT), Stroop colour and word test, and the California Verbal Learning Test-II (CVLT-II)), and self-report fatigue questionnaires (Fatigue Severity Scale and Modified Fatigue Impact Scale) were included in the test battery. It was reported that the *P. quinquefolius* treatment did not improve subjective fatigue significantly more than the placebo. Unfortunately, the short report publication failed to report the cognition and mood outcomes, so it seems likely that no benefits were observed to those measures either.

In addition to investigations of the benefits of *P. quinquefolius* for cognitive functioning in schizophrenia and multiple-sclerosis, studies have also sought to examine its efficacy on cancer-related fatigue. Such studies typically utilise subjective measures of fatigue, like those used by Kim et al. [19]. Factor analysis of these questionnaire-related measures of fatigue has shown that they typically reflect mental fatigue [22] and cognitive or emotional tiredness [23], rather than true physical fatigue, and so are considered of relevance here. However, benefits of *P. quinquefolius* to cancer-related fatigue appear somewhat equivocal.

Barton et al. [16] employed measures including the Brief Fatigue Inventory (BFI), the Pittsburgh Sleep Quality Index (PSQI), the vitality subscale of the Medical Outcome Scale Short Form-36 (SF-36), and several factors from the Linear Analogue Self-Assessment Scale (including emotional wellbeing, mental wellbeing, and spiritual wellbeing). These respective measures of fatigue, sleep, and mood revealed no significant benefit of Wisconsin ginseng at doses of 750, 1000 mg, or 2000mg daily for 8 weeks in cancer patients (mean age 60 years, n = 282). However, a subsequent larger investigation by Barton et al. [17] (mean age 55.6 years, n = 341) focussing only on the highest dose (2000mg) was observed to convey a small fatigue benefit when using the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF). It was noted however, that benefits were slow to emerge (taking longer than 4 weeks) and were most apparent in those currently undergoing aggressive treatments, i.e. those experiencing the highest levels of fatigue [17]. Guglielmo et al. [20] failed to find any further evidence to support a benefit to fatigue (measured using the BFI) in cancer patients while investigating a daily dose of 1000 mg of the *P. quinquefolius* extract Euquinax® for 8 weeks (mean age 56.5 years, n = 32). However, given the findings of Barton et al. [16, 17] it seems likely that this study was under-powered and possibly under-dosed to see an effect in this demographic. However, due to the large range in ginsenoside content and profile across different extracts, comparison of doses is difficult.

Discussion

The findings of this review suggest that extracts of *P. quinquefolius* may show the greatest benefits to cognition, mental fatigue, and mood in healthy populations, rather than those with pathology such as multiple sclerosis or cancer. Indeed, over three clinical trials (reported as four papers [12-14, 18]) it has been shown that *P. quinquefolius* extract can improve aspects of cognitive function and mood in healthy adults, with attentional processes and working memory being most sensitive to the intervention. Out of these four publications investigating benefits in healthy adults, acute memory recall benefits were only observed in one [12], but acute enhancement of attentional processes were reported in three [12-14] with one of these also reporting chronic (14-day) and acute-on-chronic effects [14]. The one study which did not report an improvement in attentional functioning (likely due to being underpowered to observe behavioural effects) did still report a tendency for changes in brain activation, possibly indicative of increased recruitment of prefrontal brain regions during working memory processing on a Continuous Performance attentional task [18]. Benefits of *P. quinquefolius* were also observed in Schizophrenia patients over a relatively short chronic time frame and with a similar dose [15]. Overall, improvements to working memory and attention following *P. quinquefolius* appear more robust than those previously reported for *P. ginseng* [8], particularly in healthy populations.

The cancer-related fatigue literature has focussed on chronic rather than acute supplementation and has investigated higher doses (750mg-2000mg) to combat high levels of fatigue during cancer treatment, but study findings have not fully supported the efficacy of this approach, with only one study reporting a benefit to fatigue [17]. A possible explanation, given the reported findings in healthy adults based on apparently lower dosing (100mg-400 mg), may be that all the fatigue-related studies in cancer patients are currently dosed too high, and that much lower doses of *P. quinquefolius* may be optimal. This possibility is

supported in part by the cognitive findings in Schizophrenia patients [15], where a lower dose of 200 mg was found to be effective on cognition in a non-healthy cohort. But a more nuanced investigation of dose is required that considers the varying ginsenoside content and profile of different extracts and considers differences in acute versus chronic applications. The most effective extracts currently appear to be Cereboost® and HT1001 which are both proprietary extracts optimised to contain 10-20% ginsenosides, including 4–8% Rg1 and Rb1. Therefore, the exact profile of the extract, such as the Rb1 content and therefore the ratio of Rb1/total ginsenosides (optimally between 0.3 and 0.6) may be important when considering the efficacy of *P.quinquefolius*. However, irrespective of extract dose or composition, it may be that *P. quinquefolius* is more effective as a cognitive boost in healthy populations rather than a treatment for deficits in unhealthy populations, as supported by the current literature.

Importantly, the specific behavioural properties observed in healthy adults may have ramifications for everyday mental functioning. In many workplaces attention and working memory are crucial to optimal functioning. Beyond the workplace, attention and working memory are also important processes involved in activities such as sports performance, where working memory capacity is associated with better goal-directed attentional control [24]. In addition to physical sports, esports (competitive organized electronic video gaming) have become a global phenomenon and participants may be advantaged by the cognitive benefits of *P. quinquefolius* extract in the context of concomitant elevations in calmness, reduced fatigue, and increased self-assurance [14]. Similar benefits may also be extended to exam performance in academia. More recently it has become evident that problems in attention are characteristic of the 'brain fog' associated with long COVID [25], although applications for *P. quinquefolius* in the treatment of pathology are less well supported by the studies reviewed here. Indeed, current evidence from cancer-related fatigue research may not support an application in the treatment of long Covid. Nevertheless, further applied research is needed to confirm benefits of *P. quinquefolius* extract across multiple activities and applications, paying careful attention to ginsenoside doses to establish optimal ranges in different populations.

Potential mechanisms of action for *P.quinquefolius* are somewhat under investigated. Pre-clinical trials have observed cognition-related mechanistic pathways, including those directly related to the CNS such as facilitation of nitric oxide synthesis/signalling, and upregulation of GABA receptors, acetylcholine neurotransmission, and cAMP/PKA/CREB signalling [5]. While these CNS-related mechanisms are difficult to investigate in human research, indirect mechanisms via antioxidant, anti-inflammatory, and glucoregulatory pathways have also been observed in animal models [5] and can be more easily investigated in humans. Indeed, several of the behavioural studies reviewed here have included measures aimed at determining potential mechanisms underlying the neurocognitive benefits of *P. quinquefolius* extract in humans, including blood glucose, electrical brain activity, and gut microbiota [12-14, 18]. It is known that fluctuations in blood glucose levels can influence cognitive performance. *P. ginseng* has been shown to both reduce blood glucose and improve cognitive functioning in healthy young adults [26, 27]. Similarly, *P. quinquefolius* has been shown to attenuate excursions in blood glucose in healthy cohorts and those with diabetes [28, 29], although effects on blood glucose were not observed in the studies reported here [12, 13]. Again, the specific extract used may be a determinant of any glucoregulatory effects, and so further research is required into this mechanism of action. Antioxidant effects (but not anti-inflammatory effects) of *P. quinquefolius* have been researched in humans [30], but not in conjunction with behavioural testing and so further research is required to link these mechanisms with observable cognitive effects.

The cohort in White et al. [18] underwent steady state visually evoked potentials (SSVEPs) measurement. SSVEPs represent a specific aspect of encephalography which has proved extremely sensitive to nutrition-type interventions [31-33]. Technical details of the methodology and analyses are beyond the scope of this review but can be found in references [34] and [18]. Importantly, during the Spatial Working Memory task *P. quinquefolius* was associated with decreased latency of SSVEP in prefrontal areas. This mechanistic effect is typically interpreted as a manifestation of increased excitatory processes. In this case the effect may be mediated by modulations in acetylcholine [35, 36]. This notion is further supported by the study of Bell et al. [14] where, following 2 weeks' daily *P. quinquefolius* supplementation, benefits were observed on an RVIP task which has known cholinergic sensitivity [37]. Indeed, like other working memory/attentional tasks, RVIP activates a fronto-parietal circuit [38, 39] and is known to be sensitive to cholinergic modulation [35]. Moreover, upregulation of acetylcholine has been observed following supplementation with *P. quinquefolius* extract in rodents [40]. It may be relevant that, compared with *P. ginseng*, *P. quinquefolius*

has higher levels of ginsenosides which upregulate acetylcholine namely Rb1, Re and Rg, which supports its calming effect to the CNS [41].

In addition, the paper by Bell et al. [14] also reports an *in vitro* experiment demonstrating increases in gut microbiota and their short chain fatty acids (SCFAs) in a simulation of the human colon, suggesting enhanced metabolic activity in the gut following ongoing treatment with *P. quinquefolius* extract. It should be noted that measures of SCFA in faecal samples may not be representative of circulating SCFA but, nevertheless, gut microbiota are increasingly recognised as an important factor in cognitive function via the gut-brain axis and may impact cognitive function by several routes. These include improved digestion, metabolism, and absorption of important nutrients such as polyphenols present in many plant-based foods; direct effects of circulating metabolites such as polyphenols or SCFAs on neurochemical pathways; and indirect effects of metabolites on peripheral vascular function or glucose regulation potentially leading to improved fuelling of the brain. Indeed, *P. quinquefolius* and its associated ginsenosides have been shown in preclinical research to be effective in reversing gut dysbiosis, and even eliciting positive changes to gut microbiota in healthy models, most notably improving levels of *Lactobacillus* and Bacteroides, and increasing production of acetate and propionate [4]. Certainly, future *in vivo* research into the gut microbiota effects of *P. quinquefolius* is warranted to confirm potential mechanisms of action in human subjects, in addition to further investigation into regulation of glucose and acetylcholine.

Conclusions

P. quinquefolius (American ginseng) extract appears to improve performance across varying tests of attention and working memory in healthy adults and may also increase memory recall. Importantly, there is some evidence of increased mental alertness, and mental concentration. General mental wellbeing appears to be promoted by support of cognitive function and decreases in fatigue following supplementation with *P. quinquefolius*, although these fatigue-related benefits do not appear to translate to pathologies often associated with increased levels of fatigue. Underlying mechanisms may include increased activation of fronto-parietal neural circuits and, in the context of the gut-brain axis, positive alterations in gut microbial composition. The effects are also consistent with cholinergic modulation. Nevertheless, while the apparent cognitive and mood benefits of *P. quinquefolius* appear promising, the conclusions of this review are drawn from a limited pool of small scale studies. If supported in larger studies, this profile of cognitive effects, along with elevated calmness, healthy mood balance, reduced mental fatigue and increased self-assurance suggest that *P. quinquefolius* extract may have benefits to every-day cognitive function as well as potential applications in the context of academic and sports or esports performance. However, more research is needed to determine efficacy in these areas.

Disclosure statement

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Data availability statement

Data sharing is not applicable to this review article as no new data were created or analyzed.

Notes on contributors

Lynne Bell, PhD, is a postdoctoral researcher in the School of Psychology & Clinical Language Sciences at the University of Reading. She is an experienced researcher and has worked on many industry funded projects with a focus on nutritional psychology.

Pascale Fança-Berthon, PhD, is a Nutrition & Health Food engineer. Pascale obtained her PhD in Physiology and Nutrition in 2009 and has worked for more than 16 years in research and development for the Health and Nutrition industry, with a good track record of peer-reviewed, published preclinical and clinical studies and approved health claims. She was Global Category Technical Leader for the Health Ingredients at Givaudan, in charge of translating business needs into a technical strategy and leading a team of scientists to develop improved and new botanical products and solutions with clinically demonstrated health benefits.

Romain Le Cozannet, PhD, is a passionate clinical scientist, with a PhD in neuroscience, leading innovation in the Mind & Women's health platform within Givaudan's Health Ingredients division. Based in Avignon, France, he aims to deliver innovative solutions with proven benefits backed by clinical evidence that positively influence mental and women's health.

David Ferguson, PhD FACSM ACSM-CEP, is an Associate Professor of Kinesiology at Michigan State University. He has two distinct research interests in the field of exercise physiology. The first focuses on the effects of early life growth-restriction on chronic disease risk. Children who are malnourished in early life have a higher incidence of cardiovascular disease in adulthood. The goal of his laboratory is to investigate the molecular mechanisms that occur due to growth-restriction and propose therapeutic countermeasures to increase cardiovascular function and decrease mortality rates. The second area of research focuses on the health and human performance of race car drivers. During competition, race car drivers are exposed to elevated temperatures and gravitational forces which can induce fatigue. The goal of his laboratory is to document these stressors so that interventions can be designed to increase safety and performance of race car drivers.

Andrew Scholey, PhD CPsychol AFBPsyS, is Professor of Human Psychopharmacology at Northumbria University. He has led over 100 clinical trials into the neurocognitive effects of natural products, metabolic substrates, recreational drugs, hangover, nutraceuticals and nutrients. This work has included neuroimaging and biomarker techniques to better understand the mechanisms of cognitive impairment and enhancement and neuroprotection. His current work focuses on translating research findings into evidence-based, end-user benefits to brain and mental health.

Claire M. Williams, PhD, is Professor of Neuroscience in the School of Psychology & Clinical Language Sciences at the University of Reading. Her laboratory studies the interplay between dietary intake and cognitive and mental health across the lifespan using a wide range of techniques (e.g. animal studies, randomised controlled trials, neuroimaging). She has published more than one hundred peer-reviewed research articles, five book chapters and is listed as an inventor on six international patent families, including 34 worldwide granted patents.

ORCID

Lynne Bell http://orcid.org/0000-0003-0677-021X
Pascale Fança-Berthon http://orcid.org/0000-0003-2250-2346
Romain Le Cozannet http://orcid.org/0000-0002-3357-8701
David Ferguson http://orcid.org/0000-0003-1203-0920
Andrew Scholey http://orcid.org/0000-0003-4484-5462
Claire Williams http://orcid.org/0000-0003-4452-671X

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