HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2010; **25**: 462–471.
Published online in Wiley Online Library
(wileyonlinelibrary.com).**DOI**: 10.1002/hup.1138

Panax ginseng (G115) improves aspects of working memory performance and subjective ratings of calmness in healthy young adults

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Objective There is a lack of research into the cognitive and mood effects of repeated ginseng ingestion. The present study assessed the effects of *Panax ginseng* (G115) on subjective mood and aspects of 'working' memory processes, following a single dose and following sub-chronic (7 days) ingestion, in healthy volunteers.
Methods A placebo-controlled, double-blind, randomised, crossover was utilised. Thirty volunteers (mean age 22.87 years; SD 4.01) received each treatment (200 mg; 400 mg; placebo) for 8 days, in a counter balanced order, with a 6-day wash-out period. Testing was on days 1 and 8 of each treatment period, at pre-dose, 1, 2.5 and 4 h post-dose.
Results Results revealed dose-related treatment effects ($p < 0.05$). Two hundred milligrams slowed a fall in mood at 2.5 and 4 h on day 1 and at 1 and 4 h on day 8, but slowed responding on a mental arithmetic task across day 1 and at 1 and 2.5 h on day 8. The 400 mg dose also improved calmness (restricted 2.5 and 4 h on day 1) and improved mental arithmetic across days 1 and 8.
Conclusions We found no evidence of additional benefits, nor attenuation of acute effects following repeated ingestion of *Panax ginseng* (G115). Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — Panax; Ginseng; G115; Memory; Acute; Chronic

INTRODUCTION

Over the last decade a number of studies have revealed that a single dose of *Panax Ginseng* (G115) can modulate aspects of cognitive function (see Kennedy and Scholey, 2003); electrical brain activity (Kennedy *et al*., 2003) and peripheral blood glucose levels (Reay *et al*., 2005, 2006), in healthy young volunteers.

With regards to cognitive function, these placebo-controlled, double-blind, balanced, crossover studies have identified both positive and negative effects; however, the most consistent finding is one of improved secondary memory performance (and also a null effect on working memory) following G115 alone (Kennedy *et al*., 2001, 2002, 2004), and in combination with both *Ginkgo biloba* (Kennedy *et al*., 2002) and guaraná (*Paullinia cupana*) (Kennedy *et al*., 2004). Despite the fact that these studies have consistently reported a null effect upon 'traditional' test of working memory, other studies have demonstrated *Panax ginseng's* (G115) ability to modulate mental arithmetic performance (a task that loads heavily on working memory resources) in healthy volunteers (Scholey and Kennedy, 2002; Reay *et al*., 2005, 2006) and attentional processes (Sünram-Lea *et al*., 2005). These findings suggest that further research, focusing specifically upon the psychological construct of working memory, may reveal effects of *Panax ginseng's* (G115) administration.

Additionally, despite the evidence supporting *Panax ginseng's* (G115) ability to modulate cognitive processes following a single dose, only three empirical studies have directly investigated the cognitive and mood effects following more extended ginseng ingestion periods (only one of these studies using the standardised G115 extract). Two early studies revealed improved speed of performing a mental arithmetic task following 12 weeks administration of *Panax ginseng* (200 mg G115 per day) in young volunteers (D'Angelo *et al*., 1986), and faster reaction times on the most rapid auditory reaction time

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Received 29 March 2010
Accepted 29 June 2010

task following 8–9 weeks of ginseng ingestion (400 mg standardised Gerimax ginseng extract; Dansak Droge A/S, Denmark) in middle-aged participants (Sorensen and Sonne, 1996). In the most recent, Kennedy *et al*. (2007) reported improved working memory performance following 4 and 8 weeks administration of a less widely used and researched standardised Korean *Panax ginseng* extract (200 mg/day), in healthy (mean age 39 years) volunteers.

Given the above, it seemed timely to further investigate *Panax Ginseng's* (G115) effects upon working memory processes, in more detail, following single and repeated ingestion. The present placebo-controlled, double-blind, randomised, crossover study therefore investigated the effects of both a single dose and 7 consecutive days of *Panax Ginseng* (G115) ingestion, on aspects of working memory processes, in healthy young volunteers.

SUBJECTS AND METHODS

Participants

Thirty adult volunteers (M 15/F 15; mean age 22.87 years; SD 4.01) participated in the study which was approved by the Northumbria University Department of Psychology Ethics committee and conducted in accordance with the Declaration of Helsinki. Prior to participation, each participant gave informed consent and completed a medical health questionnaire. All participants reported that they were in good health, and that they were free from heart disorders, high blood pressure, respiratory disorders, epilepsy, panic attacks and diabetes. Additionally, they reported being free from 'over the-counter' treatments, illicit social drugs and prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Heavy smokers (>10 cigarettes/day) were excluded from the study. Of the 30 participants, 4 where light smokers (<3 per day) and agreed to abstain from smoking on the days of testing. All participants were alcohol and caffeine free for 12 h prior to baseline assessment, and agreed to abstain from products containing caffeine on the days of testing. Volunteers were paid £100 for participation. Participants were randomly allocated to a position on a Latin Square which counterbalanced the treatment order, by the computerised generation of random numbers. Sample size was based upon previous research that has successfully reported significant effects of G115, in healthy young populations, using 20–30 participants.

Due to a data capture error the number of useable data sets was reduced to 28 on the Corsi block task and the delayed word recognition task; reduced to 24 on the N-back task and to 23 on the random number generation task. In these cases, the participants were removed from the analysis.

COGNITIVE BATTERY

Subjective mood

Bond–Lader visual analogue scales (Bond and Lader, 1974). Scores from the 16 items, comprising 100 mm visual analogue scales anchored at each end by pairs of mood antonyms (e.g. calm-tense), were combined as recommended by the authors to form three mood factors: Alert, Calm and Contented.

Working memory

Computerised Corsi block tapping task. The Corsi blocks task was developed as a non-verbal counterpart to the verbal-memory span task and has frequently been used to assess non-verbal short-term memory performance in healthy adults and patients with neuropsychological deficits (see Berch *et al*., 1998). The present study implemented a computerised version of the task. Nine identical blue squares (each square was 93×93 pixels; screen resolution was set at 1024–768) appeared in random pattern on the computer screen. A predetermined number of squares would change colour, from the original blue to red and then back to blue, at the rate of one per second, thus identifying the sequence of spatial locations to be remembered. The participant would then repeat the sequence by moving the mouse and cursor and clicking each square in the sequence. The sequence span increased until the participant could no longer correctly recall the sequence, resulting in a span measure of non-verbal working memory. Participants were presented with five trials at each span level and were required to correctly recall at least three of the five trials to proceed to the next level. Non-verbal memory span was measured as an average of the last five correct sequences recalled.

N-back task. Imaging studies have demonstrated the involvement of the prefrontal cortex (an area thought to underpin working memory performance) in completing the N-back task and positive relationship between brain activity and memory load (e.g. Jonides *et al*., 1997). In the present study participants engaged in the N-back task at four levels of difficulty. In the most difficult version (3-back) participants had to indicate whether or not the letter currently on the screen was the same as that which had been presented on screen 3

DOI: 10.1002/hup

letters before. In the easier versions volunteers had to engage in '2-back' (2 letters before) and '1-back' (the letter immediately before) matching. In the least demanding version (0-back) participants had to identify in the series presented, a target letter that was specified prior to the beginning of the series. For each level of difficulty there were 14 targets and 41 non-targets. Each letter remained on screen until a response was made, there was an inter-stimulus interval (ISI) of 2.5 s. Responses were made via the 'M' key (match) and 'Z' key (no match). The task was scored according to receiver operating characteristics (ROC curves) to ascertain an indication of task accuracy (referred to as the 'sensitivity index' in the current paper) using the non-parametric index of signal detection p(A) (see Pastore *et al*., 2003). Reaction time for correct responses was also recorded.

Random number generation task. Random number generation is considered an indication of executive function and draws heavily on processes responsible for inhibition, a process that is thought to rely on the left dorsolateral pre-frontal cortex (Jahanshahi *et al*., 2000). In this task participants were instructed to produce a string of random numbers, using the linear number keys (0–9). Participants were instructed to generate responses in pace with an asterisk that appeared on the computer screen, once per second for 100 s. Participants' responses were scored for randomness using RG calc (Towse and Neil, 1998), which is a computerised algorithm generating scores representing indicators of randomness, in strings of digits.

Treatments

Active treatments and placebo capsules, matched for size, colour, opacity and odour were provided by the manufacturer (Pharmaton SA, Lugano, Switzerland). Prior to the commencement of the study, a disinterested third party, who had no other involvement in the study, prepared the capsule treatments for each of the individual participants (in accordance with the study's Latin Square) and sealed them in containers marked only with the participant code and study day numbers (days 1–8). On each morning participants ingested four capsules (on days 1 and 8 the capsules were administered in the lab, after a pre-dose cognitive assessment session). The individual capsules contained either an inert placebo, or 100 mg of *Panax ginseng* extract (G115, Pharmaton SA, Lugano, Switzerland). Depending on the condition to which the participant was allocated to during that particular period, the combination of capsules corresponded to a dose of 0 mg (placebo), 200 mg (G115), or 400 mg (G115) per day.

Procedure

The study commenced with a practice day that was identical to subsequent study days with the exception that no treatment was offered and the data acquired were not entered into any analysis. This served to familiarise participants with the tasks, minimise practice effects and establish that they were capable of engaging with the cognitive tasks. Participants received each treatment (placebo, 200 and 400 mg) for 8 days in total, with a wash-out period of 6 days between treatments (see Figure 1). Testing took place in a suite of laboratories with participants visually isolated from each other. Participants were assessed on the first day (day 1) and last day (day 8) of each treatment period (i.e. 6 assessment days in total across the three treatments) (see Figure 1). On each day participants attended the laboratory between 8:30 am and 9:00 am and made a baseline completion of the cognitive/mood assessment described above. This was followed immediately by the ingestion of that day's treatment. Post-dose assessments then commenced at 1, 2.5, and 4 h post-dose (see Figure 2). Upon completion of the last post-dose

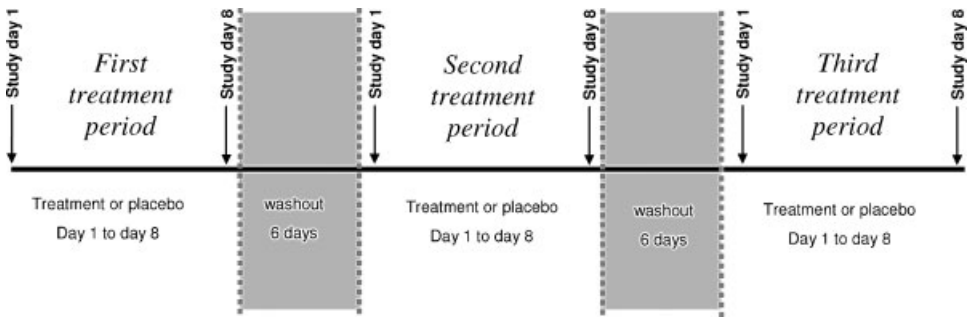

Figure 1. Timeline depicting the overall study protocol. Participants received either placebo or ginseng (200 or 400 mg G115) during each treatment period of the study. All participants received placebo during the washout periods.

DOI: 10.1002/hup

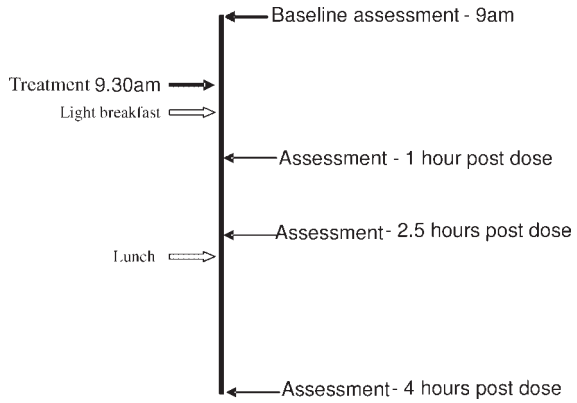

Figure 2. Timeline depicting the running order of each study day (days 1 and 8) for all treatments.

testing session on the first testing day (day 1) for each treatment period, participants were provided with six identical containers, containing treatments for each day (days 2–7) until the next laboratory visit. Treatments on days 1 and 8 of each period were consumed in the laboratory. On study day 1, a record was taken of every participant's choice of breakfast (a typical breakfast reported was either cereal with milk or toast with spread) and lunch (a typical lunch reported was a Sandwich with various fillings, crisps/fruit and water). On all subsequent assessment days each participants consumed the identical breakfast and identical lunch as that consumed on the first study day. Participants abstained from caffeinated foods and drinks on all testing days.

Statistics

Post-dose treatment effects, for each individual outcome measure (Bond–Lader mood scale; N-Back; Random Number Generation and the Corsi-Block task) were analysed as 'change from baseline' (pre-dose scores on day 1 of each treatment period). Planned comparisons were made between placebo and each of the active treatments utilising *t* tests with MSError (from an omnibus ANOVA) as the error term (Keppel, 1991). To ensure the overall protection level, comparisons were strictly planned prior to commencement of the study and only conducted on those outcome measures that reached statistical significance on the initial ANOVA (using Minitab statistical package version 13.1). Additionally, only probabilities associated with planned comparisons were calculated, and all testing was two-tailed. Differences were considered significant at $p < 0.05$.

Pure sub-chronic effects. In order to assess the effects of 7 day's treatment with ginseng, but without the potential confounding acute effects of the day's treatment, pre-dose data on day 8 (scored as 'change from day 1 baseline') were analysed by one-way repeated measures ANOVA (treatment condition as the independent variable).

Acute, sub-chronic and superimposed effects. In order to assess the acute, sub-chronic and superimposed effects of ginseng, a three way repeated measures ANOVA (treatment [0, 200, 400 mg] × session [1, 2.5, 4 h post-dose] × day [1, 8]) was performed on the post-treatment data collected at days 1 and 8. All data were scored as 'change from day 1 pre-dose baseline'.

Using this analysis a main effect of 'treatment' or a significant 'treatment' × 'session' interaction would indicate an acute effect of ginseng across both assessment days. A treatment × day interaction would indicate a differential effect of sub-chronic and acute dosing (superimposed with one another).

RESULTS

Baseline scores

Prior to analysis of 'change from baseline' data, raw baseline scores for all three conditions (placebo, 200 and 400 mg) for each of the outcome measures were subject to one-way repeated-measures ANOVAs. There were no significant differences in baseline performance on any measure. Mean pre-dose baseline raw scores and change from baseline scores, for each treatment, at each post-time point following commencement of treatment, are presented in Table 1.

Sub-chronic effects

There were no significant treatment related effects for any outcome measure. Mean pre-dose data for day 8 (change from day 1 baseline), for each treatment (placebo, 200 and 400 mg), for each outcome measure are presented in Table 1.

Acute effects

Bond–Lader visual analogue scale. The initial ANOVA revealed a significant main effect of treatment [$F(2, 116) = 4.64$, $p = 0.014$] on subjective self-report ratings of calmness (see Figure 3, Panel 1a and Table 1). Planned comparisons (Figure 3, panel 1b and Table 1) comparing each treatment to placebo, at each time point, on days 1 and 8 revealed that 200 mg significantly improved self report ratings of calmness at

DOI: 10.1002/hup

Table 1. Effects of 200 mg (G115), 400 mg (G115) and placebo on working memory performance and mood

			Post-dose day 1								Post-dose day 8					
	Baseline day 1	SE	1 h	SE	2.5 h	SE	4 h	SE	Pre-dose day 8	SE	1 h	SE	2.5 h	SE	4 h	SE
Bond–Lader mood scale ($N = 30$)																
Alert (mm)																
Placebo	55.76	4.45	4.98	3.60	4.56	3.39	2.00	3.82	2.72	3.29	4.86	3.96	5.43	3.79	6.23	4.90
200 mg	59.66	2.95	0.29	1.95	2.52	2.35	−0.81	2.99	0.78	2.67	1.63	2.78	−0.22	3.00	1.18	2.57
400 mg	61.79	3.04	3.29	1.66	1.74	2.14	−2.65	2.89	−2.94	2.90	0.23	2.36	−0.22	3.25	−1.37	3.22
Calm (mm)																
Placebo	65.69	2.25	−2.63	2.29	−5.93	2.29	−14.74	2.56	−1.98	1.63	−3.56	1.65	−3.85	2.41	−4.15	2.49
200 mg	60.69	2.53	0.92	2.51	0.43	2.53	−2.33	2.70	1.40	2.29	1.93	2.54	−1.43	2.72	1.99	2.38
400 mg	62.88	2.92	1.99	1.35	0.87	2.08	−3.38	2.72	1.98	2.51	1.02	2.68	0.89	2.21	0.44	3.24
Content (mm)																
Placebo	67.37	2.97	−10.03	3.02	−3.58	3.32	−8.85	3.46	−2.57	2.93	−5.83	2.94	−8.07	2.98	−9.32	6.23
200 mg	61.92	2.81	1.47	3.14	−1.28	3.15	−1.83	3.88	0.77	3.20	−3.02	3.75	−3.87	3.50	−1.42	3.42
400 mg	65.60	3.65	−2.75	2.59	−5.33	2.14	−3.93	3.35	−0.85	3.11	−6.85	2.55	−3.88	2.56	−5.05	3.47
Corsi block task ($N = 28$)																
Span (No)																
Placebo	6.04	0.19	0.26	0.18	0.11	0.25	0.07	0.22	0.23	0.21	0.01	0.26	0.12	0.20	0.33	0.23
200 mg	6.10	0.22	−0.15	0.19	0.09	0.18	−0.01	0.22	0.21	0.23	0.09	0.22	−0.01	0.23	−0.01	0.20
400 mg	6.31	0.21	−0.38	0.24	−0.24	0.16	−0.24	0.19	−0.22	0.19	−0.28	0.20	−0.02	0.16	−0.26	0.21
Zero back ($N = 24$)																
S/(p(A))																
Placebo	0.97	0.01	0.00	0.01	−0.01	0.01	−0.01	0.01	0.00	0.01	−0.06	0.04	0.01	0.01	−0.03	0.02
200 mg	0.94	0.03	0.01	0.02	0.02	0.03	0.03	0.02	0.03	0.03	0.02	0.03	0.02	0.03	0.02	0.03
400 mg	0.97	0.01	−0.02	0.01	0.00	0.01	−0.01	0.01	−0.01	0.01	−0.01	0.01	−0.01	0.01	−0.01	0.01
Average RT (sec)																
Placebo	0.59	0.03	−0.01	0.02	−0.05	0.02	−0.02	0.03	0.01	0.03	−0.02	0.03	−0.03	0.03	−0.03	0.04
200 mg	0.63	0.04	−0.03	0.03	0.01	0.03	−0.04	0.02	0.00	0.02	−0.01	0.04	−0.04	0.02	−0.06	0.03
400 mg	0.61	0.03	−0.04	0.03	−0.07	0.03	−0.05	0.03	−0.03	0.02	−0.06	0.03	−0.07	0.02	−0.04	0.03
One back ($N = 24$)																
S/(p(A))																
Placebo	0.85	0.04	0.02	0.04	−0.04	0.03	−0.02	0.05	0.02	0.03	0.00	0.03	−0.02	0.03	0.01	0.04
200 mg	0.88	0.02	−0.01	0.02	−0.09	0.03	−0.05	0.03	0.01	0.02	−0.05	0.02	−0.04	0.02	−0.03	0.02
400 mg	0.85	0.03	−0.03	0.04	−0.04	0.03	−0.01	0.03	0.01	0.02	0.02	0.04	0.03	0.04	−0.02	0.04
Average RT (sec)																
Placebo	0.64	0.04	−0.02	0.03	−0.05	0.03	−0.03	0.03	−0.03	0.03	−0.03	0.04	−0.03	0.04	−0.03	0.04
200 mg	0.67	0.04	−0.01	0.02	0.06	0.04	−0.04	0.03	−0.03	0.03	−0.05	0.03	−0.03	0.03	−0.05	0.03
400 mg	0.66	0.03	−0.03	0.02	−0.03	0.03	−0.04	0.03	−0.04	0.03	−0.08	0.03	−0.06	0.04	−0.03	0.05
Two back ($N = 24$)																
S/(p(A))																
Placebo	0.81	0.05	0.01	0.03	0.04	0.03	−0.02	0.03	0.04	0.03	0.04	0.05	−0.02	0.05	0.02	0.05
200 mg	0.85	0.03	0.02	0.02	−0.05	0.02	−0.06	0.03	0.02	0.03	−0.04	0.03	0.00	0.02	−0.03	0.03
400 mg	0.80	0.07	0.06	0.07	0.05	0.08	0.04	0.08	0.04	0.07	0.03	0.08	0.06	0.06	0.02	0.07
Average RT (sec)																
Placebo	0.74	0.04	−0.01	0.02	−0.01	0.03	−0.01	0.04	−0.02	0.02	0.00	0.03	−0.01	0.03	−0.04	0.03
200 mg	0.80	0.05	−0.04	0.03	−0.07	0.03	−0.04	0.04	−0.05	0.03	−0.07	0.04	−0.01	0.04	−0.08	0.03
400 mg	0.80	0.05	−0.03	0.04	−0.08	0.04	−0.09	0.05	−0.07	0.04	−0.09	0.05	−0.10	0.05	−0.11	0.05
Three back ($N = 24$)																
S/(p(A))																
Placebo	0.69	0.04	−0.05	0.04	−0.09	0.04	−0.05	0.04	0.00	0.04	0.02	0.04	0.02	0.05	0.02	0.03
200 mg	0.69	0.05	−0.05	0.06	−0.04	0.04	−0.01	0.03	0.03	0.03	−0.05	0.04	−0.01	0.05	−0.06	0.04
400 mg	0.55	0.08	0.11	0.07	0.10	0.06	0.13	0.06	0.16	0.07	0.17	0.05	0.18	0.05	0.12	0.06
Average RT (sec)																
Placebo	0.88	0.06	−0.10	0.03	−0.10	0.04	−0.13	0.04	−0.06	0.04	−0.08	0.04	−0.08	0.03	−0.11	0.03
200 mg	0.81	0.05	0.00	0.03	−0.04	0.03	−0.05	0.03	0.01	0.04	−0.01	0.03	0.02	0.04	−0.09	0.03
400 mg	0.92	0.06	−0.11	0.03	−0.16	0.04	−0.14	0.03	−0.08	0.03	−0.13	0.04	−0.17	0.05	−0.12	0.06
Random number generation ($N = 23$)																
R																
Placebo	4.09	0.79	0.56	0.44	0.14	0.49	−0.76	0.61	0.07	0.35	0.50	0.44	0.30	0.61	0.95	0.64
200 mg	3.56	0.51	0.61	0.44	1.05	0.40	1.16	0.54	0.52	0.37	1.87	1.20	1.09	1.14	2.46	1.32
400 mg	3.69	0.48	−0.02	0.62	0.98	0.61	−0.11	0.52	1.16	0.74	1.04	0.81	1.24	0.82	−0.60	0.32
RNG																
Placebo	0.30	0.02	0.01	0.01	−0.01	0.02	−0.01	0.01	0.01	0.01	0.00	0.02	−0.01	0.02	−0.01	0.01
200 mg	0.31	0.01	−0.01	0.01	0.00	0.02	0.00	0.01	0.01	0.01	0.00	0.02	−0.01	0.01	0.02	0.02
400 mg	0.31	0.01	−0.01	0.02	0.00	0.02	−0.02	0.01	−0.01	0.02	0.01	0.02	0.00	0.02	−0.01	0.01

(*Continues*)

DOI: 10.1002/hup

Table 1. (Continued)

			Post-dose day 1								Post-dose day 8					
	Baseline day 1	SE	1 h	SE	2.5 h	SE	4 h	SE	Pre-dose day 8	SE	1 h	SE	2.5 h	SE	4 h	SE
NSQ																
Placebo	53.20	1.37	0.75	1.16	1.19	1.93	−0.83	1.28	−0.83	1.16	2.46	1.24	0.48	1.32	1.49	1.62
200 mg	54.00	1.17	−0.35	1.26	0.26	1.49	1.67	1.26	0.28	1.54	0.70	1.62	0.04	1.73	1.62	1.83
400 mg	52.48	1.10	0.48	1.32	1.67	1.29	−0.66	1.18	0.76	1.20	2.99	1.25	1.71	1.70	0.13	0.98
RNG2																
Placebo	0.25	0.01	0.01	0.01	−0.01	0.02	−0.01	0.01	0.01	0.01	0.00	0.02	0.01	0.01	0.01	0.01
200 mg	0.26	0.01	−0.01	0.01	0.00	0.01	0.00	0.01	−0.02	0.01	0.01	0.02	−0.01	0.01	0.02	0.02
400 mg	0.26	0.01	−0.02	0.01	0.00	0.02	−0.01	0.01	−0.02	0.01	0.01	0.01	−0.02	0.02	−0.02	0.01
TPI																
Placebo	0.72	0.07	−0.03	0.07	0.15	0.09	−0.01	0.11	0.25	0.07	0.19	0.11	0.07	0.10	0.05	0.09
200 mg	0.79	0.10	0.00	0.11	0.02	0.11	0.06	0.12	−0.06	0.07	0.04	0.11	−0.04	0.11	0.10	0.18
400 mg	0.75	0.07	−0.01	0.09	0.06	0.06	0.06	0.06	0.05	0.08	0.03	0.11	0.07	0.08	0.10	0.07
Runs																
Placebo	19.07	1.94	1.16	2.15	1.36	2.65	2.06	2.06	5.18	3.72	3.56	2.90	4.37	2.90	2.60	3.18
200 mg	22.92	2.84	−0.37	2.82	−2.89	3.47	−1.42	2.77	−2.07	3.13	4.54	4.54	−1.10	2.90	−2.07	3.37
400 mg	20.90	2.46	4.33	4.95	0.35	3.17	−0.90	2.96	−3.30	2.39	5.04	3.68	0.81	1.63	3.72	3.56

Values represent mean baseline performance score and mean change from baseline performance score at each post-dose testing session on day 1; mean change from baseline performance score at pre-dose on day 8 and at each post-dose testing session on day 8.

2.5 h [$t(116) = 2.56$, $p = 0.012$; $d = 0.5$], and 4 h [$t(116) = 4.99$, $p < 0.0001$; $d = 0.9$] post-treatment on day 1. The same dose also led to significantly improved ratings of calmness at 1 h [$t(116) = 2.21$, $p = 0.029$; $d = 0.6$], and 4 h [$t(116) = 2.46$, $p = 0.015$; $d = 0.5$] post-treatment on day 8. The higher dose, 400 mg G115, improved calmness at 2.5 h [$t(116) = 2.74$, $p = 0.007$; $d = 0.5$] and 4 h [$t(116) = 4.57$, $p < 0.0001$; $d = 0.8$] post-treatment on day 1 only.

Three back (RT). There was a significant main effect of treatment on average reaction times [$F(2, 92) = 5.64$, $p = 0.006$] (Figure 3, panel 2a and Table 1). Planned comparisons revealed (Figure 3, panel 2b and Table 1) that, compared with placebo, 400 mg led to significantly faster response times at 2.5 h post-dose on day 1 [$t(92) = 2.30$, $p = 0.023$; $d = 0.3$] and day 8 [$t(92) = 3.37$, $p = 0.001$; $d = 0.5$]. However, 200 mg led to significantly slower response times on day 1 at 1 h [$t(92) = 3.664$, $p = 0.0004$; $d = 0.6$], 2.5 h [$t(92) = 2.021$, $p = 0.046$; $d = 0.3$] and 4 h [$t(92) = 3.046$, $p = 0.003$; $d = 0.5$] post-dose. Similarly, on day 8, 200 mg led to significantly slower response times at 1 h [$t(92) = 3.938$, $p = 0.004$; $d = 0.4$] and 2.5 h [$t(92) = 4.017$, $p = 0.0001$; $d = 0.6$] post-dose.

Three back (SI). There was a significant main effect of treatment on sensitivity index (SI) [$F(2, 92) = 6.57$, $p = 0.003$] (Figure 1, panel 3a and Table 1). Planned comparisons (Figure 1, panel 3b and Table 1) revealed that, compared with placebo, the 400 mg dose led to significantly improved SI on day 1 at 1 h [$t(92) = 4.229$, $p = 0.00006$; $d = 0.7$], 2.5 h [$t(92) = 5.15$, $p = 0.0000015$; $d = 0.9$] and 4 h [$t(92) = 4.866$, $p = 0.000005$; $d = 0.8$] post-dose. The same dose also led to significantly improved sensitivity on day 8 at 1 h [$t(92) = 4.384$, $p = 0.00003$; $d = 0.9$], 2.5 h [$t(92) = 4.38$, $p = 0.00003$; $d = 0.6$] and 4 h [$t(92) = 2.91$, $p = 0.004$; $d = 0.6$] post-dose. However, 200 mg led to a significant impairment in SI on day 8 at the 4 h [$t(92) = 2.25$, $p = 0.02$; $d = 0.5$] post-dose testing session.

The initial ANOVAs showed that no other measure was significantly modulated by the treatment. The lack of any treatment × day interaction suggested that there was no evidence of a 'superimposed' effect, by which any treatment related effects following the day's dose either increased or attenuated over the course of the 8-day treatment period.

DISCUSSION

The results of the present study confirm that an acute dose of *Panax ginseng* (G115) can modulate cognitive function and mood in young healthy volunteers; however, the study revealed no effects following a 7-day dosing regimen.

With regards to mood, planned comparisons revealed that an acute dose of 200 and 400 mg of *Panax ginseng* (G115) significantly slowed the fall in subjective ratings of calmness at the last two testing session on day 1 and at the first and last testing session on day 8 following 200 mg only. Whilst the present study is the first to report an acute effect of *Panax ginseng* (G115) on subjective ratings of 'calmness',

DOI: 10.1002/hup

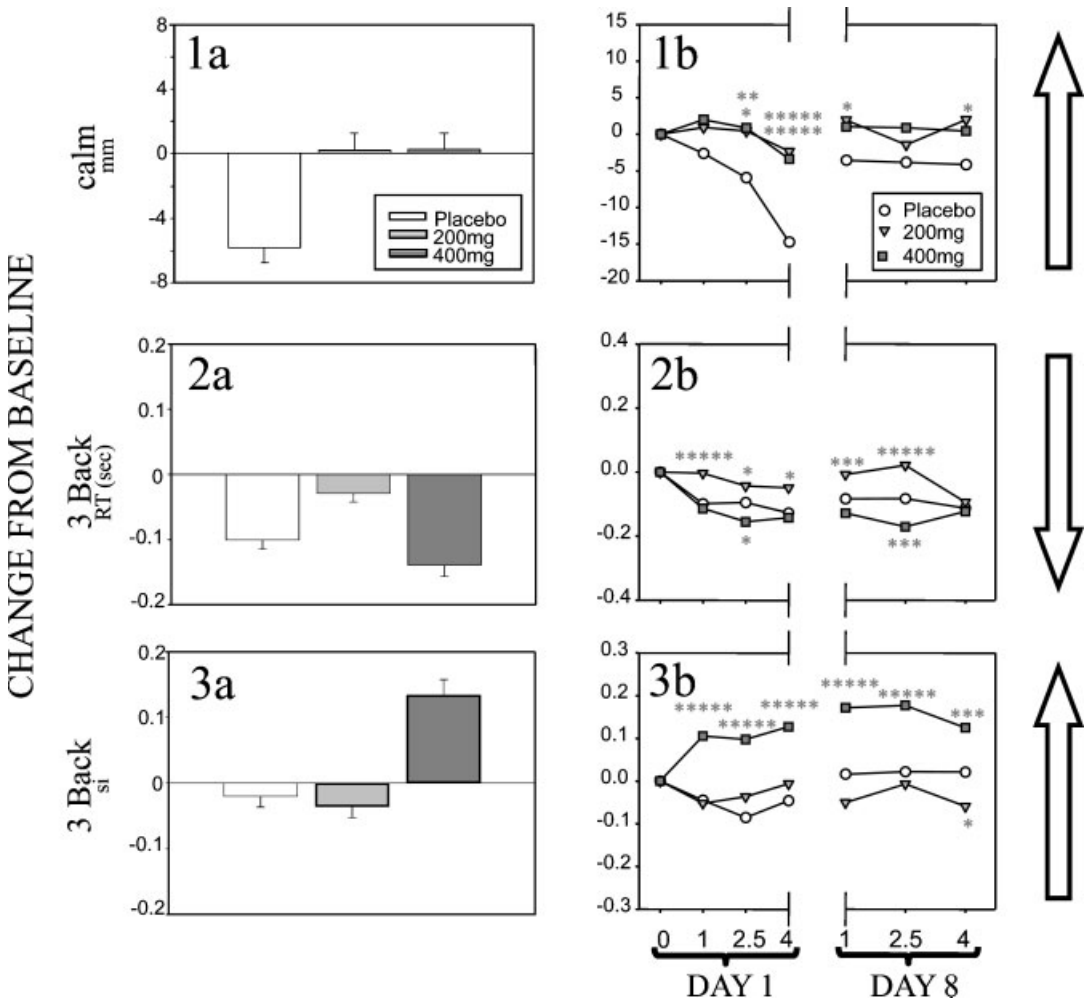

Figure 3. Panel 1a, 2a, and 3a depict a significant main effect of ginseng treatment on self-reported ratings of calmness, average reaction time for the 3 back and sensitivity index for the 3 back task respectively, in young healthy volunteers. Values represent 'change from baseline' group means summed across day (post-dose day 1 and post-dose day 8) and session (1, 2.5, 4 h post-dose). Panels 1b, 2b and 3b depicts the pattern of results broken down over day (days 1 and 8) and session (1, 2.5 and 4 h post-dose) for placebo, 200 and 400 mg of *P. ginseng* (G115). Asterisks represent significance of planned comparison as compared to placebo. Values represent 'change from day 1 pre-dose baseline'. Directional arrows indicate improvements on those measures. ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.005$; $^{*****}p < 0.0005$). Significance is compared with placebo.

previous acute studies (utilising different methodologies and assessments batteries) have reported *Panax ginseng*'*s* (G115) abilities to ameliorate subjective ratings of mental fatigue during 60 min of sustained cognitive processing (Reay *et al*., 2005, 2006) and its ability to reduce subjective feelings of 'alertness' in healthy young volunteers (Kennedy *et al*., 2001). Although these mood dimensions are considered somewhat independent of each other, we speculate that the acute changes in subjective mood may be related to the purported anxiolytic properties of ginseng, and that volunteers are expressing such feelings within the constraints of the available mood measures utilised. To date, no human study has directly assessed the purported anxiolytic properties of ginseng, despite a wealth of animal data suggestion such effects (see Kennedy and Scholey, 2003) and literature of other herbal products (with similar *in vitro* biological actions to that of ginseng) showing anxioloytic actions in human trials (see Weeks 2009 for review).

The present results suggest that there is no effect of seven consecutive days consumption of *Panax ginseng* (G115) on subjective mood; however, the present study is the first to investigate repeated administration over this period of time (i.e. 7 days). We have previously suggested that the underlying mechanisms of action driving the behavioural and mood effects, following a single dose, may include modulation of glucose availability (Reay *et al*., 2005, 2006). These mechanisms may attenuate with repeated 7-day dosing. On the

DOI: 10.1002/hup

other hand the 7-day regime may be too short to capture longer-term effects resulting from, for example neuroprotection, free-radical scavenging properties.

Whilst the modulation of mood *per se* by extended treatment with ginseng has received little attention, the related constructs of 'quality of life' and 'well-being', which include a consideration of mood, have been investigated in a number of placebo-controlled trials, when administered alone (Sotaniemi *et al*., 1995; Wiklund *et al*., 1999; Cardinal and Engles, 2001; Ellis and Reddy, 2002) and in conjunction with vitamins and minerals (Wiklund *et al*., 1994; Neri *et al*., 1995; Ussher *et al*., 1995; Caso Marasco *et al*., 1996; Ussher and Swann, 2000). Effects have been evaluated using doses ranging from 80 to 400 mg in populations of various ages and stress levels (Wiklund *et al*., 1994; Neri *et al*., 1995; Sotaniemi *et al*., 1995; Ussher *et al*., 1995; Caso Marasco *et al*., 1996; Ussher and Swann, 2000; Cardinal and Engles, 2001; Ellis and Reddy, 2002), with study duration ranging between 2 and 9 months (see Coleman *et al*., 2003 for review). Findings are by no means unequivocal (see Kennedy and Scholey, 2003), even when considering only those studies that have investigated the effects of *Panax ginseng* supplements alone (i.e. free from added vitamin, minerals, etc.). For example, improvements have been reported following 16 weeks administration of *Panax ginseng* in several subscales of the Psychological General Well Being Index (Wiklund *et al*., 1999); improvements have been reported following two doses of ginseng (100 and 200 mg/day for 8 weeks) on self-ratings of mood, vigour and well-being (Sotaniemi *et al*., 1995). However, Cardinal and Engles (2001) reported no significant differences on the Positive Affect–Negative Affect Scale (PANAS) or Profile of Mood States (POMS) following 8 weeks daily ingestion of 200 mg (G115) or 400 mg (G115). Clearly, more research is needed.

With regards cognitive performance, the lack of any treatment × day (1/8) interaction in the present study would again suggest 'simple' acute effects of *Panax ginseng* on the most demanding version of the N-back ('working' memory) task (3 back). On this task the most striking finding was the significant improvement in the accuracy of performing the 3 back task at all post-dose testing sessions on days 1 and 8 following 400 mg ginseng, accompanied by significant speeding in performance of the same task at the mid-testing session on days 1 and 8 following the same dose. However, planned comparisons revealed that 200 mg led to significant slowing of performance of the same 3 back task at all but the very last testing session on day 8, as compared with placebo. Planned comparisons also showed that 200 mg led to a significant decrement in the accuracy of performing the same task at the final testing session on day 8. The present study includes the first comprehensive global assessment of working memory performance following *Panax ginseng* (G115) and is in contrast with those studies that have continually failed to report any effect upon this memory construct following a single dose (see Kennedy and Scholey, 2003; Kennedy *et al*., 2007); however, the present study is in line with those studies that have shown improved mental arithmetic performance (which can be viewed as an indirect indicator of working memory performance) following a single dose of *Panax ginseng* (G115) (Reay *et al*., 2005, 2006) and a further study that has reported working memory improvements following 4 and 8 weeks of *Panax ginseng* (Korean) ingestion on the same 'working' memory task (Kennedy *et al*., 2007) The significant slowing in working memory performing revealed in the present study, following 200 mg, is consistent with reports of slower performance in other cognitive domains following the same 200 mg dose in healthy volunteers. For example, Kennedy *et al*. (2001) reported slower reaction times during an attention task and Scholey and Kennedy (2002) reported slower mental arithmetic performance. However, this slowing in performance is not consistent with the recent findings of faster memory, attention, and serial subtraction task performance (Kennedy *et al*., 2004; Reay *et al*., 2005, 2006), and decreased latency of the P300 component of auditory evoked potentials following the same 200 mg dose (Kennedy *et al*., 2003).

The previous failure to educe an affect on working memory performance may have been due to the 'under loaded' nature of the working memory tasks utilised in the previous studies. Indeed, this suggestion is supported by the observation that, in the present study ginseng only exerted its effects on the most cognitively demanding level on the N-Back task (3 back) and in previous studies the more demanding version of the serial subtraction task (Reay *et al*., 2005), or on an easier version of the subtraction task but only when concomitant subjective self reported mental fatigue was at its greatest (Reay *et al*., 2006).

It is difficult, if not impossible, with the present knowledge of the mechanism responsible for ginseng effects, to explain the disparity in results obtained from study to study following 200 mg of *Panax ginseng* or even the non-linear dose response relationship. However, in the present study, the slowed performance following the 200 mg dose was associated with a

DOI: 10.1002/hup

concomitant increased in subjective reports of calmness. This improved state of calmness may be accountable for the slowed speed of performance (although this pattern was not evident for the 400 mg dose). Unfortunately, the study was not designed to delineate any cause/effect relationship between mood and cognitive performance. Therefore the most parsimonious explanation is that of a simple cohort effect (all studies report data from cohorts drawn from the healthy young population). Alternatively, whilst the extract used is standardised to total ginsenoside content, it is possible that even minor differences in the levels of single ginsenosides, or groups of ginsenosides (e.g. the ratio of protopanaxadiols to protopanaxatriols), may have exerted an effect. Additionally, while the effect following 200 mg may appear curious, previous ginseng research, both in humans and animals, is replete with dose-specific effects and non-linear dose response profiles (see Kennedy and Scholey, 2003).

As mentioned earlier the mechanisms underlying ginseng's cognitive effects are, as yet, not well understood. Potential candidate mechanisms include effects on the cardiovascular and Hypothalamic Pituitary Adrenal (HPA) systems, deceleration of platelet aggregation, cardio- and neuro protective effects, modulation of neurotransmission, promotion of nitric oxide synthesis and gluco-regulatory effects (Kennedy and Scholey, 2003). With reference to the latter, in Reay *et al*. (2005) and Reay *et al*. (2006) an attempt was made to relate ginseng's acute gluco-regulatory effects to its cognitive efficacy, reporting cognitive enhancement in the presence of concomitant reduction in circulating blood glucose levels in a healthy young cohort. However, there was a lack of any clear relationship between the modulation of blood glucose levels and changes in cognitive performance.

In conclusion, the present study has revealed that 7 consecutive days of ginseng ingestion has no affect on mood or cognitive performance as assessed in the present study. However, results did reveal, for the first time, that single doses (administered on days 1 and 8) of *Panax ginseng* can modulate working memory performance and improve participants' subjective self-reports of calmness. Given that ginseng is typically ingested repeatedly by members of the public, further research is needed to investigate the behavioural effects following longer periods of ginseng ingestion.

CONFLICT OF INTEREST

The study sponsor had no role in the design, data collection, analysis, interpretation, writing the report or in the decision to submit for publication.

Reay JL has no conflict of interest.

During the last 3 years D Kennedy has received payment for academic presentations conducted for Bayer healthcare, Nestle (UK) and Unilever Ltd. He declares that he has not received any payment, and has no personal holdings, that could be perceived as constituting a potential conflict of interests.

Scholey has acted as a consultant/expert advisor to: Barilla, Bayer Healthcare, Danone, GlaxoSmithKline Healthcare, Masterfoods, Martek, Novartis, Unilever, Wrigley. He has held research grants from: Bayer Healthcare, Danone, GlaxoSmithKline Healthcare, Nestlé, Martek, Masterfoods, Novartis, Unilever, Wrigley. He has accepted travel/hospitality for speaking engagements by Bayer Healthcare, Blackmores, Danone, Flordis, Ginsana/Pharmaton, GlaxoSmithKline Healthcare, Naturex, Unilever, Wrigley, YuYu Industries.

ACKNOWLEDGEMENTS

The authors would like to thank Pharmaton SA, Lugano, Switzerland for their financial support.

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