

## THE EFFECT OF ACUTE ADMINISTRATION OF 400MG OF *PANAX GINSENG* ON COGNITIVE PERFORMANCE AND MOOD IN HEALTHY YOUNG VOLUNTEERS

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**ABSTRACT:** *Recent evidence suggests that single dose administration of ginseng can improve certain aspects of cognitive performance and mood in healthy young volunteers in a dose and time dependent manner. The aim of this study was to investigate the effect of acute administration of 400 mg of a standardised Panax ginseng extract (G115<sup>®</sup>, Pharmaton SA) on mood and cognitive performance. Following a double-blind, placebo controlled, balanced, cross-over design, thirty healthy young adult volunteers received 400 mg of ginseng, and a matching inert placebo, in a counterbalanced order, with a 7-day washout period between treatments. Following baseline evaluation of cognitive performance and mood measures, participants' cognitive performance and mood was assessed again 90 minutes after drug ingestion. Ginseng improved speed of attention, indicating a beneficial effect on participants' ability to allocate attentional processes to a particular task. No significant effect was observed on any other aspect of cognitive performance and on self-reported mood measures. Previous research demonstrated no improvement on attentional processes, but significant improvements on tasks associated with episodic memory performance following administration of 400 mg of ginseng when participants were tested 1h, 2.5h, 4h and 6h post ingestion. Consequently, it may be the case that ginseng offers alternative windows of therapeutic opportunity on different aspects of cognitive performance at different time points.*

**KEY WORDS:** Cognition, Healthy young adults, Mood, *Panax ginseng*, Single-dose administration

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### INTRODUCTION

In Asian countries, ginseng has been used as a dietary supplement to enhance cognitive performance and reduce mental fatigue for thousands of years (Huang, 1999). Reports of its various therapeutic actions, including beneficial effect on cognition and mood date back as far as 101 B.C. claiming that it can "...support the five visceral organs, calm the nerves, tranquilize the mind, stop convulsion, expunge evil spirits, clear the eyes, and improve memory..." ("The Herbal Classic of the Divine Plowman", published around 101 B.C., author unknown, cited in Huang, 1999). Traditionally it was thought that ginseng needed to be taken over a period of time in order to have beneficial effects on various physiological and behavioural parameters, including cognition and mood. This assumption influenced scientific research that initially focussed on chronic dosing regimes. Such research demonstrated that chronic or sub-chronic ginseng administration can ameliorate cognitive impairments in both animals and humans and facilitate certain aspects of cognitive performance in healthy young adults with no pre-existing cognitive impairments (for a review see Kennedy and Scholey, 2003). For example, ginseng administration has been shown to attenuate learning deficits in rodents caused by brain damage or by normal ageing processes (e.g. Wen et al., 1996; Nitta et al., 1995). Moreover, facilitation of certain aspects of cognitive function following chronic administration of a multivitamin preparation-containing ginseng has been observed in human participants with age-related memory impairments (Neri et al., 1995) and has been shown to attenuate memory impairments in a sample of non-insulin dependent diabetic patients (Soteniemi et al., 1995). Chronic ginseng administration has also been shown to improve cognitive performance in healthy young adults with no pre-existing cognitive impairments (for a review see Kennedy and Scholey, 2003). D'Angelo et al. (1986) demonstrated that twice daily administration of 100mg of standardized ginseng over a period of twelve weeks improves performance on a mental arithmetic test in volunteers aged 20 – 24 years compared to placebo. In a further placebo-controlled study,

healthy young participants received 400mg of standardized ginseng extract or placebo daily for 8-9 weeks. Significant improvements following ginseng administration were seen on a simple reaction time task and on a task pertaining to executive function (Sorensen and Sonne, 1996).

However, recent evidence suggests that even single dose administration of ginseng can improve certain aspects of cognitive performance and mood in healthy young volunteers in both a dose- and time-dependent manner (Kennedy and Scholey, 2003; Kennedy et al., 2001; 2002; 2003; Scholey and Kennedy, 2002). Employing a double blind placebo-controlled balanced crossover design, healthy young participants were given different single doses of Panax ginseng extract (G115®, Pharmaton SA). Using the Cognitive Drug Research (CDR) computerised test battery and a computerised working memory task to assess both cognitive performance and mood, a complex picture of findings emerged. Single doses of 200, 400, and 600 mg standardised ginseng were associated with improvements on tasks relating to episodic memory processes, with improvements being most pronounced following administration of 400mg when assessed 1, 2.5, 4 and 6 h post ingestion (Kennedy et al., 2001). Enhancement of tasks relating to episodic memory was observed at all but the 6h post session for 600mg, however, for 200mg this was restricted to 4h post ingestion (Kennedy et al., 2001). Interestingly, at the later test sessions (4h and 6h post ingestion) both the 200 and 600mg dose were associated with decreased performance on reaction time tasks, and 200 and 400mg of ginseng were associated with declines in subjective alertness 4 and 6h post ingestion (Kennedy et al., 2001). In addition, 200mg of ginseng led to performance decrements on a numeric working memory task when assessed 1h, 2.5h, and 6h post ingestion, whilst 4h post ingestion an improvement was observed on this task (Scholey and Kennedy, 2002). Moreover, potential fractionation in the cognitive enhancement effects of ginseng has been observed, as 400mg of ginseng led to significant improvements in tasks associated with episodic memory performance, but had no effect on tasks pertaining to attentional processes and even led to decrements in performance on a numeric working memory task 2.5 and 6h post ingestion (Kennedy et al., 2001). A further study replicated improvements in episodic memory performance following administration of 400mg of ginseng when assessed 4 and 6h post ingestion, but not 1 and 2.5 h following consumption (Kennedy et al., 2002). Moreover, 400mg of ginseng resulted in improved performance 4h post ingestion on 'speed of memory' on episodic recognition tasks and working memory tasks, i.e. the speed with which participants are able to identify whether or not an item was presented to them earlier (Kennedy et al., 2002). Interestingly, in that particular study attentional processes were also facilitated following administration of 400mg of ginseng when assessed 2.5h post ingestion (Kennedy et al., 2002).

Consequently, current data suggest that single dose administration of ginseng can improve certain aspects of cognitive performance and mood in healthy young volunteers and that the degree of facilitation is both dose and time

dependent. Moreover, it has also been found that task difficulty can moderate the degree of cognitive facilitation following ginseng administration (Scholey and Kennedy, 2002). Manipulation of the cognitive load on a working memory task (Serial Sevens and Serial Threes) revealed improved accuracy on the more demanding Serial Sevens task following administration of 400mg of ginseng, whereas 200mg of ginseng led to reduced speed of performance on the same task (Scholey and Kennedy, 2002).

Given the complex picture of previous findings, the aim of this study was to further investigate the effect of ginseng administration on cognitive performance and mood in healthy young volunteers. Because of the previously observed fractionation of enhancement on different aspects of cognitive performance after administration of 400mg of ginseng extract, this dose was chosen for further investigation regarding its effect on cognitive performance and mood. Moreover, it was decided to implement a 90-min post treatment delay. This decision was made on two grounds: i) a 90-min delay has not been implemented before, and ii) animal research suggests that serum and tissue levels of ginsenoside Rg1 peak 30 and 90 minutes following ginseng administration (Spinella, 2001).

## MATERIALS AND METHODS

### Participants

Thirty healthy young male and female participants took part in this study (15 males, 15 females). Ages ranged from 18-25 years (mean 20 years). Each participant completed a medical health-screening questionnaire. All participants self-reported that they were in good health and that they were not taking medication or herbal supplements. Of the 30 participants two were light smokers (<5 cigarettes per day and <2 per week, respectively). Participants agreed to refrain from smoking, and caffeine and alcohol consumption throughout each study day. No other dietary restrictions were implemented. The study was approved by the Ethics Committee of the Department of Psychology, Lancaster University, and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant prior to participation.

### Study design and treatment

Following a double-blind, placebo controlled, balanced, cross-over design, participants received on each study day two capsules of identical appearance, each containing either an inert placebo or 200mg of Panax ginseng extract (G115®, Pharmaton SA, Switzerland), in a counterbalanced order. A 7-day washout period between treatments was foreseen. Treatment order was randomly assigned and double blind. A person not involved in the trial carried out randomisation manually using a randomisation table. The trial material was dispensed in the laboratory prior to testing.

### Procedure

Each participant was required to attend the laboratory on four occasions. At their first visit participants were randomly

allocated to a treatment regime on arrival with the order of treatments across the two active days of the study being counterbalanced. Participants received no treatment (active or placebo) on the first two visits as these were intended to familiarize participants with the test battery and procedure, and data from these training sessions were not included in the statistical analysis. Completion of the training sessions was followed by two study days. Each visit was at the same time of day (between 10.00 and 18.00) with a 7-day washout period between study days. Each study day consisted of two identical testing sessions. The first was a pre-dose testing session for baseline evaluation of cognitive performance and mood, which was immediately followed by administration of the day's treatment. The second test session was carried out 90 minutes after ingestion of the day's treatment. Both test sessions (pre and post-dose testing) comprised completion of the CDR test battery (cognitive performance) followed by the Bond-Lader visual analogue scales (mood measures).

### *Cognitive tests*

A tailored version of the Cognitive Drug Research (CDR) computerised assessment system was used to evaluate cognitive performance. A selection of computer-controlled tasks from the system was administered with parallel forms of the tests being presented at each test session. Task presentation was via VGA colour monitors, and, with the exception of written word recall tests, all responses were recorded via two-button (YES/NO) response boxes. The entire selection of tasks presented took approximately 20 minutes and in each session tests were administered in the following order:

- (a) Word Presentation: A list of 15 words matched for frequency, concreteness and imagery was presented on the monitor at the rate of 1 every 2 seconds for participants to remember.
- (b) Immediate Word Recall: Participants were given 60 seconds to recall as many of the words as possible. Recall was scored as number correct, number of intrusions and errors and the resulting score was converted into a percentage.
- (c) Picture Presentation: A series of 20 pictures was presented on the monitor at a rate of one every 3 seconds, with stimulus duration of 1 second, for participants to remember.
- (d) Simple Reaction Time: Participants were instructed to press the "YES" button as quickly as possible every time the word "YES" was presented on the monitor. Fifty stimuli were presented with varying inter-stimulus intervals of between 1 and 3.5 seconds. The outcome measure was the average reaction time in milliseconds.
- (e) Digit Vigilance: A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was presented in the centre of the screen at a rate of 80 per minute. Participants were instructed to press the "YES" button as quickly as possible every time the digit in the series matched the target. The task lasted one minute. Task outcome measures were the percentage of targets correctly detected, the average reaction time of these detections (in milliseconds), and

the number of false alarms.

(f) Choice Reaction Time: Either the word "NO" or "YES" was presented on the monitor and participants were required to press the corresponding button as quickly as possible. There were 50 trials during which the stimulus word was chosen randomly with equal probability, with a randomly varying inter-stimulus interval of between 1 and 3.5s. Task outcome measures were the percentage of correct responses and the average reaction time of these responses in milliseconds.

(g) Spatial working memory: A picture of a house was presented on the screen with four of its nine windows lit. Participants were instructed to memorise the position of the illuminated windows. In 36 successive presentation of the house, one of the windows was illuminated and participants decided whether or not this matched one of the lighted windows in the original presentation and pressed the "YES" or "NO" button as appropriate as quickly as possible. The outcome measures were mean reaction times (milliseconds), and accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages.

(h) Numeric working memory: 5 digits were presented sequentially for participants to retain in memory. This was followed by a series of 30 probe digits for each of which participants decided whether or not it had been in the original series and had to press the "YES" or "NO" response button as appropriate as quickly as possible. This was repeated two further times with different stimuli and probe digits. Stimuli were on the screen for 1150 milliseconds and there was a 500-millisecond interval between each presentation. Accuracy of responses to both novel (distractor) and original stimuli were recorded as percentages, and mean reaction times were measured in milliseconds.

(i) Delayed word recall: Participants were given 60 seconds to write down as many of the words as possible. The task was scored as number correct, intrusions and errors and the resulting score was converted into percentage.

(j) Delayed word recognition: The original words presented plus 15 distractor items were presented one at a time in a randomised order. For each word participants indicated whether or not they recognised it as being included in the original list by pressing the "YES" or "NO" button as appropriate as quickly as possible. Accuracy of responses for both novel (distractor) and original stimuli were recorded as percentages, and mean reaction times were measured in milliseconds.

(k) Delayed picture recognition: The original pictures plus 20-distractor pictures were presented sequentially in random order. For each picture participants indicated whether or not they recognised it as being from the original series by pressing the "YES" or "NO" button as appropriate as quickly as possible. Accuracy of responses for both novel (distractor) and original stimuli were recorded as percentages, and mean reaction times were measured in milliseconds.

### *Subjective Mood Measures*

The Bond and Lader Visual Analogue Scales (VAS): 16 visual analogue scales (Bond and Lader, 1974) were presented

on the monitor. A joystick was used to measure subjective responses. Participants were instructed to “use the joystick to position the arrow at the point on the scale that represents how you feel at the present time”. The 16 scales were combined as recommended by Bond and Lader (1974) to form three mood factors: ‘alertness’, ‘calmness’ and ‘contentment’.

### *Statistical Analyses*

Scores from individual measures were combined to form four primary outcome measures (‘quality of memory’, ‘speed of memory’, ‘quality of attention’, and ‘speed of attention’) and two secondary cognitive outcome measures (‘working memory sub-factor’, and ‘secondary memory sub-factor’) derived from factor analysis of the Cognitive Drug Research computerised test battery (Wesnes et al., 1999; 2000), and previously used by Wesnes et al. (1997; 1999; 2000), and Kennedy et al. (2000; 2001; 2002).

### *Primary Outcome Measures*

(a) Quality of Memory Factor: Derived by calculating the combined percentage accuracy scores (adjusted for proportion of novel and new stimuli where appropriate) of all working memory tests and secondary memory tests: spatial working memory, numeric working memory, word recognition, picture recognition, immediate word recall, delayed word recall (with adjustment to the total percentage correct for errors and intrusions on the latter two tasks). 100 percent accuracy across the six tasks would generate a maximum score of 600.

(b) Speed of Memory Factor: Derived by combining reaction times of the numeric working memory task, spatial memory task, delayed word recognition and delayed picture recognition task (units are summed milliseconds for the four tasks).

(c) Speed of Attention Factor (also termed ‘Power of Attention’, Wesnes et al., 2000): Derived by combining reaction times of three attentional tasks: simple reaction time, choice reaction time, and digit vigilance (units are summed milliseconds for the three tasks).

(d) Accuracy of Attention: Derived by calculating the combined percentage accuracy across choice reaction time and digit vigilance tasks (with adjustment for false alarms on the latter test). 100 percent accuracy across the two tasks would result in a maximum score of 100.

### *Secondary Outcome Measures*

(a) Working Memory Sub-factor: Derived by combining percentage accuracy scores from the two working memory tests: spatial working memory and numeric working memory. 100 percent accuracy across the two tasks would result in a maximum score of 200.

(b) Secondary Memory Sub-factor: Derived by calculating the combined percentage accuracy scores (adjusted for proportion of novel and new stimuli where appropriate) from all secondary memory tests: word recognition, picture recognition, immediate word recall, delayed word recall (with adjustment to the total percentage correct for errors and intrusions on the latter two tasks). 100 percent accuracy across the four tasks

would result in a maximum score of 400.

(c) CDR Factor Scores were analysed as “change from baseline” scores and comparisons between ginseng and placebo were made using repeated measures t-test. Individual outcome measures from each CDR test and the three mood outcomes derived from the Bond-Lader scales were also analysed as “change from baseline” scores using repeated measures t-test.

## **RESULTS**

### *1. Primary Cognitive Outcome Measures*

Ginseng administration had a significant effect on ‘speed of attention’ [ $t(29)=2.37$ ;  $p=0.03$ ]. However, there were no significant effects on ‘continuity of attention’ [ $t(29)=0.47$ ;  $p=0.64$ ], ‘quality of memory’ [ $t(29)=0.17$ ;  $p=0.86$ ], and ‘speed of memory’ [ $t(29)=0.50$ ;  $p=0.62$ ] (see table 1 for absolute scores and change from baseline scores on the four combined factor scores).

### *2. Secondary Cognitive Outcome Measures*

Repeated measures t-test demonstrated that ginseng had no significant effect on both the working memory sub-factor [ $t(29)=1.32$ ;  $p=0.20$ ] and on the secondary memory sub-factor [ $t(29)=0.18$ ;  $p=0.86$ ] (see table 2 for absolute scores and change from baseline scores on the two combined factor scores).

### *3. Individual Task Analysis*

Whilst there were no significant improvements on any of the tasks associated with the ‘quality of memory’, ‘speed of memory’ and ‘accuracy of attention’ factors, one single task measure loading on the ‘speed of attention’ factor revealed significant improvements following ginseng administration in comparison with placebo. Ninety minutes after ginseng ingestion, participants had significantly faster reaction times on the Choice Reaction Time task compared to baseline performance [ $t(29)=2.92$ ;  $p=0.006$ ] (see table 3 for absolute scores and change from baseline scores on individual tasks).

### *4. Subjective Mood Measures*

Ginseng administration had no effect on any of the factors derived from the Bond-Lader visual analogue scales (‘alertness’ factor:  $t(29)=0.40$ ;  $p=0.70$ ; ‘contentedness’ factor:  $t(29)=0.23$ ;  $p=0.81$ ; ‘calmness’ factor:  $t(29)=0.48$ ;  $p=0.64$ ) (see table 4 for absolute scores and change from baseline scores on the factor scores from the Bond-Lader visual analogue scales).

## **DISCUSSION**

In this study 400mg of ginseng improved speed of attention, indicating a beneficial effect on participants’ ability to allocate attentional processes to a particular task. No effect was observed on any other aspect of cognitive performance, including tasks pertaining to episodic memory processes. In addition, participants’ self-reported mood measures did not differ significantly across treatments. Yet, it is important to

**Table 1: Effect of Ginseng on Primary Cognitive Outcome Measures.** Table presents means (with standard errors in italics) of absolute scores and change from baseline scores for ginseng and placebo. For factors "Quality of Memory" and "Accuracy of Attention" positive change scores indicate improved performance following drug administration. For "Speed of Memory" and "Speed of Attention" negative change scores indicate improved performance following drug administration. \* $p < 0.05$  compared to placebo.

Primary Outcome Factor		Pre-dose		Post-dose		
Quality of Memory	Ginseng	Absolute Score	220.85	<i>10.54</i>	204.94	<i>9.69</i>
		Change from baseline			-15.91	<i>8.15</i>
	Placebo	Absolute Score	223.71	<i>10.86</i>	210.08	<i>8.62</i>
		Change from baseline			-13.63	<i>11.29</i>
Speed of Memory	Ginseng	Absolute Score	2529.87	<i>64.25</i>	2464.57	<i>58.87</i>
		Change from baseline			-65.29	<i>35.97</i>
	Placebo	Absolute Score	2582.59	<i>82.24</i>	2489.14	<i>61.34</i>
		Change from baseline			-93.46	<i>45.75</i>
Speed of Attention	Ginseng	Absolute Score	1042.36	<i>21.75</i>	1028.46	<i>21.36</i>
		Change from baseline			-13.90*	<i>6.44</i>
	Placebo	Absolute Score	1015.01	<i>16.17</i>	1026.72	<i>19.06</i>
		Change from baseline			11.71	<i>7.69</i>
Continuity of Attention	Ginseng	Absolute Score	89.92	<i>0.69</i>	89.73	<i>0.66</i>
		Change from baseline			-0.19	<i>0.52</i>
	Placebo	Absolute Score	90.33	<i>0.59</i>	90.47	<i>0.57</i>
		Change from baseline			0.13	<i>0.54</i>

**Table 2: Effect of Ginseng on Secondary Cognitive Outcome Measures.** Table presents means (with standard errors in italics) of absolute scores and change from baseline scores for ginseng and placebo. Positive change scores indicate improved performance following drug administration.

Secondary Outcome Factor		Pre-dose		Post-dose		
Working Memory	Ginseng	Absolute Score	1.79	<i>0.03</i>	1.83	<i>0.02</i>
		Change from baseline			0.03	<i>0.03</i>
	Placebo	Absolute Score	1.82	<i>0.03</i>	1.80	<i>0.02</i>
		Change from baseline			-0.02	<i>0.02</i>
Secondary Memory	Ginseng	Absolute Score	219.06	<i>10.53</i>	203.11	<i>9.69</i>
		Change from baseline			-15.94	<i>8.15</i>
	Placebo	Absolute Score	221.89	<i>10.86</i>	208.28	<i>8.62</i>
		Change from baseline			-13.61	<i>11.30</i>

note that the only task loading on the speed of attention factor where an improvement after ginseng administration compared to baseline performance has been demonstrated was the choice reaction time task. Closer inspection of choice reaction times demonstrates poorer performance at baseline in the ginseng condition for this task (see table 3). Consequently, in this experiment it might be more accurate to describe the effect of ginseng administration on speed of accuracy (and the choice reaction time task) as stabilizing performance to "normal" levels rather than absolute improvement.

However, it is interesting to note that previous research demonstrated no facilitation on the ability to allocate attentional processes to a particular task following administration of 400mg of ginseng, but significant improvements on accuracy of attention, i.e. the ability to sustain attention over a period

of time without making any mistakes (Kennedy et al., 2002). In addition, earlier studies demonstrated improvement on episodic memory tasks ('quality of memory' factor) following administration of 400mg of Ginseng when participants were tested 1h, 2.5h, 4h and 6h post ingestion (Kennedy et al., 2001). It is important to note that the different performance profile observed in this study compared to earlier investigations cannot be due to differences in sensitivity of tasks employed, as the same cognitive test battery (CDR) was used. Consequently, it might be the case that assessing individuals' cognitive performance 90 minutes post ingestion missed the therapeutic window of opportunity for observing significant improvements on memory tasks.

Previous experiments have also demonstrated that the same dose of ginseng can have different effects on cognition and mood at different times post ingestion. For example, administration of 200mg of ginseng improved accuracy of attention 6h post ingestion, but had no beneficial effect on that aspect of cognition 1, 2.5, and 4h post ingestion (Kennedy et al., 2001). Facilitation of episodic memory performance following 400mg of ginseng was observed 4 and 6h post ingestion, but not 1 and 2.5 h following consumption (Kennedy et al., 2002). 600mg of ginseng facilitated performance on tasks pertaining to episodic memory when tested 1, 2.5, and 4h post administration, but not 6h post ingestion and 200mg of ginseng only facilitated memory performance 4h post ingestion, but not at any other time point (Kennedy et al., 2001). Furthermore, following administration of 400mg of ginseng improved accuracy on all memory tasks ('quality of memory factor') was only observed 4h post ingestion, but not 1, 2.5, and 6h after ginseng was taken and improved accuracy of attentional processes was only observed 2.5h after administration of 400mg of ginseng (Kennedy et al., 2002). Moreover, 200mg of ginseng led to performance decrements on the Serial Sevens Task when assessed 1h, 2.5h, and 6h post ingestion, whilst 4h post ingestion an improvement was observed on this task (Scholey and Kennedy, 2002). Taken together the data suggests that ginseng may offer alternative windows of therapeutic opportunity on different aspects of cognitive performance and mood at different time points. This may be due to different chemical constituents of ginseng displaying different pharmacokinetic properties and psychopharmacological actions.

Ginseng contains multiple active chemical constituents including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids (Attele et al., 1999; Spinella, 2001). However, the majority of its pharmacological actions are being attributed to the ginsenosides (Huang, 1999). To date more than twenty such ginsenosides have been isolated (Gillis, 1997) and some of these appear to have important mechanisms of action in the central nervous system, including interactions with neurotransmitter systems involved in the neural mediation of memory and cognition (see Kennedy and Scholey, 2003; Attele et al., 1999 for recent reviews).

Moreover, ginseng has peripheral effects, which may indirectly lead to facilitation of cognitive performance. For example, in large doses ginseng has a vasodilating effect in

**Table 3: Effect of Ginseng on individual task outcome measures from the CDR battery.** Results are shown as mean baseline and change from baseline scores, with standard errors in italics. The units are milliseconds for reaction times and percentages for accuracies. †Adjustment to the total % correct for errors and intrusions. ‡Adjusted for proportion of novel and new stimuli where appropriate \* $p < 0.01$  compared to placebo.

Measure		Pre-dose Baseline Score		Post-dose Change from Baseline Score	
Immediate Word Recall Accuracy adjusted † (%)	Ginseng	52.78	<i>3.14</i>	-5.11	<i>3.26</i>
	Placebo	48.78	<i>3.30</i>	0.22	<i>3.19</i>
Delayed Word Recall Accuracy adjusted † (%)	Ginseng	30.89	<i>4.53</i>	-1.11	<i>3.60</i>
	Placebo	33.00	<i>4.64</i>	8.33	<i>4.65</i>
Simple Reaction Time (ms)	Ginseng	249.56	<i>5.75</i>	-1.75	<i>3.07</i>
	Placebo	242.00	<i>5.62</i>	5.59	<i>3.30</i>
Digit Vigilance Accuracy (%)	Ginseng	96.57	<i>4.46</i>	-0.57	<i>4.74</i>
	Placebo	96.89	<i>3.67</i>	0.37	<i>3.74</i>
Digit Vigilance False Alarms (number)	Ginseng	0.97	<i>0.24</i>	-0.30	<i>0.25</i>
	Placebo	0.50	<i>0.13</i>	0.00	<i>0.19</i>
Digit Vigilance Reaction Time (ms)	Ginseng	397.15	<i>7.94</i>	1.83	<i>2.81</i>
	Placebo	393.32	<i>6.74</i>	-1.99	<i>3.34</i>
Choice Reaction Time Accuracy (%)	Ginseng	94.87	<i>0.75</i>	-0.47	<i>0.63</i>
	Placebo	94.47	<i>0.69</i>	-0.07	<i>0.67</i>
Choice Reaction Time (ms)	Ginseng	395.65	<i>10.13</i>	-13.98*	<i>4.40</i>
	Placebo	379.69	<i>7.01</i>	8.11	<i>4.85</i>
Spatial Memory Accuracy (%)	Ginseng	95.15	<i>0.92</i>	0.68	<i>1.01</i>
	Placebo	93.96	<i>1.29</i>	0.42	<i>0.99</i>
Spatial Working Memory Sensitivity Index	Ginseng	0.915	<i>0.016</i>	0.0191	<i>0.017</i>
	Placebo	0.913	<i>0.020</i>	0.0028	<i>0.018</i>
Spatial Memory Reaction Time (ms)	Ginseng	565.18	<i>27.33</i>	-57.86	<i>14.47</i>
	Placebo	572.54	<i>27.50</i>	-69.36	<i>21.16</i>
Numeric Working Memory Accuracy (%)	Ginseng	91.49	<i>1.47</i>	1.10	<i>1.17</i>
	Placebo	93.04	<i>1.18</i>	-1.11	<i>1.09</i>
Numeric Working Memory Sensitivity Index	Ginseng	0.8801	<i>0.023</i>	0.0124	<i>0.019</i>
	Placebo	0.9100	<i>0.012</i>	-0.0210	<i>0.015</i>
Numeric Working Memory Reaction Time (ms)	Ginseng	551.01	<i>20.22</i>	-19.77	<i>10.20</i>
	Placebo	569.12	<i>26.75</i>	-26.00	<i>14.12</i>
Word Recognition Accuracy adjusted ‡ (%)	Ginseng	64.89	<i>3.85</i>	-3.56	<i>3.68</i>
	Placebo	66.44	<i>3.48</i>	-3.33	<i>3.86</i>
Word Recognition Reaction Time (ms)	Ginseng	667.69	<i>15.46</i>	7.75	<i>16.26</i>
	Placebo	689.78	<i>25.17</i>	14.23	<i>17.64</i>
Picture Recognition Accuracy adjusted ‡ (%)	Ginseng	70.50	<i>3.86</i>	-6.17	<i>3.02</i>
	Placebo	73.67	<i>3.49</i>	-2.17	<i>3.85</i>
Picture Recognition Reaction Time (ms)	Ginseng	745.99	<i>16.59</i>	4.59	<i>17.85</i>
	Placebo	751.16	<i>22.15</i>	-12.32	<i>21.31</i>

**Table 4: Effects of Ginseng on self-rated mood as measured by Bond-Lader Visual Analogue Scales.** Table presents means (with standard errors in italics) of absolute scores and change from baseline scores for ginseng and placebo. Positive change scores indicate increased feeling of alertness, contentedness, or calmness following drug administration.

Mood Factor		Pre-dose				Post-dose					
		Absolute Score	<i>50.44</i>	<i>2.26</i>	<i>51.96</i>	<i>2.29</i>	Absolute Score	<i>50.06</i>	<i>2.74</i>	<i>50.38</i>	<i>2.34</i>
Alertness	Ginseng	Absolute Score	<i>50.44</i>	<i>2.26</i>	<i>51.96</i>	<i>2.29</i>	Absolute Score	<i>50.06</i>	<i>2.74</i>	<i>50.38</i>	<i>2.34</i>
		Change from baseline					Change from baseline			1.52	2.54
	Placebo	Absolute Score	<i>50.06</i>	<i>2.74</i>	<i>50.38</i>	<i>2.34</i>	Absolute Score	<i>50.06</i>	<i>2.74</i>	<i>50.38</i>	<i>2.34</i>
		Change from baseline					Change from baseline			0.32	2.39
Contentedness	Ginseng	Absolute Score	<i>59.68</i>	<i>2.43</i>	<i>59.55</i>	<i>2.54</i>	Absolute Score	<i>54.67</i>	<i>2.34</i>	<i>55.17</i>	<i>2.54</i>
		Change from baseline					Change from baseline			-0.13	2.03
	Placebo	Absolute Score	<i>54.67</i>	<i>2.34</i>	<i>55.17</i>	<i>2.54</i>	Absolute Score	<i>54.67</i>	<i>2.34</i>	<i>55.17</i>	<i>2.54</i>
		Change from baseline					Change from baseline			0.50	1.78
Calmness	Ginseng	Absolute Score	<i>56.77</i>	<i>3.10</i>	<i>55.82</i>	<i>2.67</i>	Absolute Score	<i>59.22</i>	<i>2.43</i>	<i>60.15</i>	<i>2.10</i>
		Change from baseline					Change from baseline			-0.95	3.51
	Placebo	Absolute Score	<i>59.22</i>	<i>2.43</i>	<i>60.15</i>	<i>2.10</i>	Absolute Score	<i>59.22</i>	<i>2.43</i>	<i>60.15</i>	<i>2.10</i>
		Change from baseline					Change from baseline			0.93	2.56

coronary and cerebral vessel, resulting in increased coronary and cerebral and blood flow (Huang, 1999). This might in turn lead to increased fuel-supply to the brain, including increased central availability of oxygen and glucose. Both glucose and oxygen administration have previously been shown to facilitate certain aspects of cognitive performance (see for example Kennedy and Scholey, 2000; Scholey et al., 2001; Sünram-Lea et al., 2001; 2002a; 2002b, for glucose effects on cognition and Moss and Scholey, 1996; Moss et al., 1998; Scholey et al., 1998 for effect of oxygen on cognition). Consequently, one might speculate that one of the mechanisms by which ginseng improves cognitive performance could be by increasing central glucose and oxygen availability. This notion is supported by the fact that direct effects of ginseng on glucose metabolism have previously been observed. For example, ginseng has been shown to increase intracellular glucose transport (Hasegawa et al., 1994; Ohnishi et al., 1996), and to modulate insulin secretion (Kimura et al., 1981). It is important to note that facilitation of cognitive performance following either chronic or acute administration of ginseng is likely to be of a multifactorial nature; that is, it may well be the case that ginseng administration exerts its cognitive facilitation effects via different routes. Yet, these different routes might “operate” at different time points, which may explain the time dependency of the effects observed following administration of the same dose of ginseng. Moreover, taken the multitude of mechanisms of action ginseng exerts both peripherally and centrally it is not surprising that a complex picture of cognitive effects emerges.

Although the exact nature of the central and/or peripheral mechanisms leading to cognitive facilitation remain speculative at the moment, a recent study elucidated that single-dose administration results in “visible” changes in cerebral bioelectrical activity as measured by electroencephalograph (EEG; Kennedy et al., 2003). Administration of 200mg of

Panax ginseng resulted in significant decreases in theta, beta and alpha activity in frontal areas 4 hours post ingestion. Moreover, ginseng administration resulted in decreased latency for the P300 wave demonstrating that it also is able to modulate evoked potentials (Kennedy et al., 2003).

To date little is known about the pharmacokinetic profile and bioavailability of the main ginsenosides. Ginsenosides are absorbed from the upper gastrointestinal tract, however absorption time differs depending on the type of ginsenosides, dose, preparation and stomach acidity (Spinella, 2001). Odani et al. (1983a;b) found that 2-30% of Rg1 is absorbed within 30-60 minutes, whereas little of Rb1 is absorbed. However, a more recent study investigating the pharmacokinetics and bioavailability of ginsenoside Rb1 and Rg1 (extracted from *Panax notoginseng*) in rodents demonstrated that orally administered Rg1 is faster absorbed through the gastrointestinal tract than Rb1 (Xu et al., 2003). Rg1 reached peak concentration of 7.29 µg/ml 1 hour after oral administration, whereas Rb1 was relatively slowly absorbed through the digestive tract reaching peak concentration in 1.5h of 47.13 µg/ml (Xu et al., 2003). Yet, Rb1 peak concentration was maintained for 72 h in blood, whilst Rg1 was not quantifiable beyond 24h post dose (Xu et al., 2003). Consequently, at the moment there is conflicting evidence regarding the exact time course of absorption, distribution, and biotransformation of different ginsenosides. However, the fact that differences in the pharmacokinetic profile and bioavailability of different ginsenosides have been observed (Odani et al., 1983a;b; Xu et al., 2003) strengthens the notion that ginseng may offer alternative windows of therapeutic opportunity on different aspects of cognitive performance at different time points. This may be due to different chemical constituents of ginseng displaying different pharmacokinetic properties and psychopharmacological actions. Further research is clearly needed to better our understanding of the pharmacokinetics of the different chemical constituents of ginseng.

In summary, our findings suggest that ginseng may offer alternative windows of therapeutic opportunity on different aspects of cognitive performance and mood at different time points. This may be due to different chemical constituents of ginseng displaying different pharmacokinetic properties and psychopharmacological actions. More carefully controlled studies, using standardized ginseng products, are needed to further elucidate the effects of acute (and chronic) ginseng administration on cognitive performance. Future research should also aim to identify the optimal dose and preparation needed for demonstration of cognitive enhancement in different populations. For example, it might be the case that detecting an effect of acute ginseng administration is inherently more difficult due to individual differences in speed of metabolism; i.e. ginseng may not have been sufficiently metabolised by some participants at that time in the experiment in order to demonstrate cognitive facilitation, which may also explain some of the conflicting findings. Moreover, there are a number of methodological issues, which may have obscured a more robust pattern of results in this experiment. These include

the failure to control for a number of potentially intervening factors such as circadian rhythms, diet, and exercise. Future studies that carefully control for such factors may permit a more comprehensive evaluation of ginseng-related effects on cognitive performance.

**CONFLICT OF INTEREST DISCLOSURE:** O. Petrini is employed by Pharmaton SA, the producer of the standardised ginseng extract G115 used in the trial.

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