The Effects of Ginseng on Memory and Mood

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Taken alone, the wealth of both *in vitro* and *in vivo* research, demonstrating a plethora of both microscopic and macroscopic physiological consequences of ginseng administration, would seem to suggest that there should be behavioural consequences to the ingestion of ginseng. To a certain extent this is borne out in the animal literature, with a number of behavioural changes demonstrated in animals following ginseng administration. These include not only adaptogenic physiological effects, but also attenuation of learning deficits due both to age (e.g. Nitta *et al.,* 1995) and experimentally induced brain damage (e.g. Wen *et al.,* 1996; Zhao and McDaniel, 1998); and dose-dependent improvements in learning and memory in both young and old rodents (e.g. Petkov and Mosharrof, 1987; Petkov *et al.,* 1993).

Regarding humans the evidence is less clear cut, with an equivocal literature as to ergogenic benefits (see: Bahrke and Morgan 1994; 2000), but some evidence of improvements in subjective ratings of well being or quality of life following chronic administration of ginseng, both alone and in combination with vitamins (e.g. Neri *et al.,* 1995; Wiklund *et al.,* 1994; Marasco *et al.,* 1996; Sotaniemi *et al.,* 1995; Ussher *et al.,* 1995). Several studies have included some form of cognitive assessment. These have demonstrated enhanced performance, in comparison to placebo, on various cognitive measures. Such improvements include faster completion of a timed diagram drawing test in non-insulin dependent diabetics (Sotaniemei *et al.,* 1995), improved performance on a tapping test for fatigued night nurses (Hallstrom *et al.,* 1982) and better performance on the Randt Memory Test in a cohort suffering age-related memory impairment (Neri *et al.,* 1995).

Two investigations have also focussed directly on ginseng's effects on cognition. Both employed a double blind, placebo controlled design. In the first D'Angelo *et al* (1986) examined the effects of 12 weeks daily administration of 200 mg of ginseng to healthy young volunteers.

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Tests included those assessing motor performance, speed of performance on attentional tasks, mental arithmetic and logical reasoning. The result showed that performance was significantly improved for the *Ginseng* group, in comparison to placebo, only on the mental arithmetic test. A later study by Sorensen and Sonne (1996), examined the effects of 400 mg of ginseng daily for 9 weeks in a cohort of 40 to 70 year olds, utilising a slightly more comprehensive battery. There were statistically significant performance improvements for the ginseng group, in comparison to placebo, only on the fastest trials of an auditory simple reaction time test, and on a computerised version of the Wisconsin Card Sort Test.

In summary, the evidence of beneficial behavioural and mood effects of *Ginseng* in humans tends to be somewhat equivocal (Bahrke and Morgan, 2000; Vogler *et al.,* 1999). However, to a great extent this may be attributed to methodological considerations, in particular both the rigour of experimental designs and methods utilised, and the variations in doses, regimens, types and fractions of ginseng (see Bahrke and Morgan 1994; 2000).

It is also interesting to note that, by convention, the investigation of the effects of *Ginseng* in humans has been almost exclusively restricted to chronic regimens, with testing typically occurring only after a minimum of several weeks of administration.

In our own laboratory we are currently investigating the cognitive and physiological effects of a range of herbal products. Most germane here are three experiments that have assessed the cognitive and mood effects of single doses of *Panax ginseng*, and a *Panax ginseng/Ginkgo biloba* combination.

The three experiments employed an identical randomised, double-blind, placebo controlled, balanced-crossover design.

In each experiment 20 young (average age approximately 21 years) participants attended the laboratory on five separate occasions, each separated by 7 days to allow an adequate 'wash-out' period. The first day of the study was identical to the other four, with the exception that participants did not receive a treatment. This was to allow familiarisation with the experimental protocol and attenuate any possible practice effects. On the other four days of the study participants received either a placebo, or one of three separate single doses of the days treatment, with the order counterbalanced across the four days by allocation to a Latin square.

Each day of the experiment had the same running order. Participants attended at the laboratory at either 8.30am or 9am and underwent a baseline run through the cognitive battery. This was immediately followed on days 2 to 5 by the days treatment, and thereafter by further completion

of the cognitive battery at 1 hour, 2.5 hours, 4 hours and 6 hours post-dose.

The cognitive testing was undertaken using a tailored version of the Cognitive Drug Research (CDR) computerised assessment battery. The CDR battery has been used in over 500 clinical trials throughout the world, and has been utilised in several hundred published academic studies. It has also previously been shown to be sensitive to the cognitive effects of herbal remedies (Wesnes *et al.,* 1997; 2000; Kennedy *et al.,* 2000; 2002a).

The particular advantages of this testing system include: 60 parallel forms of the test stimuli, allowing the multiple retesting necessary for this experimental design; a proven lack of practice effects following the first three completions of the battery; speed of use, with the entire battery (in the form used here) taking approximately 18 minutes; and simplicity of use, with all responses (except word recall) being recorded on a simple yes/no response box.

The tailored version of the computerised battery used here comprised the following tasks: immediate word recall; picture presentation; simple reaction time; digit vigilance task; choice reaction time; spatial working memory; numeric working memory (Sternberg); delayed word recall; delayed word recognition; and delayed picture recognition.

A further advantage is that the above measures can be collapsed into five global outcome factors that can be derived from the battery's outcome scores by factor analysis (Wesnes *et al,* 2000), These formed the primary outcome measures in these studies. The five factors are: 'Secondary Memory' (% accuracy of immediate and delayed word recall, delayed word recognition, delayed picture recognition); 'Working Memory' (% accuracy of the spatial and numeric working memory tasks); 'Speed of memory' (summed reaction times on all four timed memory tasks); 'Speed of Attention' (summed reaction times on three attention tasks); and 'Accuracy of Attention' (% accuracy on the three attention tasks).

Following each run through the CDR battery mood was also assessed using Bond-Lader (Bond and Lader, 1974) visual analogue scales.

In the first experiment (Kennedy et al, 2001a) we assessed the acute effects of a placebo and doses of 200 mg, 400 mg and 600 mg of ginseng extract G115 (Pharmaton SA, Switzerland).

The most striking cognitive effect was an improvement, in comparison to placebo, in performance on the Secondary Memory factor for all three doses of ginseng. This effect was most pronounced for the middle dose (400 mg) with improvements at all four post-dose testing sessions. The 'Working Memory' factor was not affected.

In contrast to this the lowest (200 mg) and highest (600 mg) doses, both of which evinced less

mnemonic improvement, resulted in slowing of performance on the 'Speed of Attention' factor at the later testing sessions (4 hours and 6 hours post-dose). Self ratings of 'Alertness', as measured by the Bond-Lader mood scales, were also reduced towards the end of testing for the two lowest doses (200 mg and 400 mg), with this effect achieving significance at the last testing session.

What was particularly interesting here was that in a previous experiment (Kennedy et al, 2000) we demonstrated that single doses of *Ginkgo biloba* (GK501) led to a milder improvement on the 'Secondary Memory' factor, but a clear, linear, dose-dependent improvement on the 'Speed of Attention factor'. This naturally raised the question as to whether single doses of a combination of *Panax ginseng* and *Ginkgo biloba*, chronic regimens of which have previously been shown to improve memory performance in neurasthenic and middle aged cohorts (Wesnes et al, 1997, 2000), would lead to improved memory in a young cohort without decrements on the speed of performing attention tasks seen following ginseng alone.

In the second experiment (Kennedy et al 2001b) we therefore investigated three single doses of a 100:60 combination of ginseng (G115) and ginkgo (GK501) using the same methodology as the previous studies.

What was most interesting about the results of this experiment was that the cognitive effects of the combination were strikingly similar to those following *Panax ginseng* alone, and were dissimilar to those following *Ginkgo biloba* (Kennedy et al, 2000). As in the previous ginseng experiment the most marked finding was an enhancement of secondary memory performance, in this case following the highest (960 mg) dose. As with the previous experiment decrements in the speed of performing the attention tasks were also evident, in this case again restricted to a dose that saw no mnemonic improvements (320 mg). There were no decrements evident on the mood scales.

Having demonstrated secondary memory improvements following single doses of *Panax ginseng* alone and in combination with *Ginkgo biloba*, it seemed timely at this point to replicate these novel findings. The third experiment, again utilising the same methodology, was therefore a direct comparison of the most cognitively advantageous doses utilised in the previous studies (Kennedy *et al,*. 2000; 2001a; 2001b) of *Ginkgo biloba* (360 mg), *Panax ginseng* (400 mg), and the combination of the two (960 mg).

Once again the most striking result was an improvement, in comparison to placebo, in secondary memory performance following all three treatments. Whilst this effect was evident following

ginkgo, it was more pronounced for both ginseng and the combination, although they differed in that the effect was more pronounced at the first two testing sessions for the combination, and at the latter two testing sessions for ginseng alone. As would be expected from the previous studies for these specific doses, there were no decrements on the speed of attention task performance. Interestingly the *Panax ginseng* condition also outperformed the other conditions at all time points on the 'Speed of Memory' factor and the 'Quality of Attention' factors, with these effects reaching significance at one time point in each case.

In summary, the results of these three experiments suggest for the first time that single doses of both *Panax ginseng* and a *Panax ginseng/Ginkgo biloba* combination can consistently improve secondary memory performance in cohorts of young adults.

As yet the mechanisms underlying both these improvements and the decrements seen on the speed of attention task performance (for the less mnemonically active doses) remain to be elucidated. However, the results presented here, in concert with other studies from our laboratory that have examined the physiological consequences of single doses of *Panax ginseng* (to be presented by Dr Scholey), suggest that ginseng, in the correct dose, has great potential as a cognition enhancer.

Whilst all of the experimentation from our laboratory to date has concentrated on single doses of ginseng, we are currently seeking funding to extend this research into an examination of the effects of chronic regimens of *Panax ginseng* in both healthy and cognitively challenged populations.

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