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Modulation of cognitive performance following single doses of 120 mg Ginkgo biloba extract administered to healthy young volunteers

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Previous research from our laboratory demonstrated that administration of single doses (120, 240, 360 mg) of standardised Ginkgo biloba extract (GBE) had linear, dose-dependent, positive effects on the speed of performing attention tasks in comparison to placebo. However, whilst the lowest dose, which is typical of a recommended daily dose, had no effect on the speed of attention task performance it did engender mild improvements in secondary memory performance. The current study presents a reanalysis of data from three methodologically identical studies that each included a treatment of 120 mg GBE and matched placebo.

All three studies were of a multiple dose, placebo-controlled, double-blind, balanced-crossover design, employing four or five treatment arms in total. Across the studies 78 healthy young participants received 120 mg GBE and placebo in randomly counterbalanced order, separated by a wash-out period of at least 7 days. On each study day participants' performance on the Cognitive Drug Research (CDR) computerised cognitive assessment battery was measured immediately prior to dosing and at 1, 2.5, 4 and 6 hr following treatment, with scores collapsed into the six measures (speed of attention, accuracy of attention, secondary memory, working memory, speed of memory, quality of memory) which have previously been derived by factor analysis of the data from CDR subtests.

The results showed that 120 mg of Ginkgo engendered a significant improvement on the 'quality of memory' factor that was most evident at 1 and 4 hr post-dose, but had a negative effect on performance on the 'speed of attention' factor that was most evident at 1 and 6 hr post-dose.

The current study confirmed the previous observation of modestly improved memory performance following 120 mg of GBE, but suggests that acute administration of this typical daily dose may have a detrimental effect on the speed of attention task performance which is opposite to that seen previously following higher doses.

KEY WORDS — Ginko biloba; memory; attention; acute; young; healthy

INTRODUCTION

Extracts derived from Ginkgo biloba leaves are almost unique within the herbal medicinal products field in that they are generally well-defined and consistent between major manufacturers, in terms of the nature and proportions of their active principles. They are sold both 'over the counter' and/or on prescription across Western markets. The active constituents, a range of species specific flavonoids and the terpenoids—bilobalide and ginkgolides A, B, C and J (Kleijnen and Knipschild, 1992)—are believed to be responsible for a number of physiological effects potentially relevant to the enhancement of cognition. These include a number of effects that may underlie any acute behavioural effects in humans. For instance: scavenging and inhibition of free radicals (for reviews see: Droy-Lefaix, 1997; Ramassamy, 2006), a potential antagonism of platelet activating factor (e.g. Akiba *et al*., 1998; Krane *et al*., 2003), modulation of a number of neurotransmitter systems (e.g. Ahlemeyer

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Measure		Pre-dose Baseline score	Change from baseline score 1 hr post-dose	2.5hr post-dose	4 he post-dose	6hr post-dose
Quality of Memory *(% X 6)*	placebo	**408.66** *7.24*	**-46.20** *5.42*	**-48.89** *6.21*	**-52.24** *5.75*	**-57.45** *5.67*
	ginkgo	**396.00** *7.37*	**-30.49** *5.38*	**-42.91** *5.56*	**-40.28** *5.60*	**-46.99** *5.66*
Secondary Memory (% X 4)	placebo	**226.56** *6.96*	**-37.03** *5.05*	**-39.51** *5.76*	**-43.48** *5.17*	**-48.40** *5.52*
	ginkgo	**215.75** *7.00*	**-22.80** *4.75*	**-33.52** *4.70*	**-34.51** *5.43*	**-41.73** *4.98*
Working Memory (% X 2)	placebo	182.10 *1.53*	-9.17 *2.25*	-9.39 *2.26*	-8.75 *2.35*	-9.06 *2.14*
	ginkgo	180.25 *1.77*	-7.69 *2.81*	-9.38 *2.47*	-5.77 *1.72*	-5.26 *2.03*
Speed of Memory *(msecs X 4)*	placebo	2472.69 *38.51*	13.78 *22.61*	-5.50 *23.87*	-30.32 *19.48*	-46.59 *25.71*
	ginkgo	2469.58 *40.12*	-2.19 *21.58*	12.12 *23.97*	23.51 *20.53*	-36.39 *27.74*
Speed of Attention *(msecs X 3)*	placebo	**1114.07** *13.86*	**18.35** *6.46*	**25.07** *7.75*	**29.22** *7.85*	**22.50** *7.35*
	ginkgo	**1105.66** *12.08*	**35.41** *8.37*	**36.16** *9.86*	**42.83** *8.76*	**42.45** *10.10*
Accuracy of Attention (% X 2)	placebo	358.77 *1.47*	0.06 *1.34*	0.87 *1.21*	-0.35 *1.66*	-1.87 *1.38*
	ginkgo	359.57 *1.54*	-0.70 *1.36*	-1.14 *1.54*	-0.19 *1.56*	-3.28 *1.54*

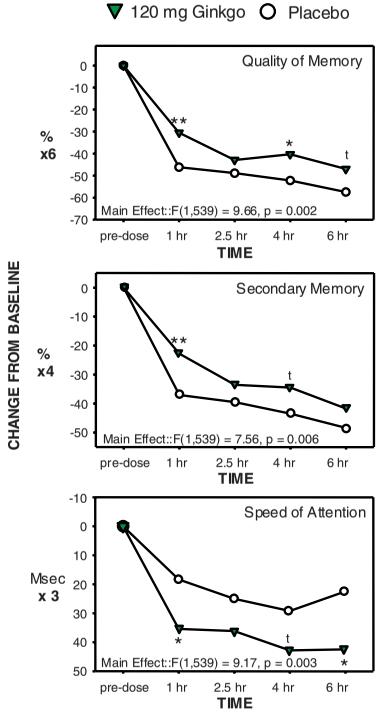

Figure 1. Effects of the treatments on the cognitive factor outcomes derived from the CDR battery across the study day assessments. Mean baseline and change from baseline scores (with standard errors) are presented, with a graphical representation of the factors generating significant differences on the initial ANOVA and subsequent planned comparisons ($^{*}p = 0.05$; $^{**}p = 0.01$; $t =$ trend, $p < 0.1$ in comparison to placebo at each time-point)

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and Krieglstein, 2003; Ahmad *et al*., 2005; DeFeudis and Drieu, 2004; Lee *et al*., 2004; Shah *et al*., 2003), beneficial effects on blood circulation (e.g. Ahlemeyer and Krieglstein, 2003; Chung *et al*., 1999; Jung *et al*., 1990; Koltringer *et al*., 1993; Krieglstein *et al*., 1986; Santos *et al*., 2003; Topp *et al*., 2001), with the latter including increased cerebral perfusion in humans (Santos *et al*., 2003). The above mentioned effects may also contribute to demonstrations of both *in vitro* and *in vivo* protection against hypoxic challenges (e.g. Jannsens *et al*., 1999; Klein *et al*., 1997; Oberpichler *et al*., 1988) and *in vivo* neuro-protective properties in animal models (see Ahlemeyer and Krieglstein, 2003; Lee *et al*., 2002; Tadano *et al*., 1998).

Accumulating evidence suggests that chronic administration of Ginkgo biloba may be effective in the amelioration of the cognitive declines associated with ageing and dementia. In this respect, a comprehensive Cochrane review (Birks *et al*., 2002) meta-analysed the 33 extant studies involving cohorts suffering from dementia or age-related cognitive impairment that met their inclusion criteria. The authors concluded that 'Overall there is promising evidence of improvement in cognition and function associated with Ginkgo'.

There is also some evidence of cognitive enhancement in both younger (Stough *et al*., 2001) and older (Mix and Crews, 2000, 2002) 'cognitively intact' populations administered 12 or 180 mg of Ginkgo extract for 7 days or longer, although evidence in this respect is not unequivocal (e.g. Moulton *et al*., 2001; Solomon *et al*., 2002).

Several placebo-controlled experiments have assessed the effects of single doses of Ginkgo extract on cognitive performance (Elsabagh *et al*., 2005; Hindmarch, 1986; Kennedy *et al*., 2000, 2002a; Warot *et al*., 1991), although the evidence from these studies is less than compelling (for review see Canter and Ernst, 2007). However, these studies include two (Hindmarch, 1986; Warot *et al*., 1991) that adopted a balanced cross-over design, but utilised small sample sizes ($n = 8$ and 12, respectively). No clear pattern of results emerged across the two studies. Of particular relevance here, a double-blind, placebo-controlled, balanced cross-over study involving 20 healthy young participants from our own laboratory also investigated single doses (120 mg, 240 mg, 360 mg) of standardised Ginkgo biloba extract (GBE) (Kennedy *et al*., 2000). The results demonstrated a clear, linear, dose-dependent increase in performance of a 'speed of attention' factor (comprising the speed of performing three separate attention tasks) derived from tasks within the Cognitive Drug Research (CDR) computerised assessment battery. This effect only reached significance following the two higher doses, and at the later three (out of four—1, 2.5, 4, 6 hr) post-dose testing sessions. The lowest dose (120 mg), whilst having no effect on the speed of attention task performance, was associated with a significant but less marked improvement on a 'quality of memory' factor (comprising scores from six memory tasks assessing 'working' memory and 'secondary' memory—for details see Method section below) at 2 and 4 hr post-dose.

Given that 120 mg, rather than the higher doses, is a typical recommended daily dose of standardised GBE, the acute cognitive effects of this dose warrant further investigation. To this end the current study took advantage of the inclusion of a 120 mg dose of GBE, identical to the initial study, as a reference treatment in two further studies (Kennedy *et al*., 2007; Kennedy *et al*., in preparation) which investigated possible potentiation of the effects of Ginkgo biloba by its combination with the phospholipids—phosphatidylcholine and phosphatidylserine. Both of these later studies were identical to the original study (Kennedy *et al*., 2000) in terms of their double-blind, placebo-controlled, balanced-crossover design, their utilisation of exactly the same assessment schedule and cognitive assessment, and the similarity of their healthy young cohorts. Given that the placebo and Ginkgo (120 mg) conditions were presented in exactly counterbalanced (by Latin square) order within each study, and that there was an adequate wash-out period between treatments in all cases (7 days), it seems sensible to take advantage of the greatly increased power allowed by the combined analysis of the relevant data from each study to conduct a more comprehensive assessment of the acute cognitive effects of an average daily dose of 120 mg GBE.

The current study assessed the cognitive effects of a single typical daily dose of standardised GBE (120 mg) in healthy young adults via a secondary analysis of previously obtained data sets from three studies which employed identical methodology.

METHOD

Participants

Data were combined from three previous studies that included a total of 78 participants (none of whom took part in more than one of the studies).

Study 1 included 20 participants (F 18/M 2, Mean age 19.9 years); Study 2 included 28 participants (F

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18/M 10, Mean age 20.4 years) and Study 3 included 30 participants (F 17/M 13, Mean age 21.68 years).

In each case, the study was approved by the ethics committee of Northumbria University Division of Psychology and was carried out in accordance with the Declaration of Helsinki. Prior to participation each volunteer signed an informed consent form and completed a medical health questionnaire. All participants reported that they were in good health, and were taking no illicit social drugs. Additionally they were free of any food supplements, 'over the counter' or prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Smokers were excluded from the study. All participants abstained from alcohol for a minimum of 12 hr prior to the first testing session of the morning.

Cognitive and mood measures

Cognitive Drug Research computerised assessment battery. The CDR computerised assessment battery has been used in over 500 European and North American drug trials.

The tailored version of the CDR battery utilised here, including a detailed description of the constituent tasks, are described in detail by Kennedy *et al*. (2000, 2001a, 2001b, 2002b, 2003). This battery has previously been found to be sensitive to modulation of cognitive function as a consequence of acute ingestion of herbal extracts, including *Melissa officinalis* (Kennedy *et al*., 2002b, 2003), Ginkgo biloba (Kennedy *et al*., 2000, 2002a) and *Panax Ginseng* (Kennedy *et al*., 2001a, 2002b), and acute and chronic administration of a Ginkgo biloba/Panax ginseng combination (Kennedy *et al*., 2001b, 2002a; Wesnes *et al*., 1997, 2000). The selection of computer-controlled tasks from the system was administered with randomly ordered parallel forms of the tests being presented at each testing session. Presentation was via desktop computers with high-resolution 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 took approximately 20 min to perform.

Primary cognitive outcome measures

As with the previous study assessing multiple doses of Ginkgo biloba (Kennedy *et al*., 2000), the single task outcomes from the CDR battery were collapsed into four cognitive outcome measures derived from the battery by a factor analysis conducted and described by Wesnes *et al*. (2000). In addition, the original 'quality of memory' factor has also been fractionated into its two component factors: 'secondary memory' and 'working memory' to allow more detailed scrutiny of any effects. The factor composition is described briefly below.

Quality of memory. Quality of memory is a global measure of mnemonic performance derived by combining scores from the 'secondary memory' and 'working memory' factors (percentage correct scores from six memory tasks, with a maximum score of 600).

Secondary memory factor. Secondary memory factor is derived by combining the percentage accuracy scores from delayed word recognition, delayed picture recognition, immediate word recall and delayed word recall tasks. One hundred per cent accuracy across the four tasks would generate a maximum score of 400 on this index.

Working memory factor. Working memory factor is derived by combining the percentage accuracy scores from the two working memory tests—spatial working memory and numeric working memory. One hundred per cent accuracy across the two tasks would generate a maximum score of 200 on this index.

Speed of memory factor. Speed of memory factor is derived by combining the reaction times of numeric working memory, spatial memory, delayed word recognition and delayed picture recognition (units are summed milliseconds for the four tasks).

Speed of attention factor. Speed of attention factor is derived by combining the reaction times of the three attentional tasks—simple reaction time, choice reaction time and digit vigilance (units are summed milliseconds for the three tasks).

Accuracy of Attention factor. Accuracy of attention factor is derived by calculating the combined percentage accuracy across the choice reaction time and digit vigilance tasks. Hundred per cent accuracy across the two tasks would generate a maximum score of 100.

Treatments

During each of the three multiple-dose trials the participants received two hard-gelatin capsules that were of identical appearance on each visit to the laboratory. In each case, the treatments included: 120 mg of Gingko biloba extract standardised to 24% ginkgo-flavone glycosides and 6% terpene lactones

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(Indena SpA, Milan), and an apparently identical placebo. The counterbalanced order of presentation of the treatments within each study was dictated by random allocation of the participant to a position on a Latin Square. This assured that within each study, and therefore the entire dataset, the presentation of the 120 mg Ginkgo and placebo treatments were exactly counterbalanced across visits.

For each study a disinterested third party was responsible for preparing the individual participants' treatments in identical containers, as per the study's Latin square. The codes remained unbroken until initial statistical analysis had been completed. All treatments were identical in appearance and scent.

Procedure

Each participant was required to attend a total of five or six (study 3) study days that were conducted 7 days apart, to ensure a sufficient wash-out between conditions. Testing took place, commencing at 9 am on each day, in a suite of laboratories with participants visually isolated from each other.

On arrival at their first session on the first day participants were randomly allocated to a treatment regime using a Latin square design which counterbalanced the order of treatments across the four active days of the study.

The first day was identical to the following 4 days (5 days for study 3) to allow familiarisation with the test battery and procedure. However, no treatment (active or placebo) was offered, and data from the five sessions of this practice day were not included in any analysis.

Each active study day comprised five identical cognitive/mood testing sessions. The first was a pre-dose testing session that established baseline performance for that day, and was immediately followed by the day's treatment on all days (except the practice day). Further testing sessions began at 1, 2.5, 4 and 6 hr following consumption of the day's treatment.

Statistics

Scores for the four primary factors and the two memory sub-factors were analysed as 'change from baseline' using the Minitab statistical package.

Prior to carrying out planned comparisons, an ANOVA (general linear model), with terms fitted to the model for dose, visit, dose × visit and subject, was carried out to identify main effects and interaction effects on change from baseline data for each measure. The primary statistical analysis of the 'change from baseline' data for each measure was carried out using planned comparisons, utilising *t*-tests with MSError from an omnibus ANOVA as an error term (Keppel, 1991). At each time-point (1, 2.5, 4 and 6 hr post-dose) data from the placebo condition were compared to the Ginkgo biloba condition. To ensure the overall Type I error protection level only those planned comparisons associated with measures that generated a significant main effect or interaction effect on the initial ANOVA are reported. Furthermore, all testing was two-tailed; comparisons were strictly planned prior to the study, were restricted to the number of conditions minus one at each time-point, and only probabilities associated with these pre-planned comparisons were calculated (see Figure 1).

RESULTS

Quality of memory

The initial ANOVA showed a significant main effect [F (1539) = 9.66, $p = 0.002$] of Ginkgo biloba on the accuracy of memory performance across tasks. Reference to the planned comparisons showed that this positive effect was significant at 1 hr [t (231) = 2.6, $p = 0.01$] and 4 hr [t (231) = 1.98, $p = 0.049$] with a trend towards the same effect at 6 hr post-dose [t (231) = 1.73, $p = 0.08$].

Secondary memory

The initial ANOVA showed a significant effect of treatment across the secondary memory tasks [F (1539) = 7.56, $p = 0.006$]. Reference to the planned comparisons showed that this positive effect was significant at 1 hr post-dose [t (231) = 2.6, $p = 0.01$] with a trend towards the same effect at 4 hr post-dose [t (231) = 1.63, $p = 0.1$].

Working memory

There was no significant effect of treatment on this factor.

Speed of memory

There was no significant effect of treatment on this factor.

Speed of attention

The initial ANOVA showed a significant effect of Ginkgo on the speed of performing attention tasks [F

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(1539) = 9.17, $p = 0.003$]. The planned comparisons showed that this effect comprised a slowing of performance that reached significance at 1 hr [t (231) = 2.18, $p = 0.03$] and 6 hr [t (231) = 2.55, $p = 0.012$] with a trend towards the same effect at 4 hr post-dose [t (231) = 1.74, $p = 0.084$].

Accuracy of attention

There was no significant effect of treatment on this factor.

DISCUSSION

The results of the current study confirm the previous observation (Kennedy *et al*., 2000) of significant improvements in memory performance following a single dose of 120 mg of GBE administered to healthy young volunteers. The results here also suggest that this effect is largely due to improved performance on secondary memory tasks rather than those assessing working memory. Unexpectedly, the analysis also revealed a significant slowing of the speed of attention task performance. This effect is directly the opposite of that seen following higher doses (240 and 360 mg) in the original multiple single dose study.

It is also notable that, whilst accuracy of memory task performance was improved and attention task performance was slowed there was no direct effect on either the speed of memory task performance or accuracy of attention task performance. This suggests that the effects evinced here are not due to a trade off between speed and accuracy.

Regarding potential mechanisms underlying these effects, Ginkgo has been shown to modulate a plethora of physiological parameters that could individually, or in concert, have repercussions for cognitive performance. These include directly increased cerebral blood circulation (for review see Ahlemeyer and Krieglstein, 2003) and perfusion (Santos *et al*., 2003). However, it seems unlikely that the delivery of additional blood borne metabolic substrates to the brain would lead both to improved mnemonic performance and concomitant reductions in the speed of performing attention tasks, particularly as these effects are seen here in largely discrete cognitive domains. It seems more likely that the effects are underpinned by differing mechanisms. Given the complicated pattern of effects seen on attention task performance, with slowing seen here for 120 mg, but faster performance seen to increase with dose for 240 and 360 mg previously (Kennedy *et al*., 2000) a potential mechanism that might accommodate complicated behavioural response such as this would be modulation of neurotransmitter synthesis and/or functionality. To this end Ginkgo has been shown to interact with adrenergic, cholinergic, dopaminergic, glutamatergic, serotonergic and GABAergic parameters (for reviews see Ahlemeyer and Krieglstein, 2003; DeFeudis and Drieu, 2004). However, this possibility does not preclude a behavioural influence of any of the wide range of other microscopic cellular effects exerted by Ginkgo or their concordant modulation of physiological parameters.

It has to be conceded that the modulation of memory seen here is of a similar modest magnitude to that seen previously across the same tasks. The slowing of speed, while statistically significant, could also be characterised as being modest in comparison to the increased speed seen following the higher doses. However, the current study utilised data from a comparatively large sample for a within subjects design (78, as compared to 20 in the initial study) and therefore possessed enough statistical power to detect mild but consistent effects due to treatment.

While this demonstration of the acute effects of Ginkgo extract confirms its psychoactive nature, and the observation of impaired performance is an interesting addition to the current literature, it tells us little of the potential effects of chronic dosage. Our limited understanding of the effects of complex herbal products does not allow us to speculate as to whether these effects will attenuate or increase over time, or whether, for instance, the modest decrements in speed represent a platform for a beneficial rebound effect following a longer duration of dosage.

Given that the dose investigated here is typical of many manufacturers' recommended daily dose of standardised Ginkgo extract for consumption by healthy humans, it would seem expedient to extend the research presented here with an investigation of the cognitive effects of chronic regimens in a sufficiently large sample which includes a comprehensive assessment of the speed of task performance.

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REFERENCES

Ahlemeyer B, Krieglstein J. 2003. Neuroprotective effects of Ginkgo biloba extract. *Cell Mol Life Sci* **60**(9): 1779–1792.

Ahmad M, Saleem S, Ahmad AS, *et al*. 2005. Ginkgo biloba affords dose-dependent protection against 6-hydroxydopamine-induced parkinsonism in rats: neurobehavioural, neurochemical and immunohistochemical evidences. *J Neurochem* **93**(1): 94–104.

Akiba S, Kawauchi T, Oka T, Hashizume T, Sato T. 1998. Inhibitory effect of the leaf extract of Ginkgo biloba L. on oxidative stress-induced platelet aggregation. *Biochem Mol Biol Int* **46**(6): 1243–1248.

Birks J, Grimley EV, Van Dongen M. 2002. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev* **4**: CD003120

Canter PH, Ernst E. 2007. Ginkgo biloba is not a smart drug: an updated systematic review of randomised clinical trials testing the nootropic effects of G. biloba extracts in healthy people. *Hum Psychopharmacol Clin Exp* **22**: 265–278.

Chung HS, Harris A, Kristinsson JK, Ciulla TA, Kagemann C, Ritch R. 1999. Ginkgo biloba extract increases ocular blood flow velocity. *J Ocul Pharmacol Ther* **15**(3): 233–240.

DeFeudis FV, Drieu K. 2004. ''Stress-alleviating'' and ''vigilance-enhancing'' actions of Ginkgo biloba extract (EGb 761). *Drug Dev Res* **62**(1): 1–25.

Droy-Lefaix MT. 1997. Effect of the antioxidant action of Ginkgo biloba extract (Egb 761) on aging and oxidative stress. *Age* **20**: 141–149.

Elsabagh S, Hartley DE, Ali O, Williamson EM, File SE. 2005. Differential cognitive effects of Ginkgo biloba after acute and chronic treatment in healthy young volunteers. *Psychopharmacology* **179**: 437–446.

Hindmarch I. 1986. Activity of Ginkgo biloba extract on short-term memory. *Presse Med* **15**(31): 1592–1594.

Jannsens D, Remacle J, Drieu K, Michiels C. 1999. Protection of mitochondrial respiration activity by bilobalide. *Biochem Pharmacol* **58**(1): 109–119.

Jung F, Mrowietz C, Kiesewetter H, Wenzel E. 1990. Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers. *Arzneimittelforschung* **40**(5): 589–593.

Kennedy DO, Scholey AB, Wesnes K. 2000. The dose dependent cognitive effects of acute administration of Ginkgo biloba to healthy young volunteers. *Psychopharmacology* **151**: 416–423.

Kennedy DO, Scholey AB, Wesnes K. 2001a. Differential, dose dependent changes in cognitive performance following acute administration of a Ginkgo biloba/Panax ginseng combination to healthy young volunteers. *Nutr Neurosci* **4**: 399–412.

Kennedy DO, Scholey AB, Wesnes K. 2001b. Dose dependent changes in cognitive performance and mood following acute administration of Ginseng to healthy young volunteers. *Nutr Neurosci* **4**: 295–310.

Kennedy DO, Scholey AB, Wesnes KA. 2002a. Modulation of cognition and mood following administration of single doses of Ginkgo biloba, Ginseng and a Ginkgo/Ginseng combination to healthy young adults. *Physiol Behav* **75**: 739–751.

Kennedy DO, Scholey AB, Tildesley NTJ, Perry EK, Wesnes KA. 2002b. Modulation of mood and cognitive performance following acute administration of single doses of Melissa officinalis (Lemon Balm). *Pharmacol, Biochem Behav* **72**: 953–964.

Kennedy DO, Wake G, Savelev S, *et al*. 2003. Modulation of mood and cognitive performance following administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor binding properties. *Neuropsychopharmacology* **28**(10): 1871–1881.

Kennedy DO, Haskell CF, Mauri PL, Scholey AB. 2007. Acute cognitive effects of standardised Ginkgo biloba extract complexed with phosphatidylserine. *Hum Psychopharmacol Clin Exp* **22**: 199–210.

Keppel G. 1991. *Design and Analysis*. Prentice Hall: New Jersey.

Kleijnen J, Knipschild P. 1992. Ginkgo biloba. *Lancet* **340**(8833): 1474.

Klein J, Chatterjee SS, Loffelholz K. 1997. Phospholipid breakdown and choline release under hypoxic conditions: inhibition by bilobalide, a constituent of Ginkgo biloba. *Brain Res* **755**: 347–3350.

Koltringer P, Langsteger W, Klima G, Reisecker F, Eber O. 1993. Hemorrheologic effects of ginkgo biloba extract EGb 761. Dose-dependent effect of EGb 761 on microcirculation and viscoelasticity of blood. *Fortschr Med* **111**(10): 170–172.

Krane S, Kim SR, Abrell LM, Nakanishi K. 2003. Microphysiometric measurement of PAF receptor responses to ginkgolides. *Helv Chim Acta* **86**(11): 3776–3786.

Krieglstein J, Beck T, Seibert A. 1986. Influence of an extract of Ginkgo biloba on cerebral blood flow and metabolism. *Life Sci* **39**(24): 2327–2334.

Lee EJ, Chen HY, Wu TS, Chen TY, Maynard KI. 2002. Acute administration of Ginkgo biloba extract (EGb 761) affords neuroprotection against permanent and transient focal cerebral ischemia in Sprague-Dawley rats. *J Neurosci Res* **68**(5): 636–645.

Lee TF, Chen CF, Wang LCH. 2004. Effect of ginkgolides on beta-amyloid-suppressed acetylocholine release from rat hippocampal slices. *Phytother Res* **18**(7): 556–560.

Mix JA, Crews WD. 2000. An examination of the efficacy of Ginkgo biloba extract EGb761 on the neuropsychologic functioning of cognitively intact older adults. *J Altern Complement Med* **6**(3): 219–229.

Mix JA, Crews WD. 2002. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 (R) in a sample of cognitively intact older adults: neuropsychological findings. *Hum Psychopharmacol Clin Exp* **17**: 267–277.

Moulton PL, Boyko LN, Fitzpatrick JL, Petros TV. 2001. The effect of Ginkgo biloba on memory in healthy male volunteers. *Physiol Behav* **73**: 659–665.

Oberpichler H, Beck T, Abdel-Rahman MM, Bielenberg GW, Krieglstein J. 1988. Effects of Ginkgo biloba constituents related to protection against brain damage caused by hypoxia. *Pharmacol Res Commun* **20**(5): 349–368.

Ramassamy C. 2006. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. *Eur J Pharmacol* **545**(1): 51–64.

Santos RF, Galduroz JCF, Barbieri A, Castiglioni MLV, Ytaya LY, Bueno OFA. 2003. Cognitive performance, SPECT, and blood viscosity in elderly non-demented people using Ginkgo biloba. *Pharmacopsychiatry* **36**(4): 127–133.

Shah ZA, Sharma P, Vohora SB. 2003. Ginkgo biloba normalises stress-elevated alterations in brain catecholamines, serotonin and plasma corticosterone levels. *Eur Neuropsychopharmacol* **13**(5): 321–325.

Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. 2002. Ginkgo for memory enhancement—a randomized controlled trial. *JAMA* **288**: 835–840.

Stough C, Clarke J, Lloyd J, Nathan PJ. 2001. Neuropsychological changes after 30-day Ginkgo biloba administration in healthy participants. *Int J Neuropsychopharmacol* **4**(2): 131–134.

Tadano T, Nakagawasai O, Tan-no K, Morikawa Y, Takahashi N, Kisara K. 1998. Effects of ginkgo biloba extract on impairment oflearning induced by cerebral ischemia in mice. *Am J Chin Med* **26**(2): 127–132.

Topp S, Knoefel WT, Schutte S, Brilloff S, Rogiers X, Gubdlach M. 2001. Ginkgo biloba (Egb761) improves microcirculation after warm water ischemia of the rat liver. *Transplant Proc* **33**: 979–981.

Warot D, Lacomblez L, Danjou P, Weiller E, Payan C, Puech AJ. 1991. Comparative effects of ginkgo biloba extracts on psychomotor performances and memory in healthy subjects. *Therapie* **46**(1): 33–36.

Wesnes KA, Faleni RA, Hefting N, *et al*. 1997. The cognitive, subjective and physical effects of a combination of panax ginseng and ginkgo biloba in healthy volunteers with neurasthenic complaints. *Psychopharmacol Bull* **33**: 603–603.

Wesnes KA, Ward T, McGinty A, Petrini O. 2000. The memory enhancing effects of a Ginkgo-biloba/Panax ginseng combination in healthy middle aged volunteers. *Psychopharmacology* **152**: 353–361.

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