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Pharmacology, Biochemistry and Behavior 75 (2003) 687–700
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Review article

# Ginseng: potential for the enhancement of cognitive performance and mood

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Received 11 November 2002; received in revised form 3 March 2003; accepted 11 April 2003

**Abstract**

Ginseng has been used medicinally in the Far East for several millennia and is currently one of the most widely taken herbal products throughout the world. It has been attributed with a plethora of physiological effects that could potentially benefit cognitive performance or mood. Studies involving animals show that ginseng and its constituent ginsenosides can modulate indices of stress, fatigue, and learning. However, there is a lack of adequately controlled research showing behavioural effects following chronic administration to humans. Recent research has demonstrated that single doses of ginseng most notably engender cognitive benefits in terms of improved memory, but can also be associated with 'costs' in terms of attention task deficits following less mnemonically beneficial doses. A single dose of ginseng has also been shown to modulate cerebroelectrical (EEG) activity. It is suggested that ginseng would benefit from rigorous research further delineating its acute effects and exploring the relationship between acute effects and those seen during and following chronic administration regimens.


*Keywords:* Ginseng; Panax; Memory; Attention; Mood; Cognition

## 1. Introduction

'Ginseng' is generally taken to refer to the dried root of several species in the plant genus *Panax* (Araliaceae family). The most widely used family member is *Panax ginseng*, which is indigenous to the Far East (most notably China and Korea). It was first cultivated around 11 BC and has a medical history (as a wild herb) stretching back more than 5000 years (Yun, 2001). Other members of the genus include *Panax quinquefolius* (American), *Panax notoginseng*, and *Panax japonicus*.

The man-shaped ginseng root was initially taken as a whole body treatment according to the 'doctrine of signatures.' This indication as a general tonic, along with those of physical performance enhancer, 'adaptogen,' and aphrodisiac has survived to this day (O'Hara et al., 1998). Extensive recent in vitro, in vivo, and epidemiological research also suggests that ginseng may have a cancer-preventative effect (Yun, 2001).

Whilst it is difficult to quantify the exact prevalence of ginseng use, it is sufficient to say that it occupies a permanent and prominent position in the herbal 'best-sellers' list throughout the world and has been estimated to have the second highest financial turnover of any herb (after *Ginkgo biloba*) in the USA marketplace (Blumenthal, 2001). It also seems likely that the widespread undocumented use of ginseng throughout a number of societies and traditional medicinal systems may well make it the most widely taken herbal product in the world. Given that the overall quantified retail sales of herbal products worldwide for 1997 were estimated at US$16.5 billion (Scimone, 1997; Scimone and Scimone, 1998), with estimates reaching US$3 billion for Germany alone in 1996 (Brown, 1996) and US$4 billion for the USA in 2000 (Ernst, 2000), it can be seen that ginseng is not only big business but also widely consumed on a global scale.

What is particularly relevant here is that ginseng products are purchased by consumers who believe not only that they will engender physical benefits, but also that they will have a positive effect on their cognitive performance and well-being. As an example of this, the Hartman Group's Natural Products Census Supplement Report (July 1998–July 1999) shows that *G. biloba* and members of the *Panax* genus were

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0091-3057/03/$ – see front matter 
doi:10.1016/S0091-3057(03)00126-6

the first and third (vitamin E being second) most frequently taken products for 'memory loss' and 'absentmindedness.' This figure was derived from 116.3 million surveyed incidents of herbal medicine usage in the Unites States.

Whilst a reasonably well-supported case for such a role for *G. biloba* can be made, the same cannot be said for ginseng. Indeed, the extant literature, whilst voluminous, is notable in that there is little solid, methodologically adequate evidence at present for ginseng's efficacy as a medical treatment (see Vogler et al., 1999) or for roles in general health or cognition enhancement. The following review does, however, attempt to pull together a number of suggestive strands of evidence, including recent observations of modulation of cognitive performance following single doses of *P. ginseng*, in arguing that adequately focussed and controlled research may well show that ginseng has potential for the beneficial modulation of cognitive performance.

## 2. Constituents and extracts

The major active constituents of the *Panax* genus are thought to be triterpenoid glycosides or saponins, also known as ginsenosides, of which over 30 individual examples, many of which exist only in minute amounts, have been identified (Tachikawa et al., 1999). Ginsenosides can be classified into three groups on the basis of the chemical structure of their sapogenins (aglycones): the panaxadiol group (e.g., $Rb_1$, $Rb_2$, $Rb_3$, Rc, Rd, $Rg_3$, $Rh_2$, $Rs_1$); the panaxatriol group (e.g., Re, Rf, $Rg_1$, $Rg_2$, $Rh_1$); and the oleanolic acid group (e.g., Ro) (Tachikawa et al., 1999).

The ginsenoside content of ginseng can vary depending on the species, the age and part of the plant, the preservation method, the season of harvest, and the extraction method (Liberti and Der Manderosian, 1978; Phillipson and Anderson, 1984). Russo (2001) also notes that no herb is more subject to adulteration and misrepresentation than ginseng and notes that ginsenoside content in many brands on the US market is low to negligible. This latter point is largely confirmed by Cui et al. (1996) and Cui (1995) who found a huge variation in ginsenoside content across several dozen commercial ginseng preparations and extracts. Ginseng products have also been found to contain naturally occurring methylxanthines (Vaughan et al., 1999) and contaminants such as pseudoephedrine (Bahrke and Morgan, 2000).

The most widely used standardised ginseng extract, both commercially and for research purposes, is G115 (Pharmaton, Switzerland), a concentrated aqueous extract of *P. ginseng* contained in the marketed product Ginsana, which is standardised to contain an invariable 4% of ginsenosides (Soldati and Sticher, 1980).

As a practical example of how poor standardisation in many ginseng products might confound research involving ginseng, recent research has shown that ginsenosides from the three groups (panaxadiol, panaxatriol, and oleanolic acid groups) exert markedly different pharmacological and behavioural effects. These include differing influences on the in vitro responses to various receptor stimuli (e.g., Kudo et al., 1997; Tachikawa et al., 1999) and demonstrations of improvements in scopolamine-induced learning deficits as a consequence of panaxatriol, but not panaxadiol, administration (Yamaguchi et al., 1995, 1996). In keeping with this, a memory-enhancing effect was observed in rodents using ginseng extracts with a high, but not low, ratio of panaxatriol/panaxadiol ginsenoside content. Thus, Jin et al. (1999) suggest that the ratio of ginsenosides may be an important factor in the pharmacological effects of ginseng extracts. Indeed, the research outlined below has involved the use of a wide variety of ginseng products and components. These include standardised extracts, ginseng total saponins (all of the ginsenosides), single or multiple ginsenosides extracted from either the root or the leaves/stem, and different extractions of ginseng (e.g., ether, ethanol, aqueous). By and large the human experimentation and much of the animal behavioural research reviewed below have involved the use of whole or standardised ginseng extracts, in many cases the standardised ginseng extract G115. The use of a well-standardised extract such as G115 allows replicable scientific research to a certain extent. However, it should be noted that real progress in this area will not be possible until the active components of the *Panax* genus are better understood.

Possibly due to the lack of satisfactory analytical methods to detect plasma and tissue concentrations, there has been little research published on the pharmacokinetics of the absorption, distribution, and excretion of ginseng saponins. However, Odani et al. (1983) report that in rats, ginsenoside Rg1 was absorbed rapidly from the upper digestive tract, reached peak serum and tissue concentrations at 30 min and 90 min respectively, and was widely distributed throughout the body but was not detected in the brain. Cui et al. (1996), using gas-chromatography mass spectroscopy, also confirmed the uptake of ginsenosides in humans by demonstrating the presence of metabolites in the urine samples of athletes that had consumed ginseng within the last 10 days.

## 3. Possible mechanisms of action

The ginseng literature contains a large number of studies examining a plethora of mechanisms supposedly underlying ginseng's efficacy. Some of the physiological effects may confer a general benefit to health. For instance, there are reports of a general bolstering of the immune system (Scaglione et al., 1996), anti-inflammatory effects (Matsuda et al., 1990, 1991), antihepatoxicity effects (Zuin et al., 1987), and a protective action against mammalian tumour cell lines (Ong and Yong, 2000) and nonorgan specific cancers (Yun and Choi, 1995, 1998; Yun, 2001), with these latter effects potentially related to antimutagenic and DNA protective properties (Ong and Yong, 2000). Whilst these

general benefits are of undoubted interest in their own right, there are a number of central and peripheral physiological effects that are potentially relevant to the modulation of mood and cognitive performance.

### 3.1. Cardiovascular and haemorrheological effects

Intravenous ginseng administration to anaesthetised dogs has been shown to produce a number of effects including a reduction, followed by an increase, in blood pressure, and transient vasodilation (Wood et al., 1964). Lee et al. (1981) administered ether, ethanol, and aqueous extracts of ginseng to anaesthetised dogs. Both ether and ethanol extracts decreased total peripheral resistance and caused vasodilation and bradycardia, whilst the aqueous extract of ginseng led to a significant increase in total peripheral resistance.

Lei and Chiou (1986) found that extracts of *P. notoginseng* decreased systemic blood pressure in rats and rabbits. They suggested that ginseng could be a useful treatment for angina since it dilates coronary vessels, but that it would not be a useful treatment for hypertension since it can induce both vasodilation and vasoconstriction depending on dose and target vessel. Kang et al. (1995b) suggest that vasorelaxation is induced by ginsenosides via the release of nitric oxide (NO) from endothelial cells, and that this may contribute to the beneficial effect of ginseng on the cardiovascular system. This is, in part, substantiated by the findings of other researchers (Gillis, 1997).

Research also suggests that several of ginseng's active ingredients also have a beneficial influence on platelet aggregation. Shi et al. (1990) demonstrated an antiatherosclerotic action of total ginsenosides, apparently mediated by a correction in the imbalance between prostacyclin and thromboxane. Kimura et al. (1988) tested six ginsenosides and found that only Rg1 inhibited 5-HT release from, and adrenaline and thrombin-induced aggregation of, platelets. Kuo et al. (1990) found that ginsenosides Ro, $Rg_1$, and $Rg_2$ all suppressed the 5-HT release action of rabbit platelets, but that panaxynol, a nonginsenoside fraction, inhibited aggregation, release reaction, and thromboxane formation. This finding is in agreement with several other studies that have found panaxynol or the lipophilic fraction to be the most potent antiplatelet agent in ginseng, chiefly due to an inhibition of thromboxane formation (Teng et al., 1989). This possibly occurs via regulation of cGMP and cAMP levels and prolongation of the time interval between the conversion of fibrinogen to fibrin (Park et al., 1996). Ginsenosides have also been shown to be relatively potent platelet activating factor antagonists (Jung et al., 1998).

### 3.2. Cardioprotection and neuroprotection

A cardioprotective effect has also been reported, with a protection of endothelial function in aortic rings in ginseng-treated animals (Gillis, 1997). Enhanced recovery of cardiac haemodynamic performance and lowered mitochondrial swelling in cardiopulmonary patients has also been shown as a consequence of including ginseng extract in cardioplegic solution during open heart surgery (Zhan et al., 1994). It has been suggested that these cardiovascular protective effects of ginseng may be mediated by the release of NO (Gillis, 1997; Lim et al., 1997; Scott et al., 2001).

Neuroprotective properties of ginsenosides have also been demonstrated in vitro (Rudakewich et al., 2001) and in vivo. Such effects include protection of hippocampal CA1 neurons (Chen, 1999; Wen et al., 1996), reduction of infarct area (Zhang and Liu, 1996), and preservation of local cerebral glucose utilisation (Choi et al., 1996) following ischaemia in rodents.

Possible ginseng-mediated neuroprotective mechanisms include a defence against overproduction of NO (Kim et al., 1998a), glutamate and kainic acid-induced excitotoxicity (Liao et al., 2002). Protection against free radical-mediated lipid peroxidation (Huong et al., 1998; Zhang et al., 1996), and a blockade of calcium overinflux into neurons (Liu and Zhang, 1995; Zhong et al., 1995). Ginsenosides also engender cerebrovascular relaxation via a NO pathway (Chen et al., 1997), and modulation of cellular energy metabolism (Jiang and Qian, 1995).

### 3.3. Hypothalamic–pituitary–adrenal system regulation

Some of the 'adaptogenic' effects of ginseng are attributed to its actions on the hypothalamic–pituitary–adrenal system (Sonnenborn and Proppert, 1990). Both situation-dependent increases and decreases in corticosterone levels as a consequence of ginseng administration have been demonstrated. Evidence indicates that both oral administration (Filaretov et al., 1988) and interperitoneal injection of ginseng can increase plasma levels of ACTH and corticosterone, with this effect being abolished by hypophysectomy (Hiai et al., 1983).

Conversely, ginseng total saponins have been found to inhibit the stress-induced increase in plasma corticosterone levels as a consequence of their intra-cerebro-ventricular injection into mice. This inhibitory action of ginseng was blocked by a co-administered inhibitor of NO synthase, suggesting that ginsenosides modulate the stress-induced hypothalamo–pituitary–adrenal response by inducing NO production in the brain (Kim et al., 1998b).

Kim et al. (1998c) found that ginseng total saponins and ginsenosides exerted inhibitory effects on $Ca2^+$ currents in rat adrenal chromaffin cells. They suggest that the cellular basis of the antistress effects of ginseng may be the regulation of catecholamine secretion from adrenal cells. However, it should also be noted that Luo et al. (1993) demonstrated that whilst cold water swim stress raised levels of serum corticosterone in rats and mice, both total root saponins and ginsenoside $Rb_1$ inhibited this increase of serum corticosterone in rats. However, the same dosage/kilogram of ginseng/ginsenosides produced an opposite effect in mice, producing raised serum corticosterone levels.

In an attempt to explain the biphasic effects of ginseng, Gaffney et al. (2001) suggest that ginsenosides may inhibit catalytic enzymes resulting in increased occupancy of both negative and positive feedback stress hormone receptors. This would lead to an existing stress response in either direction being increased.

### 3.4. Modulation of glucose levels

It has been demonstrated that ingestion of a number of different types of ginseng, including Asian, American, Korean Red, and Canadian white ginseng, can lead to a reduction in fasting blood glucose levels in rodents (Liu and Xiao, 1992; Martinez and Staba, 1984; Ohnishi et al., 1996; Oshima et al., 1987) and improvement in the glucose tolerance curve of diabetic mice (Oshima et al., 1987).

In humans, a reduction in fasted blood glucose levels and glycated haemoglobin, in comparison to placebo, has been reported following 8 weeks administration of 200 mg of an unspecified *P. ginseng* extract to 18 participants with type 2 diabetes mellitus (Sotaniemi et al., 1995). A number of studies have also demonstrated reductions in blood glucose levels following a 25-g glucose challenge in both diabetic patients who had ingested 3, 6, and 9 g (Vuksan et al., 2000a,b) and nondiabetics administered 1, 2, and 3g (Vuksan et al., 2000a, 2001) of *P. quinquefolius*. Vuksan et al. (2000a) suggest three possible mechanisms underlying these effects: a ginseng-related slowing of the rate of digestion of food (Suzuki et al., 1991; Yuan et al., 1998); an increase in intracellular glucose transport (Hasegawa et al., 1994; Ohnishi et al., 1996); and modulation of insulin secretion (Kimura et al., 1981). It is also noted that the latter two putative mechanisms may well be mediated by increased NO production (Roy et al., 1998; Spinas et al., 1998).

### 3.5. Modulation of neurotransmission

Extracts of *P. ginseng* (Hsieh et al., 2000; Jin et al., 1999; Nitta et al., 1995) and *Panax quinquefolium* (Sloley et al., 1999) have been reported to improve the memory deficits associated with scopolamine administration to rodents. The latter of these studies showed increased choline uptake in synaptosomal preparations. An in vitro investigation of displacement of radio-labelled nicotine and scopolamine also showed that crude extracts of *P. ginseng* exhibited an affinity for both nicotinic and muscarinic receptors in human brain cerebral cortex membranes (Lewis et al., 1999).

A number of studies have identified cholinergic properties associated with single ginsenosides, including a direct interaction between $Rg_2$ and nicotinic receptor subtypes (Sala et al., 2002) and modulation by $Rb_1$ of acetylcholine release and reuptake, and the number of choline uptake sites in the hippocampus, and to a lesser extent, the cortex (Benishin, 1992). Both ginsenosides $Rg_1$ (Zhang et al., 1990) and $Rb_1$ (Salim et al., 1997; Zhang et al., 1990) have also been shown to increase choline acetyltransferase levels in rodent brains.

Petkov (1978) found that ginseng administration (50 mg/kg) led to increases in brainstem dopamine and norepinephrine and increases in serotonin in the cortex. This action was abolished by administration of either a serotonin receptor agonist or a specific serotonin antagonist, suggesting that serotonergic transmission was involved in the memory-enhancing effect. It has also been shown that ginseng total saponin can modulate dopaminergic activity at both presynaptic and postsynaptic dopamine receptors (Kim et al., 1995a), and can block behavioural sensitisation induced by psychostimulants such as morphine (Kim et al., 1995b), cocaine (Kim et al., 1995a), methamphetamines (Kim et al., 1998c), and nicotine (Kim et al., 1999a,b; Shim et al., 2000). The latter authors suggest that these effects are mediated by the inhibition of drug-related dopamine release by the action of ginseng total saponins on presynaptic dopamine terminals.

Wang et al. (1995) also found that both root and stem/leaf saponins improved learning and raised the levels of biogenic monoamines in normal rats' brains. Ginseng has also been shown to attenuate pentylenetetrazole-induced decreases in rat brain monoamine oxidase, possibly accounting for its demonstrated antianxiety effect in rodents (Bhattacharya and Mitra, 1991).

### 3.6. NO synthesis

It has previously been suggested that many of ginseng's physiological effects are as a consequence of enhanced synthesis of NO throughout a number of organs and tissues (Gillis, 1997). The range of cells and tissue in which such an effect has been observed includes activated macrophages (Fan et al., 1995; Friedl et al., 2001), peripheral (Chen, 1996; Maffei-Facino et al., 1999; Sung et al., 2000), cardiac (Kang et al., 1995a,b), and vascular tissue, the kidneys (Han and Kim, 1996), muscle tissue (Chen and Lee, 1995; Choi et al., 1998; Kim et al., 1998a,b,c,d; Tamaoki et al., 2000), and cerebral tissue (Toda et al., 2001; Chen et al., 1997; Kim et al., 1998d).

Increased NO synthesis has been repeatedly proposed to partially underlie many of the physiological effects of ginseng and ginsenosides, including antioxidant and cardiovascular effects (Gillis, 1997), cardioprotection (Maffei-Facino et al., 1999), neuroprotection (Kim et al., 1998d), hypothalamic–pitiuitary–adrenal axis modulation (Kim et al., 1998b), glucoregulatory effects (Vuksan et al., 2000a,b), and enhancement of immune function (Friedl et al., 2001).

The enzyme NO synthase has been shown to be present throughout the brain with a particular prevalence in the cerebellum. It is reported to be involved in hippocampal long-term potentiation (LTP) (Salemme et al., 1996) and general memory processes (Prast and Philippu, 2001). It is therefore tempting to speculate that ginseng may exert any effects on cognition through the same pathway. In line with

this proposition, a number of previous studies have implicated NO synthesis in the efficacy of several other nootropic treatments (Corasaniti et al., 1995; Maurice and Privat, 1997; Reddy and Kulkarni, 1998). It may well also be significant that following ginsenosides, the release of NO from endothelial cells has been shown to be specific to the panaxatriol rather than the panaxadiol ginsenosides (Kang et al., 1995b), whilst it has been suggested that memory-enhancing effects in rodents are also restricted to extracts with a high, but not a low, ratio of panaxatriol to panaxadiol ginsenoside content (Jin et al., 1999).

## 4. Behavioural and psychological effects

Given such a wide range of physiological effects, it would be expected that ginseng might exert an effect on both cognitive performance and mood. In this respect, a number of studies have examined behavioural consequences. A brief review of some of the relevant evidence from animal studies is included prior to an evaluation of the evidence in humans.

### *4.1. Animal studies*

#### *4.1.1. Relief of stress and fatigue*

A number of studies have demonstrated a reduction of stress or its physiological concomitants in animals. Examples include the suppression of psychological and foot shock stress-induced antinociception in mice (Nguyen et al., 1995); an attenuation of the disruption of pentobarbital-induced sleep produced by 30 min of psychological stress in mice, with no change in sleep duration in unstressed mice (Nguyen et al., 1996); protection against psychological stress-induced gastric lesions in mice (Huong et al., 1998); and an inhibition of intra-cerebro-ventricular injection stress-induced increases in plasma corticosterone levels in mice (Kim et al., 1998b). One of the concomitants of such psychological stress in rodents is an enhancement of lipid peroxidation activity, and Yobimoto et al. (2000) demonstrated the suppression by Vietnamese ginseng of oxidative damage to brain membranes as a result of a stressful experience (placing of the mouse in a chamber in which it had observed the extended electric shocking of another mouse).

A number of studies have also demonstrated that administration of ginseng or its active components can attenuate fatigue in rodents. For instance, Filaretov et al. (1988) found that a single administration of ginseng leads to significant increases in endurance time to exhaustion on a treadmill running test, with a concomitant increase in the basal level of ACTH and corticosteroids, with this effect disappearing by the end of 7 days treatment. Avakian and Evonuk (1979) also demonstrated that administration of 2 mg crude ginseng extract to rats did not affect glycogen levels prior to exercise but significantly increased glycogen levels after 1.5 h (39%) and 3 h (115%) of prolonged swimming. Similarly, Avakian et al. (1984) demonstrated no effect at rest but higher levels of blood glucose following 60 min of exercise and lower concentrations of lactic acid, pyruvic acid, and free fatty acid after 30 min of exercise for rats treated with ginseng as opposed to placebo.

However, Martinez and Staba (1984) found no increase in endurance times and no effects of ginseng extract on plasma lactic acid, glucagon, insulin, or liver glycogen levels in rested or exercised rats. Similarly, whereas several of the aforementioned studies had not been blinded, Lewis et al. (1983) utilised a blind design and found no adaptogenic effects during exercise for four ginseng infusions during a series of trials over 3 months.

Several recent studies suggest that this variability in results may possibly be attributed either to the quality of the extract of ginseng used and/or to the dose investigated, and a possible habituation either to the effects of ginseng or exercise. For example, Wang and Lee (1998) found that short-term (4 days) but not chronic treatment with ginseng total saponin significantly prolonged the aerobic endurance of nontrained rats compared to saline-treated controls. Ginseng treatment significantly increased the plasma free fatty acid level and maintained plasma glucose level during exercise. They also found that a preparation devoid of ginsenosides $Rg_1$ and $Rb_1$ failed to enhance, whereas injection of either $Rg_1$ or $Rb_1$ enhanced, aerobic exercise performance. Ferrando et al. (1999a) found that both ginseng (G115) and treadmill exercise alone improved a number of haematological parameters in rats, but that the combination of ginseng and exercise produced a smaller improvement. These results suggest a clear physiological response due to the administration of ginseng extract similar to that obtained after long-term exercise, but no synergistic effect of ginseng and exercise. This possibility was borne out by Fernando et al. (1999b) who found that prolonged treatment with ginseng (G115) increased the capillary density and the oxidative capacity of rat forelimb muscles, thereby providing greater aerobic potential in a manner similar to the performance of physical exercise. As with the previous research, the combination of exercise and treatment failed to potentiate the separately obtained effects.

#### *4.1.2. Memory and learning*

A number of studies suggest that ginseng can be effective in the attenuation of learning deficits due to brain damage and ageing in rodents. Examples include a demonstration, following 5 min of forebrain ischemia in gerbils, of both neuroprotective properties (i.e., rescue of hippocampal CA1 pyramidal neurons) and amelioration of learning deficits (passive avoidance step down) as a consequence of 7 days administration (prior to ischemia) of red ginseng powder, crude ginsenosides, and ginsenoside $Rb_1$. A lesser effect was observed for crude ginseng nonginsenosides, and no effect was observed for ginsenosides $Rg_1$ and Ro (Wen et al., 1996). Similarly, a dose-dependent attenuation of learn-

ing deficits in brain-lesioned (medial prefrontal cortex) rats, and significant strategic learning improvements in sham control rats, have been shown as a consequence of 30 days postoperative administration of 40 and 80 mg/kg crude ginseng extract (Zhao and McDaniel, 1998). Age-related deterioration in performance on a radial maze task has also been attenuated by administration of ginseng extract. No such effect was evident, however, on an operant discrimination task (Nitta et al., 1995).

Ginseng-related improvements in the learning and memory of normal and young rats tend to be both dose dependent and sensitive to the nature of the task. As an example, Petkov and Mosharrof (1987) administered mice with 3, 10, 30, 100, and 300 mg/kg G115 and found an inverted U dose–response relationship on some tasks, with 10 mg the most effective in facilitating 'shuttle box' active avoidance learning, whilst 30 mg significantly improved retention of 'step down' passive avoidance. However, only the 10 mg dose improved performance on staircase maze training with positive (alimentary) reinforcement, whilst 100 mg increased locomotor activity. Similarly Petkov et al. (1993) demonstrated variations in learning as a function of method of assessment, age of rats, and dosage (17, 50 or 150 mg/kg G115 for 7 days). Consequently, for instance, young rats showed the greatest improvement in retention of 'shuttle box' passive avoidance with the lowest and highest doses (17 and 150 mg/kg) but only showed significant improvement on 'step down' passive avoidance with the middle dose (50 mg/kg), whilst neither 'step through' passive avoidance nor water maze learning was significantly affected by any dose of G115.

It is also particularly noteworthy that different fractions or doses of ginseng extract have been shown to impair learning. For instance, Saito et al. (1977) found that extracts of ginseng inhibited conditioned avoidance response and discrimination behaviour on pole climbing and shuttle box tests. Similarly, Petkov and Mosharrof (1987) found that high doses of ginseng G115 impaired rather than improved conditioned reflex activity, and Takagi et al. (1972a,b) demonstrated decreased exploratory activity and a specific blocking action of conditioned responses following administration of a crude ginsenoside fraction.

Interestingly, Smriga et al. (1995), in an investigation into the individual ingredients in the putatively nootropic Chinese prescription DX-9386, found that a single oral administration of ginseng (500 mg/kg) significantly increased hippocampal LTP in anaesthetised rats. This finding was broadly in line with similar demonstrations in vivo of modulation of LTP in the hippocampal formation by ginsenoside $Rb_1$ (Abe et al., 1994).

The above literature suggests that ginseng may have the potential to benefit cognitive performance. However, systematic research using standardised extracts, multidosing regmines, and a variety of task domains will be necessary in order to determine dose–response relationships and the circumstances under which positive and negative effects on learning and memory are realised.

## 5. Human studies involving chronic administration

### 5.1. Human ergogenic benefits

The extant literature includes a number of studies investigating ginseng's effects on physical or 'ergogenic' performance in humans. Whilst not directly relevant to cognitive performance and mood, it seems reasonable to suggest both that demonstrations of improvements in this domain may well have psychological concomitants, and that any beneficial effect on mood or perceived 'well-being' may well in itself affect performance.

Unfortunately, methodological difficulties make interpretation of several of the studies difficult. For instance, a study by Knapik et al. (1983) demonstrated no effects but had a very small sample size (5 ginseng, 6 placebo); Pieralisi et al. (1991) demonstrated substantial ergogenic effects but for ginseng combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements. In two separate studies, Forgo and Kirchdorfer (1981, 1982) demonstrated significant aerobic capacity, lactate level, and heart rate effects but failed to include either placebo or control conditions.

Forgo (1983) did, however, extend these studies with a double blind placebo-controlled investigation into the effects of 9 weeks administration of ginseng (G115), ginseng plus tocopherol, or placebo, on physiological and hormonal measures in athletes. He reported significant increases in oxygen uptake and significant decreases in both exercise blood lactates and heart rate, but no change in hormone levels for both of the active treatments in comparison to placebo. This was followed by a further double blind study (Forgo and Schimert, 1985) investigating the duration of the effects of 9 weeks administration of ginseng (G115-100 mg twice daily) during exercise. Results reported include significant increases in oxygen uptake and forced expiratory volume and significant decreases in heart rate and visual reaction times. Some of these differences persisted at testing 3 weeks after cessation of treatment.

Several recent studies do not, however, offer any support to this role of ginseng as an ergogenic aid. Morris et al. (1996), in a placebo-controlled, cross-over study, found that 1 week administration of two different doses of ginseng had no more effect on any of the physiological indices under investigation (oxygen, free fatty acids, lactate, glucose) than placebo. Allen et al. (1998) reported, in a randomised double-blind, placebo-controlled study involving 28 healthy young adults, that the administration of 200 mg ginseng extract for 21 days did not significantly affect heart rate or perceived exertion at 150 and 200 W ergometric exercise; and that it did not affect $VO_2$, exercise time, workload, plasma lactate, or haematocrit at peak levels of exercise. Similarly, Engels and Wirth (1997), again in a randomised double blind placebo-controlled trial involving 36 healthy men, failed to demonstrate any effect of 8 weeks administration of ginseng on $O_2$ consumption, respiratory exchange

ratio, minute ventilation, blood lactic acid levels, heart rate, or perceived effort; whilst Engels et al. (2001) found no effect of 400 mg/day G115 for 8 weeks on supramaximal exercise performance and postexercise heart rate in 19 healthy women. Bahrke and Morgan (1994, 2000), in comprehensive reviews of this area, suggest that the equivocal nature of the evidence pertaining to the putative ergogenic benefits of ginseng can be attributed in the most part to methodological problems with the majority of studies, including ineffectively controlled experimental paradigms and small sample sizes.

### 5.2. Human 'quality of life' and 'well-being'

For understandable reasons, no research has been conducted into the relief of experimentally induced stress in humans by ginseng. However, a number of studies deal with the more generalised question of 'quality of life' or 'well-being.'

Neri et al. (1995), in a double blind placebo-controlled trial involving a cohort suffering age-related memory impairment, investigated the effect of a standardised ginseng/vitamin complex on ratings of quality of life, ratings of symptoms, and performance on a memory test (Randt Memory Test). Both ratings of quality of life and memory performance were improved in the ginseng/vitamin group. Similarly, a study by Wiklund et al. (1994) demonstrated a more pronounced improvement from baseline in ratings of well-being (Psychological General Well Being Index) for the 205 healthy participants in a ginseng/vitamin group as opposed to the 185 participants taking a placebo for 12 weeks. However, an examination of the efficacy of a ginseng containing complex (Gericomplex) in the treatment and rehabilitation of geriatric patients found no positive effect on any of the objective or subjective measures that were utilised (Thommessen and Laake, 1996), and a further double blind placebo-controlled trial utilising a combination product (Ussher et al., 1995) also found no significant self-reported 'quality of life' improvements in comparison to placebo in 95 middle managers taking a ginseng/vitamins combination for 2 months.

Whilst, in these preceding studies, the utilisation of ginseng in combination with other compounds makes the attribution of experimental effects (or lack thereof) difficult; a number of studies have administered ginseng alone or attempted to isolate the effects of ginseng administered with other compounds. These include a double blind study by Wiklund et al. (1999) using the same primary endpoint as their previous (1994) study, which demonstrated significant improvements in comparison to placebo on several subscales of the Psychological General Well Being Index, but not on the whole index, following 16 weeks administration of ginseng (or placebo) to 394 symptomatic postmenopausal women. This finding is offered some qualified support by the results of an inadequately controlled trial by Tode et al. (1999), which showed that 12 postmenopausal women with climacteric syndrome showed improvements both in an imbalance of hormones and on measures of mood following 30 days administration of 6g of ginseng. However, whilst suggestive, this result is difficult to interpret as the control group utilised was a cohort of nine postmenopausal women without climacteric syndrome who were offered no treatment.

The effects of *P. ginseng* have also been studied in non-insulin-dependent diabetes mellitus (NIDDM) patients. Sotaniemi et al. (1995), in an 8-week double blind placebo-controlled study, investigated the effects of two doses (100 and 200 mg/day) of ginseng on 36 NIDDM patients. They demonstrated improvements in self ratings of mood, vigour, and well-being, as well as improved performance on a psychophysical test (timed diagram drawing) and reductions in fasted blood glucose levels in comparison to placebo. There was, however, no improvement on a working memory test (digit span). In keeping with the physiological response to *P. ginseng* reported in the previous study, Vuksan et al. (2000a,b, 2001) demonstrated reductions in postprandial blood glucose levels in both normal participants and non-insulin-dependent diabetic patients following administration of *P. quinquefolium*.

Several studies have addressed the effects of ginseng in healthy populations. These include a study by Marasco et al. (1996), who attempted to isolate the effect of ginseng on the well-being of subjectively stressed and fatigued participants ($n = 625$), in a double blind study administering either multivitamin capsules or multivitamin/ginseng capsules taken for 12 weeks. Both treatments induced a significant increase in a quality of life index in comparison to placebo, but the increase was significantly higher for the ginseng/vitamins group. Using ginseng by itself, Ellis and Reddy (2002) administered 200 mg G115/day or placebo to a small cohort of 30 healthy young adults and assessed 'quality of life' following 4 and 8 weeks of treatment with the Short Form-36 Health Survey. They found improvements on the social functioning and mental component scales at 4 weeks, with these differences attenuating by the 8-week end point. Using a similar but slightly larger cohort of 83 healthy young adults administered 200 mg G115, 400 mg G115, or a placebo daily, Cardinal and Engels (2001) found no significant differences on the Positive Affect–Negative Affect Scale (PANAS) or Profile of Mood States (POMS) at their 8-week end point.

One study (Hallstrom et al., 1982) also investigated the role of ginseng in work-related fatigue, with a double blind crossover study involving 12 night nurses. The two conditions involved administration of 1200 mg ginseng or placebo during night work, with a further comparison made with day time work. Measures included self-rating scales (mood, lethargy, sleep quality), psychophysiological performance tests (tapping and cancellation tests), and haematological and biochemical tests. Night duty in itself impaired performance on all of the mood and most of the somatic measures. There were, however, no significant changes in the ginseng group on any of the measures, except for

improved performance on the tapping test and deterioration in sleep quality and duration.

### 5.3. Cognitive effects

Whilst there is a good body of work attesting to the cognition-enhancing effects of ginseng with regard to animals, the evidence of such effects following chronic administration is scarce with regard to humans.

Several of the studies outlined above assessing 'well-being' or 'quality of life' effects included a cognitive element. For instance, Neri et al. (1995) found improved mnemonic performance (Randt Memory Test) in their cohort suffering from age-related memory impairment, whereas Thommessen and Laake (1996) found no improvement in geriatric patients on performance of the Mini-Mental State Examination, the Kendrick Object Learning test, or the Trail Making test. Non-insulin-dependent diabetic patients exhibited an improvement in psychophysical performance (timed diagram completion) but no working memory improvement (digit span) (Sotaniemi et al., 1995).

Only two investigations have focussed directly on the effect of chronic administration of ginseng on cognition. Both employed a double blind placebo-controlled design. The first study, by D'Angelo et al. (1986), involved 32 healthy young (20–24) volunteers who were given either 100 mg of G115 or placebo twice a day. Testing took place prior to and following 12 weeks of treatment. Tests included those assessing motor performance (finger tapping), auditory and visual simple reaction times, choice reaction times, attention (digit cancellation and digit symbol substitution), mental arithmetic performance, and logical deduction performance. Within-groups analysis showed that performance in the ginseng, but not the placebo group, was significantly improved above baseline on choice reaction time, logical deduction, and cancellation tests. However, between-groups analysis revealed that performance was only significantly improved for the ginseng group in comparison to placebo on the mental arithmetic test, which involved calculation of whether the sum of four two digit numbers was odd or even.

The second study was by Sorensen and Sonne (1996) and involved 112 healthy participants over 40 years (40–70) who received either 400 mg of standardised ginseng extract or placebo daily for 8–9 weeks. Tests included the finger tapping test, both auditory and visual simple reaction time tests, a 5-min letter and symbol cancellation test, a verbal fluency test (naming as many animals as possible in 1 min), a Logical Memory and Reproduction Test (reproducing units of linguistically meaningful information), the Rey-Ostreith Complex Figure Test, and a computerised Wisconsin Card Sort Test. Results showed statistically significant performance improvements for the ginseng group, in comparison to placebo, only on the fastest trials of the auditory simple reaction time tests, and on the Wisconsin Card Sort Test, a putative test of 'executive' function.

### 5.4. Methodological considerations

The literature briefly reviewed above suggests that the behavioural effects seen in humans following chronic administration of ginseng could at best be described as suggestive. Bahrke and Morgan (1994, 2000), in comprehensive reviews, suggest that the equivocal nature of the evidence is due to fundamental shortcomings in the methodology employed in this research rather than a preponderance of negative data. In particular, they emphasise inadequate research designs, the use of nonstandardised, combined, and adulterated treatments, small sample sizes, and inadequate statistical approaches. On a similar note, Vogler et al. (1999), in a review of randomised-controlled ginseng trials, conclude that the evidence from the few adequately controlled trials that met their inclusion criteria was not compelling for the efficacy of ginseng with regard to any indication for which it might be taken. The authors of these reviews are unanimous in a call for more methodologically rigorous research to be undertaken.

A further two criticisms could be added to those identified in these previous reviews. The first is the curious convention throughout the ginseng/human behavioural literature that only chronic treatment regimens, typically of eight or more weeks duration, be investigated (two exceptions are included above, Hallstrom et al., 1982 and Morris et al., 1996 who used subchronic administration regimens of 3 and 7 days, respectively). The second is the complete absence of any intermediate assessments between commencing treatment and the final end point (exceptionally, Ellis and Reddy, 2002 included an assessment at the 4-week midpoint of their 8 weeks experiment). This reliance on extended chronic regimens with a single assessment at the end of the study period obviously tells us nothing of any acute behavioural effects of ginseng or the time course of any effects. Similarly, given several instances of short-term physiological effects in rodents attenuating with chronic administration (e.g., Filaretov et al., 1988; Wang and Lee, 1998), the foregoing can tell us nothing of any potential physiological habituation to ginseng in humans.

## 6. Human studies involving acute administration

In order to lay the groundwork for a thorough investigation of the cognitive and mood effects of *P. ginseng*, our own laboratory has recently completed a series of experiments that included an investigation of the acute effects of the most widely taken and researched standardised ginseng extract (G115) in healthy young participants (Kennedy et al., 2001a,b, 2002a, 2003;[1] Scholey and Kennedy, 2002).

These studies shared the same randomised double blind placebo-controlled balanced crossover design. In all of these studies (with the exception of Kennedy et al.,

[1] This volume.

2003), 20 participants received three different single doses of the relevant extract and an identical placebo on separate occasions, with random allocation to a Latin square counterbalancing the order of presentation of treatments over the four study days. Each study day was separated by a 7-day 'washout' period. The first three of these studies (Kennedy et al., 2001a,b, 2002a) utilised the Cognitive Drug Research (CDR) computerised assessment battery. This battery has been used in over 500 clinical trials worldwide and has been shown to be sensitive to the cognitive and mood effects of a number of herbal products (Kennedy et al., 2000, 2002b; Wesnes et al., 1997, 2000). Mood changes were concurrently assessed by completion of Bond–Lader Mood scales.

On each testing day, participants performed a baseline completion of the CDR battery and mood scales. They then took the day's treatment and were retested 1, 2.5, 4, and 6 h postdose. The resulting 'change from baseline' data were analysed with respect primarily to the cognitive domain factors ('secondary memory,' 'working memory,' 'speed of memory,' 'accuracy of attention,' and 'speed of attention') previously derived by factor analysis of outcome data generated from this tailored version of the CDR battery (Wesnes et al., 2000).

The first study (Kennedy et al., 2001a) involved administration of 200, 400, and 600 mg of the standardised *P. ginseng* extract G115 and an identical placebo. The results showed that all three doses of ginseng were associated with improvements on the 'secondary memory' factor (comprised of percentage accuracy scores from four secondary memory tasks). However, these improvements were most pronounced for the middle (400 mg) dose, with significantly enhanced performance at all four postdose testing sessions. In contrast to these improvements, both of the less mnemonically active doses (200 and 600 mg) were associated at the later testing sessions with slowed performance on the 'speed of attention' factor (comprising reaction times on three attention tasks). Both the 200- and 400-mg doses were also associated with declines in subjective alertness that reached significance by the last testing session of the day (6 h postdose).

In the second, methodologically identical, study (Kennedy et al., 2001b), three doses (320, 640, 960 mg) of a 100:60 combination of *P. ginseng* extract (G115) and *G. biloba* extract (GK501) were compared to an identical placebo. This particular combination has previously been shown to improve memory performance in neurasthenic patients and healthy middle-aged participants following chronic regimens (Wesnes et al., 1997, 2000). The pattern of results of the study was strikingly similar to those following single doses of *P. ginseng* alone in the previous study, but was dissimilar to those found following *G. biloba* alone in an earlier study (Kennedy et al., 2000). Once again, memory performance was significantly improved for the optimum dose of the combination (960 mg of the combined treatment) with this effect isolated to secondary memory, whilst the less than optimum doses (320 and 640 mg) again led to decrements in terms of speed on the attention tasks.

In order to confirm these novel observations of secondary memory improvement, a further study (Kennedy et al., 2002a) was carried out; again using the same methodology but this time comparing the most cognitively advantageous single dose of extract from the previous studies to placebo (400 mg *P. ginseng*; Kennedy et al., 2001a), 960 mg ginseng/ginkgo (Kennedy et al., 2001b), and 360 mg *G. biloba* (Kennedy et al., 2000)). Again, both *P. ginseng* alone and in combination with *G. biloba* improved secondary memory performance. Following 400 mg of ginseng alone, there was also evidence of improved performance on the 'speed of memory' and 'accuracy of attention' factors.

Whilst this last experiment replicated and confirmed the beneficial mnemonic effects of 400 mg of G115, it is also interesting to note that a further study (Scholey and Kennedy, 2002) examined the effects of three doses of G115 (200, 400, 600 mg) on the performance of serial subtraction mental arithmetic tests where the cognitive 'load' was manipulated. The results showed that the cognitively beneficial 400 mg dose of G115 led to improved accuracy on the demanding Serial 7s task, whilst the detrimental 200 mg dose led to a reduced speed of performance on the same task.

In order to confirm the peripheral and CNS effects of *P. ginseng*, two further studies also examined its acute effects on blood glucose levels and EEG. In the first study (unpublished data), 200 mg, but not 400 mg, of G115 was found to reduce the blood glucose levels of healthy young volunteers during measurements spanning a time period from 60 to 120 min postadministration. In the second study (Kennedy et al., 2003, this issue), the electroencephalograph (EEG) effects of 200 mg of *P. ginseng* G115, 360 mg of *G. biloba* GK501, and placebo were assessed in 15 healthy young volunteers. The results suggested that there were similarities in the topographic EEG effects elicited by both extracts (in comparison to placebo) with reduction in the power of 'eyes closed' frontal theta and beta wavebands. However, these effects were more marked for ginseng, with a main effect of treatment within these wavebands across the whole scalp, and were accompanied by reductions in frontal alpha waveband activity and decreased latency of the P300 component of the auditory-evoked potential.

## 7. Conclusions

The evidence reviewed above from in vitro, in vivo, and animal behavioural studies suggests that ginseng and its component ginsenosides can modulate a number of physiological mechanisms and may improve indices of stress, fatigue, and learning in rodents. This review has concentrated on behaviour-relevant indices. However, it is interesting to note that most of this research has been undertaken in regions of the world with indigenous *Panax*

cultivation and a long history of usage. By contrast, the human behavioural studies, which have produced equivocal results, have been largely undertaken in Western areas of the world to which the *Panax* genus is a relative newcomer to the armoury of the behavioural pharmacopoeia. This interesting dichotomy suggests two distinct philosophical approaches. In the case of the former, the research would seem to be driven by a curiosity as to the mechanisms underlying what is taken to be the known efficacy of a traditional medication; and in the case of the latter, the impetus is a desire to 'prove' the putative effects in humans of a potentially beneficial herb. Unfortunately, whilst these two approaches are mutually beneficial in the long run, the literature pertaining to the chronic effects of ginseng in humans is riddled with so many methodological inadequacies that the question of efficacy remains open (see Bahrke and Morgan, 1994, 2000; Vogler et al., 1999).

The results of the recent acute dosage studies from our laboratory do, however, suggest not only that single doses of *P. ginseng* extract G115 can robustly affect cognitive performance, but also that they exert a direct effect on CNS functioning, as seen in the modulation of cerebroelectrical activity. These findings are entirely unsurprising given the plethora of ginseng's potential physiological effects. It is clear from this that further rigorous methodologically adequate research is required to clarify the chronic effects of ginseng and to bridge the unresearched void between acute and chronic studies.

Another issue that the acute studies also highlight is that of dosage. In the multiple single dose studies of *P. ginseng* G115 (Kennedy et al., 2001a) and the *P. ginseng*/*G. biloba* combination (Kennedy et al., 2001b), the beneficial secondary memory effects were most pronounced for specific doses (400 and 960 mg, respectively) with cognitive 'costs' in terms of slowing of the performance of attention tasks becoming evident at the later testing sessions for the less mnemonically beneficial doses (including 200 mg of G115). Again, the dose-specific nature of these results and the potential for decrements are not unexpected given similar findings in the rodent literature (reviewed above). Unfortunately, although G115 is the most widely consumed and researched standardised ginseng extract in the world, the chronic dosage research has almost exclusively involved administering the recommended daily dose of 200 mg (Coon and Ernst, 2002). Whilst it would be premature to anticipate the longer term effects of the overwhelmingly beneficial acute dose of 400 mg, it would seem sensible to either use this dose or preferably multiple doses in future chronic studies.

One of the most notable aspects of the results from the acute studies is that *P. ginseng* would appear to be more active and to have a more profound CNS effect (as assessed by EEG) than *G. biloba*. However, the two treatments differ markedly in the level and quality of research that they have attracted. Both treatments share a number of physiological actions that are potentially beneficial in groups showing cognitive decline, and it seems reasonable to suggest that research directed towards identifying the most beneficial preparation and dose of ginseng, and subsequent assessment of its efficacy as a nootropic treatment, is long overdue.

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