



Review Article

Panax ginseng Meyer Herbal Preparation HRG80 for Preventing and Mitigating Stress-Induced Failure of Cognitive Functions in Healthy Subjects

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Abstract

A large body of evidence suggests that ginsenoside metabolites contribute substantially to the pharmacological effects of *ginseng*. These metabolites (rare ginsenosides) are present in minor amounts in white *Ginseng* and in larger amounts in steam processed red *Ginseng*. A recent study aimed to obtain evidence that rare ginsenosides significantly contribute in the overall efficacy of *Ginseng*. The efficacy of two *Ginseng* preparations containing approximately the same amounts of major ginsenosides but substantially different (7.8-fold) amounts of rare ginsenosides was compared in a three-arm, randomized, double-blinded, placebo-controlled, crossover trial. A hydroponically cultivated red *Panax ginseng* Meyer root preparation (HRG80®) was compared with traditionally harvested 6-year-old white *P. ginseng* (WG) and placebo for their ability to prevent symptoms of stress such as fatigue, impaired memory, reduced concentration, and attention deficit related to daily work in healthy subjects. The effects of HRG80® (daily dose: 418 mg of red *ginseng* powder, 63.5 mg of ginsenosides, and 52 mg of rare ginsenosides), PGS Arkopharma (daily dose: 764 mg of white *ginseng* powder, 19.8 mg of ginsenosides, and 6.1 mg of rare ginsenosides), and placebo capsules, taken orally once a day for 14 days in 50 tired but otherwise healthy subjects, were studied. The efficacy outcomes included the accuracy of processing in the d2 test for cognitive functions, an accuracy score obtained using a computerized memory test, and

the perceived stress score. A statistically significant interaction effect between time and treatment was observed in the d2 attention and memory tests, indicating that HRG80 was more beneficial than placebo. The effects of WG were better than those of placebo, but the difference was not statistically significant. There was a significant difference between the effects of HRG80 and WG, which was observed after both single (day 1) and repeated administration (days 5 and 12). Importantly, the effective therapeutic daily dose of HRG80 (418 mg) was at least 10-fold lower than the commonly used effective dose red *ginseng* (4500–9000 mg per day).

Keywords: Cognitive; Occupational stress; *Panax ginseng*; Rare ginsenosides

Background

Stress-induced fatigue

Fatigue is considered an alarm phase of the adaptive defense response of the neuroendocrine-immune system to stressors [1]. Fatigue, also known as weariness, tiredness, exhaustion or lethargy, is a common health complaint that may be generally defined as a lack of energy. Fatigue and sleepiness can affect performance at work and cause transportation and industrial accidents, resulting in considerable losses of property, personal injury and even death [2]. It is estimated that approximately 20% of Americans experience fatigue of sufficient intensity to interfere with the ability to enjoy a normal life, with physical causes being responsible for 20%-60% of fatigue cases and emotional causes being responsible for the balance.

Fatigue can have a physical and/or mental nature. Physical fatigue, also known as peripheral fatigue, results from repeated muscle actions followed by an inability to continue functioning at a level commensurate with normal ability. By contrast, mental fatigue represents a failure to complete mental tasks that require self-motivation and internal cues in the absence of cognitive failure or motor weakness. Mental fatigue decreases the efficiency of subjects' occupational work or learning effectiveness in daily life. Mental fatigue may manifest in the form of decreased attention, reduced concentration, or somnolence. Acute fatigue is a normal phenomenon that disappears after a period of rest. Conversely, prolonged fatigue is often irrevocable, and the recovery mechanisms that alleviate acute fatigue are no longer effective. Chronic fatigue is caused by the prolonged accumulation of acute fatigue [3]. It is well known that social stresses frequently trigger acute mental fatigue and the onset of chronic fatigue syndrome [1]. Dealing with the COVID-19 viral outbreak has created a tremendous amount of constant stress directly related to the outbreak plus the implications of the lock down, and other restrictions that are put in place as a way to contain spreading of the virus. Stress is caused fighting the virus or worrying about a family member or yourself that you may be the next victim. There could not be more stress for people today who are losing their jobs without knowing if they have an income to meet the challenges of paying the mountain of bills piling up.

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Just the uncertainty of what the future will hold for millions of people can cause stress and stress-induced fatigue. The stress today may take a greater bodily toll than the virus itself.

Many people prefer to avoid problems related to decreased attention and reduced concentration during continuous mental work and resort to the use of stimulants (caffeine), sympathomimetics (ephedrine) and tonics such as cola [4]. However, regular consumers of coffee recognize that caffeine can disrupt sleep and that caffeine withdrawal is associated with various adverse effects including fatigue and headache. Cognitive performance is adversely affected by acute caffeine withdrawal, and even in the context of alertness reduced by sleep restriction, cognitive performance is not improved by caffeine in the absence of withdrawal effects. Because caffeine use is also associated with an increased risk for various cardiovascular diseases including high blood pressure and elevated plasma homocysteine levels, it has been suggested that caffeine consumption confers little benefit. Additionally, the diterpenes present in unfiltered coffee also appear to increase the risk of coronary heart disease [5,6]. The use of sympathomimetics might efficiently improve acute fatigue; however, their long-term use might accelerate the progression of chronic fatigue because sympathetic hyperactivity based on decreased parasympathetic activity is associated with mental fatigue induced by prolonged cognitive load [3].

Many plant extracts have exhibited good stimulating and anti-fatigue effects in experiments conducted in experimental animals. Of these, adaptogens (*Panax ginseng*, *Rhodiola rosea*, *Eleutherococcus senticosus*, *Schisandra chinensis*) have exhibited significant anti-fatigue effects including increased mental performance, particularly cognitive function, in placebo-controlled, double-blind studies [7]. These adaptogenic plants extracts can enhance resistance to stress and improve performance, concentration, and endurance during fatigue [8-15].

Ginseng

Ginseng Radix et Rhizoma (*P. ginseng* CA Meyer) is air-dried to generate white *ginseng* (WG, known in China as Ren Shen) or steamed at 100°C to generate red *ginseng* (Hon Shen), both of which contain ginsenosides Rg1 and Rb1 (dried drug) at levels of at least 0.40% [16].

Traditional and current uses

Ginseng root has been traditionally used in China, Korea, and Japan for thousands of years “to tonify the original qi greatly, resume pulse and secure collapse, tonify [the] spleen and replenish [the kidneys], engender fluid and nourish blood, tranquilize the mind and replenish wisdom” [17]. The species name was derived from the Greek words “Pan” (meaning “all”) and “axos” (meaning “cure”), allowing a translation of “cure-all” or panacea. The herbal root was named “*ginseng*” to represent two Chinese ideograms: “gin” (pronounced ren) refers to “man” and “seng” (pronounced shen) refers to “essence” because it is shaped like a man. It is believed to embody man’s three mythical essences: body, mind and spirit [18].

The first medical records on efficacy of *Ginseng*, also known as Korean *ginseng*, are dated 200 CE, and its use was later summarized (in 1596 and 1959) in Chinese Materia Medica. *Ginseng* has been used to promote vitality and healthy aging, to enhance cognitive function, reverse general weakness, improve blood circulation, and restore

normal pulse in subjects with palpitations. According to ancient records, long-term *ginseng* uses increases longevity and enhances mental and visual performance. However, *ginseng* has been used primarily as a tonic to invigorate weak bodies and help restore homeostasis, a modern term associated with adaptive stress syndrome, adaptability and adaptogen concepts [7,15,19].

The effectiveness of *ginseng* has been recognized in the West since the 18th century. *Ginseng* has been used as a general tonic or adaptogen to promote longevity and treat fatigue and mental stress. Based on its multiple health applications, including increased energy, improved cognition, enhanced immunity, reduced blood sugar levels, better circulation and improved sexual health in men, Korean red *ginseng* is often considered an all-encompassing remedy by herbalists. *Ginseng* is one of the most popular nutraceuticals, with annual sales exceeding USD 200 million [18].

According to WHO, the medicinal uses of *Ginseng Radix* et Rhizoma are divided into three categories [20]:

- Uses supported by clinical data, such as prophylactic and restorative treatment for enhancing mental and physical capacities, improving weakness, exhaustion, tiredness and loss of concentration, and aiding convalescence
- Uses described in pharmacopoeias and in traditional systems of medicine such as the treatment of impotence and prevention of hepatotoxicity and gastric ulcers.
- Uses not supported by experimental or clinical data including the treatment of nervous and metabolic disorders, infectious diseases, and other conditions.

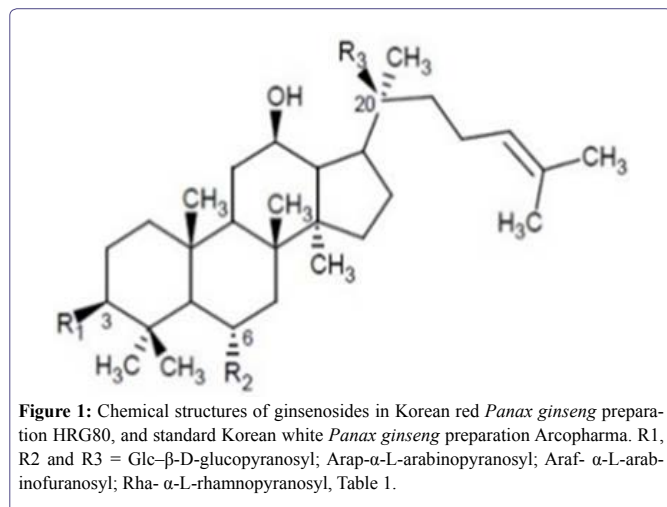
In Europe, most *ginseng* preparations are used as tonic to treat tiredness, weakness, and decreased mental and physical capacity [21].

Active constituents

Most of the pharmacological actions of *ginseng* are attributed to one type of tetracyclic triterpenoid glycosides (saponins), namely ginsenosides. Nearly 300 saponins have been reported in *Panax* species [22]. More than 200 saponins have been isolated from *ginseng*, including the roots (processed and native), leaves, stems, flower buds, berries and seeds. To date, 112 saponins have been reported as components of *P. ginseng*, including ginsenosides, which have been isolated from raw or processed *ginseng*, hydrolysates and semisynthetic saponins [23]. Most ginsenosides share a dammarane triterpenoid structure (Figure 1).

In total, 39 genuine ginsenosides have been identified and quantified in *P. ginseng* roots, leaves, stems, and berries using UPLC-QTOF/MS. The major ginsenosides in roots were M-Rb1 (0.47%), Rb1 (0.38%), Rf (0.46%), Ra2 (0.32%), Rg1 (0.31%), Re (0.3%), and Rgf (0.18%), whereas the content of other minor (rare) ginsenosides was less than 0.1% [24].

In our recent study, the content of rare ginsenosides in WG samples from Arkopham was 0.8%, compared with 12.43% in the hydroponically cultivated and processed preparation HRG80 (Figure 1 & Table 1).



The nomenclature of the ginsenosides (Ra, Rb, Rc, etc..) is associated with their decreasing polarity on TLC plates, from Ra to Rf, which correlates with the number of sugar moieties in the molecules of ginsenosides reflecting the grade of glycosylation.

In addition to ginsenosides, many other biologically active compounds have also been identified in *P. ginseng*, such as polysaccharides (*Panaxans*, ginsenans), aliphatic C17-polyacetylenes (panaxynol [also known as falcarinol], panaxydol, panaxytriol [0.002%–0.02%]), glycosides (isomaltol-α-d-glucopyranoside, ketopropyl-α-d-glucopyranoside, adenosine), alkaloids (N9-formylharman, ethyl β-carboline, perolryne, 1-carbobutoxy-β-carboline, 1-carbomethoxy-β-carboline), phenolic acids (maltol, salicylic acid, vanillic acid, p-hydroxycinnamic acid), thiazole, and lignans (gomisin N, gomisin A, gintonin

[a complex of lysophosphatidic acid and *ginseng* proteins]). In addition, numerous volatile monoterpenes and sesquiterpenes (including citral, limonene, eremophilene and β-elemene), phenolics, triglycerides, fatty acids, sugars, starch, pectins, amino acids, peptides, proteins and minerals were identified in *ginseng* roots [21,25-28].

Bioavailability of ginsenosides and their metabolism

The pharmacokinetics of different active *ginseng* compounds has been studied in both animals and humans [21]. The bioavailability of ginsenosides is low after their oral administration; however, various ginsenosides have varying pharmacokinetic behavior [29,30]. The highly glycosylated ginsenosides Rb1, Rb2, Rc, Rd., Re, Rg1 and Rg2 have poor stability in the gastrointestinal tract, and they are easily converted into monoglycosides and aglycone ginsenosides (e.g., CK, Rh2, Rh1, F1) by gastric acid and/or the intestinal flora [29-36].

After oral administration, the concentrations of ginsenosides are high in blood, but their absorption is low. The absorption profile of ginsenosides in the intestinal mucosa and the availability of both intact ginsenosides and their metabolites from the intestines are exceptionally low [29,30]. The maximal concentration of ginsenosides in plasma is reached within 2 h, suggesting that they are rapidly absorbed and distributed in tissues. Rg1, Re, Rb1 and Rc reach the brain, but their concentrations rapidly decline over time [29,37]. Rg1 and Re are more readily distributed in the brain, and they are considered the main components that directly affect central nervous system neurons [37]. The plasma level of ginsenosides indicates that protopanaxadiol ginsenosides have higher concentrations and longer half-lives than protopanaxatriol ginsenosides [29,37]. After the biotransformation of ginsenosides, microbiota in the gut produces deglycosylated products [38,39].

	Compound	R1	R2	R3	Red ginseng, %	White ginseng,%
Major ginsenosides	Rb1	O-Glc-Glc (2-1)	H	O-Glc-Glc (6-1)	0.55	0.36
	Rb2	O-Glc-Glc (2-1)	H	O-Glc-Arap (6-1)	0.31	0.33
	Rc	O-Glc-Glc (2-1)	H	O-Glc-Araf (6-1)	0.46	0.37
	Rd	O-Glc-Glc (2-1)	H	O-Glc	0.91	0.10
	Re	OH	O-Glc-Rha (2-1)	O-Glc	0.28	0.28
	Rf	OH	O-Glc-Rha (2-1)	OH	0.00	0.06
	Rg1	OH	O-Glc	O-Glc	0.25	0.30
Rare ginsenosides	Rg2	OH	O-Glc-Rha (2-1)	OH	0.37	0.02
	Rg3	O-Glc-Glc (2-1)	H	OH	1.69	0.22
	Rg6	OH	OH	O-Glc, C25-OOH	1.01	0.02
	Rh1	OH	O-Glc	OH	0.00	0.00
	Rh2	O-Glc	H	OH Δ-24	0.51	0.22
	Rh3	O-Glc	H	20-Deoxy, Δ20	1.21	0.04
	Rh4	OH	O-Glc	20-Deoxy, Δ20	1.92	0.20
	Rk1	O-Glc-Glc (2-1)	H	20-Deoxy	1.99	0.00
	CK	OH	H	O-Glc	3.52	0.02
	PDD	OH	H	OH	0.22	0.05
				Major	2.76 (18%)	1.78 (69%)
				Rare	12.43 (82%)	0.8 (31%)
				Total	15.19 (100%)	2.58 (100%)

Table 1: Content (% of dry powdered root) in Korean red *Panax ginseng* preparation HRG80 and standard Korean white *Panax ginseng* preparation Arcopharma. R1, R2 and R3 = Glc-β-D-glucopyranosyl; Arap-α-L-arabinopyranosyl; Araf- α-L-arabinofuranosyl; Rha- α-L-rhamnopyranosyl.

The intestinal bacteria isolated from human feces and some food-derived microorganisms as well as fungi from soil around *ginseng* roots convert glycosylated ginsenosides to compound K [31,40-42]. Compound K was the only ginsenoside detected in plasma and urine after the oral administration of Rb1 [43]. The deglycosylated products are better absorbed than ginsenosides based on their greater ability to permeate biological membranes [44].

It was concluded that ginsenoside metabolites contribute substantially to the pharmacological effects of *ginseng* [21].

Rare ginsenosides and hydroponically cultivated *ginseng* HRG80

The term “rare ginsenosides” has been applied to ginsenosides naturally occurring in minor amounts in *ginseng*. They are generated from major highly glycosylated ginsenosides during thermal processing as well as by intestinal microflora (gut bacteria) or gastric juice *in vivo* [18,29,32,35].

Rare ginsenosides are chemically different from major ginsenosides in various ways:

- Stereo chemical configuration of C-20 (R) compared with that in major ginsenosides (S) [18,23]
- Lack of a hydroxyl group at C-20 [35] and
- Lack of a sugar moiety at C-20 or C-3 (less glycosylated) of the tetracycline skeleton [35].

Rare ginsenosides have better bioavailability and presumably greater biological activity than their precursors containing more than one sugar moiety [18,29,30,35]. Rare ginsenosides have a wide range of bioactivities. For instance, ginsenoside CK was proved to protect against myocardial infarction and inhibit angiogenesis and the proliferation of various cancer cells [35,45,46]. Ginsenoside F2 exhibited anti-tumor and anti-obesity activities [47,48]. The rare ginsenoside 20(R)-Rg3 displayed more potent adjuvant activity than the major ginsenoside 20(S)-Rg3 [49].

High rare ginsenoside levels can be obtained in *ginseng* preparations by converting major ginsenosides using various methods such as heating, mild acid hydrolysis, alkali treatment and microbial and enzymatic biotransformation [34,50].

According to EP, the content of ginsenoside saponins in wild growing roots normally ranges 0.6–3.0% [51]. The content of active ginsenosides in a representative sample of white *P. ginseng* was approximately 2.6% of the root powder content (Figure 1 and Table 1). Seven compounds (Rg1, Rg2, Re, Rf, Rb1, Rb2, Rc and Rd) represented the major ginsenosides (1.78% dry root), comprising 69% of the root ginsenosides. They have poor bioavailability, they but easily metabolized/hydrolyzed by intestinal bacteria into active ginsenosides with higher bioavailability (Rh2, Rg3, compound K, Rg6, Rk1, Rk2, Rh1), which can be obtained via traditional cooking methods for *P. ginseng* roots.

Red *ginseng* powder in HRG80 contains 15.2% total ginsenosides (approximately 6-fold higher level than that WG), including 12.43% [15-fold higher level than that in WG) rare ginsenosides (CK, Rk1, Rh2, Rh3, Rh4, Rg2, Rg3, Rg6; Table 1).

Cultivation of *P. ginseng* in culture, including tissue (e.g., meristem, leaf tissue), cell and organ cultures (e.g., roots, hairy roots), is a promising approach to increase the content of targeted secondary metabolites under controlled conditions [52]. It is presumed that this approach is most suitable and effective for good manufacturing practices [52,53]. Soilless cultivation of *ginseng* in hydroponic and aeroponic cultures is most appropriate because of several reasons, including the fact that this method is safe and free of pesticides and agrochemicals [54-57]. Parameters including the nutrient solution composition, pH, aeration, temperature, light and numerous stressful factors are crucial for optimal plant growth and development and the increased biosynthesis of pharmacologically active secondary plant metabolites that play important roles in plant defense responses and survival [54,55,58]. Choi et al., cultivated *P. ginseng* hydroponically and observed higher ginsenoside and phenolic content in its leaves [54].

High levels of ginsenosides in HRG80 preparations were achieved by cultivating roots in stressful conditions, under which the roots produce large amounts of plant secondary metabolites and ginsenosides to adapt and survive [10]. Substantially (15.6-fold) higher rare ginsenoside content in *ginseng* roots was obtained by steaming the roots at 100°C, a traditionally used processing method [10]. Importantly, the HRG80 capsules contain 50% inactive carriers; therefore, the total content of rare ginsenosides in capsules was 6.2%, which was 7.8-fold higher than that in WG (Arkopharma) capsules used as a comparator in a study on human subjects [10].

Pharmacological activity of ginsenosides, neuroprotective effect

Many studies have examined the botanical, chemical, pharmacological, and therapeutic properties of *ginseng* extracts, fractions, and isolated compounds in animal models and *in vitro*, and more than 6000 articles have been published since the 1950s [23]. Effects on the nervous, cardiovascular, immune, endocrine, reproductive, and detoxification systems and skin have been demonstrated [19,21]. Such investigations revealed that ginsenosides are constituents with a broad set of pharmacological activities (e.g., cytoprotective effects, anti-inflammatory effects, anti-microbial effects, anti-cancer effects) in various cell culture models and animal experiments [21,24,59-61].

Numerous *in vivo* and *in vitro* studies of *ginseng* have suggested its useful effects against cardiovascular and neurodegenerative diseases, central nervous system disorders, immunodeficiency and cancer, as well as effects against aging-related diseases [19]. In general, anti-oxidant, anti-inflammatory, anti-apoptotic and immune-stimulatory defense responses primarily underlie *ginseng*-mediated protective mechanisms [24, 59-61].

Ginsenosides have been found to exhibit immunomodulatory, anti-cancer, anti-fatigue, anti-aging, anti-diabetic, anti-depressant like and neuroprotective effects [62-68]. The effects of ginsenosides Rb1, Rg1, Rg2, Rg3, Ro, Rb3, Rd, Rf, Rh2 and 20 (S)-PTon the nervous system and behavior of animals were demonstrated in numerous studies [21]. Rb1, Rd, Re, Rg1, Rg2, Rg3, Rh1, Rh2, Rh3, PF11 and NTR1, as well as gintonin and compound K, have displayed potential activity against cognitive deficits [29]. Some of these compounds modulate glutamergic and cholinergic neurotransmission and various intracellular signaling pathways with important roles in the regulation of

cognitive functions. For example, compound K inhibits mTOR signaling in astrocytes, suggesting that it may be useful for treating or preventing several age-associated conditions including neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [29]. Compound K exerts anti-inflammatory effects in microglia by inhibiting the generation of free radicals and MAPK-mediated signaling. Compound K prevents mitochondrial dysfunction and activates antioxidant signal in neurons, leading to neuroprotection and preventing neuronal cell death [29].

The major ginsenosides Rg1 and Rb1 increase neural plasticity; in particular, Rg1 increases the proliferation and differentiation of neural progenitor cells in the hippocampus of adult mice and ischemia models in gerbils. This finding suggests its great value in treating Alzheimer's disease and other neurodegenerative disorders characterized by neuronal loss. Ginsenosides Rg3, Rg1 and Rb1 can prevent neurodegeneration by modulating several adaptive stress-response signaling pathways involved in the regulation of brain cell survival [66]. Ginsenosides Rb1 and Rg1 induce the secretion of brain-derived neurotrophic factor, which promotes the growth, differentiation and survival of neuronal cells by increasing intracellular cyclic AMP levels via protein kinase, thereby augmenting new synapse formation and signaling [67]. Rg1 and Rb1 also upregulate brain anti-oxidant enzymes and inhibit apoptosis and calcium overload, which are important for neuroprotection [66].

Clinical studies

Effects on cognitive functions and anti-fatigue activity

The results of clinical trials suggesting beneficial effects of *ginseng* on stress and cognitive functions were critically summarized in several comprehensive and systematic review articles [21,69-72]. The outcomes obtained in clinical studies assessing the effects of *ginseng* extracts on cognitive functions, physical performance, and fatigues are conflicting. Most studies were hampered by poor methodology, a lack of proper controls, and the absence of extract standardization. A meta-analysis of 12 Randomized Controlled Trials (RCTs) involving 630 participants (311 participants in the intervention group and 319 participants in the placebo group) revealed a lack of sufficient clinical evidence supporting the use of *ginseng* supplements to reduce fatigue and enhance physical performance because only a few RCTs with small sample sizes have been published to date [13].

Ten trials with good methodology (Jahad scale >3 in five of the eight trials) evaluated the effects of WG or red *ginseng* on psychomotor function [73-77]. Overall, six positive and two negative results were obtained in these studies. The authors concluded that there was a strong evidence of efficacy concerning psychomotor function. The authors reported the anti-mental fatigue effects of *P. ginseng* extract (G115) based on improvements in cognitive performance and memory in healthy volunteers in serial clinical studies [78-82]. However, no significant difference in efficacy was found between *ginseng* and placebo [71,78].

The results of several studies suggested that Korean red *ginseng* improves cognitive function (performance) in patients with Alzheimer's disease when applied at daily doses of 4.5 and 9.0g for at least 12 weeks [73,74,83,84]. Maximal improvement was found around week 24.

The same dose of Korean red *ginseng* effectively enhanced cognitive function in a study of 20 healthy young males who were randomly assigned to receive a daily dose of 4500 mg of red *ginseng* or placebo for 2 weeks [85]. The cognition-enhancing effect of Korean *ginseng* powder was observed in a larger group of 90 healthy volunteers with mild cognitive impairment who received 3 g of Korean *ginseng* powder or placebo for 6 months. The subjects treated with *ginseng* displayed significant improvements of visual learning and visual recall after 6 months compared with the outcomes of placebo-treated subjects [86].

Altered mood, impaired memory and reduced concentration are the major symptoms of chronic fatigue-associated disorders. The efficacy of *P.ginseng* in the treatment of mental and chronic fatigue was demonstrated in several studies. Thus, the anti-fatigue effects of 1200 mg of *P.ginseng* in a double-blind, placebo-controlled, crossover study were evaluated in night nurses, and the results were compared with the findings in nurses engaged in daytime work [87]. *Ginseng* restored ratings on tests of mood, competence and general performance, and the study concluded that *ginseng* had anti-fatigue activity [87]. The anti-fatigue effects of 2000 mg of *P.ginseng* was demonstrated in another randomized, double-blind, placebo-controlled trial of 90 subjects with chronic fatigue [12].

The ability of red *ginseng* to decrease industrial (occupational) fatigue and improve neuro-mental symptoms was demonstrated in 43-65-year-old taxi drivers [88]. The drivers were treated with red *ginseng* or placebo before and after work and their mental fatigue was measured using the F value, which was calculated as the reaction of the brain to visual irritation. The F value decreases in proportion to the severity of mental fatigue and aging. Based on the results, the authors concluded that red *ginseng* increases the F value and improves many neuro-mental symptoms.

Overall, *ginseng* is considered a promising treatment for fatigue. *Ginseng* may be a viable treatment for fatigue in people with chronic illnesses [11].

Study of HRG80 in Stress-Induced Fatigue

The efficacy of two *ginseng* preparations containing approximately the same amounts of major ginsenosides but substantially different (7.8-fold) amounts of rare ginsenosides (Table 1 and Figure 2) was compared in 50 tired but otherwise healthy subjects in a three-arm, randomized, double-blinded, placebo-controlled crossover trial [10]. The aim of the study was to assess the efficacy of a hydroponically cultivated red *P. ginseng* root preparation (HRG80) and a traditionally harvested six-year-old white *P. ginseng* standard preparation (WG) in comparison with placebo in preventing symptoms of stress. The efficacy measures included the accuracy of processing in the d2 test for cognitive functions, the obtained accuracy score of a computerized memory test (learning, memory and attention), and the Perceived Stress (PS) score (Figures 3 & 4) [89-90].

A statistically significant interaction effect between time and treatment ($p < 0.0001$) was observed in the attention d2 and memory tests, indicating that HRG80 was more beneficial than placebo. The effects of WG were better than those of placebo, but the difference was not statistically significant. HRG80 was associated with significantly better performance than WG ($p < 0.0001$) after both single (day 1) and repeated administration (days 5 and 12).

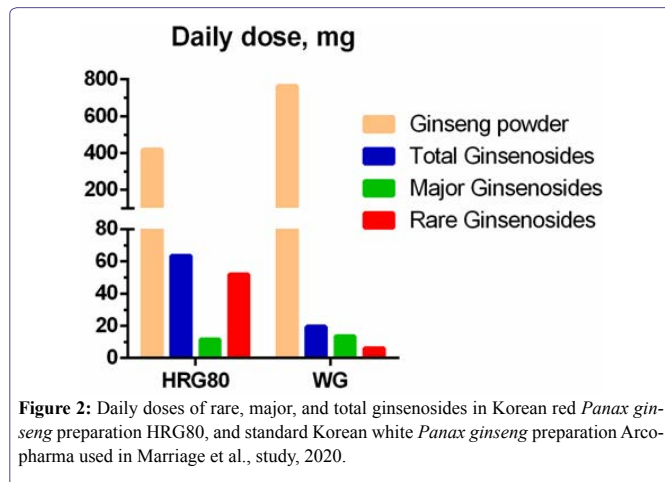


Figure 2: Daily doses of rare, major, and total ginsenosides in Korean red *Panax ginseng* preparation HRG80, and standard Korean white *Panax ginseng* preparation Arco-pharma used in Marriage et al., study, 2020.

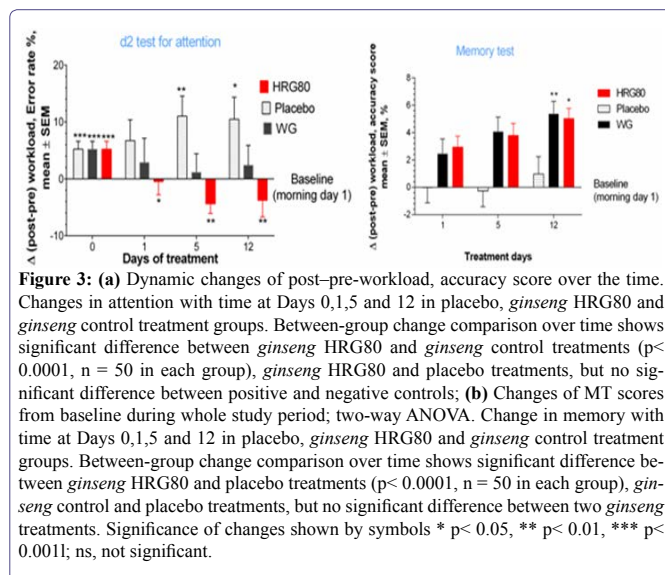


Figure 3: (a) Dynamic changes of post-pre-workload, accuracy score over the time. Changes in attention with time at Days 0,1,5 and 12 in placebo, *ginseng* HRG80 and *ginseng* control treatment groups. Between-group change comparison over time shows significant difference between *ginseng* HRG80 and *ginseng* control treatments ($p < 0.0001$, $n = 50$ in each group), *ginseng* HRG80 and placebo treatments, but no significant difference between positive and negative controls; (b) Changes of MT scores from baseline during whole study period; two-way ANOVA. Change in memory with time at Days 0,1,5 and 12 in placebo, *ginseng* HRG80 and *ginseng* control treatment groups. Between-group change comparison over time shows significant difference between *ginseng* HRG80 and placebo treatments ($p < 0.0001$, $n = 50$ in each group), *ginseng* control and placebo treatments, but no significant difference between two *ginseng* treatments. Significance of changes shown by symbols * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ns, not significant.

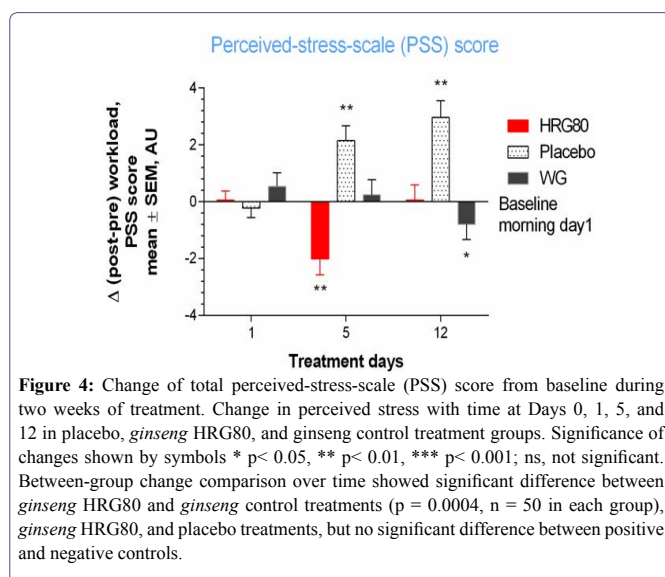


Figure 4: Change of total perceived-stress-scale (PSS) score from baseline during two weeks of treatment. Change in perceived stress with time at Days 0, 1, 5, and 12 in placebo, *ginseng* HRG80, and *ginseng* control treatment groups. Significance of changes shown by symbols * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ns, not significant. Between-group change comparison over time showed significant difference between *ginseng* HRG80 and *ginseng* control treatments ($p = 0.0004$, $n = 50$ in each group), *ginseng* HRG80, and placebo treatments, but no significant difference between positive and negative controls.

A statistically significant interaction effect between time and treatment was observed in the PS test, indicating that HRG80 was more beneficial than WG. Meanwhile, no difference in efficacy between HRG80 and WG was identified in the memory test. The number and types of adverse events were similar among the groups and no serious adverse events were observed.

Study Highlights

- Red Korean *ginseng* is useful for ameliorating occupational stress-induced fatigue in healthy subjects.
- Social stress often triggers acute mental fatigue and the onset of chronic fatigue syndrome as a result of the persistent accumulation of acute fatigue [3]. Mental fatigue is associated with decreased attention and reduced ability to concentrate, resulting in a failure to complete mental tasks, which could negatively affect work performance [3]. This is of primary importance for many healthy subjects involved in social networks, requiring regular computer use. Therefore, the participants of this study were individuals occupied in social services, including teleoperators, engineers and IT personnel who are permanently overloaded with cognitive tasks and exposed to social stress. The results of our study suggesting that *ginseng* HRG80 is a promising treatment for fatigue are in line with those of clinical studies of other adaptogenic plant extracts that exhibit anti-fatigue effects by increasing the mental performance and cognitive functions of healthy subjects and patients with chronic fatigue [8].
- The primary objective of the study was to compare the efficacy and tolerability of the hydroponically cultivated red *P. ginseng* preparation HRG80 with placebo and WG as an active control with respect to effects on cognitive function, memory and stress-induced fatigue in healthy subjects.
- HRG80 treatment exhibited significantly superior effects compared with those of WG and placebo regarding attention, memory and PS scores after single and repeated administration.
- The effective therapeutic daily dose of *P.ginseng* HRG80 of 418 mg is at least 10-fold lower than the commonly used effective doses of red *ginseng* (4500-9000 mg per day).
- A large body of evidence suggests that ginsenosidemetabolites contribute substantially to the pharmacological effects of *ginseng* [21]. These metabolites were found in minor amounts (rare ginsenosides) in WG but in larger amounts in steam-processed red *ginseng*. The results of a recently published clinical study provide evidence that rare ginsenosides significantly contribute to the overall efficacy of *ginseng* [10].

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