

Actoprotective effect of ginseng: improving mental and physical performance

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Actoprotectors are preparations that increase the mental performance and enhance body stability against physical loads without increasing oxygen consumption. Actoprotectors are regarded as a subclass of adaptogens that hold a significant capacity to increase physical performance. The focus of this article is studying adaptogen herbs of genus *Panax* (*P. ginseng* in particular) and their capabilities as actoprotectors. Some animal experiments and human studies about actoprotective properties of genus *Panax* attest that *P. ginseng* (administered as an extract) significantly increased the physical and intellectual work capacities, and the data provided suggests that ginseng is a natural source of actoprotectors. Preparations of ginseng can be regarded as potential actoprotectors which give way to further research of its influence on physical and mental work capacity, endurance and restoration after exhaustive physical loads while compared with reference actoprotectors.

Keywords: *Panax ginseng*, Ginseng, Actoprotector, Memory, Physical work capacity

INTRODUCTION

Throughout the 70's of the 20th century, investigations on a new class of pharmacologically active substances—actoprotectors (aids for improving human's physical and mental efficiency) were guided by Professor Vladimir Vinogradov. These investigations resulted from the development of the first and the most commonly used actoprotector, bemetil (chemical structure 2-ethylbenzimidazole hydrobromide) (Fig. 1). Later, other actoprotectors were created, such as bromantane [1,2].

For the last 20 yr, people synthesized and studied other compounds with actoprotective properties belonging to different chemical classes: thiazoloindole derivatives, 3-hydroxypyridine derivatives, nicotinic acid derivatives, 1-oxa-4-aza-2-silacyclanes etc [3-5].

At the same time, experimental studies and analyses of pharmacological properties of certain herbs proved that some phytochemicals, while having a very low toxicity, are also aids that improve human's physical and mental efficiency. Among such herbs, there are interesting plant adaptogens: *Panax ginseng* and other species from genus *Panax*, *Eleutherococcus senticosus*, *Pfaffia paniculata*, *Withania somnifera*, *Schisandra chinensis*, *Gynostemma pentaphyllum*, *Rhodiola rosea*, etc. [1,6-16].

DEFINITION AND CLASSIFICATION OF ACTOPROTECTORS

Actoprotectors are preparations that enhance the body

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stability against physical loads without increasing oxygen consumption or heat production, increasing the efficiency factor. Actoprotectors fall under the metabolic drugs of non-consumptive class of action and possibly possessing antihypoxic characteristics at either higher or lower extent. The agents differ from antihypoxants since actoprotectors primarily stimulate protein synthesis and increase working capacity. Moreover, the preparations exert an antihypoxic effect under hypoxic conditions, which may advance as a result of mitochondrion-decreased ability to oxidize substrates under higher physical loads. However, this is not the case in hypoxic conditions of other etiology [1,2].

The principal difference of actoprotectors and psychostimulants (caffeine, sydnocarb, phenamine, methylphenidate, modafinil, adrafinil etc.) is that actoprotectors are agents of non-exhaustive actions. In actions of actoprotectors, there is no increase in oxygen consumption or heat production; differing with nootropic agents—actoprotectors increase not only mental, but physical work capacity as well. The difference between actoprotectors and adaptogens is not so simple. Their characteristics show many similarities. Vinogradov presumed that actoprotectors did not have enough theoretical background to be labeled as a new class of pharmacological compounds. This separation appeared as a result of development of military medicine to improve physical strength [17].

Our opinion about this connection is that the actoprotectors are considered as synthetic (and possibly, natural origin) adaptogens with strong positive influence on physical work capacity. This is the most logical reasoning regarding the classification of actoprotectors. It means, for the convenience of pharmacological classification, some synthetic adaptogens that highly increase the physical performance can be determined as ‘actoprotectors,’ but this term is not applicable for other synthetic adaptogens. For example, benzimidazole derivatives dibazol (bendazol), levamisole and afobazol are all regarded in scientific literature as adaptogens. Dibazol’s adaptogenic action was initially realized in adaptation in difficult environment conditions through immune mechanisms [18-27]. Levamisole’s adaptogenic activity is also connected primarily with adaptive changes in the immune system [28-31]. Afobazol has neuroprotective properties established *in vitro* on survival of HT-22 neurons in the model of oxidative stress and glutamate toxicity [32], and its adaptogenic action was determined through central nervous system adaptation [33-35]. Since benzimidazole derivatives have adaptogenic properties, these compounds are similar to bemitil, but their influence on physical work capacity is either absent or minimal. This fact does

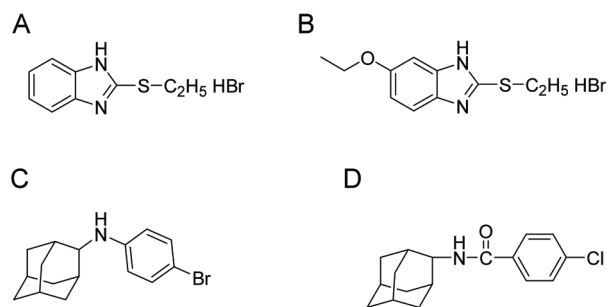


Fig. 1. Structures of actoprotectors. (A) Bemitil, (B) ethomersol, (C) bromantane, and (D) chlodantane.

not allow them to be referred as actoprotectors. We think that briefly, actoprotectors can be mentioned as ‘synthetic or natural origin adaptogens with significant capacity to increase physical and mental performance.’

The classic reference actoprotector is bemitil; in its chemical structure, bemitil is 2-ethylthiobenzimidazole hydrobromide (Fig. 1). Currently, only two compounds, among all actoprotectors, are permitted for medical administration: bemitil (commercial name Antihot, certified in Ukraine as dietary supplement) and bromantane (commercial name Ladasten, certified in Russia as a drug) (Fig. 1). Adaptogenic herbs are more available all over the world. In many countries they are certified not only as drugs but also as dietary supplements. It becomes more convenient in the usage for people with active lifestyle or whose professional activity is related with heavy physical and/or mental loads (athletes, military service men, firefighters, crew members, computer operators, night shift doctors and nurses, etc.). Therefore, adaptogenic herbs as potential actoprotectors have not just only theoretical importance for the understanding of mechanisms of their pharmacological action, but also practical applications in sport and occupational medicine.

A primary analysis of actoprotector’s effect under heavy physical loads observed its influence on carbohydrates and energy metabolism: slight decreases of glycogen and creatine phosphate content in the liver and muscles, and of glucose in the blood and lower accumulation of lactates in the tissues and blood, and lower increases in heat production and oxygen consumption. After the period of exertion ended, rehabilitation of the factors under study was accelerated, and indeed, some factors showed super compensation [1,2]. Fig. 2 illustrates the influence of benzimidazole actoprotector on glycogen content in rat liver during recovery.

Interestingly, the 4 hour time-point showed a reversed pattern for all of the parameters. The authors assumed

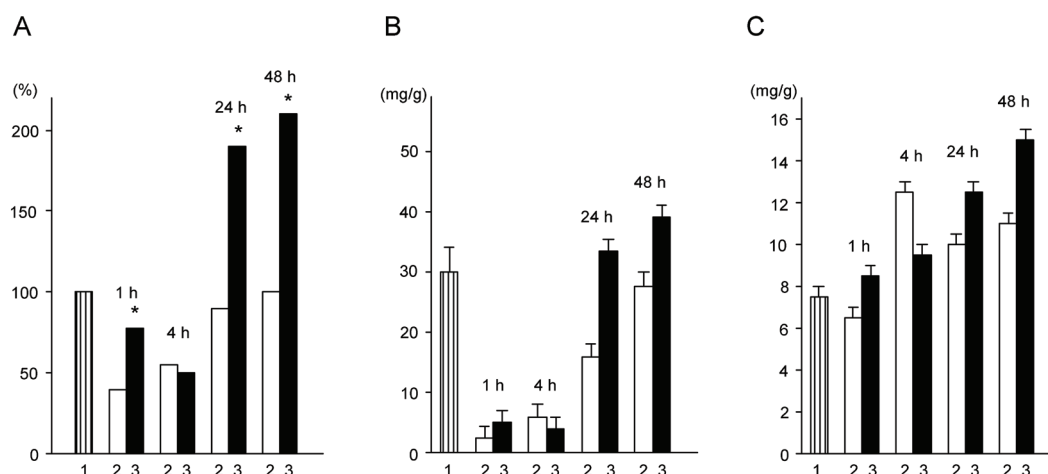


Fig. 2. Influence of benzimidazole actoprotector (50 mg/kg) on duration of repeated running (% of first running) (A), content of glycogen in liver (B), and total RNA content in liver (C) of rats during recovery after running. 1, initiative parameter (for work capacity) or parameter of intact group (for content of glycogen and RNA); 2, control group; 3, experimental group (actoprotector administration). * $p < 0.05$ in comparison with duration of repeated running of rats from control group [36].

that at this point of the recovery period, the energy resources are expended on different biosynthetic processes, leaving the energy supply for muscular activity is severely limited [36]. Thus, in this situation, “switching” of intracellular metabolism to the anabolic reactions, rather than catabolic predominantly, occurs. This is why the work capacity settles at a relatively low level and cannot be increased using pharmacological agents. Bobkov et al. [36] noted the increase of the heart and not the liver glycogen content by the 4th hour of the recovery period, and drew conclusions about the importance of the liver glycogen content to the capacity for work. However, this phenomenon reflects a more complex mechanism that cannot be explained on the aforementioned basis alone and requires further research. The significant decrease of total RNA content in the 4th hour of the recovery period in liver under benzimidazole actoprotector administration is believed to be the evidence behind this reasoning (Fig. 2).

It has been established that the therapeutic effect of actoprotectors (bemitil, as an example) is a function of its complex mechanism entailing cell genome activation, optimization of mitochondrial oxidation, oxidative stress reduction, and stimulation of cellular immune response [1,2].

COMPOSITION OF GINSENG PREPARATIONS AND THEIR STANDARDIZATION

Recently *P. ginseng* (known also as ginseng and Korean ginseng) is one of the most well-known and studied

adaptogens. It is the most studied among plants belonging to genus *Panax*. It is grown in China, Korea, Japan, and Russia while having a long-time (some thousands years) history of its administration in oriental medicine. Nowadays, *P. ginseng* as a dietary and medicinal custom is not only in Asia (especially Korea and China), but is also used world-wide. Ginseng is available in many forms: whole root, root powder (white ginseng), steamed root powder (red ginseng), heat processed root powder (sun ginseng), steamed and dried roots for 5 d and 9 times respectively (black ginseng), teas, tinctures, and standardized root extracts containing known and reproducible amounts of ginseng saponins in every batch [37-40]. In some countries, ginseng preparations are produced from *P. ginseng* cells cultivated in cell cultures. Other species from genus *Panax* (*P. bipinnatifidus*, *P. japonicus*, *P. notoginseng*, *P. pseudoginseng*, *P. quinquefolius*, *P. stipuleanatus*, *P. trifolius*, *P. vietnamensis*, *P. wangianus*, *P. zingiberensis*) are not as well-known as *P. ginseng*, but they are also used in oriental medicine.

Among the diverse constituents of ginseng, steroid-like phytochemicals with adaptogenic properties named ginsenosides have been found to be major components responsible for their biological and pharmacological actions. Ginsenosides are a special group of triterpenoid saponins that can be classified into two main groups by the skeleton of their aglycones: panaxadiol group (Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, and Rs1) and panaxatriol group (Re, Rf, Rg1, Rg2, and Rh1) [41] (Fig. 3).

Ginsenosides are found nearly exclusively in *Panax* species. More than 150 naturally occurring ginsenosides

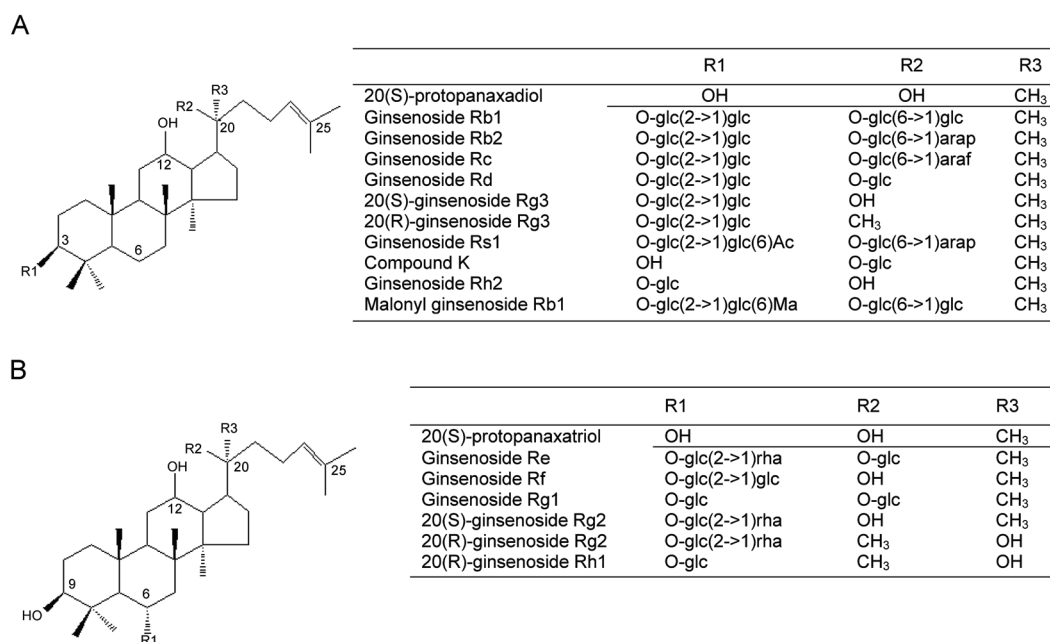


Fig. 3. Chemical structure of ginsenosides. (A) Protopanaxadiol-type ginsenoside, (B) protopanaxatriol-type ginsenoside. glc, b-D-glucopyranosyl; arap, a-L-arabinoyranosyl; araf, a-L-arabinofuranosyl; Ac, acetyl; Ma, malonyl; rha, a-L-rhamnopyranosyl.

have been isolated from roots, leaves/stems, fruits, and/or flower buds of ginseng. Ginsenosides have been the target to many researches as they are believed to be the main active components behind the claims of ginseng's efficacy. These steroid-like phytochemicals, which are known to counter the negative influence of stress, are beneficial for health property. The glycosides act on the adrenal glands, helping to prevent adrenal hypertrophy and excess corticosteroid production in response to stress. Ginsenosides increase protein synthesis and the activity of neurotransmitters in the brain. Ginseng stimulates the formation of blood vessels and improves blood circulation in the brain, thereby improving memory and cognitive abilities. Ginseng is also used as treatments of diabetes, migraines, infections, cancer, radiation and chemotherapy protection, sleep aid, and appetite stimulation [42-44].

The ginsenosides content in ginseng preparations can vary depending on the species, the age, portion of the plant, the preservation method, the season of harvest, and the extraction method [45-47]. For example, comparative study on the ginsenosides of 47 samples of ginseng products derived from different *Panax* species was conducted using a reverse-phase HPLC method. The results showed that the ginsenoside compositions in ginseng products of different origins were considerably variable [48]. Total saponin contents varied by 10-fold from the highest product to the lowest one. Chikusetsu-ninjin derived from *P. japonicus* (Japan) was found to have the highest content

(192.80-296.18 mg/g) and a product from *P. ginseng* to be the lowest (5.78-15.63 mg/g). Two main groups suggested by phytochemical data were clearly observed: group I mainly containing dammarane saponins consisted of *P. ginseng*, *P. quinquefolius*, *P. notoginseng*, *P. vietnamensis* and *P. vietnamensis* var. *fuscidiscus* and group II containing a large amount of oleanolic acid saponins was composed of *P. japonicus* (Japan), *P. zingiberensis*, *P. japonicus* (China), *P. japonicus* var. *angustifolius*, *P. japonicus* var. *major*, and *P. stipuleanatus*. The ratios of the subtotal of dammarane saponins to that of oleanolic acid saponins were found to be >1.9 and <0.25 for groups I and II, respectively [48]. The product samples derived from the same botanical origin revealed similar constituent patterns, in other words, each *Panax* taxon showed its own characteristic chromatographic profile, which appeared in the specific shape of an 11-direction radar graph constructed on the basis of the result of quantitative analysis [48]. Similarities of chemical constitution were seen among the closely phylogenetically-related taxa, including *P. ginseng* and *P. quinquefolius*, *P. vietnamensis* and *P. vietnamensis* var. *fuscidiscus*, *P. japonicus* (China) and its varieties, except for *P. japonicus* (Japan) and *P. zingiberensis* [48].

As mentioned above, except for ginsenosides, plants from genus *Panax* contain other active compounds (carbohydrates including polysaccharides, vitamins, alkaloids, fat soluble components, organic acids, microelements and macroelements, etc.) which make important

contributions in their pharmacological activity, but the quantity and composition of these compounds differ among the different species [49-53].

All together these facts explain why pharmacological properties of plants from genus *Panax* are similar, but not the same; moreover, pharmacological activity of different preparations from the same part (roots, leaves etc.) of the same species can be different depending on the season of harvest and the extraction method. Finally, differences between different ginseng preparations can have an influence not just only in their potency, but also in kinds of their pharmacological activity. Recently, the most widely standardized ginseng extracts, both commercially and for research purposes, are G115 [54] and products of Korea Ginseng Corporation (Seoul, Korea), concentrated aqueous extracts from *P. ginseng* root, which are standardized to contain a certain amount of ginsenosides.

Poor standardization can cause difficulties in evaluation of data received from the animal experiments and human studies related with pharmacological activity of adaptogens including ginseng. It means that sometimes data from different laboratories connected with pharmacological properties (including neurocognitive and actoprotective activity) of preparations from the same species cannot be compared (or, at least, their comparison is very complicated). In conclusion, data on pharmacological activity of preparations received from different species from genus *Panax* should be evaluated separately.

EFFECT ON EXERCISE PERFORMANCE

Analyses of scientific literature connected with influence of preparations from plants of genus *Panax* on physical work capacity is more complicated when compared with that of their influence on cognitive functions. Similar to the situation with memory and attention, most studies are connected with preparations from *P. ginseng*. A few group use *P. quinquefolius*, *P. notoginseng* and *P. japonicas* as well.

Results of many animal experiments attest that *P. ginseng* preparations can significantly increase physical work capacity. Administration preparations with different qualities from this plant in different dosages increase exhaustion time for swimming in mice [55-58] and rats [59] and exhaustion time for treadmill running in rats [60-62]. Short-term (4 d), although not acute, treatment with complex of ginseng saponins (10 and 20 mg/kg/d) significantly prolongs the aerobic endurance of non-trained rats exercising at approximately 70% $\text{VO}_{2\text{max}}$ [63]. Wang et al. [64] established that PEC (the oral liquid which con-

sists of *P. quinquefolius*, *Epimedium brevicornum*, *S. chinensis* Bail and *Cervus eplaphus*) administration could prolong swimming duration of mice in water tank and increase the tolerant ability against oxygen-deficiency.

However at the same time, results of some other experimental studies show no significant influence of ginseng on physical work capacity. Martinez and Staba [65] established that saponin extracts from different kinds of *P. ginseng* (Korean red, Shiu-Chi red, Kirin red and Sanchi ginseng) and *P. quinquefolius* (Canadian, American white and American red ginseng) have no influence on exhaustion time for swimming in rats.

The term 'ergogenic' stems from the Greek roots 'ergon' and 'genes,' meaning 'work' and 'born,' respectively. Any means of enhancing energy production or utilization may be described as an ergogenic aid [66]. It defines ergogenic aids as substances, foods, or training methods that enhance energy production, in use or recovery, while providing athletes with a competitive advantage. Regarding to herbs currently being used to enhance physical performance, Bucci [67] subscribed that they can have different reasons for use including their adaptogenic properties, testosterone-like (anabolic) effect, stimulating effect on central nervous system, effect on capacity to increase endogenous testosterone production (testosterone booster), and alpha-adrenergic agonist properties etc. A wide understanding of ergogenic aid makes this term a practical definition in the field of sport science and sport medicine but not pharmacology.

According to modern pharmacological classification, *P. ginseng* and most other herbs from genus *Panax* should be definite adaptogens due to their ability to increase physical work capacity in a healthy person, this being one of the important components of adaptogens' action [1]. However on the other hand, different adaptogens have different capacities to increase physical performance. That is why adaptogens with the strongest potency to increase physical work capacity are referred to actoprotectors. According to conventional wisdom [2], it is reasonable to refer agents from actoprotectors' class to synthetic adaptogens and to regard their strong actoprotective effect as one of their components of adaptogenic action. It should be stressed that the focus of this study is on the ability to enhance physical work capacity and not on the adaptogens' origins, synthetic or natural. According to this point of view, adaptogens of natural origin also can be refer to actoprotectors if they have potent influence on physical work capacity.

Some mechanisms of antifatigue action can be included into adaptogen action; but other mechanisms can be

different. As we see regarding to ginseng, its actoprotective properties are very discussible, but antifatigue properties have even more evidence supporting this along with proofs.

From the results of experimental and human studies on the influence of ginseng preparations on physical performance and restoration after loads, there are many other controversies besides those mentioned about critical points of protocols and experimental techniques, including administration of different quality and composition ginseng supplements.

Administration of ginseng preparations on physical work capacity showed controversial results in animal experiments. Detail analyses of experimental results demonstrated no influence by ginseng based on the swimming exhaustion time of rats and mice indicating critical points. For example, in one study some experimental groups included very few animals (3-4) [65]. In this study, results of the swimming test generally showed variable swimming time (205-592 min). It cannot be excluded that such various individual results can possibly be connected with methodological defects because of the difficulties in managing swimming test (water of room temperature was preferred to avoid gas sorption on hair but could not use fresh tap water) along with insufficient quantity of animals in some experimental groups. In

Jung et al.'s study [57], very high doses of ginseng extract were used (500 mg/kg/d) during a long time period (4 wk), although it is well-known that too high of dose of adaptogens can lead to inverse effects [1].

Results from numerous human studies, which are summarized in Table 1, are also controversial. Similar to animal experiments, interpretation of these studies is complicated since variable methodology was applied. For example, a study by Knapik et al. (cited in [67]) demonstrated that ginseng supplementation had no effect but had a very small sample size (5 athletes in experimental group and 6 in placebo group). Ziembra et al. [68] established that ginseng administration does improve psychomotor performance during exercise without affecting exercise capacity in their study with soccer players, but used non-specific method for this kind of sport test (incremental bicycle ergometer exercise test). Perialisi et al. [69] demonstrated substantial ergogenic effects but for ginseng combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace element. Kulaputana et al. [70] established that ginseng supplementation does not exert an ergogenic property on aerobic fitness enhancement in well-fit individuals with 60 young men (30 in experimental and 30 in control group), but used non-standardized 100% ginseng instead of any standardized ginseng preparation such as G115, products of Korea

Table 1. Results of human studies with plants from genus *Panax* on physical performance (adapted with modifications from [67])

Study (reference)	Subject (n)	Study design	Subject age range	Daily dose	Preparation type	Study duration	Effects (statistically significant unless otherwise stated)
<i>P. ginseng</i>							
Dorling et al., 1980 (cited in [67])	60	DB, PC	22-80 yr	#	G115	12 wk	Improved visual and auditory reaction times, postexercise recovery (stair climbing), 2-handcoordination, alertness, and subjective assessments
Forgo et al., 1981 (cited in [67])	20	NC	18-31 yr	200 mg	G115	9 wk	Increased aerobic capacity; reduced lactate production, and heart rate
Forgo et al., 1981 [71]	120	DB	30-60 yr	200 mg	G115	12 wk	Improved vital capacity, forced expiration volume, maximum expiratory flow, maximal breathing capacity, work output; NS for serum LH, FSH, testosterone, estradiol, blood chemistries
Forgo et al., 1982 (cited in [67])	30	NC	Elite young athletes	200 mg	Standardized extract, 4% or 7% ginsenoside content	9 wk	Improved aerobic capacity; reduced lactate production, and heart rate; NS for difference between 4% and 7% ginsenoside content
Forgo, 1983 [72]	30 Elite athletes	DB, PC	19-31 yr	200 mg	G115	9 wk	Improved oxygen uptake, maximal breathing capacity, vital capacity, and forced expiration volume; reduced lactate production, and heart rate; NS for serum LH, testosterone, and cortisol
Knapik et al., 1983 (cited in [67])	11 Marathon runners	DB, PC	#	2,000 mg	1.5% glycosides	4 wk	NS for R values, glucose, lactate, free fatty acids, glycerol, insulin, cortisol, and growth hormone

Table 1. (Continued)

Teves et al., 1983 (cited in [67])	12 Marathon runners	DB, PC	22±1 yr	2,000 mg	1.5% glycosides	4 wk	NS for run time to exhaustion, aerobic capacity, heart rate, $V_{E\dot{V}}$ and RPE
Murano et al., 1984 (cited in [67])	65	NC	18-21, 38-70 yr	2 capsules for 30 d, 1 capsule for 30 d	ARM229 standardized extract	60 d	Older group: improved performance in Cooper test (12-min run time); younger group: NS trend in Cooper and Harvard step tests
Forgo et al., 1985 (cited in [73])	28 Elite athletes	DB, PC	20-30 yr	200 mg	G115	9 wk	Improved oxygen uptake, forced expiration volume, vital capacity, visual reaction times, and heart rates
Ng et al., 1986 (cited in [67])	214	#	#	#	#	#	Improved endurance, maximal oxygen uptake, postexercise recovery, simple reaction time
Macareg et al., 1986 (cited in [67])	12	R, DB, PC, CO	#	#	#	#	NS for time to exhaustion, glucose, and lactate
Von Ardenne et al., 1987 [74]	10	NC	50 yr	200 mg	G115	4 wk	Improved resting PO_2 uptake (arteriovenous difference) by 29%
Tesch et al., 1987 (cited in [67])	38	PC	50-54 yr	80 mg	Standardized extract, vitamins, minerals	8 wk	Improved heart rate and lactate production (> 180 W), RPE (60, 80, 120 W workloads); NS for lactate production up to 180 W
McNaughton et al., 1989 (cited in [67])	15 F, 15 M	R, DB, PC, CO	#	1,000 mg	Ginseng root powder	6 wk	Improved aerobic capacity, pectoral strength (27%), quadriceps strength (18%), postexercise recovery; NS for grip strength
Gribaudo et al., 1990 (cited in [75])	12 M	R, DB, PC, CO	Young	1,000 mg	Ginseng + fenu greek	15 d	Improved total work output, NS for lactate
Gribaudo et al., 1991 (cited in [75])	14 Well trained amateur cyclists	R, DB, CO	#	1,000 mg	Ginseng + fenu greek	30 d	Improved maximal work, $VO_{2\max}$, anaerobic threshold, NS for lactate
Pieralisi et al., 1991 [69]	50	R, DB, PC, CO	21-47 yr	200 mg	Standardized extract plus DMAE, vitamins, minerals	6 wk	Improved total work load, time to exhaustion, aerobic capacity, ventilation, oxygen consumption, carbon dioxide production, lactate production, and heart rate; NS for RER
Van Schepdael 1993 (cited in [67])	43 F triathletes	R, DB, PC, CO	24-36 yr	400 mg	G115	20 wk	Prevented loss of physical fitness after 10 wk
Engels et al., 1995 (cited in [67])	19 F	DB	26±1 yr	200 mg	G115	8 wk	NS for exercise recovery (heart rate, lactate production, oxygen consumption, and ventilation)
Caso Marasco et al., 1996 [76]	625	R, DB, PC	18-65 yr	200 mg	Standardized extract plus minerals, vitamins	12 wk	Improved quality of life, prevention of increased body weight and high blood pressure
Engels et al., 1997 [78]	36 M	R, DB, PC	#	200 or 400 mg	G115	8 wk	NS for oxygen consumption, RER, RPE, lactate, and heart rate during exercise
Lifton et al., 1997 [77]	7 M, 4 F well trained	DB, CO	#	3 g	#	13 d	NS for heart rate max, $VO_{2\max}$, total workload
Allen et al., 1998 [79]	8 F, 20 M	R, DB, PC, CO	23±3 yr	200 mg	7% ginsenoside standardized extract	3 wk	NS for oxygen uptake, exercise time, workload, lactate production, hematocrit, heart rate, ratings of perceived exertion at 150 W, 200 W, or peak

Table 1. (Continued)

Kolokouri et al., 1999 [80]	24 F	DB, PC	Adult	400 mg	#	8 wk	NS for peak anaerobic power output, fatigue reate
Ziemba et al., 1999 [68]	15 Soccer players	DB	19.07±0.62 yr	350 mg	Ginseng preparation	6 wk	Improved psychomotor performance during bicycle ergometer exercise without affecting exercise capacity
Engels et al., 2001 [81]	24 F	DB	#	400 mg	G115	8 wk	No ergogenic benefits during and in the recovery from short, supramaximal exercise
Cardinal et al., 2001 [82]	83 Adults (40 F, 43 M)	R, DB, PC, CO	Mean age, 25.7	200 or 400 mg	G115	8 wk	No evidence that chronic ginseng supplementation enhancing affect or mood in healthy young adults
Kang et al., 2002 [83]	8 College students	R, PC	Young	20 g	Ginseng root extract	Acute administration, after exercise	NS after and during 2 h recovery period for cortisol, testosterone, hGH, insulin-like growth factor
Kim et al., 2005 [84]	7 M	#	#	6 g	Standardized extract	8 wk	Ginseng supplementation has ergogenic properties in facilitating recovery from exhaustive exercise
Engels et al., 2003 [85]	27	R, DB, PC	#	400 mg	G115	8 wk	No changes in secretory IgA at rest and after an exercise induced state of homeostatic disturbance. No evidence for improvement of physical performance and heart rate recovery of individuals undergoing repeated bouts of exhausting exercise
Kulaputana et al., 2007 [70]	60 M	#	17-22 yr	3 g	100% ginseng	8 wk	No changes of lactate threshold and physical performances in physically active men
Ping et al., 2011 [86]	9 Heat adapted recreational runners	R, DB, PC	25.4±6.9 yr	200 mg	#	Acute administration, 1 h before running	No influence on the endurance running performance of the heat-adapted male recreational runners in the heat
Jung et al., 2011 [87]	18 M	#	Young	20 g	Korean red ginseng extract	7 d	Reduced exercise-induced muscle damage and inflammatory responses, resulting in improvements in insulin sensitivity
<i>P. quinquefolius</i>							
Morris et al., 1996 [88]	1 F, 7 M	R, DB, PC	27±5 yr	8 or 16 mg/kg	Water-ethanol extract	7 d	NS for cycle time to exhaustion and physiologic responses
Biondo et al., 2008 [89]	#	#	#	1,125 mg	<i>P. quinquefolius</i> standardized extract	35 d	No influence on exercise-induced changes in plasma concentrations of lactate, insulin, cortisol, or growth hormone
<i>P. notoginseng</i>							
Liang et al., 2005 [90]	29 Untrained adults	#	20-35 yr	1,350 mg	#	30 d	Improves endurance time to exhaustion, and lowered mean blood pressure and VO ₂ during endurance exercise

#, data not listed or unavailable; CO, crossover; DB, double-blind; DMAE, dimethylaminoethanol; F, female; FSH, follicle stimulating hormone; LH, luteinizing hormone; M, male; NC, not controlled; PANAS, positive and negative affect schedule; PC, placebo-controlled; POMS, profile of mood survey; R, randomized; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; SB, single-blind; VE, expiratory ventilation.

Ginseng Corporation. or any other standardized extract. Two separate studies Forgo et al, 1981 and 1982 respectively (both cited in [67]), showed significant change in aerobic capacity, lactate level, and heart rate under ginseng administration but failed to show either placebo or control conditions.

Forgo [72] did, however, extend these studies with a double blind placebo-controlled investigation into the

effects of 9 weeks administration of G115, G115 plus tocopherol, or placebo, on physiological and hormonal measures (luteinizing hormone, testosterone, and cortisol) in athletes. He reported the significant increase 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 [72]. This was followed by a further double blind

study investigating the duration of the effects of 9 weeks administration of G115 (100 mg twice daily) during exercise. Results reported a significant increase in oxygen uptake and forced expiratory volume and significant decrease in heart rate and visual reaction times. Some of these differences persisted at 3 weeks at the end of administration of G115 (Forgo and Schimert, cited in [73]). Liang et al. [90] reported that 30 d administration of *P. notoginseng* improves endurance time of exhaustion, and lowers mean blood pressure and VO_2 during endurance exercise in healthy untrained adults.

Other studies do not support the view on ginseng as supplementation increases physical work capacity. Ping et al. [86] reported that acute *P. ginseng* supplementation does not affect the endurance of running performance of the heat-adapted male recreational runners in the heat. Morris et al. [88] found that 1 week administration of two different doses of ginseng does not show better effect on any of the physiological indices under investigation (oxygen, free fatty acids, lactate, and glucose) than placebo in a placebo-controlled, cross-over study. Allen et al. [79] reported, in a randomized double-blind, placebo-controlled study involving 28 healthy young adults, that the administration of 200 mg ginseng extract for 21 d did not significantly affect heart rate or perceived exertion at 150 and 200 W ergometric exercise and claimed that it did not affect VO_2 , exercise time, workload, plasma lactate, or hematocrit at peak levels of exercise. Similarly, Engels et al. did not establish any increasing of physical work capacity after its course administration in a many-years series of ergogenic properties of G115 [81]. Thus, Engels and Wirth [78] 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 in a randomized double blind placebo-controlled G115 trial involving 36 healthy men. Engels et al. [81] found no effect of 400 mg/d G115 for 8 wk on supramaximal exercise performance and postexercise heart rate in 19 healthy women. Engels et al. [85] failed to demonstrate improvement of physical performance and heart rate recovery of individuals undergoing repeated bouts of exhausting exercise of 8-weeks administration of ginseng (G115, 400 mg/d) in a double-blind, placebo-controlled, randomized study involving 38 active healthy women. Morris et al. [88] found that no influence of short (7 d) administration of *P. quinquefolius* water-ethanol extract (8 or 16 mg/kg/d) on cycle time to exhaustion and physiologic responses for loads in healthy people.

Direct increasing of physical work capacity after acute

or course administration (actoprotective properties) should be separated from increasing of recovery speed after previous physical or other heavy loads for the convenience of administration of ergogenic aids in practice of sport preparedness as well as for pharmacological study of their mechanism of action. The property of increasing of recovery speed after previous physical or other heavy loads can be defined as 'antifatigue activity' in healthy people. Drugs and dietary supplements with antifatigue properties are very important in some types of sports with demand for repeated performance after short intervals (academic rowing, kayak and canoe paddling, different styles of wrestling, etc.). Positive influence of *P. ginseng* on parameters of recovery after exhaustive physical loads has been proved by numerous animal experiments since the 1970's.

The first article published in 1974 [91] studied the effects of extracts obtained from *P. ginseng* root (50-200 mg/kg intraperitoneal, immediately following the exercise) on recovery from exhaustion (four hour oscillation movements) using six methods: exploratory movement (EM), hole cross (HC), rotating rod (RR), sliding angle (SA), spring balance (SB) and rectal temperature (RT) tests. Water extract significantly accelerated the recovery after EM, increased motor activity index in EM test, and elevated rectal temperature. However, water extract decreased the index in HC test and grip tone in SB test. Antifatigue effects of ginsenoside Rg1 were shown in every test. Lipophilic fraction significantly sped up the recovery from fatigue in EM, RR, RT, and SB tests while delaying recovery in HC and SA tests. Neutral saponin fraction had no effect on recovery in the 6 tests [91]. Later, Banerjee and Izquierdo [92] studied antistress and antifatigue properties of *P. ginseng* preparation on Swiss albino mice which were exposed to various experimental models of stress in comparison with piracetam. Both ginseng and piracetam were administered chronically in drinking water for 16 to 18 d as well as acutely 30 to 60 min prior to the experiments by injection. Reactivity of the mice, loss of body weight, amount of feces, length of endurance, and incidence of mortality were graded and measured. Both piracetam and ginseng treatment provided good protection against electroshock stress when compared to untreated mice. Fighting scores, incidence of tonic convulsion, and mortality were significantly less in the treated groups. In the heat stress experiments, both piracetam and ginseng provided significant protection to the heat-exposed mice. In the fatigue stress of forced swim test, ginseng treatment was provided to be effective on adaptation to fatigue and ginseng also increased

the endurance in both male and female mice. Piracetam, on the other hand, only showed some antifatigue effects in the male mice. In the locomotor activity tests, ginseng did not depress motility, while piracetam did as described in the later part of the tests.

From human studies on healthy people and clinical studies on patients who suffered from fatigue, the anti-fatigue property of *P. ginseng* preparations can be confirmed. Dorling et al. (cited in [67]) reported that administration of ginseng extract during 12-weeks improves postexercise recovery. Later, postexercise recovery under ginseng administration was confirmed by Ng and Ng (cited in [67]), McNaughton et al. (cited in [67]), and by other researches. Dai et al. [93] evaluated the effect of the traditional Chinese medicine Tongxinluo and ginseng which had a good effect on the excess fatigue rats using metabolomics approach. A metabolomics study was performed on the excess fatigue rats treated with traditional Tongxinluo or ginseng based on ultra-fast liquid chromatography coupled with ion trap-time of flight mass spectrometry. The plasma metabolic profiling data of the control rats, excess fatigue rats, and excess fatigue rats treated with Tongxinluo or ginseng were acquired. The orthogonal partial least squares analysis was applied for the multivariate statistics, leading to the discovery of important differential metabolites distinguishing the excess fatigue rats treated with Tongxinluo or ginseng from the control rats and excess fatigue rats. The results showed that tryptophan, bile acid, and lysophosphatidylcholine metabolism were disturbed in the excess fatigue rats. The metabolic pattern including the related metabolic pathways of the rats, after being treated with Tongxinluo or ginseng, was adjusted towards the normal state.

Clinical studies of *P. ginseng* administration in treatment of unexplained chronic fatigue of unknown etiology demonstrated as effective in 56% cases [94]; *P. ginseng* and *P. quinquefolius* preparations can be regarded also as perspective compounds to improve cancer-related fatigue [95,96].

In the last 20 yr of scientific literature, the question “Is *P. ginseng* an ergogenic aid?” has been widely discussed [67,97-101]. Based on modern understanding of pharmacology terms and definitions, it seems logical to concretize this debate by dividing it into two questions: “Is *P. ginseng* an actoprotector” and “Is *P. ginseng* an antifatigue supplementation?” Such division has a principal character and needs separate explanation.

Analyses of data from properly controlled studies on *P. ginseng* preparations (Table 1) allow us to make the preliminary conclusion that the controversies related to

this study are connected with different doses, duration of courses being used in different studies, and physical condition of subjects who participated in these studies.

Enhancement of physical work capacity was only observed in studies when: 1) higher doses of ginseng supplementation (over 200 mg/kg/d of standardized extract) were used, 2) there were longer durations of study (not less than 8 wk), 3) had larger subjects' number, indicating greater statistical power, and 4) subjects were in relatively poor physical condition.

One of the explanations that ginseng supplementation has no positive influence on physical performance was made by Ferrando et al. [102]. In their experiments, the effects of the ginseng extract on various biochemical and hematological parameters in male Wistar rats subjected to a treadmill exercise protocol were studied for 12 wk. The results showed increase in the hematological parameters. The increase was the largest for the animals treated with the extract during the third month of the study. The exercise alone also led to the increase in these parameters, while the combination of both exercise and ginseng extract produced smaller increase. This study shows a clear physiological response due to the ginseng extract administration that reproduces many of the effects obtained after long-term exercise. Authors made conclusion that the combination of exercise and treatments seems to support the theory that there is no clear synergic effect when compared with the performance of exercise. In other work, the same authors established that treatment with *P. ginseng* increases the capillary density and the mitochondrial content of the red gastrocnemius muscle of rats. The results suggest that prolonged treatment with *P. ginseng* increases the capillary density and the oxidative capacity of the muscles with greater aerobic potential in a manner similar to the performance of physical exercise. Although when exercise and treatment are combined, the effects are not potentiated [103]. This explanation can be accepted as one possibility, but it generally cannot be a foundation for the conclusion that any effects of physical training and ginseng supplementation may be obtained separately but not when combined.

The facts mentioned above allow us to conclude that *P. ginseng* (and other plants from genus *Panax*, possibly) can be regarded as a potential actoprotector and antifatigue preparation with further research of its influence on physical work capacity, endurance and restoration after exhaustive physical loads in comparing with reference actoprotector bemitil.

Possible biochemical mechanisms for increasing the endurance after ginseng administration are connected

with its influence on 1) carbohydrate and fat metabolism [57,63,104-106], 2) immune and endocrine mechanisms [60,83,87], and 3) regulation of oxidative balance [106-111].

It seems possible, that in realization of the actoprotective and antifatigue properties of ginseng preparations, saponins are not the only components that have big importance. Polysaccharides also play a large role. Wang et al. [52] established that ginseng polysaccharides have anti-fatigue activity, reflecting in the effects on the physiological markers for fatigue. The acidic polysaccharide is more potent than the neutral polysaccharide.

It seems logical that such controversies are connected with different doses, duration of courses used in different studies, as well as with administration of different quality and composition of ginseng supplements. Such a conclusion also allows ginseng to be regarded as potential actoprotector and allows for further research on its influence on physical work capacity, endurance and restoration after exhaustive physical loads in being compared to reference actoprotector, bemitil.

EFFECTS OF GINSENG ON COGNITIVE FUNCTIONS

Numerous animal experiments and clinical studies about the influence of ginseng preparations (mainly preparations from *P. ginseng*) on cognitive functions show less controversial results compared to studies connected with exercise performance. Several of them show memory improvement after ginseng administration.

Various memory-impairment models (aged animals, scopolamine-induced memory deficit, ethanol-induced memory deficit, electroconvulsive shock-induced memory disturbances, muscarinic-induced memory deficit, dopamine-induced memory deficit, brain ischemia, cerebral infarct, sham or medial prefrontal cortex lesions, reserpine-induced orofacial dyskinesia, beta-amyloid-induced amnesia model, etc.) have been used to evaluate the effects of ginseng and its active ingredients on a person's learning and memory. Results of experimental studies on normal animals and on mentioned above animal models are summarized in Table 2. In most studies, inde-

Table 2. Results of animal experiments with separated ginsenosides and preparations of plants from genus *Panax* on cognitive functions

Study (reference)	Preparation type	Animals and experimental model	Daily dose and study duration	Briefly results
Separated ginsenosides				
Zhang et al., 1990 [112]	Rg1 and Rb1	Mice, rats; one trial avoidance learning method	#	Rg1 and Rb1 improved acquisition, consolidation and retrieval of memory improved by amnesic agents
Benishin et al., 1991 [113]	Rb1	Rats, scopolamine-induced memory deficit	#	Rb1 partially prevented memory deficits
Ma et al., 1993 [114]	20(S)-ginsenoside-Rg2	Male Wistar rats, two-way active avoidance method	20 mg/kg i.p., repeatedly	Positive influence on memory function
Li et al., 1999 [115]	Pseudoginsenoside-F11 from <i>P. quinquefolium</i>	Mice, rats; scopolamine-induced memory deficit	1-4 mg/kg/d (i.p.), once time or 5 d course	Compound antagonized the memory dysfunction induced by scopolamine
Yamazaki et al., 2001 [116]	Panaxynol	Mice, scopolamine-induced memory deficit	20 mg/kg/d, i.p., for 3 d	Improvement of scopolamine-induced memory deficit
Bao et al., 2005 [117]	Rg3(R), Rg3(S) and Rg5/Rk1 (a mixture of Rg5 and Rk1, 1:1, w/w)	Mice, ethanol and scopolamine-induced memory deficit	p.o., course 4 d	Rg3(S) and Rg5/Rk1 significantly reversed the memory dysfunction induced by ethanol or scopolamine
Yang et al., 2009 [118]	Rh2	Mice, scopolamine-induced memory deficit	40 mg/kg, p.o. 1 h before the first trial session at every consecutive day	Rh2 ameliorated scopolamine-induced learning deficit in mice
Wang et al., 2010 [119]	Rg1 and Rb1	Mice, scopolamine-induced memory deficit	6 and 12 mg/kg, i.p., 7 d	Multiple administrations of Rg1 and Rb1 are effective in improving memory deficiency induced by scopolamine. Rg1 and Rb1 ameliorated cognition-deficiency in mice with dementia. Rg1 showed stronger effects than Rb1. Both Rg1 and Rb1 increased acetylcholine levels in the hippocampus, but Rg1 inhibited acetylcholinesterase activity while Rb1 had no effect on its activity. Both Rg1 and Rb1 inhibited the decrease of 5-HT induced by scopolamine, but Rb1 was more active than the same dose of Rg1. Rg1 appears to be more potent than Rb1 in improving acquisition impairment.

Table 2. (Continued)

<i>P. ginseng</i>				
Lasarova et al., 1987 [120]	G115	Rats, electroconvulsive shock-induced memory disturbances	30 mg/kg/d (p.o.), 10 d	Tendency for elimination of the memory-impairing effect of electroconvulsive shock.
Petkov et al., 1987 [121]	G115	Rats, "shuttle-box" method for active avoidance	3, 10, 30, 100 and 300 mg/kg/d (p.o.), 10 d	The results show that ginseng at appropriate doses improves learning, memory and physical capabilities. Bell-shaped dose-effect curves, reported with other nootropic drugs, were obtained.
Zhang et al., 1987 [122]	#	Mice	#	Induction of memory facilitation
Jaenicke et al., 1991 [123]	#	Female rats of two groups (6 and 27 mo), passive avoidance test	30 mg/kg/d (p.o.), 13 d	Increasing of learning ability in older rats
Petkov et al., 1992 [124]	Standardized extracts: from stem and leaves (GL), and from roots (G115)	Rats with undisturbed memory and in rats with experimentally-impaired memory (electroconvulsive shock); methods for active avoidance (shuttle-box) and passive avoidance (step-down, step-through), the water-maze method and the method for studying exploratory behavior	Multiple administration	G115 exerted favorable effects on learning and memory and on the higher nervous activity as a whole; GL had, in the majority of cases, an effect weaker than that of G115 or was without effect at all
Petkov et al., 1993 [125]	G115	Young (aged 3 months) and old (aged 26 months) rats; conditioned-reflex methods with punishment or positive reinforcement for active and passive avoidance (shuttle-box, step-down, step-through, and water maze)	17, 50, and 150 mg/kg/d (p.o.), 7 d before training	Positive influence on memory effects, similar to those of nootropic drugs
Nitta et al., 1995 [126]	Standardized extract	Aged Fischer 344 rats	8 g/kg/d, p.o. for 12-33 d	Subchronic treatment with ginseng extract improves spatial cognitive impairment in aged rats
Nitta et al., 1995 [127]	<i>P. ginseng</i> ethanol extract and its WSF and LSF fractions	Rats; scopolamine-induced disruption of radial maze performance	<i>P. ginseng</i> ethanol extract, WSF and LSF - 2-8 g dried root/kg, 90 min before testing	<i>P. ginseng</i> ethanol extract and WSF improved the maze performance disrupted by scopolamine in a dose-dependent manner, but LSF failed to attenuate the disruption. Ginseng extract possesses a beneficial effect regarding spatial cognitive impairment and that the water-soluble fraction of ginseng extract mainly contributes to the effect of the ethanol extract
Wang et al., 1995 [128]	Root saponins	Normal male Wistar rats	50 mg/kg/d (ig.), 7 d	Ginseng root saponins facilitate the learning and memory of normal male Wistar rats and significantly raise the levels of biogenic monoamines in their brain
Zhao et al., 1998 [129]	Crude ginseng extract	Normal and brain-damaged (sham or medial prefrontal cortex lesions) rats	40 or 80 mg/kg daily during 30 d after operation	administration of the higher dose resulted in better performance in the learning paradigm
Jin et al., 1999 [130]	Root saponins with a low PD/PT (1.24) and high PD/PT (1.46) ratio	Mice, scopolamine-induced memory deficit	50 and 100 mg/kg (intraperitoneally) before training	The two saponins improved the scopolamine-induced learning impairment at both dosages. The two saponins did not show a favorable effect on learning and memory in normal mice. Korean red ginseng saponin with a low PD/PT ratio had an improving effect on spatial working memory, but the saponin with a high PD/PT ratio did not
Hsieh et al., 2000 [131]	#	Rats, scopolamine-induced memory deficit	1-week course (p.o.)	Improvement of the scopolamine-induced learning and memory deficit

Table 2. (Continued)

Petkov et al., 2003 [132]	G115	Rats, experimentally-impaired memory (by alcohol or by muscarinic- and dopamine-receptor antagonists) model	#	Favorable effects on learning and memory. These effects varied with the dose and administration schedules, with the rat strain and with the behavioral method
Kurimoto et al., 2004 [133]	Nonsaponin fraction of red ginseng	Aged rats	#	Nonsaponin fraction of red ginseng contains important substances to improve learning and memory in aged rats and that this amelioration by nonsaponin might be attributed partly to augmentation of long-term potentiation in the hippocampal CA3 subfield
Lee et al., 2010 [134]	Methanol extracts of wild and cultivated ginseng	Rats; scopolamine-induced memory deficit	7 days at 30 min before scopolamine injection (2 mg/kg, i.p.)	Wild ginseng demonstrates a significant neuroprotective effect against scopolamine-induced neuronal and cognitive impairment
Sanghavi et al., 2011 [135]	Standardized extract	Rats; reserpine-induced orofacial dyskinesia	100 and 200 mg/kg, p.o., 3 wk	Korean ginseng extract could be useful in the treatment of drug-induced dyskinesia and amnesia
<i>P. quinquefolium</i>				
Sloley et al., 1999 [136]	Standardized extract (HT-1001)	Sprague-Dawley rats; scopolamine-induced memory deficit	200 mg/kg/d (p.o.), 8 d	HT-1001 demonstrates a capacity to protect against scopolamine-induced memory deficits (protected against scopolamine-induced amnesia and increased choline uptake in synaptosomal preparations; did not alter brain concentrations of norepinephrine, dopamine, serotonin, 3,4-dihydroxyphenylacetic acid or 5-hydroxyindoleacetic acid)
Zhong et al., 2000 [137]	Red ginseng powder (Ginseng Radix rubra, Seikansho, Kobe, Japan)	Young (10-12 wk) and aged (28-32 mo) Fisher-344 rats; brain ischemia model	#	Red ginseng ameliorates learning and memory deficits through effects on the central nervous system, partly through effects on the hippocampal formation
Wang et al., 2006 [138]	Ginsenosides (containing both protopanaxadiol- and protopanaxatriol-type saponins), isolated from the dry roots of <i>P. quinquefolium</i> by 80% alcohol extraction and column chromatography; the yield in ginsenosides (versus dry root weight) was found to be 4.2%–5.1%	Male Sprague-Dawley rats (3-4 months old); beta-amyloid-induced amnesia model	80 mg/kg/d p.o., 5 d before icv beta-amyloid injection and 7 d afterward; or the same dose 12 d but only after β -amyloid injection	Ginsenosides pre-treatment can functionally prevent the beta-amyloid-induced memory loss possibly by minimizing the inhibitory effect of beta-amyloid on hippocampal cholinergic transmission
Chatterjee et al., 2012 [139]	Standardized extract	Male Swiss albino mice	12.5-200 mg/kg, p.o.	<i>P. quinquefolium</i> extract administration (100 mg/kg) blocked ketamine induced memory impairment in the passive avoidance paradigm
<i>P. notoginseng</i>				
Hsieh et al., 2000 [131]	#	Rats, scopolamine-induced memory deficit	1 week course (p.o.)	Improvement of the scopolamine-induced learning and memory deficit
Chuang et al., 2008 [140]	PNB	Rats, cerebral infarct model	0.5 g/kg/d, p.o., 3 d per week for 4 wk	PNB attenuates impairment of learning and memory functions and increases ED1, BDNF and beta-secretase immunoreactive cells in chronic stage ischemia-reperfusion injured rats
Zhong et al., 2011 [141]	PNS	SAMP8	High and low doses of PNS	PNS can improve the abilities of learning and memory of SAMP8, the mechanism may be relevant to down-regulating the expression of APP gene at transcriptional level

Table 2. (Continued)

<i>P. pseudoginseng</i>				
Zhang et al., 1987 [122]	#	Mice	#	Induction of memory facilitation
#, data not listed or unavailable; i.p., intraperitoneal; p.o., per os; WSF, water-soluble fractions; LSF, lipid-soluble fractions; PD, protopanaxadiol; PT, protopanaxatriol; PNB, <i>P. notoginseng</i> Burk; BDNF, brain derivative neurotrophic factor; PNS, <i>P. notoginseng</i> saponins; SAMP8, senescence accelerated mouse prone 8.				

pendent of experimental model used, course administration of *P. ginseng* preparations had as a final result with significant anti-amnaestic effect. In addition, positive results for cognitive functions enhancement were received from preparations of *P. quinquefolium* [136,137,139], *P. notoginseng* [131,140,141] and *P. pseudoginseng* [122]. However, different fractions or doses of ginseng extract have been shown to impair learning. For example, Saito et al. [142] found that extracts of ginseng inhibits conditioned avoidance response and discrimination behavior on pole climbing and shuttle box tests. Similarly, Petkov and Mosharrof [121] found that high doses of G115 impaired, rather than improved, conditioned reflex activity, and Takagi et al. [143] and Takagi et al. [144] demonstrated decreasing exploratory activity and a specific blocking action of conditioned responses following the administration of a crude ginsenoside fraction.

Some experiments were provided with isolated components of ginseng preparations, first with ginsenosides Rg1 and Rb1. In passive avoidance test, Rg1 improved learning and memory acquisition, consolidation, and retrieval, indicating that Rg1 can improve all stages of memory [112]. Later, to study the effect of Rg1 on one's learning and memory loss induced by β -amyloid, passive avoidance and performance in the Morris water maze were assayed after the final treatment. Ginsenoside Rg1 significantly decreased the latency and swimming distance, improved corresponding changes in search strategies in the Morris water maze, and increased the step-through latency [145]. In other studies, Rg1 significantly improved memory deficits in aged rats, ovariectomized rats, and cerebral ischemia-reperfusion rats (Qiu et al., cited in [146]; Chen et al., cited in [146]). Rb1 also improved spatial cognitive performance of rats in Morris water maze [147]. These results showed that ginseng extract and ginsenosides Rg1 and Rb1 facilitated acquisition and retrieval of memory. Moreover, ginsenosides Rb1 and Rg1 also antagonized memory loss and cognitive deficit under various pathological conditions, such as cerebral ischemia and dementia (Qiu et al., cited in [146]). At the same time, other ginsenosides like Rg3(S), Rg5/Rk1 [117], and Rh2 [118] and even nonsaponin fraction of red ginseng [133] also have anti-amnaestic properties

and may have some importance on prevention of memory impairment or treatment of memory disorders.

Results of most human studies, connected with evaluation of influence of ginseng supplementation on cognitive functions, are summarized in Table 3. Some of these studies show positive effects of ginseng preparations even at acute [148-150] or short course [151,152] administration. Poor standardization of different preparations unfortunately does not allow for the comparing of results from different studies. In this connection, it is necessary to put attention on row of studies provided with G115 [152-160].

Effects of acute administration of G115 on cognition in young healthy individuals were evaluated in randomized double blind placebo-controlled studies [152,156-158] where ginseng differentially improved scores on a 'secondary memory' factor (a composite of four memory tasks). In the first study, doses of 200, 400, and 600 mg of G115 were administered. Enhancement of 'secondary memory' was found following 400 mg at four post-dose testing sessions while the lower and higher dosage reduced performance on the 'speed of attention' factor [152]. Kennedy et al. [158] replicated the finding that 400 mg dosage improved 'secondary memory.' A later study assessed the effects of 200 and 400 mg ginseng during sustained cognitive demand-repeated cycles of Serial Threes, Serial Sevens, and the Bakan Rapid Visual Information Processing (RVIP) task. Serial Sevens performance was improved by the 200 mg dose [159]. In a follow-up study, the same dose improved Serial Threes and RVIP performance [160]. It appears that *P. ginseng* or its constituents are capable of producing tangible cognitive enhancing effects and that 200 to 400 mg appears to be the optimal dose range for young healthy adults when administered acutely prior to a cognitive test.

Course administration of ginseng preparations in most studies also showed positive effect on cognitive functions (Table 3).

Detail analyses of mechanisms to determine underlying the positive impact on cognition under ginseng administration is out of the focus of this article. They are already described in numerous review articles published in recent literature [146,156,171-180]. It is necessary to

Table 3. Results of human studies with plants from genus *Panax* on neurocognitive function (adapted with modifications from [67])

Study (reference)	Subject (n)	Study design	Subject age range	Daily dose	Preparation type	Study duration	Effects (statistically significant unless otherwise stated)
<i>P. ginseng</i>							
Kochmareva, 1958 [148]	122	CO, PC, SB	Students	2 mL	Tincture	Acute	Increased quality and quantity of mental work performed
Medvedev, 1963 [149]	13	CO, PC, SB	21-23 yr	2 mL	Tincture	Acute	Decreased errors in data sent by radio operators 1 h after drug uptake
Popov et al., 1973 [150]	32 M	DB, PC	21-23 yr	2-mL extract	40% ethanol tincture	Acute	Decreased errors in radio transmission of coded messages (17% compared with 31%); NS for number of characters transmitted
Sandberg, 1974 (cited in [67])	30	DB, PC	Students	#	#	#	NS for spiral maze tracing test, letter cancellation test
Revers et al., 1976 (cited in [67])	#	DB	Elderly	#	G115	90 d	Improved vitality, alertness, rigidity, concentration, visual-motor coordination, positive outlook, visual and auditory reaction times
Simon et al., 1977 [161]	36	#	Elderly	#	G115	90 d	Improved concentration, and mental accuracy; NS for attention
Bae, 1978 (cited in [162])	32	DB, DC	21-23 yr	#	#	#	Reduced telegraphy mistakes (17% compared with 31%); NS for mental concentration, coordination
Schmidt, 1978 (cited in [162])	540	PC	#	#	#	#	Improved subjective and objective indexes; normalized blood glucose and blood pressure
Dorling et al., 1980 (cited in [67])	60	DB, PC	22-80 yr	#	G115	12 wk	Improved visual and auditory reaction times, hand coordination, alertness, and subjective assessments
Sandberg, 1980 (cited in [67])	60	DB, PC	#	#	2 Types of standardized extract	12 wk	Improved spiral maze tracing test, letter cancellation test, and oxygen metabolism (15-min step test)
Johnson, 1980 (cited in [162])	38	#	Dental students	#	#	#	NS for mathematics performance, blood cortisol and epinephrines, proofreading error detection, mood, and fatigue indexes
Forgo et al., 1981 [71]	120	DB	30-60 yr	200 mg	G115	12 wk	Improved vital capacity, forced expiration volume, maximum expiratory flow, maximal breathing capacity, reaction times, subjective assessments of mood, work output, sleep, concentration, vitality; NS for serum LH, FSH, testosterone, estradiol, blood chemistries
Hallstrom et al. 1978 [151]	12 Nightshift nurses	DB, PC, CO	21-27 yr	1200 mg	Korean white ginseng powder	3 d	Improved tapping rate test; NS for mood, somatic symptoms, blood glucose (all trends); negative effects on sleep quality
D'Angelo et al., 1986 [163]	32	DB, PC	20-24 yr	200 mg	G115	12 wk	Improved mental arithmetic calculations; NS trend for attention, choice reaction time, auditory reaction time; NS for tapping test, recognition, and visual reaction time
Zhao, 1990 [164]	481	#	50-85 yr	150 mg	Sugar-coated tablets of GRS	2 months	GRS possessed antisenility effect and marked effect on relieving the symptoms of aging, adjusting organic metabolism and improving physiological function, etc., such as promoting memory, raising the amount of white cells and improving organic immunity function.
Wiklund et al., 1994 [165]	390	PC	Middle-age	200 mg	G115 + vitamins, minerals	12 wk	Improved alertness, relaxation, appetite, overall score, and general well-being (3 scales)
Smith et al., 1995 (cited in [67])	19 F	DB	26 ±1 yr	200 mg	G115	8 wk	NS for POMS and PANAS (psychological tests) and RPE
Sorensen et al., 1996 [166]	112 Healthy volunteers	R, DB, PC	>40 yr	400 mg	G115	8-9 wk	Faster reaction times, better abstract thinking; NS for memory, concentration, well-being
Ziemba et al., 1999 [68]	15 Soccer players	DB	19.07±0.62 yr	350 mg	Ginseng preparation	6 wk	Improved psychomotor performance during bicycle ergometer exercise without affecting exercise capacity
Kennedy et al., 2001 [152]	40	R, DB, PC, CO	Young	200, 400, and 600 mg	G115	7 d	Significant improvement in "quality of memory" and the associated "secondary memory" factor at all-time points following 400 mg of ginseng. Both the 200 and 600 mg doses were associated with a significant decrement of the "speed of attention" factor at later testing times only

Table 3. (Continued)

Lee et al., 2008 [167]	97	#	Alzheimer's disease patients	4.5 g/d	<i>P. ginseng</i> powder	12 wk	<i>P. ginseng</i> is clinically effective in the cognitive performance of Alzheimer disease patients
Reay et al., 2010 [154]	30	R, DB, PC, CO	Healthy young adults (22.87±4.01)	200 and 400 mg	G115	8 d	No evidence of additional benefits, or attenuation of acute effects following repeated ingestion of G115
Heo et al., 2011 [168]	61	#	Alzheimer's disease patients 50-80 yr	4.5, 9 g	Korean red ginseng	96 wk	Improvement of cognitive deficit in Alzheimer's disease patients
Yeo et al., 2012 [169]	15 M	R, DB, PC	Healthy young adults	4.5 g	Korean red ginseng	2 wk	Decreased latency in event-related potential test associated with improved cognitive function
<i>P. quinquefolius</i>							
Scholey et al., 2010 [170]	32	R, DB, PC, CO	Healthy young adults	100, 200, 400 mg	Cereboost (<i>P. quinquefolius</i> standardized to 10.65% ginsenosides)	Acute administration	This study has identified robust working memory enhancement following administration of Cereboost

#, data not listed or unavailable; CO, crossover; DB, double-blind; DMAE, dimethylaminoethanol; F, female; FSH, follicle stimulating hormone; GRS, ginseng-rhizome saponin; LH, luteinizing hormone; M, male; NC, not controlled; PANAS, positive and negative affect schedule; PC, placebo-controlled; POMS, profile of mood survey; R, randomized; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; SB, single-blind; VE, expiratory ventilation.

subscribe that among these mechanisms is the capacity of ginsenosides to potentiate the cholinergic system in central nervous system [112,113,119,181,182]. Other important neurotransmitters for learning, memory, and cognitive functions involved in mechanism action of ginsenosides are glutamate [183,184] and 5-HT [175].

Similar to studies connected with physical performance, it seems logical that such inconsistencies in the results of different studies are connected with different doses, duration of courses used in different studies, as well as with administration of different quality and composition ginseng supplements. Despite that, most studies show positive influences of ginseng supplementation on intellectual work capacity in normal subjects and those of decreased cognitive functions. Such conclusion also allows ginseng to be regarded as potential actoprotector and opens the way for further research of its influence on mental work capacity and cognitive functions in comparing with reference actoprotector, bemitil, and reference nootropic drug, piracetam.

CONCLUSION

Related to the capacity of many plant adaptogens to increase physical and mental performance, the question that arose about actoprotectors class including not just only synthesized but also natural origin compounds has importance for fundamental theory of pharmacological science and practical administration of many phytochemicals.

The ginsenosides content in ginseng preparations can vary depending on the species, the age and part of the plant, the preservation method, the season of harvest, and the extraction method. In this connection, poor standardization can cause some difficulties in the evaluation of data received from animal experiments and human studies about the pharmacological activity of adaptogens including ginseng.

Despite these difficulties, large quantities of data received from animal experiments and human studies allow for making some preliminary conclusions about potential actoprotective properties of ginseng preparations: 1) results of some animal experiments and human studies attest that *P. ginseng* (administered as extract) can significantly increase physical and intellectual work capacity and the data allow ginseng to be referred as an actoprotector of natural origin; 2) results related to the influence of ginseng on physical performance are more controversial than those connected with its influence on intellectual work capacity; and 3) ginseng preparations can be regarded as potential actoprotectors and allow for further research of its influence on physical and mental work capacity, endurance, and restoration after exhaustive physical loads in comparing with reference actoprotectors (bemitil) and nootropic drugs (piracetam).

Pharmacological activity of preparations received from different species from genus *Panax* should be evaluated separately, but extract preparation should be standardized. Comparison of ginseng preparations with preparations of other adaptogenic herbs will allow the decision

of the most effective herbal actoprotectors. Composition based on additive effects of herbal actoprotectors and synthesized ones can become the more useful in clinical and preventive medicine.

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