Vol.5, No.9, 1509-1515 (2013)
http://dx.doi.org/10.4236/health.2013.59205

Eleutherococcus senticosus: Studies and effects*

Aline Arouca, Dora Maria Grassi-Kassisse#

Department of Structural and Functional Biology, Laboratory of Stress Study, Institute of Biology, University of Campinas, Campinas, Brazil; #Corresponding Author: doramgk@unicamp.br, alineb.arouca@gmail.com

Received 13 June 2013; revised 14 July 2013; accepted 19 August 2013

ABSTRACT

Ginseng is one of the most popular herbal supplements in the world. It is a plant widely used in folk and traditional medicines for cardiovascular, immune, nervous and endocrine systems, and according to the researchers, it has the ability to increase the non-specific resistance state, which characterizes it as an adaptogenic substance. There are different species of ginseng, such as the American, Chinese, Korean and Japanese ginseng; the Korean species (*Panax ginseng*) is being used for thousands of years as a tonic, prophylactic and "restorative" agent, with powerful antioxidant properties. For a long time, its use was empirical, because people used to believe that it was a panacea that promoted longevity, with beneficial effects for the treatment of physical fatigues. Nowadays, the active components of *Eleutherococcus senticosus* are well described, however, there are no data on the quantity of a certain class of these secondary compounds produced in each species. Although the *Eleutherococcus senticosus* extract may contain several substances, including vitamins, minerals, cellulose, and ethanol, the substances responsible for inducing various physiological responses are the eleutherosides (in the root) and ciwujianosides (in the leaf). As *Eleutherococcus senticosus* receives great attention by showing that its active components can provide protection against oxidative stress, among other benefits, contributing to health and the prevention and treatment of diseases, such as diabetes, cancer, cardiovascular disease and inflammation. The purpose of this article is to describe the main, adverse and toxicological effects of *Eleutherococcus senticosus* recently related in the literature.

Keywords: *Eleutherococcus senticosus*; Ginseng; Eleutherosides; Ciwujianosides

1. INTRODUCTION

Eleutherococcus senticosus, world widely known as *Acanthopanax senticosus* (Rupr. et Maxim), belongs to the *Araliaceae* plant family, as well as other types of ginseng (Latin name), a generic term given to all species of *Panax* [1]. It is also known as Siberian or Russian ginseng, ciwujia, eleuthero, eleuthero ginseng, touch-me-not and devil's shrub [2,3].

Ginseng is one of the most popular herbal supplements in the world [2]. It is a widely used plant in folk and traditional medicines for the cardiovascular, immune, nervous, and endocrine systems, and according to the researchers Brekhman & Dardymov (1969) [4], it has the ability to increase the non-specific resistance state, which characterizes it as an adaptogenic substance.

There are other species of ginseng, such as the American, Chinese, Korean and Japanese ginseng [5]; the Korean species (*Panax ginseng*) is being used for thousands of years as a tonic, prophylactic and "restorative" agent (3), with powerful antioxidant properties [6]. For a long time, its use was empirical, because people used to believe it was a panacea that promoted longevity, with beneficial effects for the treatment of physical fatigue [7].

The use of *Panax* as a source of raw materials for pharmaceuticals was very expensive for many years [2,5]. Therefore, a group of Russian researchers looked for alternatives, and after the discovery, many years later, at the end of 1950, *Eleutherococcus senticosus* (ES) was recognized as a new medicinal plant [2,3]. Despite having been described only in 1950, *Eleutherococcus senticosus* is a plant used by the Chinese for over 2000 years. Some reports describe its use as a medicinal remedy for the treatment of infections, resistance to fatigue and for immunological improvement [8].

*This study was supported by CAPES.

In 1982, Baranov [9] concluded that the chronic administration of *Eleutherococcus senticosus* was more advantageous when compared to *Panax*, because it does not cause arousal in patients. It has a more intense protective effect on the immune system; in addition, it does not lead to the development of a similar stress syndrome. The seasonality influences the effects of these two types of ginseng, but there is not much variation in *Eleutherococcus senticosus* (ES) [3].

ES was recently included in the European Pharmacopoeia as a medicine derived from plants and it is, therefore, suitable for use in traditional herbal medicines and associations [10].

The 1994 DSHEA (Dietary Supplement Health and Education Act) regulation allows a direct commercialization of ES as a supplement for consumption in the United States without the regulation of the FDA (Food and Drug Administration) [11].

2. ACTIVE COMPONENTS OF *ELEUTHEROCOCCUS SENTICOSUS*

The active components of *Eleutherococcus senticosus*, the eleutherosides, were initially coded from A to F [12], and years later, Hikino *et al*. (1986) [13] studied seven eleutherosides coded as A, B, C, D, E, F and G, and through acid hydrolysis of these components, obtained the formation of glycosides, such as rhamnose, arabinose, xylose, mannose, galactose and glucose.

Based on several studies by Wagner *et al*. (1994) [14], the ES components were rated as phenylpropanes, compounds, lignans, coumarins, polysaccharides and other compounds, such as oleanolic acid, aromatic oils and sugar [8]. In an attempt to bring order to these chemicals compounds, ES was divided into two classes: 1. Triterpenoid saponins, which are glycosides of oleanolic acid (referred to as eleutherosides I, K, L and M), and 2. Phenylpropane derivatives (eleutherosides B, B1, D and E), which are mostly glycosylated [15].

The ES root extract is standardized in 0.6% to 0.8% of eleutherosides, depending on the extraction method of solids [16,17].

Unfortunately, there are no data on the quantity of a certain class of these secondary compounds produced in each species. These compounds include, but are not limited to, phenylpropanoids (siringina, caffeic acid, sinapyl alcohol, and coniferyl aldehyde), lignans (sesamin, syringaresinol and its glycoside), saponins (daucosterol, β-sitosterol, and hederasaponine-B), coumarins (isofraxidine and its glycoside) and vitamins (vitamin E and beta-carotene) [15].

Eleutherococcus not only synthesizes lignans, but also siringina, syringaresinol and sesamin; it produces and accumulates precursors of lignans, such as hydroxycinnamic caffeic acid and other intermediate compounds, as coniferaldehyde. These precursors have shown a significant antioxidant activity [15].

Although the *Eleutherococcus senticosus* extract may contain several substances, including vitamins, minerals, cellulose and ethanol [14], the substances responsible for inducing various physiological responses are the eleutherosides (in the root) and ciwujianosides (in the leaf) [1].

3. MAIN EFFECTS OF *ELEUTHEROCOCCUS SENTICOSUS*

Eleutherococcus senticosus, as well as *Panax ginseng*, seems to have a stimulating effect on the metabolism of substrates, as it significantly alters the mobilization and utilization of carbohydrates and fatty acids. Since the metabolism of substrates is essential, different types of ginseng can have ergogenic effect [5]. **Table 1** shows several studies performed in humans, using a supplementation made from ES, among other types of ginseng. According to the studies, we may observe that the acute supplementation has no effect on physical performance, whereas chronic supplementation can provide significant changes in various biochemical parameters.

Some studies, using the supplementation of *Eleutherococcus senticosus*, report an improvement in heart rate recovery after physical exercise, improvement of the lactate removal ability, greater ability to obtain energy from aerobic metabolism (by increasing the oxygen consumption and utilization of fatty acids as a source of energy) and, therefore, an improvement of the performance [3,8, 18-20]. These authors believe that these improvements are due to the action of eleutherosides, responsible for inducing various physiological responses, which are present in the root of *Eleutherococcus senticosus* [1].

The extracts from different parts of ES have been considered good for health [21]. The ES antioxidant effect is related to improvements in the treatment of diabetes, cancer and inflammatory state, in addition to their immunoregulatory and immunomodulatory property, and antimicrobial and antiviral activity [11].

Six secondary compounds found in *Eleutherococcus senticosus* have demonstrated antioxidant effects (such as siringina, caffeic acid, ethyl aldehyde, coniferyl aldehyde), four had antioxidant effects in cancer (sesamin, β-sitosterol, isofraxidine), and three had hypocholesterolemic activities (sesamin, β-sitosterol and β-sitosterol 3-D-glucoside) [15].

Sesamin and siringina demonstrated immunostimulatory activity, while isofraxidine showed choleretic activity. Siringina demonstrated radioprotective property, and antibacterial activity of caffeic acid [15].

The hypocholesterolemic activity of sesamin, β-sitosterol compounds and its glycoside β-sitosterol β-D-glucopyranoside can be explained by their participation in antioxidant reactions on LDL (low density lipoprotein),

Table 1. Effects of some types of ginseng on physical performance in humans.

Ginseng	Experimental design	Results
Standardized extract of *Panax ginseng* 200 mg/day, during 9 weeks. [28]	Men, n = 20, data collected-aerobic capacity.	Increased aerobic capacity, reduced lactate production and heart rate.
Standardized extract of *Panax ginseng* containing 4% or 7% of ginsenosides, during 9 weeks. [29]	Young men, n = 30, data collected-aerobic capacity	Improved aerobic capacity, reduced lactate production and heart rate, there was no difference between 4% and 7% of the content of ginsenosides.
Standardized extract of *Panax ginseng* 200 mg/day, during 9 weeks. [30]	High performance athletes, n = 30, data collected-O_2 uptake.	Improved O_2 uptake, maximum breathing capacity, vital capacity and forced expiratory volume, reduced lactate production and heart rate; no significant changes for serum LH, testosterone, and cortisol.
Glycosides, 2000 mg/day; 1.5%, during 4 weeks. [31]	Marathon runners, n = 12, data collected-aerobic capacity.	No significant difference on the running time to exhaustion, aerobic capacity, heart rate, VE, and RPE.
Standardized extract of ARM229, 2 capsules per 30 days; 1 capsule per 30 days. [32]	Young people (18 - 21 years), and adults (38 - 70 years), n = 65, data collected-performance in Cooper Test.	In the adult group, there was an improved performance in the Cooper test (12 min race), and in the young group there was no significant difference.
Standardized extract of *P. ginseng* (G115), 200 mg/day, during 9 weeks. [33]	High performance athletes, n = 28, data collected-effects on the health of athletes.	Improved O_2 uptake, forced expiratory volume, vital capacity, reaction time and heart rate.
E. senticosus M, during 8 days. [34]	Young men, n = 6, data collected-maximal work capacity.	Significant increase in total work, time to exhaustion
Chinese ginseng and *Eleutherococcus senticosus*, during 6 weeks. [35]	Marathon runners, n = 15 (M) and n = 15 (W), data collected-aerobic performance, physical strength.	Significant increase in VO_2max, physical strength.
Ginseng and fenu-greco 0.5 g twice a day, during 15 days. [36]	Young men, n = 12, data collected-strength and muscle fatigue.	Significant increase in the production of work, significant differences in the lactate level.
Ginseng and fenu-greco 0.5 g twice a day, during 30 days. [37]	Well-trained amateur cyclists, n = 14, data collected-training, endurance performance.	Significant increase in anaerobic threshold, blood ferritin, work, RER, VEmax, VO_2max; blood lactate is not significant.
Standardized extract of *P. ginseng*, 200 mg/day, DMAE, vitamins, minerals, during 6 weeks. [38]	People (21 - 47 years), n = 50, data collected-work and aerobic capacity.	Improved the total workload, time to exhaustion, aerobic capacity, ventilation, VO_2, carbon dioxide production, lactate production and heart rate; no significant RER.
Standardized extract of *P. ginseng*, 400 mg/day during 20 weeks. [39]	Female triathletes (24 - 36 years, n = 43), data collected-physical performance.	Prevented the decrease in the physical performance after 10 km.
P. ginseng C.A. Meyer 200 mg/day at 4% ginsenosides, during 8 weeks. [40]	Healthy adult women, n = 19, data Collected-Metabolic responses.	No significant difference in the sub maximal and maximal exercise.
E. senticosus M 3.4 mL during 8 weeks. [41]	People trained in distance running, n = 20, data collected-Maximal and sub maximal aerobic exercise.	No significant difference in the heart rate, VO_2, VE, VE/VO_2, RER, RPE, time to exhaustion and lactate level.
P. ginseng C.A. Meyer 200 mg/day at 4% ginsenosides during 8 weeks. [42]	Healthy adult women, n = 19, data collected-work performance and energy metabolism.	No significant difference in the performance of maximum work, rest, exercise, recovery of O_2, RER, VE, heart rate, blood lactate levels.
Standardized extract of *P. ginseng*, vitamins, minerals, 200 mg/day during 12 weeks. [43]	Volunteers (18 - 65 years), n = 625, data collected-quality of life.	Improved quality of life, preventing weight gain and increased blood pressure.
P. quinquefolium 8 or 16 mg/Kg/ day during 7 days. [44]	Well-trained amateur cyclists, n = 7 (M), n = 1 (W), data collected-exhaustion at 75% VO_2 max	There was no significant difference in time to exhaustion, lactate levels and glucose, RPE, VE, VO_2

Continued

P. ginseng C.A. Meyer 200 ou 400 mg/day, during 8 weeks. [45]	Healthy adult men, n = 31, data collected-psychological and physiological responses.	No significant difference in maximal and submaximal O_2 uptake, RER, VE, blood lactate, heart rate and RPE.
Ginseng not especified 3 g/day, during 13 days. [46]	Well-trained amateur cyclists, n = 7 (M) and n = 4 (W), data collected-aerobic exercise maximum.	There was no significant difference in maximal heart rate, VO_2max, workload, RER.
P. ginseng 200 mg/day, 7% ginsenosides, during 3 weeks. [47]	Moderately trained healthy young adults, n = 20 (M) and n = 8 (W), data collected-maximum aerobic performance.	There was no significant difference in VO_2, workload, exercise time, lactate, levels of hematocrit, heart rate, RPE.
E. senticosus 1200 mg/day, during 7 days before data collection [3]	Well-trained men, n = 10, data collected-substrate utilization, maintenance of performance.	No significant difference in VO_2, RER, RPE, rate, heart rate, level of lactate and glucose.
P. ginseng C.A. Meyer 400 mg/day, during 8 weeks. [48]	Healthy adult women, n = 24, data collected-aerobic capacity, fatigue.	There was no significant difference in the supramaximal work of short duration.
Extract fluid of Taiga Wurzel-25 drops 3 x/day (1 mL equivalent to 1 g root) during 30 days. [8]	Healthy volunteers (n = 50, W and M), data collected-total cholesterol, LDL cholesterol, free fatty acids, triacylglycerol, glucose, VO_2max.	Significant reduction in total cholesterol and LDL cholesterol levels, reduction of free fatty acids, triacylglycerol, blood glucose, and significant increase in peak VO_2max.
Panax not ginseng 1350 mg/day, during 30 days. [49]	Young adults, n = 29, data collected-aerobic capacity, endurance, mean arterial pressure and VO_2.	Significant improvement in endurance, time to exhaustion, decrease in the mean arterial pressure and VO_2.
Standardized extract of *E. senticosus* 800 mg/day, during 8 weeks. [20]	Men in recreational cycling training, n = 9, data collected-aerobic capacity, maximum heart rate, VO_2, RPE, RER, free fatty acids and glucose in the plasma.	Significant increase in peak VO_2, heart rate and improvement in endurance time. The production of free fatty acids in the plasma was increased, and the glucose level decreased significantly ($P < 0.05$) in 30 min within 75% of peak VO_2.
Panax ginseng 200 mg, 1 hour before running on a treadmill, acute study. [50]	Recreational athletes racing (n = 9, 25 - 32 years), data collected-aerobic capacity, VO_2, heart rate, body temperature, RPE, glucose, lactate, plasma insulin, free fatty acids.	Acute supplementation did not affect any of the parameters analyzed in the study.
Korean ginseng extract, 20 g, mixed with 200 mL of water 3x/day, during 7 days before the test, and four days after the test. [51]	Male college students, n = 18, data Collected-Exercise-induced muscle damage, inflammatory response, insulin sensitivity.	Significant decrease in creatine kinase and interleukin 6 in the group supplemented with ginseng, and a significant decrease in plasma insulin and glucose, suggesting reduced muscle damage and decreased inflammatory response, resulting in improvements in insulin sensitivity.

W = women; M = men; O_2 = oxygen; RER = respiratory exchange ratio; RPE = rate of perceived exertion; VE = expiratory volume; VEmax = forced expiratory volume; VO_2 = oxygen uptake; VO_2max = maximum oxygen uptake; LH = luteinizing hormone, n = number of volunteers. Reference number between [ ], Source: Adapted and updated from Barke & Morgan [2] and Bucci [52].

and also, the sesamin has a direct effect on cholesterol re-synthesis. *β*-sitosterol also has an important effect on the cholesterol structure, reducing its absorption (as demonstrated in humans) and the ability to reduce insulin concentrations, as well as and antioxidant effects regarding cancer. *β*-sitosterol also has anti-inflammatory and antipyretic activities [15].

The antihyperglycaemic action of *β*-sitosterol and its glycoside can be explained by the competitive enzyme inhibition in glucose breakdown, but it does not end the possibilities for this property [15].

The study by Rhie and Won (2004) [22] demonstrated the potent effect on body weight gain of mice treated with ES, which was significantly reduced, besides demonstrating a significant reduction in the plasmatic cholesterol concentration. One hypothesis for this important effect in reducing weight could be explained by the action of ES on glucose and insulin metabolism [20], besides the effect of lower concentrations of corticosterone in rats [11,23].

4. ADVERSE EFFECTS OF *ELEUTHEROCOCCUS SENTICOSUS*

A case was reported on the use of *Eleutherococus senticosus* in a man who used digoxin and who had high plasmatic concentration (digoxin). When the supplementation was interrupted, the plasmatic concentration decreased [24]. Diabetics who use ES should monitor blood glucose concentrations, due to the hypoglycemic effects reported in animals [25].

5. TOXICOLOGICAL EFFECTS

The safety and efficacy of the ES supplement were evaluated on the activities of CYP2D6 of the cytochrome P450 and CYP3A4 [26], suggesting that the ES extract at a dose as it is usually recommended does not affect the metabolism of CYP2D6 and CYP3A4, and, therefore, it is not harmful to the health of individuals [11,27].

6. CONCLUSION

ES may receive great attention by showing that its active components can provide protection against oxidative stress, among other benefits, contributing to health and the prevention and treatment of diseases such as diabetes, cancer, cardiovascular disease and inflammations. However, the researches comprise mostly *in vitro* tests or animals tested *in vivo* in the laboratory, and the studies may not necessarily apply to humans. When they apply, there may be no reliable results due to factors such as diet, lifestyle, exercise and the administration of other drugs, and also the actual health of the participants. Nevertheless, it is expected that further controlled studies in humans are performed for a better understanding of the ES effects and its implementation, conferring it an economic importance, since it may help in the treatment of several diseases.

REFERENCES

[1] Goulet, E.D.B. and Dionne, I.J. (2005) Assessment of the effects of *Eleutherococcus senticosus* on endurance performance. *International Journal of Sport Nutrition and Exercise Metabolism*, **14**, 75-83.

[2] Bahrke, M.S., Morgan, W.P. and Stegner, A. (2009) Is Ginseng an ergogenic aid? *International Journal of Sport Nutrition and Exercise Metabolism*, **19**, 298-322.

[3] Eschbach, L.C., Webster, M.J., Boyd, J.C., McArthur, P.D. and Evetovich, T.K. (2000) The effect of Siberian ginseng (*Eleutherococcus senticosus*) on substrate utilization and performance during prolonged cycling. *International Journal of Sport Nutrition and Exercise Metabolism*, **10**, 444-451.

[4] Brekhman, I.I. and Dardymov, I.V. (1969) New substances of plant origin which increase nonspecific resistance. *Annual Review of Pharmacology and Toxicology*, **9**, 419-430. doi:10.1146/annurev.pa.09.040169.002223

[5] Bahrke, M.S. and Morgan, W.P. (2000) Evaluation of the ergogenic properties of ginseng. *Sports Medicine*, **2**, 113-133. doi:10.2165/00007256-200029020-00004

[6] Fu, Y. and Ji, L.L. (2003) Chronic Ginseng consumption attenuates age-associed oxidative stress in rats. *Journal of Nutrition*, **11**, 3603-3609.

[7] Atelle, A.S., Wu, J.A. and Yuan, C. (1999) Ginseng pharmacology, multiple constituents and multiple actions. *Biochemical Pharmacology*, **58**, 1685-1693. doi:10.1016/S0006-2952(99)00212-9

[8] Szolomicki, J., Samochowiec, L., Mójcicki, J. and Drozdzik, M. (2000) The influence of active components of *Eleutherococcus senticosus* on cellular defense and physical fitness in man. *Phytotherapy Research*, **14**, 30-35. doi:10.1002/(SICI)1099-1573(200002)14:1<30::AID-PTR543>3.3.CO;2-M

[9] Baranov, A.I. (1982) Medicinal uses of ginseng and related plants of the Soviet Union: Recent trends in the Soviet literature. *Journal of Ethnopharmacology*, **6**, 339-353. doi:10.1016/0378-8741(82)90055-1

[10] (2010) *Official Journal of the European Union*, **53**. http://eur-lex.europa.eu/JOHtml.do?uri=OJ%3AL%3A2010%3A012%3ASOM%3AEN%3AHTML

[11] Yan-Lin, S., Lin-De, L. and Soon-Kwan, H. (2011) *Eleutherococcus senticosus* as a crude medicine: Review of biological and pharmacological effects. *Journal of Medicinal Plants Research*, **5**, 5946-5952. http://www.academicjournals.org/JMPR

[12] Elyakov, G.B., Strigina, L.I., Uvarova, N.I., Vaskovsky, V.E., Dzizenko, A.K. and Kochetkov, N.K. (1964) Glycosides from ginseng roots. *Tetrahedron Letters*, **48**, 3591-3597. doi:10.1016/S0040-4039(01)89378-3

[13] Hikino, H., Takahashi, M., Otake, K. and Konno, C. (1986) Isolation and hypoglycemic activity of eleutherans A, B, C, D, E, F, and G: Glycans of *Eleutherococcus senticosus* roots. *Journal of natural products*, **49**, 293-297. doi:10.1021/np50044a015

[14] Wagner, H., Norr, H. and Winterhoff, H. (1994) Plant adaptogens. *Phytomedicine*, **1**, 63-76. doi:10.1016/S0944-7113(11)80025-5

[15] Davydov, M. and Krikorian, A.D. (2000) *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: A closer look. *Journal of Ethnopharmacology*, **72**, 345-393. doi:10.1016/S0378-8741(00)00181-1

[16] Yat, P.N., Arnason, J.T. and Awang, D.V.C. (1998) An improved extraction procedure for the rapid, quantitative high-performance liquid chromatographic estimation of the main eleutherosides (B and E) in *Eleutherococcus* (Eleuthero). *Phytochemical Analysis*, **9**, 291-295. doi:10.1002/(SICI)1099-1565(199811/12)9:6<291::AID-PCA417>3.0.CO;2-K

[17] Apers, S., Naessens, T., Van Miert, S., Pieters, L. and Vlietinck, A. (2005) Quality control of roots of *Eleutherococcus senticosus* by HPLC. *Phytochemical Analysis*, **16**, 55-60. doi:10.1002/pca.811

[18] Campbell, T.C., Wu, Y.N., Lu, C.Q., Li, M. and Kaman, R.L. (1997) Effects of Radix *Acanthopanax senticosus* (ciwujia) on exercise. *The Journal of Strength & Conditioning Research*, **11**, 278.

[19] Wu, Y.I.N., Wang, X.Q., Zhao, Y.F., Wang, J.Z., Chen, H.J., Liu, H.Z., Li, R.W., Campbell, T.C. and Chen, J.S. (1996) Effect of ciwujia (*Radix Acanthopanax senticosis*) preparation on human stamina. *Wei Sheng Yan Jiu*, **25**, 57-61.

[20] Kuo, J., Chen, K.W.C., Cheng, I.S., Tsai, P.H., Lu, Y.J. and

Lee, N.Y. (2010) The effect of eight weeks of supplementation with *Eleutherococcus senticosus* on endurance capacity and metabolism in human. *The Chinese Journal of Physiology*, **53**, 105-111. doi:10.4077/CJP.2010.AMK018

[21] Han, J.H., Jung, I.C., Cho, H.E. and Park, S.H. (2006) Total polyphenol, water soluble antioxidants contents and antioxidative activity from a composite with *Eleutherococcus senticosus* and several oriental medicine herbs. *Korean Journal of Oriental Physiology & Pathology*, **20**, 1275-1281.

[22] Rhie, S.G. and Won, H.R. (2004) Effect of hot water soluble extract from *Eleutherococcus senticosus* and dietary carnitine on the lipid metabolism and antioxidant defense system of rats on hypercholesterol diet. *The Korean Journal of Community Living Science*, **15**, 105-113.

[23] Kimura, Y. and Sumiyoshi, M. (2004) Effects of various *Eleutherococcus senticosus* cortex on swimming time, natural killer activity and corticosterone level in forced swimming stressed mice. *Journal of Ethnopharmacology*, **95**, 447-453. doi:10.1016/j.jep.2004.08.027

[24] Huang, L.Z., Zhao, H.F., Huang, B.K., Zheng, C.J., Peng, W. and Qin, L.P. (2011) *Acanthopanax senticosus*: Review of botany, chemistry and pharmacology. *Pharmazie*, **66**, 83-97.

[25] Brinker, F. (1998) Herb contraindications and drug interactions. 2nd Edition, Eclectic Medical Publications, Sany, 123.

[26] Brosen, K. (1996) Drug-metabolizing enzymes and therapeutic drug monitoring in psychiatry. *Therapeutic Drug Monitoring*, **18**, 393-396. doi:10.1097/00007691-199608000-00014

[27] Donovan, J.L., Devane, C.L., Chavin, K.D., Taylor, R.M. and Markowitz, J.S. (2003) Siberian ginseng (*Eleutherococcus senticosus*) effects on CYP2D6 and CYP3A4 activity in normal volunteers. *Drug Metabolism and Disposition*, **31**, 519-522. doi:10.1124/dmd.31.5.519

[28] Forgo, I. and Kirchdorfer, A.M. (1981) Ginseng steigert die körperliche Leistung. Kreislaufphysiologische Untersuchungen an Spitzensportlern beweisen: Der Stoffwechsel wird aktiviert. (On the question of influencing the performance of top sportsmen by means of biologically active substances). *Arztl Prax*, **33**, 1784-1791.

[29] Forgo, I. and Kirchdorfer, A.M. (1982) The effect of different ginsenoside concentrations on physical work capacity. *Notabene Medicine*, **12**, 721-727.

[30] Forgo, I. (1983) Effect of drugs on physical performance and the hormonal system of athletes. *MMW*: *Munchener Medizinische Wochenschrift*, **125**, 822-824.

[31] Teves, M.A., Wright, J.E., Welch, M.J., Patton, J.F., Mello, R.P., Rock, P.B., Knapik, J.J., Vogel, J.A. and derMarderosian, A. (1983) Effects of ginseng on repeated bouts of exhaustive exercise. *Medicine & Science in Sports & Exercise*, **15**, 162. doi:10.1249/00005768-198315020-00350

[32] Murano, S. and Lo Russo R. (1984) Experiencia con ARM 229. *Prensa Medical Argent*, **71**, 178-183.

[33] Forgo, I. and Schimert, G. (1985) The duration of effect of the standardized ginseng extract G115 in healthy competitive athletes. *Notabene Medicine*, **15**, 636-640.

[34] Asano, K., Takahashi, T., Miyashita, M., Matsuzaka, S., Muramatsu, S., Kuboyama, M., Kugo, H. and Imia, J. (1986) Effect of *Eleutherococcus senticosus* extract on human physical working capacity. *Planta Medica*, **3**, 175-177. doi:10.1055/s-2007-969114

[35] McNaughton, L., Egan, G. and Caelli, G. (1989) A comparison of Chinese and Russian ginseng as ergogenic aids to improve various facets of physical fitness. *International Journal of Clinical and Nutrition Reviews*, **9**, 32-35.

[36] Gribaudo, C.G., Ganzit, G.P. and Verzini, E.F. (1990) Effetti sulla forza e sulla fatica muscolare di un prodotto ergogenico di origine naturale. *Medicina Dello Sport*, **43**, 241-249.

[37] Gribaudo, C.G., Ganzit, G.P., Biancotti, P.P. and Meda, C. (1991) Effetti della soministrazione di un prodotto naturalle ergogenico sulle doti aerobiche di ciclisti agonisti. *Medicina Dello Sport*, **44**, 335-343.

[38] Pieralisi, G., Ripari, P. and Vecchiet, L. (1991) Effects of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements on physical performance during exercise. *Clinical Therapy*, **13**, 373-382.

[39] Van Schepdael, P. (1993) Les effets du ginseng G115 sur la capacité physique de sportifs d'endurance. *Acta Therapeutica*, **19**, 337-347.

[40] Engels, H.-J., Said, J.M., Wirth, J.C. and Zhu, W. (1995) Effect of chronic ginseng intake on metabolic responses during and in the recovery from graded maximal exercise (abstract). *Medicine & Science in Sports & Exercise*, **27**, S147. doi:10.1249/00005768-199505001-00830

[41] Dowling, E.A., Redondo, D.R., Branch, J.D., Jones, S., McNabb, G. and Williams, M.H. (1996) Effect of *Eleutherococcus senticosus* on submaximal and maximal exercise performance. *Medicine & Science in Sports & Exercise*, **28**, 482-489. doi:10.1097/00005768-199604000-00013

[42] Engels, H.-J., Said, J.M. and Wirth, J.C. (1996) Failure of chronic ginseng supplementation to affect work performance and energy metabolism in healthy adult females. *Nutrition Research*, **16**, 1295-1305. doi:10.1016/0271-5317(96)00138-8

[43] Marasco, C., Vargas, R., Villagomez, S. and Infante, B. (1996) Double-blind study of a multivitamin complex supplemented with ginseng extract. *Drugs under Experimental and Clinical Research*, **22**, 323-329.

[44] Morris, A.C., Jacobs, I., McLellan, T.M., Klugerman, A., Wang, L.C.H. and Zamecnik, J. (1996) No ergogenic effect of ginseng ingestion. *International Journal of Sport Nutrition*, **6**, 263-271.

[45] Engels, H.J. and Wirth, J.C. (1997) No ergogenic effects of ginseng (*Panax ginseng* C.A. Meyer) during graded maximal aerobic exercise. *Journal of the American Dietetic Association*, **97**, 1110-1115. doi:10.1016/S0002-8223(97)00271-X

[46] Lifton, B., Otto, R.M. and Wygand, J. (1997) The effect of ginseng on acute maximal aerobic exercise (abstract). *Medicine & Science in Sports & Exercise*, **29**, 249. doi:10.1097/00005768-199705001-01413

[47] Allen, J.D., McLung, J., Nelson, A.G. and Welsch, M. (1998) Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance. *Journal of the American College of Nutrition*, **17**, 462-466. doi:10.1080/07315724.1998.10718795

[48] Kolokouri, I., Engels, H.-J., Cieslak, T. and Wirth, J.C. (1999) Effect of chronic ginseng supplementation on short duration, supramaximal exercise test performance. *Medicine & Science in Sports & Exercise*, **31**, S117. doi:10.1097/00005768-199905001-00445

[49] Liang, M.T., Podolka, T.D and Chuang, W.J. (2005) Panax not ginseng supplementation enhances physical performance during endurance exercise. *Journal of Strength & Conditioning Research*, **19**, 108-114. doi:10.1519/00124278-200502000-00019

[50] Ping, F.W., Keong, C.C. and Bandyopadhyay, A. (2011) Effects of acute supplementation of *Panax ginseng* on endurance running in a hot & humid environment. *Indian Journal of Medical Research*, **133**, 96-102.

[51] Jung, H.L., Kwak, H.E., Kim, S.S., Kim, Y.C., Lee, C.D., Byurn, H.K. and Kang, H.Y. (2011) Effects of *Panax ginseng* supplementation on muscle damage and inflammation after uphill treadmill running in humans. *The American Journal of Chinese Medicine*, **39**, 441-450. doi:10.1142/S0192415X11008944

[52] Bucci, L.R. (2000) Selected herbals and human exercise performance. *The American Journal of Clinical Nutrition*, **72**, 624-636.

