Int J Neurosci, 2013; 00(00): 1–7

ISSN: 0020-7454 print / ISSN: 1543-5245 online
DOI: 10.3109/00207454.2013.764499

informa
healthcare

Orginal Article

Ginseng in the treatment of fatigue in multiple sclerosis: a randomized, placebo-controlled, double-blind pilot study

Masoud Etemadifar,[1,2,3] Farnaz Sayahi,[3] Seyed-Hossein Abtahi,[1,2,3,4] Hamidreza Shemshaki,[5] Gholam-Ali Dorooshi,[6] Mohammad Goodarzi,[7] Mojtaba Akbari,[1] and Mahboobeh Fereidan-Esfahani[1,2,3,4]

[1]Medical School, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Neurology, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Isfahan Research Committee of Multiple Sclerosis (IRCOMS), Isfahan University of Medical Sciences, Isfahan, Iran, [4]Medical Students' Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran, [6]Department of Clinical Toxicology and Forensic Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, and [7]Student Research Committee, School of Nursing and Midwifery, Medical Students Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Fatigue is one of the common complaints of multiple sclerosis (MS) patients, and its treatment is relatively unclear. Ginseng is one of the herbal medicines possessing antifatigue properties, and its administration in MS for such a purpose has been scarcely evaluated. The purpose of this study was to evaluate the efficacy and safety of ginseng in the treatment of fatigue and the quality of life of MS patients. *Methods:* Eligible female MS patients were randomized in a double-blind manner, to receive 250-mg ginseng or placebo twice daily over 3 months. Outcome measures included the Modified Fatigue Impact Scale (MFIS) and the Iranian version of the Multiple Sclerosis Quality Of Life Questionnaire (MSQOL-54). The questionnaires were used after randomization, and again at the end of the study. *Results:* Of 60 patients who were enrolled in the study, 52 (86%) subjects completed the trial with good drug tolerance. Statistical analysis showed better effects for ginseng than the placebo as regards MFIS ($p = 0.046$) and MSQOL ($p \leq 0.0001$) after 3 months. No serious adverse events were observed during follow-up. *Conclusions:* This study indicates that 3-month ginseng treatment can reduce fatigue and has a significant positive effect on quality of life. Ginseng is probably a good candidate for the relief of MS-related fatigue. Further studies are needed to shed light on the efficacy of ginseng in this field.

KEYWORDS: multiple sclerosis, ginseng, fatigue, quality of life, Isfahan, Iran

Introduction

Multiple sclerosis (MS) is one of the most common non-traumatic causes of disability in the world. It is a chronic inflammatory and demyelinating disorder of the central nervous system (CNS), which affects individuals in the productive age range and causes a large burden for years to come. During the last decade, serial population-based studies have shown a sharp increase in the prevalence and incidence of MS in our population [1,2]. Fatigue is a common complaint and one of the least understood symptoms of MS [3]. It lowers the quality of life (QOL) in MS patients [4]. Among the immunomodulation drugs used in the treatment of the relapsing form of MS, only natalizumab can reduce MS-related fatigue, but it has serious adverse effects [5].

Ginseng is one of the most well-known herbal medicines, widely used as a tonic, restorative and antiaging agent in traditional Chinese medicine [6]. The plant contains ginsenosides as major bioactive compounds, which are known to exert complex and multiple pharmacological effects. It also contains a number of important bioactive constituents like polysaccharides, triterpenoids and flavonoids [7,8]. Ginseng affects the CNS, cardiovascular, reproductive and metabolic [9,10] systems and has antifatigue [11], antihyperglycemic [12–14], antiobesity [15, 16], anticancer [17], antioxidant [18,19] and antiaging [20] properties. Some studies have shown that ginseng might be beneficial in the treatment of cancer-related fatigue [21]. The results of some clinical and

Received 23 October 2012; revised 4 January 2013; accepted 4 January 2013.
Correspondence: Mahboobeh Fereidan-Esfahani, Isfahan Multiple Sclerosis Society, No. 2, Behesht Building, Bozorgmehr Ave., Isfahan, Iran. Tel: +98.9380283952. E-mail: mf.esfahani@yahoo.com

experimental studies indicate that ginseng can increase work efficiency, energy and physical stamina [22,23]. At ordinary levels of administration, it is shown to be safe [12,24], adverse effects occurring only when it is overused [25,26]. Notwithstanding such findings, to date, there is only one study by Kim et al. [27] evaluating the safety and efficacy of ginseng for the treatment of MS-related fatigue. This study suggested that escalating doses of American ginseng (100 mg/day, 200 mg/day, 400 mg/day) are safe; however, they did not provide any benefit over that seen with the placebo.

We conducted this trial, a 3-month, randomized, double-blind, placebo-controlled pilot study, to evaluate the efficacy and safety of ginseng in the treatment of fatigue in patients with MS.

Methods and materials

Setting and patients

This randomized double-blind trial was conducted from December 2010 to April 2011 by Isfahan MS Society (IMSS) and Isfahan University of Medical Sciences, Isfahan, Iran. Inclusion criteria were definite diagnosis of relapsing-remitting MS (RRMS) as defined by McDonald's criteria [28] with a baseline of Expanded Disability Status Score (EDSS) of less than 5.0 [29]. Female MS patients (between 18 and 50 years old) undergoing treatment with the type of interferon beta-1a (IFNB-1a) were enrolled. Exclusion criteria were as follows: (1) patients with a clinical relapse of MS during the last 30 days; (2) prior use of ginseng or any other tonic agents, glucocorticoids, warfarin, digoxin, aspirin, furosemide, caffeine, Ephedra and antiplatelet agents within 1 month prior to enrollment; (3) pregnancy or lactation; (4) history of renal failure and (5) lack of appropriate adherence to the study protocol.

The study was implemented in accordance with the tenets of the declaration of Helsinki. The study protocol was approved by the institutional ethics board, and all participants provided us with written informed consents prior to inclusion. The study was registered at ClinicalTrials.gov (Identifier: NCT01712373).

Intervention

Using simple random allocation software [30], eligible patients were assigned into two arms of 3-month drug regimen: (1) 250-mg Korean ginseng tablets (Martec Industries Inc., Huntington Beach, CA, USA) twice daily after breakfast and evening meal; (2) placebo tablets having the same shape and color. Participants were followed by a 2-week washout. Compliance and adverse events were assessed during the study with non-leading questions in clinical visits by investigators every 4 weeks. During data collection, neither the assessors nor the patients were aware of the treatment allocation.

Assessment

To evaluate fatigue, we used the Modified Fatigue Impact Scale (MFIS) [31] in its validated Persian translation. MFIS is a 21-item (score range of each item: 0–4) questionnaire with the total score computed from 0 (no impact of fatigue) to 84 (maximum impact of fatigue) in three subscales containing physical (9 items), cognitive (10 items) and psychosocial (2 items), aspects. To determine quality of life, we used the Iranian version of the Multiple Sclerosis Quality Of Life Questionnaire (MSQOL-54), once after randomization, and later at the end of the study. The validity and reliability of this questionnaire has been published elsewhere [32], by which, it has been shown that reliability, as measured by Cranach's alpha coefficient, is acceptable for all subscales ($\alpha \geq 0.7$) except those for social function and health perception having alpha coefficients of 0.654 and 0.696, respectively. It consisted of 54 questions (items), each one assigned to a score ranging from 0 to 100.

Statistical measures

The statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were adopted for demographic and clinical characteristics, reporting the variables as means ± 1, standard deviation (SD). The Kolmogrov–Smirnov test was used to test for normal distribution of quantitative data. To compare MFIS/MSQOL-54 subscales between two groups, we used a paired t test. A parametric independent sample t test and the Mann–Whitney test were employed for comparing the distribution of demographic variables. Differences among groups were assessed by analysis of covariance (ANCOVA), using the baseline score as a covariate. All statistical tests were two-tailed, and a p value of less than 0.05 was considered the significance threshold.

Results

Study sample

Participant's flow is shown in the CONSORT diagram (Figure 1). Among 60 RRMS female patients who were enrolled, 8 were excluded from the final analysis. Five patients were not initially included; 3 with an EDSS score of more than 5, 1 with concomitant use of digoxin, and another who was pregnant. A total of 52 patients completed the trial, of whom 26 received ginseng and 26 received the placebo. The baseline demographic and disease variables of the participants are summarized in Table 1. At inclusion, according to an independent

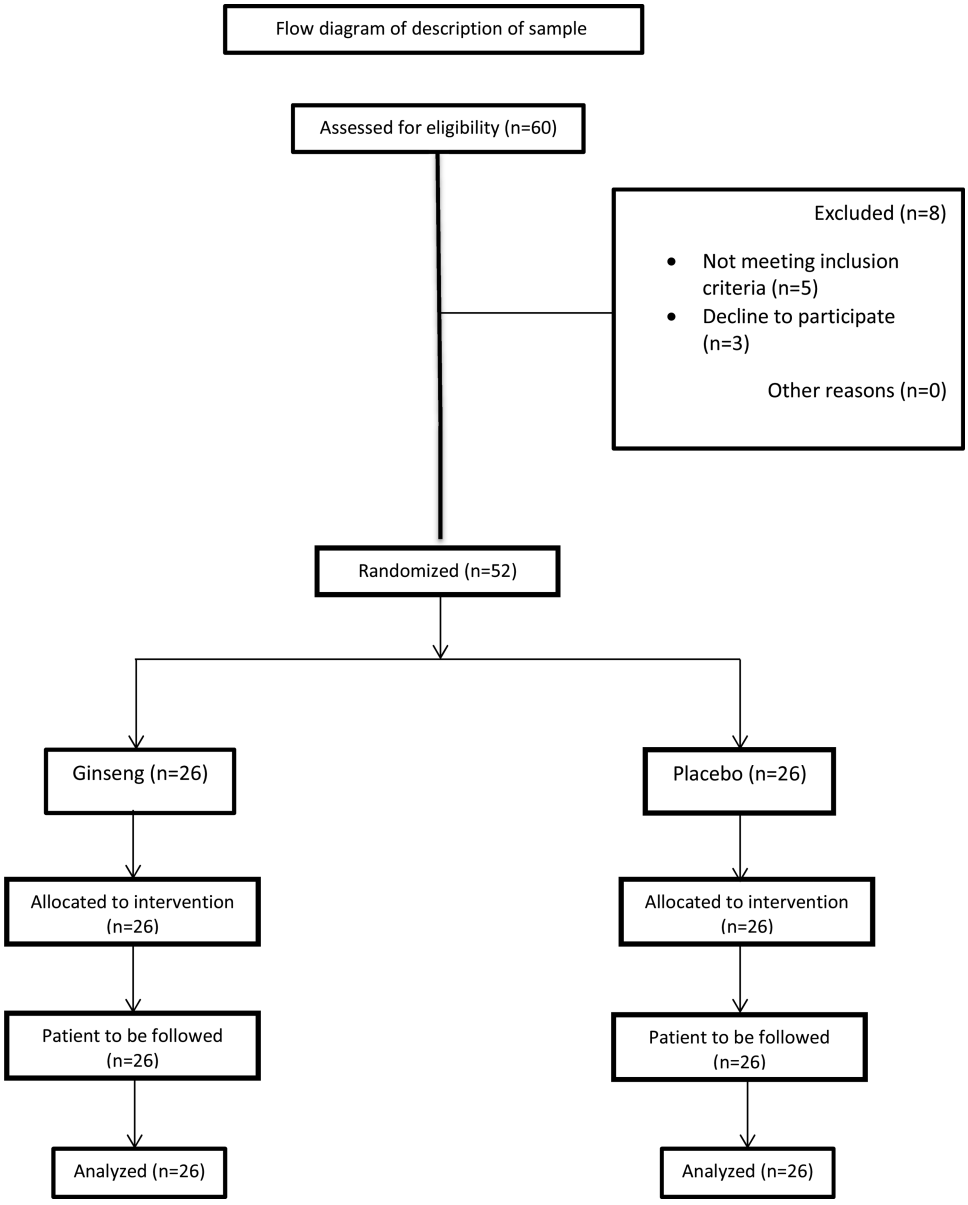

Figure 1. Participants' flow in the CONSORT diagram.

sample *t* test, the mean ± SD age was 33.9 ± 8.2 years. The median [interquartile range (IQR)] time from diagnosis to the study onset was 3.75 [1.5–5.75] years, and the median [IQR] score of EDSS was 1.5 [1–2]. The Mann–Whitney test showed no statistical difference between the two groups for age, duration of MS and EDSS.

Fatigue

Changes in the MFIS score before and after treatment were compared between the two groups. The mean total score after treatment with 500 mg/day ginseng decreased by 8.04, from 31.69 to 23.65 versus an increase from 22.23 to 23.69 in the placebo group ($p =$

Table 1. Baseline demographic and clinical characteristics of patients.

Characteristics	Ginseng group ($n = 26$)	Placebo group ($n = 26$)
Age (mean ± SD), years	33.3 ± 7.5	34.5 ± 8.9
Mean duration of MS [IQR*], years	3.5 [1.5–5.5]	3.75 [1.15–6.25]
EDSS [IQR]	1.5 [1–2]	1.5 [1–2]

MS, multiple sclerosis; EDSS, Kurtzke Expanded Disability Status Scale; Median [IQR] → median [Interquartile range]; SD, standard deviation.

AQ3

Table 2. Comparing scores of Modified Fatigue Impact Scale subscales between two groups.

Subscale	Baseline	After intervention	p Value (within group*)	p Value (between group**)
Physical dimension score				
Ginseng group	17.08 ± 6.93	15.28 ± 7.73	<0.001	0.042
Placebo group	11.54 ± 7.26	12.31 ± 6.96	0.41	
Cognitive dimension score				
Ginseng group	12.12 ± 7.59	9.15 ± 6.47	0.01	0.12
Placebo group	9.35 ± 7.03	9.65 ± 6.15	0.07	
Psychosocial dimension score				
Ginseng group	2.46 ± 2.47	1.65 ± 1.90	0.11	0.13
Placebo group	2.00 ± 2.04	1.38 ± 1.67	0.8	
Total MFIS score				
Ginseng group	31.69 ± 14.9	23.65 ± 12.8	0.042	0.046
Placebo group	22.23 ± 13.21	23.69 ± 12.94	0.68	

*Paired t test; **ANCOVA test.

0.046). The mean scores for the "physical" subscale of the MFIS were significanty improved after treatment with ginseng compared with the placebo ($p = 0.042$), although no significant differences in "cognitive" ($p = 0.12$) and "psychosocial" ($p = 0.13$) subscales were observed before and after treatment (Table 2).

Quality of life

Most of the scores for the individual domains of the MSQOL questionnaire were markedly increased after intervention. The total score for the MSQOL was increased (19.2 scores) in the ginseng treatment group. The MSQOL subscales of "physical health" ($p \leq 0.001$), "role limitations due to physical problems" ($p \leq 0.001$), "emotional well being" ($p = 0.003$), "energy" ($p \leq 0.001$), "cognitive function" ($p = 0.004$), "health distress" ($p = 0.014$) and "change in health" were desirably affected by ginseng. Overall, according to the ANCOVA test, patients treated with ginseng had an improvement in the quality of life compared with those given the placebo ($p < 0.0001$) (Table 3).

Safety

The drug was well tolerated and no serious adverse events were observed during the follow-up; however, 1 patient suffered from constipation, which was resolved with a dose adjustment.

Discussion

Our findings suggest significant differences in the MFIS between the ginseng group before and after intervention. Fatigue is one of the most common complaints of MS patients, and its treatment is difficult and unclear. On the one hand, there are a number of clinical trials that evaluate the safety and efficacy of various drugs in this field (amantadine, modafinile, acetyl L-carnitine, glatiramer acetate, etc.) [33–36]; on the other hand, the role of ginseng in cancer-related fatigue and chronic fatigue syndrome has been previously investigated [37,38]; however, there are no convincing studies on the effects of ginseng in MS-related fatigue. The mechanism by which MS causes fatigue has not been completely understood. In this regard, however, some theories for the roles of oxidative stress and free radicals have been postulated in the pathogenesis of MS lesions [39,40]. In experimental studies, related properties of ginseng, such as its neuroprotective effect [18,41] and scavenging affinity to the 2, 2-diphenyl-1-picrylhydrazyl (DPPH)-stable free radical and hydroxyl free radicals [18] have been shown. Hence, the mechanism behind the antifatigue property of ginseng may be due to its antioxidant feature, although such a notion needs further research to obtain objective evidence. Moreover, its ability to regulate dopamine, serotonin, noradrenaline and gamma-amino butyric acid (GABAergic) neurotransmissions might be another speculative explanation in support of our findings [42].

In the literature, there is only one pilot study by Kim et al. [27] on the treatment of fatigue in 47 MS patients using ginseng. In this report, patients received escalating doses of the drug during 6 weeks. This research evaluated the safety and efficacy of ginseng in this regard; results showed it to be safe but not effective. This is in contrast to our findings, which may originate from various features differing from those of our study, e.g., inclusion criteria (high score of EDSS [3.1 ± 1.8]), long duration from the onset of MS course (10.1 ± 8.6 years), short follow-up duration (6 weeks) and the use of different types of ginseng.

In our study, the reduction in the total MFIS score (8.04) during 3 months was relatively higher than that reported by Ziemssen et al. on the use of glatiramer acetate for 12 months (7.6) [36]. Iarlori et al. [43], in their related report on glatiramir acetate, found this drug to be effective in reducing fatigue in MS. To justify, they adhered to the notion that "it can prevent free radical

Table 3. Comparing scores of Multiple Sclerosis Quality of Life subscales between two groups.

Subscale	Baseline	After intervention	p Value whitin group*	p Value between group**
Physical health				
Ginseng group	42.12 ± 26.65	71.35 ± 23.85	<0.0001	<0.0001
Placebo group	51.35 ± 30.41	49.81 ± 27.58	0.63	
Role limitations due to physical problems				
Ginseng group	52.88 ± 41.42	81.73 ± 37.12	0.01	<0.0001
Placebo group	59.62 ± 34.69	47.12 ± 31.88	0.051	
Role limitations due to emotional problems				
Ginseng group	39.74 ± 49.00	79.49 ± 40.09	<0.0001	0.06
Placebo group	57.69 ± 50.38	61.54 ± 47.79	0.72	
Pain				
Ginseng group	63.27 ± 24.66	79.17 ± 22.50	<0.0001	0.25
Placebo group	79.68 ± 20.92	80.19 ± 19.90	0.86	
Emotional well being				
Ginseng group	48.00 ± 16.51	63.23 ± 13.38	<0.0001	0.003
Placebo group	56.15 ± 19.18	56.77 ± 16.47	0.82	
Energy				
Ginseng group	37.85 ± 14.54	58.15 ± 9.94	<0.0001	<0.0001
Placebo group	43.08 ± 16.79	45.54 ± 13.62	0.41	
Health perception				
Ginseng group	53.85 ± 15.83	62.88 ± 15.75	0.05	0.65
Placebo group	56.54 ± 18.64	62.88 ± 17.78	0.03	
Social function				
Ginseng group	75.64 ± 14.12	81.73 ± 8.83	0.01	0.13
Placebo group	76.92 ± 13.39	78.78 ± 11.48	0.33	
Cognitive function				
Ginseng group	68.55 ± 16.79	86.35 ± 13.08	<0.0001	0.004
Placebo group	71.82 ± 18.44	75.19 ± 19.56	0.28	
Health distress				
Ginseng group	64.23 ± 18.09	86.92 ± 17.44	<0.0001	0.014
Placebo group	72.88 ± 27.31	80.38 ± 21.35	0.06	
Sexual function				
Ginseng group	70.31 ± 38.60	81.24 ± 21.19	0.18	0.11
Placebo group	75.88 ± 33.32	74.99 ± 35.24	0.6	
Change in health				
Ginseng group	51.92 ± 24.41	75.19 ± 20.02	<0.0001	0.01
Placebo group	52.88 ± 23.79	58.65 ± 21.14	0.13	
Satisfaction with sexual function				
Ginseng group	60.94 ± 38.69	76.56 ± 21.34	0.76	0.49
Placebo group	68.42 ± 40.69	68.42 ± 38.94	1.00	
Overall quality of life				
Ginseng group	75.30 ± 17.25	79.80 ± 11.81	0.05	0.24
Placebo group	73.06 ± 20.44	74.67 ± 18.62	0.062	
Total Multiple Sclerosis Quality of Life				
Ginseng group	53.64 ± 15.51	73.56 ± 13.27	<0.0001	<0.0001
Placebo group	62.42 ± 14.64	66.60 ± 13.12	0.28	

*Paired t test; **ANCOVA test.

production during MS," which is similar to one of our explanations in favor of the association between antioxidant agents and relief of fatigue in MS.

In conclusion, this randomized, controlled, double-blind study indicates that 3-month administration of ginseng can relieve fatigue and improve the quality of life in MS cases. Ginseng can be considered as a safe option for the treatment of MS-related fatigue. The interpretation of our results is limited by the small sample size, simple randomization, short duration of follow-up, and also, inclusion of only one gender (females). Further studies in years to come are warranted to clarify the disputed effects and mechanisms of ginseng for such a purpose.

Acknowledgements

The authors would like to thank the participating patients and their relatives for their collaboration with this research. The results of this study are dedicated to MS patients who bravely cope with the illness.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. AQ4

This study was funded by the Isfahan Multiple Sclerosis Society (IMSS) as a private health care sector and Isfahan University of Medical Sciences.

References

1. Wallin MT, Page WF, Kurtzke JF. Epidemiology of multiple sclerosis in US veterans. VIII. Long-term survival after onset of multiple sclerosis. Brain (a journal of neurology) 2000;123:1677–87.
2. Etemadifar M, Abtahi SH. Multiple sclerosis in Isfahan, Iran: past, present and future. Int J Prev Med 2012;3(5):301–2.
3. Flensner G, Ek AC, Landtblom AM, et al. Fatigue in relation to perceived health: people with multiple sclerosis compared with people in the general population. Scandinavian J Caring Sci 2008;22(3):391–400.
4. Lintern TC, Beaumont JG, Kenealy PM, et al. Quality of life (QoL) in severely disabled multiple sclerosis patients: comparison of three QoL measures using multi-dimensional scaling. Qual Life Res (an international journal of quality of life aspects of treatment, care and rehabilitation) 2001;10(4):371–8.
5. Foley J. Recommendations for the selection, treatment, and management of patients utilizing natalizumab therapy for multiple sclerosis. Am J Manag Care 2010;16(6):178–83.
6. Kim YK, Guo Q, Packer L. Free radical scavenging activity of red ginseng aqueous extracts. Toxicology 2002;172(2):149–56.
7. Hou JP. The chemical constituents of ginseng plants. Comp Med East West 1977;5(2):123–45.
8. Yip TT, Lau CN, But PP, et al. Quantitative analysis of ginsenosides in fresh Panax ginseng. Am J Chin Med 1985;13(1–4):77–88.
9. Saito H, Morita M, Takagi K. Pharmacological studies of Panax ginseng leaves. Jpn J Pharmacol 1973;23(1):43–56.
10. Wang BX, Cui JC, Liu AJ. The action of ginsenosides extracted from the stems and leaves of Panax ginseng in promoting animal growth. Yao Xue Xue Bao (Acta pharmaceutica Sinica) 1982;17(12):899–904.
11. Wang BX, Cui JC, Liu AJ, et al. Studies on the anti-fatigue effect of the saponins of stems and leaves of panax ginseng (SSLG). J Tradit Chin Med (Chung i tsa chih ying wen pan / sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese Medicine) 1983;3(2):89–94.
12. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. Diabetes care 1995;18(10):1373–5.
13. Chung SH, Choi CG, Park SH. Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKAy mice. Arch Pharm Res 2001;24(3):214–8.
14. Davydov VV, Molokovskii DS, Limarenko A. Efficacy of ginseng drugs in experimental insulin-dependent diabetes and toxic hepatitis. Patologicheskaia fiziologiia i eksperimental'naia terapiia 1990;(5):49–52.
15. Xie JT, Wang CZ, Ni M, et al. American ginseng berry juice intake reduces blood glucose and body weight in ob/ob mice. J Food Sci 2007;72(8):S590–4.
16. Xie JT, Aung HH, Wu JA, et al. Effects of American ginseng berry extract on blood glucose levels in ob/ob mice. Am J Chin Med 2002;30(2–3):187–94.
17. Kitts DD, Popovich DG, Hu C. Characterizing the mechanism for ginsenoside-induced cytotoxicity in cultured leukemia (THP-1) cells. Can J Physiol Pharmacol 2007;85(11):1173–83.
18. Kitts DD, Wijewickreme AN, Hu C. Antioxidant properties of a North American ginseng extract. Mol Cell Biochem 2000;203(1–2):1–10.
19. Li J, Huang M, Teoh H, et al. Panax quinquefolium saponins protects low density lipoproteins from oxidation. Life Sci 1999;64(1):53–62.
20. Zhou L, Hao R, Jiang L. Clinical study on retarding aging effect of tongbu recipe to traditional Chinese medicine. Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi (Chinese journal of integrated traditional and Western medicine / Zhongguo Zhong xi yi jie he xue hui, Zhongguo Zhong yi yan jiu yuan zhu ban) 1999;19(4):218–20.
21. Elam JL, Carpenter JS, Shu XO, et al. Methodological issues in the investigation of ginseng as an intervention for fatigue. Clin Nurse Spec 2006;20(4):183–9.
22. Tadano T, Aizawa T, Asao T, et al. Pharmacological studies of nutritive and tonic crude drugs on fatigue in mice. Nihon yakurigaku zasshi Folia pharmacologica Japonica1992;100(5):423–31.
23. Bahrke MS, Morgan WP, Stegner A. Is ginseng an ergogenic aid? Int J Sport Nutr Exerc Metab 2009;19(3):298–322.
24. Singh B, Chandan BK, Gupta DK. Adaptogenic activity of a novel with anolide-free aqueous fraction from the roots of Withania somnifera Dun. (Part II) 2003;17(5):531–6.
25. Siegel RK. Ginseng abuse syndrome. Problems with the panacea. JAMA (the journal of the American Medical Association) 1979;241(15):1614–5.
26. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. JAMA (the journal of the American Medical Association) 2001;286(2):208–16.
27. Kim E, Cameron M, Lovera J, et al. American ginseng does not improve fatigue in multiple sclerosis: a single center randomized double-blind placebo-controlled crossover pilot study. Mult Scler 2011;17(12):1523–6.
28. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001 Jul;50(1):121–7.
29. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444–52.
30. Saghaei M. Random allocation software for parallel group randomized trials. BMC Med Res Methodol 2004;4:26.
31. Guidelines MSCfCP. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Washington, DC: Paralyzed Veterans of America; 1998.33 p.
32. Ghaem H, Borhani Haghighi A, Jafari P, et al. Validity and reliability of the Persian version of the multiple sclerosis quality of life questionnaire. Neurol India 2007;55(4):369–75.
33. Rammohan KW, Rosenberg JH, Lynn DJ, et al. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry 2002;72(2):179–83.
34. Krupp LB, Coyle PK, Doscher C, et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. Neurology 1995;45(11):1956–61.
35. Tomassini V, Pozzilli C, Onesti E, et al. Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial. J Neurol Sci 2004;218(1–2):103–8.
36. Ziemssen T, Hoffman J, Apfel R, et al. Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis. Health Qual Life Outcomes 2008;6:67–72.
37. Barton DL, Soori GS, Bauer BA, et al. Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. Support Care Cancer (official journal of the Multinational Association of Supportive Care in Cancer) 2010;18(2):179–87.
38. Hartz AJ, Bentler S, Noyes R, et al. Randomized controlled trial of Siberian ginseng for chronic fatigue. Psychol Med 2004 Jan;34(1):51–61.

39. Fischer MT, Sharma R, Lim JL, et al. NADPH oxidase expression in active multiple sclerosis lesions in relation to oxidative tissue damage and mitochondrial injury. Brain 2012;135(Pt 3):886–99.
40. Powell T, Sussman JG, Davies-Jones GA. MR imaging in acute multiple sclerosis: ringlike appearance in plaques suggesting the presence of paramagnetic free radicals. Am J Neuroradiol 1992;13(6):1544–6.
41. Lian XY, Zhang Z, Stringer JL. Protective effects of ginseng components in a rodent model of neurodegeneration. Ann Neurol 2005;57(5):642–8.
42. Yuan CS, Attele AS, Wu JA, Liu D. Modulation of American ginseng on brainstem GABAergic effects in rats. J Ethnopharmacol 1998;62(3):215–22.
43. Iarlori C, Gambi D, Lugaresi A, et al. Reduction of free radicals in multiple sclerosis: effect of glatiramer acetate (Copaxone). Mult Scler 2008;14(6):739–48.