Ginkgo biloba for Improvement of Memory and Quality of Life in Multiple Sclerosis: an Open Trial

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Abstract

Background: Multiple sclerosis (MS) is a chronic demyelinating disease that can affect cognitive function. The purpose of this study was to assess the efficacy of *Ginkgo biloba* (GB) on improvement of memory impairment and quality of life in patients with MS.

Methods: This study was an 8-week, open study of patients with MS. Thirty patients was recruited from a variety of outpatient settings. All participants met McDonald's diagnostic criteria for MS and had Wechsler score of<80. All subjects received Ginkgo 240 mg/day, TDS except one that received 120 mg/day, TDS due to history of gastritis Participants were assessed by Wechsler memory scale, MSIS-29 test and Beck Depression Inventory (BDI) which measure memory, quality of life and depression respectively at baseline and after 8 weeks of treatment.

Results: Administration of Ginkgo significantly improved Wechsler and MSIS-29 scores. Subjects who were less impaired at baseline on the Wechsler test experienced more improvement with GB.

Conclusion: The present study indicates *Ginkgo biloba* as a very well tolerated medication for improvement of cognitive impairments in people suffering from MS.

Keywords: *Ginkgo biloba*, Multiple Sclerosis, Memory impairment, Wechsler test

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Introduction

Multiple Sclerosis (MS) is a chronic demyelinating disease that usually occurs in young adults and it is more common in women [1]. MS can cause sensory, motor and visual defects, lack of coordination and cognitive disabilities resulting in quality of life reduction which is reported to be markedly impaired in patients with MS compared to the general population [2]. Additionally, the ever-present threat of further relapses and deteriorations in the course of the disease can have a significant effect on quality of life [3]. During the past two decades, cognitive impairments due to MS has received increasing attention from neuroscientists [4]. Cognitive impairment affects approximately 40% of MS cases [5] and induces an impact on working skills, familial responsibilities and social interactions.

Severe cognitive impairment that makes everyday coping difficult is reported in 10 percent of patients with MS, whereas an estimated 40-50 percent experience mild to moderate disturbances [6, 7]. The domains of cognitive functioning that are commonly affected in MS include memory, attention, concentration and word finding [8]. Despite the heavy burden of cognitive impairments in MS, treatment options remain limited [9]. Acetylcholinesterase inhibitors (AChEIs) have been the most promising class of medications tested in MS [10]. During the last decade, several trials have been performed with the deriavatives of *Ginkgo biloba* (GB) including EGb761. GB is commonly used in the treatment of early stage of Alzheimer's disease, vascular dementia, peripheral claudication and tinnitus of vascular origin [11].

Several trials have been performed to examine the efficacy of GB for treating cerebrovascular disease and dementia [12-16]. Comparing *Ginkgo biloba* with acetylcholinesterase inhibitors in meta-analytical studies has shown a similar clinical efficacy for both regimens with an additional drug safety benefit for Ginkgo [17, 18].

A trial that was performed to determine whether GB would improve functional performance in patients with MS, has shown that GB has modest beneficial effects on selective functional measures among patients with MS. No adverse event or side effect was reported [19]. In addition, a trial was performed by Lovera to determine the effect of GB on improvement of cognitive performance of patients with MS. This study showed that GB was very well tolerated and provided preliminary evidence that GB improves the cognitive performance of patients with MS on at least some cognitive domains such as attention, concentration, mental flexibility and interference susceptibility [9]. There are few published trials that have evaluated the efficacy of GB on cognitive impairment of MS patients. As a result we designed this study to evaluate the possible effects of Ginkgo biloba on memory as a major cognitive domain affected in multiple sclerosis and also to assess the effect of this medication on life quality of MS patients.

Materials and Methods

Study design

This investigation was an 8-week, open trial of patients with MS and was performed between May 2006 and June 2008 in MS Clinic of Sina Hospital affiliated to Tehran University of Medical Sciences and Iran MS Society (Tehran, Iran).

Study Samples

All participants met McDonald diagnostic criteria for multiple sclerosis. The level of

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cognitive impairment required for participation was defined as a Wechsler Score below 80 on the Wechsler test (WMS-Subscale of Memory) [20-22]. The Beck Depression Inventory II (BDI II) for depression was administered to assess the presence of depression as it can affect cognitive performance [23]. The exclusion criteria included any relapse of the disease in the last 30 days before the onset of study, any physical or nonphysical problem, including auditory or visual problems that could probably interfere with tests performance. In addition, participants were excluded if they had a score of 20 or higher on the Beck Depression Inventory II (BDI II), any gastrointestinal, coagulative or significant medical problem. History of alcoholism, any psychiatric disorder and drug abuse as well as any other condition that the investigators thought would make a patient unfitting for the study resulted in his /her exclusion.

Non educated participants and participants under medications that might have affected cognitive performance were also excluded. The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant Number: 7414). The participants provided informed consent in accordance with the procedures outlined by the local IRB. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions [24].

Treatment

All participants received *Ginkgo biloba* (GTD produced by Tolid Daru, 120 mg to 240 mg if it was tolerable) in three divided doses. The duration of the study was 8 weeks. Before the beginning of the drug therapy, all participants were administered the Wechsler memory scale test and were requested to complete BDI II and MSIS-29 questionnaires [25]. The data gathered from this visit was considered as the baseline. The tests were again administered after 8 weeks of treatment. Participants that had BDI score of >19 were referred to a psychiatrist to diagnose clinical depression and after this diagnosis they were treated with SSRI drugs. Participants who became symptom free after treatment and had BDI score≤19 and Wechsler score<80, initiated the study after wash out time of SSRI drug. The reason of exclusion of subjects with BDI score>19 was the role of depression as a confounder in this study.

A physician assessed side-effects at four weeks after treatment started. The same way and at the end of the study, side effect checklist was completed by a physician. All participants received 240mg/daily Ginkgo TD except one that received 120mg/daily due to history of gastritis.

Measurement

All participants were interviewed by a physician to collect demographic and medical history information. The rate of variations were detected in terms of age, gender, duration of disease, type of disease, educational status, mental activity and treatment protocol for further analysis. The Persian version of Beck (BDI II), MSIS-29 and Wechsler tests measured depression, quality of life and memory, respectively.

Beck and MSIS-29 questionnaires were completed by participants and Wechsler test was conducted by a trained physician.

Statistical Analysis

SPSS software version 15 was used to perform the statistical analysis. The significant level was considered at $p \leq 0.05$. Student T test was used to compare results of baseline and post-treatment tests. Fisher Exact Test was used to assess the effect of gender, educational status, type of treatment of Multiple sclerosis

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and mental activity on GTD efficacy; Pearson Test was used to assess the effect of age and duration of the disease on GTD efficacy. Linear regression analysis was done to assess the relationship between baseline Wechsler score and treatment response rate.

Results

Characteristics of patients

The flow diagram of participants was shown in Figure 1. Seven subjects had BDI score>19 before the study that were treated with SSRI drugs after diagnosis of clinical depression by the psychiatrist. Three of them did not refer again and four of them had BDI score>19 after 10 weeks of follow up. After all considerations for exclusion and inclusion criteria were met, forty subjects initiated the study. Thirty participants completed the trial to the end while 25% of participants (n=10) were dropped out during the study that were shown in Figure 1. Table 1 shows the demographic characteristics of the participants. Twenty five participants used Interferon Avonex (7), Rebif (5) and Betafron (13)), two participants used Novantrone and 3 participants used no drug as the treatment of the MS. The mean value of baseline Wechsler score was 68.8±8.942 (SD). All participants were divided into 4 groups of memory impairment: borderline (70-80 scores), mild (60 - 69 scores), moderate (50-59 scores) and severe (49 scores or less). 17 participants had borderline, 6 participants had mild and 7 participants had moderate memory impairment. There was no subject with severe memory impairment. The mean value of baseline BDI score was 12.8±3.3 (SD) and the

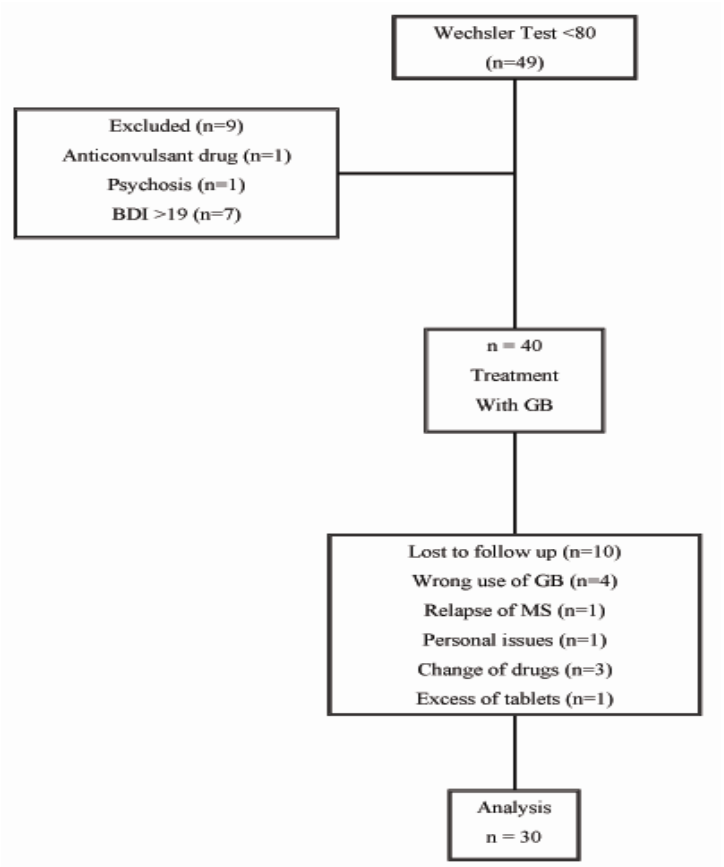


Fig 1- Study profile
BDI: Beck's depression inventory

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Table 1- Baseline characteristics

		Number (percent)
Sex	Female	20 (67 %)
	Male	10 (33 %)
Marital status	Married	11 (37 %)
	Single	19 (63 %)
Occupation	High mental activity	10 (33 %)
	Low mental activity	20 (67 %)
Educational status	Non university educated	22 (73 %)
	University educated	8 (27 %)
Type of MS	Relapsing Remitting (RRMS)	26 (87%)
	Secondary Progressive (SPMS)	4 (13%)
Age	Mean (SD) 33.7 ± 8.5	
Years since MS onset	6.23 ± 3.6	

mean value of baseline MSIS-29 score was 61 ± 21 (SD). There was no significant difference in baseline BDI score (p=0.67) and Wechsler score (p=0.37) between men and women, whereas the mean value of baseline MSIS - 29 score had significant difference (p=0.028) between men (mean=73.00) and women (mean=55.00).

Outcome measures

The tests were administered after 8 weeks of treatment. Regarding Wechsler test, an improvement of 14.10 points were observed (p<0.001). All participants except one had improvement on Wechsler test results. Regarding MSIS-29, an improvement of 4.80 points were observed after 8 weeks of treatment (p = 0.001). There was, however, no significant correlation between the results of post treatment Wechsler and MSIS-29 tests.

No significant difference was found in variation of Wechsler score between men and women (p=0.35). The efficacy of GB on improvement of quality of life of the men was more than women (Figure 2). In the other words, the mean value of MSIS-29 score had an improvement of 9.70 points in men (p=0.001) and it had an improvement of 2.35 points without significant difference in women (p=0.10). The efficacy of GB on improvement of memory impairment and quality of life had no significant difference between age groups (p=0.07 and p=0.16) [for group A and group B]. There was no significant difference in efficacy of GB in improving memory impairment (p = 0.12) and quality of life (p=0.70) comparing RRMS and SPMS participants. Type of MS drug had no effect on improvement of memory impairment (p=0.73) and quality of life (p=0.70). The mean value of memory improvement was 17.30 points in participants with high mental activity and this was more than that of participants with low mental activity (12.50 points). This difference was, however, not statistically significant (p=0.10). Quality of life also had no significant difference between these two groups (p=0.50). The mean value for

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improvement of memory impairment was 18.60 points in university educated participants (who had more than 12 years of education) and 12.40 points in non university educated participants (who had less than 12 years of education); this was also statistically significant (p=0.05). The efficacy of GB on quality of life improvement, on the other hand, had no significant difference between these two groups (p=0.93). Linear regression analysis showed that less impairment at baseline indicated by lower score on the Wechsler test is associated with a greater treatment effect (p=0.028, B=0.346) (Figure 3).

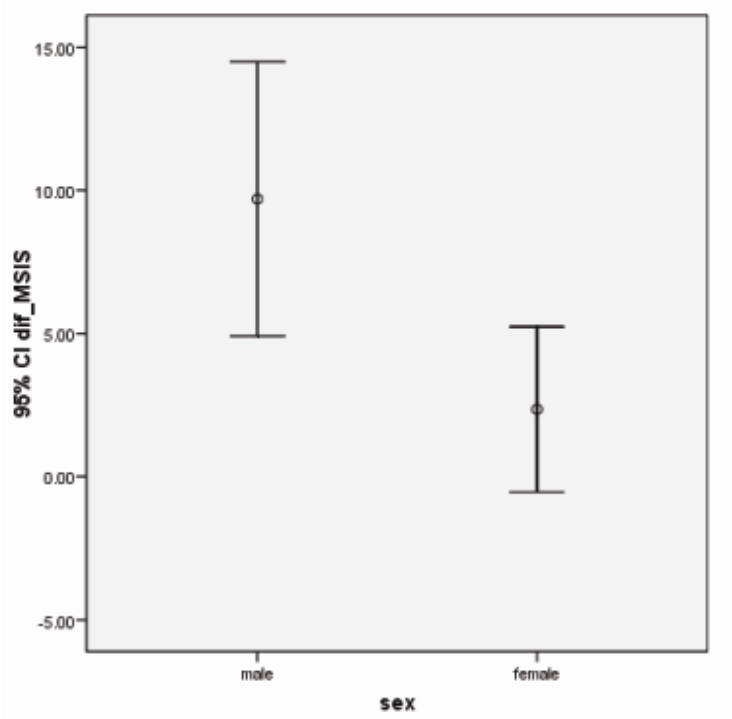


Fig 2- The efficacy of GB on improvement of quality of life of the men was more than women

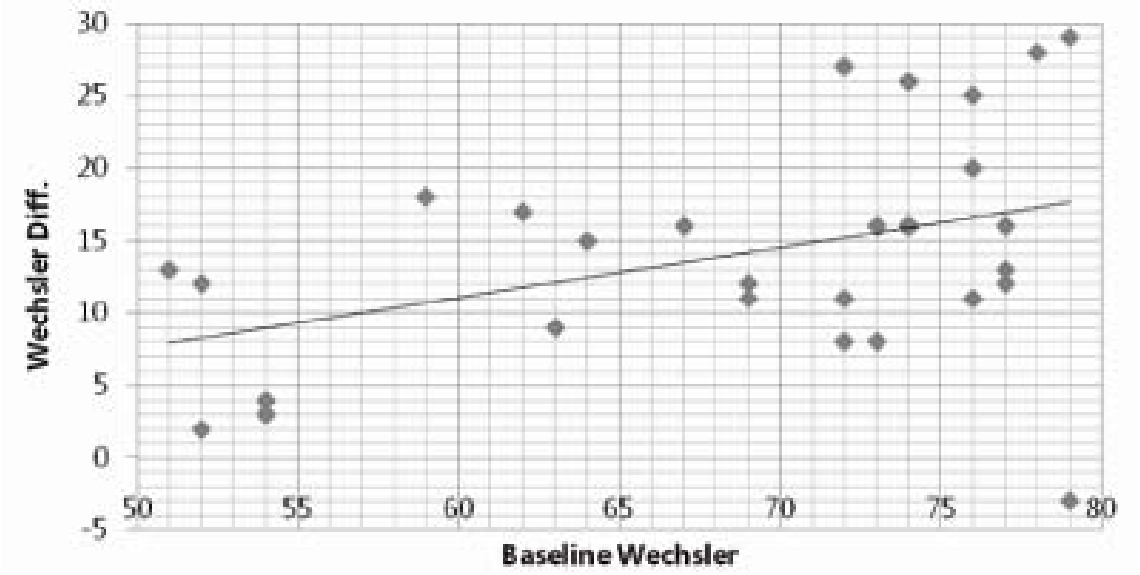


Fig 3- Less impairment at baseline on the Wechsler test is associated with a greater treatment effect

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Side effects

Six participants had side effects over the course of the trial. One participant had mild daytime drowsiness and mild nervousness. Three participants had mild nausea. One participant reported mild restlessness and one reported mild abdominal pain. All these six participants were followed up and their symptoms resolved spontaneously while no treatment was necessary. No severe side effects were observed.

Discussion

Cognitive alterations are considered a major problem for MS patients in a way that can have a bearing on their lives parallel and beyond physical disabilities imposed by the disease. Because of the limited therapeutic options, it is always useful to look for effective and well-tolerated new drug regimens to be considered whenever approved by trials. Regarding Wechsler test in this trial, a significant improvement of 14.10 points were observed after 8 weeks of treatment with GTD ($p<0.001$) without any observed difference between men and women. Regarding MSIS-29 test, the mean value of the test score had a significant improvement of 9.70 points in men ($p=0.001$) and it had improvement of 2.35 points without significant difference in women ($p=0.10$). The mean value of improvement of memory impairment was 18.6 points in patients with academic educational background while it was only 12.4 points in those without an academic education ($P=0.05$). The efficacy of GB on improvement of quality of life, however, had no significant difference between these two groups ($p=0.93$). Six participants had mild side effects over the trial and their symptoms resolved spontaneously. No severe side effects were observed throughout the study.

Lovera in 2007 performed a trial to determine the effects of GB on improvement of cognitive performance of patients with MS [9]. The battery in Lovera's trial included multiple tests to measure several cognitive domains. He also observed a significant difference in at least one of the scales assessing quality of life which favored the group under GB treatment; a finding that our study also managed to report. Treatment effect trend, limited to the Stroop test and suggested that GB may have an effect on some cognitive domains such as attention, concentration, mental flexibility, interference susceptibility and information processing speed. There was no effect on verbal memory, working memory and learning. Follow up period was 12 weeks. No serious side effects relating to treatment occurred in this trial and GB was well tolerated just as in our trial.

There was a negative correlation between severity of memory impairment and treatment response rate in our study: less memory impairment in beginning of the study based on the Wechsler test associated with a greater treatment effect. This opposed Lovera study results that showed that more impairment at baseline on the Stroop test would be associated with a greater treatment effect. In another trial that was performed by Jian to examine the effect of GB on cognitive improvement of Alzheimer Dementia (AD) and Multi Infarct Dementia (MID) total effective rate was reported to be 65%. MID was influenced more than AD, the same way that mild cases got better outcomes than severe cases [13]. The results of our study were inline with the Jian's study.

In multiple studies, depression has been reported in patients with MS because of chronic and relapsing symptoms of the disease. Depressive symptoms have detrimental effect on neuropsychological

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performance [26]. In our study, all participants that had BDI score>19 were excluded. As a result, our study was not comparable with Johnson's study that was performed to determine whether GB would improve functional performance such as depression in patients with MS. Johnson's study also showed that GB exerted very modest beneficial effects among some individuals with MS. No side effects or adverse events were reported or observed throughout the course of his study [27]; a finding that was also supported in our study. In our study, GB was reported not to influence the MSIS-29 score in women (mean=2.35, CI95%= (-0.54)-5.24) while GB had significant effect on MSIS-29 score in men (mean=9.7, CI95%= 4.9-14.5).We also found a significant difference between university educated and non university educated participants that may be due to having been exposed to more mental stimuli in the first group. This study was a test-retest trial and did not have control group with placebo administration which can be considered as a limitation. There was a difference between participants with low and high mental activity in efficacy of GB on memory impairment but it was not statistically significant that may be due to small sample size in these subgroups. With this consideration, we recommend a larger trial using larger sample size that select participants based on mental activity to determine if GB has a different effect in terms of mental activity. The difference between treatment and baseline MSIS-29 scores was statistically significant but may not be important clinically. This can be due to short follow up period of our study. GB may also have other effects on quality of life that would not be evident over a short period of follow up. Follow up period of Johnson's study was 4 weeks and he had said that the follow up period of their study is not long enough to detect the effects of the drug. Longer follow up period of our study and Lovera's study was one of the positive points. We measured only one cognitive domain whereas Lovera measured several cognitive domains.

Future studies must be designed as randomized, placebo controlled, double-blind trials with larger sample size and longer follow up period to confirm these results.

Conclusion

In conclusion this study showed that 8 weeks of treatment with Ginkgo Biloba in people with multiple sclerosis with memory impairment may improve memory and quality of life. The present study indicates Ginkgo Biloba as a very well tolerated drug.

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References

1. Debouverie M. Pittion-Vouyovitch S. Louis S. Guillemin F. LORSEP Group. Natural history of multiple sclerosis in a population-based cohort. *Eur. J. Neurology* 2008; 15: 916 - 21.

2. Patti F, Cacopardo M, Palermo F, Ciancio MR, Lopes R, Restivo D, Reggio A. Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J. Neurol. Sci.* 2003; 211: 55 - 62.

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3. Chopra P, Herrman H, Kennedy G. Comparison of disability and quality of life measures in patients with long-term psychotic disorders and patients with multiple sclerosis: an application of the WHO Disability Assessment Schedule II and WHO Quality of Life-BREF. *Int. J. Rehabil. Res.* 2008; 31: 141 - 9.

4. Hoffmann S, Tittgemeyer M, Von Cramon DY. Cognitive impairment in multiple sclerosis. *Curr. Opin. Neurol*. 2007; 20: 275 - 80.

5. Rao SM, Leo GJ, Bernardin L,Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41: 685 - 91.

6. Akhondzadeh S, Stone TW. Interaction between adenosine and GABAA receptors on hippocampal neurones. *Brain Res.* 1994; 665: 229 - 36.

7. Akhondzadeh S. Hippocampal synaptic plasticity and cognition. *J. Clin. Pharm. Ther.* 1999; 24: 241 - 8.

8. LaRocca Nicholas. Introducing MS-related emotional and cognitive issues. *MS in focus* 2004; 4: 4 – 6.

9. Lovera J, Bagert B, Smoot K, Morris CD, Frank R, Bogardus K, Wild K, Oken B, Whitham R, Bourdette D. Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial. *Mult. Scler*. 2007; 13: 376 - 85.

10. Christodoulou C, MacAllister WS, McLinskey NA, Krupp LB. Treatment of cognitive impairment in multiple sclerosis: Is the use of acetylcholinesterase inhibitors a viable option? *CNS Drugs* 2008; 22: 87 - 97.

11. Sierpina VS. Wollschlaeger B. Blumenthal M. *Ginkgo biloba*. *Am. Family Physician* 2003; 68: 923 – 6.

12. Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. *Br. J. Clin. Pharmacol*. 1992; 34: 352 – 8.

13. Salehi B, Imani R, Mohammadi MR, Fallah J, Mohammadi M, Ghanizadeh A, Tasviechi AA, Vossoughi A, Rezazadeh SA, Akhondzadeh S. Ginkgo biloba for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. *Prog. Neuropsychopharmacol Biol. Psychiatry* 2010; 34: 76 - 80.

14. Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch. Neural.* 1998; 55: 1409 – 15.

15. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen*. 2006; 21: 113-8.

16. Mazza M, Capuano A, Bria P, Mazza S. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur. J. Neurology* 2006; 13: 981 - 5.

17. Akhondzadeh S. The 5-HT hypothesis of schizophrenia. *IDrugs* 2001; 4: 295 - 300.

18. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR, Akhondzadeh S. Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. *BJOG* 2008; 115: 515 - 9.

19. Freedman MS, Thompson EJ, Deisenhammer F, Giovannoni G, Grimsley G, Keir G, Ohman S, Racke MK, Sharief M,

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Sindic CJ, Sellebjerg F, Tourtellotte WW. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiplesclerosis: a consensus statement. *Arch. Neurol.* 2005; 62: 865 - 70.

20. Wechsler D. Wechsler memory scale – Revised. The Psychological Corporation, New York, 1987.

21. Akhondzadeh S, Gerami M, Noroozian M, Karamghadiri N, Ghoreishi A, Abbasi SH, Rezazadeh SA. A 12-week, double-blind, placebo-controlled trial of donepezil adjunctive treatment to risperidone in chronic and stable schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2008; 32: 1810 - 5.

22. Akhondzadeh S, Mohammadi N, Noroozian M, Karamghadiri N, Ghoreishi A, Jamshidi AH, Forghani S. Added ondansetron for stable schizophrenia: a double blind, placebo controlled trial. *Schizophr. Res.* 2009; 107: 206 - 12.

23. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Ebrahimkhani N. Psychometric properties of Persian language version of the Beck Depression Inventory-Second Edition: BDI II Persian. *Depression Anxiety* 2005; 21: 185 - 92.

24. World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. Available at: http://www.wma.net. 2000.

25. Ayatollahi P, Nafissi S, Eshraghian MR, Kaviani H, Tarazi A. Impact of depression and disability on quality of life in Iranian patients with multiple sclerosis. *Mult. Scler*. 2007; 13: 275 - 7.

26. Landro NI, Celius EG, Sletvold H. Depressive symptoms account for deficient information processing speed but not for impaired working memory in early phase multiple sclerosis (MS). *J. Neurological Sci.* 2003; 217: 211 – 6.

27. Johnson SK, Diamond BJ, Rausch S, Kaufman M, Shiflett SC, Graves L. The effect of Ginkgo biloba on functional measures in multiple sclerosis: a pilot randomized controlled trial. *Explore (NY)*. 2006; 2: 19 - 24.

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