WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 337-345. Research Article ISSN 2277– 7105

THE EFFECTS OF GINKGO BILOBA EXTRACT ON COGNITIVE DEFICIT IN SCHIZOPHRENIC PATIENTS

[1]Hamid Jafari, [2]*Ali Nazeri Astaneh, [3]Omid Rezaei, [4]Behrooz Dolatshahi, and [5]Sahel Hemmati Garakani

[1]Psychiatrist ,Tehran,Iran

[2]Assistant Professor of Psychiatry, Psychosis Research Center, Unuversity of Social Welfare and Rehabilitation Science, Tehran, Iran.

[3]Associate professor of psychiatry, Unuversity of Social Welfare and Rehabilitation, Tehran, Iran.

[4]PhD,Psychologist, Unuversity of Social Welfare and Rehabilitation, Tehran, Iran.

[5]Associate professor of psychiatry,Pediatic Neurorehabilitation Research Center , Unuversity of Social Welfare and Rehabilitation, Tehran, Iran.

Article Received on
12 June 2015,

Revised on 03 July 2015,
Accepted on 24 July 2015

***Correspondence for Author**
Dr. Ali Nazeri Astaneh
Assistant professor of psychiatry, Psychosis Research Center, Unuversity of Social Welfare and Rehabilitation Science, Tehran, Iran.

ABSTRACT

Background: Recent human and animal studies have presented new evidences on beneficial effects of some herbs on improving cognitive function. The present study aimed to assess therapeutic effects of Ginkgo biloba on cognitive function in hospitalized schizophrenic patients. **Methods:** This randomized double-blinded controlled trial was conducted on 40 consecutive patients with the diagnosis of schizophrenia who were hospitalized in rehabilitation wards at Razi Psychiatric center in Tehran in 2014. The study subjects were randomly assigned to two groups receiving Ginkgo biloba extract (120 mg/day) or placebo for three months. On admission and also after completing treatment protocol, neurobehavioral cognitive status was assessed using the NCSE tool in both groups. **Results:** Among eight aspects of cognitive ability including attention, perception, repetition, naming, visual memory, short memory, similarities and judgment, our study showed significant improvement in the components of perceptual skill, short memory, and reasoning following treatment with this herb when compared to the placebo group. Regarding drug-related side effects, 10% of treated patients suffered gastrointestinal

complications such as nausea and gastric pain led to discontinuing the treatment protocol in these patients. **Conclusion:** Significant improvement is expectable in some aspects of neurobehavioral cognitive status including perceptual skill, short memory, and reasoning by administrating Ginkgo Biloba extract. However, administrating the drug with the maximal effective dose and achieving minimal side effects should be considered.

KEY WORDS: perceptual skill, short memory, and reasoning, Ginkgo biloba extract.

INTRODUCTION

Persistent and pervasive cognitive decline is a major manifestation in schizophrenic patients characterized by deficit in processing speed, episodic memory, working memory, and executive function observable throughout the course of the illness leading disability in daily living activities, lowering level of quality of life, and disturbing social functioning.[1] Almost all schizophrenic patients are affected by cognitive deficit.[2] This abnormality is accompanied with alteration in the neural systems involve in cognition abilities including medial temporal lobes as well as prefrontal cortex.[3] Finding a cost-effective treatment modality that improves cognitive ability in schizophrenic patients has been accelerating in recent years. Although antipsychotic drugs have been shown to have strong evident effects on psychosis in these patients, but these types of drugs have very little palliative effects on cognitive impairment.[4] In this regard, recent trials have focused new generation drugs and also alternative medicine to improve cognition in schizophrenic patients.

Some recent human and animal studies have presented new evidences on beneficial effects of some herbs on improving cognitive function. One of the most used herbal drugs recently applied to improve cognition is Ginkgo biloba.[5] Some mechanisms have been described in the physiological effects of this herb on cognitive function. Some experimental studies could demonstrate therapeutic effects of this herb on cognitive function by reducing oxidative damage and elevating the level of brain-derived neurotrophic factor.[6] Some evidences emphasized the effects of ginkgo biloba extract EGb761 on promotes proliferation of endogenous neural stem cells in cells in the subventricular zone and dentate gyrus of the brain. Furthermore, other described mechanisms of its action are increasing cerebral blood flow, antioxidant, anti-inflammatory and anti-platelet effects[7], In this regard; pharmacological investigations showed that the terpene trilactones (TTL) and the flavonoids of this herb are responsible for pharmacological effects of the extract in the improvement of cognitive decline.[8]

Recent meta-analyses have described therapeutic effects of Ginkgo biloba extract on cognitive ability in patients with neuropsychiatric disorders especially dementia.[9,10] However, the effects of this herb on cognitive function in schizophrenic patients remain unclear. The present study aimed to assess therapeutic effects of Ginkgo biloba on cognitive function in hospitalized schizophrenic patients.

METHODS

This randomized double-blinded controlled trial was conducted on 44 consecutive patients with the diagnosis of schizophrenia who were hospitalized in rehabilitation wards at Razi Psychiatric center in Tehran in 2014. Schizophrenia was diagnosed based on the criteria of the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM)-IV. All included patients had clinical stability and all patients were subjected in a non-acute phase of disease. The subjects with acute physical problems, with changes in type or doses of antipsychotic drugs within the last six months, with concurrent neurological disturbances, history of seizure or history of substance use within the last six months, with history of mental disorders or simultaneous use of aspirin, varfarin or other anti-platelet therapy were excluded. The main tool employed to psychologically assess the patients was the neurobehavioral cognitive status exam (NCSE). The examiner recorded the patient's responses on the form provided and generates a graphic profile. The test typically takes 15-20 minutes to administer. This tool is a cognitive screening instrument that assesses the five major ability areas including language, spatial skills, memory, calculations and reasoning and, with separate measures, assesses levels of consciousness, orientation, and attention. The 25-minute screening test generates a profile of cognitive abilities, rather than one global score[11,12], and it is designed so that a patient's successful performance in several cognitive domains does not obscure deficits in others. The scoring system calculates values, ranging from 0 to 12, for each cognitive domain. Several studies have shown that Cognistat has good sensitivity and specificity in predicting organic brain impairment and moderate overall validity in screening for cognitive impairment.[13] The study subjects were randomly assigned to two groups receiving Ginkgo biloba extract (120 mg/day) or placebo for three months. On admission and also after completing treatment protocol (3 months later), neurobehavioral cognitive status was assessed using the NCSE in both groups and the change in cognition score was compared across the two groups.

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using t test or non-parametric Mann-Whitney U test or whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. All statistical tests were 2-sided and were performed at a significance level of 0.05. All analyses were performed using SPSS version 21.0 for windows (SPSS Inc., Chicago, IL).

RESULTS and DISCUSSION

Of 22 patients in Ginkgo biloba group, one patient suffered severe gastrointestinal complications including nausea and severe gastric pain that could not continue the study. also, another patient in this group was excluded because of the increase of aggression and was thus excluded. In placebo group, two patients were initially excluded because of nausea and gastric pain that were excluded. In this regard, 20 patients in each group continued the study that were finally analyzed. The mean age of participants in case and placebo groups was 42.40 ± 7.89 years and 44.30 ± 5.95 with no significant difference (p = 0.352). the mean duration of medical therapy was also 16.45 ± 7.34 years and 17.40 ± 7.47 years with no difference (p = 0.601).

Regarding effects of treatment protocols on different components of neurobehavioral cognitive status, the mean score for attention in Ginkgo biloba group was 4.95 ± 1.28 and 5.25 ± 1.16 with no significant difference between them (p = 0.316). However, the mean score for perceptual skill was significantly improved in the group received Ginkgo biloba when compared with placebo group (5.15 ± 0.58 versus 5.45 ± 0.69, p = 0.030). there was no difference in repetition score between Ginkgo biloba group and control group (9.30 ± 1.49 versus 0.60 ± 1.42, p = 0.301). also, no difference was revealed in mean naming score between Ginkgo biloba group and control group (7.90 ± 0.45 versus 8.00 ± 0.01, p = 0.330). Although mean score for visual memory did not differ between Ginkgo biloba and control groups (3.55 ± 0.83 versus 3.75 ± 0.79, p = 0.104), but short memory was significantly improved in former group (5.00 ± 1.52 versus 5.90 ± 2.20, p = 0.001). With regard to changes in subcomponents of reasoning, the mean scores for similarities (2.75 ± 0.72 versus 3.60 ± 0.85, p = 0.001) and for judgment (2.55 ± 0.76 versus 3.25 ± 0.64, p = 0.003) were more improved in Ginkgo biloba group than in control group.

Table 1: Change in scores for different components of cognition in case and placebo groups

Component	Ginkgo biloba group (n = 20) (Mean difference)	Placebo group (n = 20) (Mean difference)	p-value
Attention	4.95 ± 1.28	5.25 ± 1.16	0.316
Perception	5.15 ± 0.58	5.45 ± 0.69	0.030
Repetition	9.30 ± 1.49	0.60 ± 1.42	0.301
Naming	7.90 ± 0.45	8.00 ± 0.01	0.330
Visual memory	3.55 ± 0.83	3.75 ± 0.79	0.104
Short memory	5.00 ± 1.52	5.90 ± 2.20	0.001
Similarities	2.75 ± 0.72	3.60 ± 0.85	0.001
Judgment	2.55 ± 0.76	3.25 ± 0.64	0.003

DISCUSSION

Assessing beneficial effects of Ginkgo biloba on different subcomponents of neurobehavioral cognitive status in our study showed significant improvement in some components including perceptual skill, short memory, and reasoning following treatment with this herb when compared to the control group. On the other hand, the administration of this herbal drug could improve perception and understanding, short memory, and also power of judging in patients with schizophrenia. Because of the minimal effects of antipsychotic drugs that prescribe for a long time in these patients, the use of such herbal medicines can effectively improve cognition level in these patients. Although reviewing the literature reveals different effects of Ginkgo biloba on different components of cognition in patients with dementia, however a little evidences are available in its effects among schizophrenic patients. In a study by Brondino et al[14] and by analyzing recent studies on the effects of this herb on cognitive impairment, it was found that Ginkgo biloba could improve cognitive function and activities of daily living in patients with dementia. In another study by Zhang et al[15], the use of Ginkgo biloba could not improve cognitive level from baseline to week 12 after beginning of the treatment. The inconsistent results revealed in the studies can be due to some reasons such as employing different dosages of the drug in trials as well as evaluation of the patients of self-reported cognitive complaint with uncertain diagnostic criteria.[16]

The beneficial effects of Ginkgo biloba on cognition ability seems to be related to its neuroprotection action such as reducing amyloid-β aggregation and also reducing Aβ toxicity.[17-19] EGb761 as the standardized Ginkgo biloba extract containing flavonol glycosides, terpene lactones, and ginkgolic acids, is a polyvalent radical scavenger that improves mitochondrial function[20], decreases blood viscosity, and enhances

microperfusion.[21] Some studies on animal models showed that EGb761 improves neurotransmission, in particular glutamatergic[22], dopaminergic, and cholinergic systems.[23] Therefore, standardized Ginkgo biloba extract EGb761 could be considered as a multi-target drug.

In our study, a number of patients could not initially continue the trial because of its some side effects including gastrointestinal complications. In this context, 10% of included patients did not continue the study. Despite the observed these drug-related side effects and due to its considerable beneficial therapeutic effects, it seems that by managing the optimal dose of the drug, its therapeutic effects can be optimized in parallel with minimizing its side effects. Although uncommon, serious side effects have been reported with the use of Ginkgo Biloba including allergic reactions manifested by difficulty breathing, irregular heartbeats; muscle cramps; seizures; loss of consciousness; headache; dizziness; and stomach upset.[24,25] Thus, considering minimal doses of the drug is essential with observing evidences of serious side effects. In this regard and to discover optimal therapeutic dosages of Ginkgo Biloba extract, further animal and experimental studies are recommended.

CONCLUSION

Our study shows significant improvement in some aspects of neurobehavioral cognitive status including perceptual skill, short memory, and reasoning by administration of 120 mg/day of Ginkgo Biloba extract for three months. However, administrating the drug with the maximal effective dose and achieving minimal side effects should be considered.

ACKNOWLEDGEMENT

At the end we would like to thank from all Razi psychiatric hospital and Akhavan clinic staff who cooperated in this project.

REFERENCES

1. Vöhringer PA[1], Barroilhet SA, Amerio A, Reale ML, Alvear K, Vergne D, Ghaemi SN Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. Front Psychiatry. 2013 Aug 8; 4: 87.
2. Kitchen H[1], Rofail D, Heron L, Sacco P. Cognitive impairment associated with schizophrenia: a review of the humanistic burden. Adv Ther. 2012 Feb; 29(2): 148-62. doi: 10.1007/s12325-012-0001-4. Epub 2012 Feb 10.

3. Inoue K[1], Meguro K, Akanuma K, Meguro M, Yamaguchi S, Fukuda H. Impaired memory and executive function associated with decreased medial temporal and prefrontal blood flow in Clinical Dementia Rating 0.5 status: the Osaki-Tajiri project. Psychogeriatrics. 2012 Mar; 12(1): 27-33. doi: 10.1111/j.1479-8301.2011.00384.x.
4. Kołaczkowski M[1], Mierzejewski P, Bienkowski P, Wesołowska A, Newman-Tancredi A Antipsychotic, antidepressant, and cognitive-impairment properties of antipsychotics: rat profile and implications for behavioral and psychological symptoms of dementia. Naunyn Schmiedebergs Arch Pharmacol. 2014 Jun; 387(6): 545-57. doi: 10.1007/s00210-014-0966-4. Epub 2014 Mar 6.
5. Belviranlı M[1], Okudan N[2]. The effects of Ginkgo biloba extract on cognitive functions in aged female rats: The role of oxidative stress and brain-derived neurotrophic factor. Behav Brain Res. 2014 Oct 30; 278C: 453-461. doi: 10.1016/j.bbr.2014.10.032. [Epub ahead of print]
6. Wang J[1], Chen W[2], Wang Y[2]. A ginkgo biloba extract promotes proliferation of endogenous neural stem cells in vascular dementia rats. Neural Regen Res. 2013 Jun 25; 8(18): 1655-62. doi: 10.3969/j.issn.1673-5374.2013.18.003.
7. Diamond BJ[1], Bailey MR. Ginkgo biloba: indications, mechanisms, and safety. Psychiatr Clin North Am. 2013 Mar; 36(1):73-83. doi: 10.1016/j.psc.2012.12.006.
8. Ude C[1], Schubert-Zsilavecz M, Wurglics M. Ginkgo biloba extracts: a review of the pharmacokinetics of the active ingredients. Clin Pharmacokinet. 2013 Sep; 52(9): 727-49. doi: 10.1007/s40262-013-0074-5.
9. Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of Ginkgo biloba in dementia: systematic review and meta-analysis. BMC Geriatr. 2010 Mar 17; 10:14. doi: 10.1186/1471-2318-10-14.
10. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009 Jan 21; (1): CD003120.
11. Kiernan RJ, Mueller J, Langston JW, Van Dyke C. The Neurobehavioral Cognitive Status Examination: A brief but quantitative approach to cognitive assessment. Ann Intern Med. 1987; 107: 481–485.
12. Mueller J, Kiernan R, Langston W. Manual for Cognistat (Neurobehavioral Status Exam; NCSE). Fairfax, CA: The Northern California Neurobehavioral Group Inc. Oakley; 2001.
13. Logue PE, Tupler LA, D'Amico C, Schmitt FA. The Neurobehavioral Cognitive Status Examination: Psychometric properties in use with psychiatric inpatients. J Clin Psychol. 1993; 49: 80–89

14. Brondino N1, De Silvestri A, Re S, Lanati N, Thiemann P, Verna A, Emanuele E, Politi P. A Systematic Review and Meta-Analysis of Ginkgo biloba in Neuropsychiatric Disorders: From Ancient Tradition to Modern-Day Medicine. Evid Based Complement Alternat Med. 2013; 915691. doi: 10.1155/2013/915691. Epub 2013 May 28.
15. Zhang WF1, Tan YL, Zhang XY, Chan RC, Wu HR, Zhou DF. Extract of Ginkgo biloba treatment for tardive dyskinesia in schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011 May; 72(5): 615-21. doi: 10.4088/JCP.09m05125yel. Epub 2010 Sep 21.
16. Tan MS, Yu JT, Tan CC, Wang HF, Meng XF, Wang C, Jiang T, Zhu XC, Tan L. Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: asystematic review and meta-analysis. J Alzheimers Dis. 2015; 43(2): 589-603.
17. Kampkotter A, Pielarski T, Rohrig R, Timpel C, Chovolou Y, WatjenW, Kahl R The Ginkgo biloba extract EGb761 reduces stress sensitivity, ROS accumulation and expression of catalase and glutathione S-transferase 4 in Caenorhabditis elegans. Pharmacol Res, 2007; 55: 139-147.
18. Eckert A, Keil U, Kressmann S, Schindowski K, Leutner S, Leutz S, Muller WE (2003) Effects of EGb 761 Ginkgo biloba extract on mitochondrial function and oxidative stress. Pharmacopsychiatry 36(Suppl 1), S15-S23.
19. Abdel-Kader R, Hauptmann S,Keil U, Scherping I, Leuner K, Eckert A, Muller WE Stabilization of mitochondrial function by Ginkgo biloba extract (EGb 761). Pharmacol Res, 2007; 56: 493-502.
20. K¨oltringer P, Langsteger W, Eber O Dose-dependent hemorheological effects and microcirculatory modifications following intravenous administration of Ginkgo biloba special extract EGb 761. Clin Hemorheol, 1995; 15: 649-656.
21. Williams B,Watanabe CM, Schultz PG, Rimbach G, Krucker T Age-related effects of Ginkgo biloba extract on synaptic plasticity and excitability. Neurobiol Aging, 2004; 25: 955-962.
22. Kehr J, Yoshitake S, Ijiri S, Koch E, Noldner M, Yoshitake T Ginkgo biloba leaf extract (EGb 761(R)) and its specific acylated flavonol constituents increase dopamine and acetylcholine levels in the rat medial prefrontal cortex: Possible implications for the cognitive enhancing properties of EGb 761(R). Int Psychogeriatr, 2012; 24(Suppl 1): S25-S34.

23. Yoshitake T, Yoshitake S, Kehr J The Ginkgo biloba extract EGb 761(R) and its main constituent flavonoids and ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex. Br J Pharmacol, 2010; 159: 659-668.
24. Montes P, Ruiz-Sánchez E, Rojas C, Rojas P. Ginkgo biloba Extract 761: A Review of Basic Studies and Potential Clinical Use in Psychiatric Disorders. CNS Neurol Disord Drug Targets. 2015 Feb 2
25. Di Lorenzo C, Ceschi A, Kupferschmidt H, Lüde S, De Souza Nascimento E, Dos Santos A, Colombo F, Frigerio G, Nørby K, Plumb J, Finglas P, Restani P. Adverse Effects of Plant Food Supplements and Botanical Preparations: A Systematic Review with Critical Evaluation of Causality. Br J Clin Pharmacol. 2014 Sep 24.