Journal of Herbal Medicine 6 (2016) 119–127

Contents lists available at ScienceDirect

Journal of Herbal Medicine

journal homepage: www.elsevier.com/locate/hermed

Research paper

Effect of *Boswellia serrata* on cognitive impairment in multiple sclerosis patients

Nastaran Majdinasab[a], Amir Siahpush[b], Seyedeh Khatoon Mousavinejad[a,*], Alireza Malayeri[b], Seyed Aidin Sajedi[a], Parisa Bizhanzadeh[c]

[a] Department of Neurology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[b] Medicinal Plants Research Center and Deparment of Pharmacognosy, Faculty of Pharmacy, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran
[c] Department of Psychology and Educational Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran

ARTICLE INFO

Article history:
Received 2 June 2015
Received in revised form 22 November 2015
Accepted 23 May 2016
Available online 24 May 2016

Keywords:
Multiple sclerosis
Relapsing-remitting
Cognitive impairment
Boswellia serrata
MACFIMS

ABSTRACT

Background: Boswellia Serrata (BS) has been shown to have anti-inflammatory effects and neuroprotective activity.
Objective: To determine whether BS improves cognitive performance among patients with multiple sclerosis (MS) related cognitive impairment (CI).
Method: This was a double-blind, randomized, placebo-controlled study, in which 60 patients who had subjective cognitive complaints (according to multiple sclerosis neuropsychological questionnaire) were selected and categorized in two groups (each with 30 persons). These groups were compared on the basis of the effect of 450 mg of BS or placebo capsules twice a day. A series of MACFIMS (minimum assessment of cognitive function in MS) tests were conducted on the patients at the beginning of the treatment process and after 2 months of the study. Results of the mentioned tests were analyzed and recorded.
Results: Considering changes in brief visuospatial memory test (BVMT) ($p < 0.05$) and the California verbal learning test (CVLT) second edition ($p < 0.05$), differences between the two groups were significant. But on the basis of paced auditory serial addition test, symbol digit modalities test, controlled oral word association test, judgment of line orientation test and Delis-Kaplan executive function system, differences between the two groups were negligible ($p > 0.05$).
Conclusion: BS improved CVLT and BVMT in relapsing remitting (RR)MS patients without major depression who had subjective complaints of CI.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system and the most common cause of chronic neurologic disorders, which normally occurs when people are aged 20–40 years old (Hauser and Oksenberg, 2006; Trapp and Nave, 2008; Messina and Patti, 2014). The cause of MS is not clearly known, but most likely demyelination and neurodegeneration via an autoimmune process could be the cause of disease (Hauser and Oksenberg, 2006).

Cognitive impairment (CI) is a major problem in MS patients (Browne et al., 2014) and in all subtypes of MS, it can be detected in the early stages of the disease (Robert et al., 2012; Messinis et al., 2010). Mild to moderate CI is observed in 40–60% of patients (Jongen et al., 2012). CI is associated with the disease type and duration, although disease duration and physical disability do not predict the presence of CI (DeLuca et al., 2015; Shkil'niuk et al., 2013). Mood disorders such as depression can affect performance of CI measurement. Since depression disorder is common in MS patients (50%), depression needs to be measured in such patients. In addition, drugs, such as corticosteroids and particularly high-dose intra-venous methylprednisolone used in new MS attacks, may have a negative impact on cognition (Sahraian and Etesam, 2014).

CI can affect patients' quality of life (Akbar et al., 2010), decrease employment or cause unemployment and affects daily activities, general progress, coping, and rehabilitation progress (Langdon et al., 2012; Benedict et al., 2012). CI can lead to full disability and thus imposes heavy personal and social costs (Patti, 2009).

In neuropsychological assessment of MS, the complex attention, information processing speed, episodic memory and executive function have typical changes, but language and general intelligence show no changes (Langdon et al., 2012). Clinical,

* Corresponding author.
E-mail address: mousavinejad.skh@ajums.ac.ir (S.K. Mousavinejad).

http://dx.doi.org/10.1016/j.hermed.2016.05.003
2210-8033/

radiographic, and pathological data suggests that both white matter and gray matter pathology play roles in the pathogenesis of MS-related CI (DeLuca et al., 2015).

Thus neurological assessment and cognitive screening for monitoring the cognitive impairments of patients are important (Sahraian and Etesam, 2014).

Boswellia serrata (BS) is a resinous extract from *Boswellia* species of Burceracea *Boswellia* genus trees (Archier and Vieillescazes, 2000). It has been used for thousands of years in traditional medicine in India, Italy, China, Greece and Iran (Behnamrasuli et al., 2001). It has been used for its anti- inflammatory, anti-nociceptive, anti-oxidant, anti-bacterial, cancer drug sensitizing, cardio-protective, insulin-resistance lowering and anti-arthritis properties (Jung et al., 2007; Mathe et al., 2004; Poeckel and Werz, 2006; Sudharsan et al., 2005; Syrovets et al., 2005). The most important pharmacological effect of BS is suppression of leukotriene from arachidonic acid by inhibition of 5-lipoxygenase which has anti-inflammatory properties (Ammon et al., 1991; Safayhi et al., 1992). Several studies have reported the anti-inflammatory effects of BS in the management of inflammatory diseases such as ulcerative colitis, crohn's disease, rheumatoid arthritis and asthma. In a study on a group of patients with advanced ulcerative colitis, 6 weeks of supplementation with Boswellia gum resin extract (350 mg three times daily) showed significant improvements in stool properties, microscopic appearance of the bowel wall, and blood tests of inflammation (Moussaieff et al., 2008a,b; Omura et al., 2009; Ring et al., 2006; Glaser et al., 1999; Arnett and Strober, 2011; Ammon, 2006; Gupta et al., 1997).

Boswellia also has neuroprotective activity and can increase structural formation of new nerve networks (Moussaieff et al., 2008a; Omura et al., 2009). It also inhibits degenerative changes in the hippocampus, which is one of the brain's chief memory-processing areas (Ring et al., 2006).

It should be noted that based on the toxicology studies of BS resin conducted on animals, significant pathological, hematologic and genotoxic changes were not observed at concentrations of up to 1000 mg/kg. In addition, the side effects are negligible in humans, and only in some cases have nausea, reflux and digestive disorders been reported in patients (Sharma et al., 2009; Singh and Atal, 1986).

Treatment for patients with MS and cognitive impairment usually involves disease-modifying drugs (DMD) in combination with a pharmacological cognitive-enhancement strategy (Patti, 2012).

Considering the above review of literature and anecdotes of traditional experiments, the aim of this paper is to compare therapeutic effects of BS with placebo in treatment of CI of MS patients.

2. Material and methods

This is a single-center, randomized, double-blind and placebo-controlled study.

2.1. Patient selection

The authors screened 125 clinically confirmed MS patients (MS diagnosis by revised McDonald criteria (Polman et al., 2011)) who were receiving care in the MS association of Khuzestan province Iran.

Patients that had relapsing remitting (RR) MS and were relapse free for the last 6 weeks before the start of assessments were included in this study.

Patients with current major depression, pre-existing medical or psychiatric disorders associated with cognitive dysfunction, developmental disease, drug or alcohol abuse, expanded disability status scale (EDSS) >3, new MS attacks and those who had received corticosteroids up to 6 weeks before the study or were pregnant or breastfeeding were excluded.

First, Persian beck depression inventory-fast screen (BDI-FS) questionnaire (Ghassemzadeh et al., 2005) was given to patients (see Appendix A). Patients with positive beck test results were omitted from this study. Remaining patients were given a multiple sclerosis neuropsychological questionnaire (MSNQ) to determine cognitively impaired participants in which score should be equal or higher than 22 (Akbar et al., 2010) (see Appendix A).

In this study 60 patients were finally selected; another 65 patients were excluded, among them 36 were without CI, 18 had depression, 8 were subtypes of MS (PP, PR and SP) and 3 had received corticosteroids.

2.2. Test procedure

MACFIMS battery was carried out after obtaining informed consent.

Various batteries to measure CI in MS patients such as the brief repeatable battery of neuropsychological tests (BRB-N) (Bever et al., 1995), the minimal assessment of cognitive function in MS (MACFIMS) (Benedict et al., 2002) and the brief international cognitive assessment for multiple sclerosis (BICAMS) were carried out (Langdon et al., 2012). MACFIMS proved to be more comprehensive in neuropsychological assessments in MS patients because the BRB-N did not have a measure of visual/spatial ability or executive function. (DeLuca et al., 2015) (Table 1) MACFIMS is a battery of seven neuropsychological tests (Benedict et al., 2002). This battery is a collection of the paced auditory serial addition test (PASAT) (Gronwall, 1977), the symbol digit modalities test (SDMT) (Smith, 1982), the California verbal learning test second edition (CVLT-II) (Delis et al., 2000), the brief visuospatial memory test-revised (BVMT-R) (Benedict, 1997), the controlled oral word association test (COWAT) (Benton, 1994), the judgment of line orientation test (JLO) (Benton, 1994) and the Delis-Kaplan executive function system (D-KEFS) sorting test (Delis et al., 2001). It is worth mentioning that a standard Persian version of The MACFIMS which was validated by Arman Eshagh et al. in 2012 was used in this study (Eshaghi et al., 2012).

Table 1
Neuropsychometric batteries commonly used to measure CI in MS.

Domain	BRN-B	MACFIMS	BICAMS
Processing speed (auditory) and working memory	PASAT [1]	PASAT	–
Processing speed (visual)	SDMT [2]	SDMT	SDMT
Verbal memory (learning and recall)	SRT [3]	CVLT-II [4]	CVLT-II
Visual/spatial memory (learning and recall)	SPART [5]	BVMT-R [6]	BVMT-R
Verbal fluency	COWAT [7]	COWAT	–
Spatial processing	–	JLO [8]	–
Executive function	–	D-KEFS [9]	–

BVMT-R, brief visuospatial memory test-revised; COWAT, controlled oral word association test; CVLT-II, California verbal learning test second edition; D-KEFS, Delis-Kaplan executive function system; JLO, judgment of line orientation test; PASAT, paced auditory serial addition test; SDMT, symbol digit modalities test; SPART, spatial recall test; SRT, selective reminding test.