Original Article

Evaluation of the Effectiveness of an Herbal Formulation of *Boswellia sacra Flueck*. In Improving Cognitive and Behavioral Symptoms in Patients with Cognitive Impairment and Alzheimer's Disease

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ABSTRACT

Objective: This study aimed to assess the efficacy of an herbal formulation based on *Boswellia sacra* in improving cognitive and behavioral symptoms in patients with mild cognitive impairment (MCI) and mild-to-moderate stages of Alzheimer's disease (AD). **Methods:** A 3-month, parallel-group, placebo-controlled trial was implemented from October 2021 to April 2022. Patients with MCI and mild-to-moderate stages of AD aged above 50 years (n = 60; 40 women, 20 men) enrolled in the study using clinical diagnosis and a score of 10–30 on the mini-mental state examination (MMSE) test. They were assigned into two groups; one receiving a herbal formulation) include *B. sacra, Melissa officinalis*, *Piper longum, Cinnamomum verum,* and *Physalis alkekengi*) three times a day and the other receiving a placebo for 3 months. The main efficacy measures were the changes in cognitive domains based on the MMSE and changes in behavioral and psychiatric symptoms based on neuropsychiatric inventory (NPI) scores compared with baseline. Side effects were also recorded. **Findings:** Results of this study showed significant differences between the two groups after 3 months in terms of all the assessed variables, including the overall result of the mean score of MMSE and NPI tests ($P \leq 0.001$). The herbal formulation had the most considerable effects on the domains of orientation, attention, working memory, delay recall, and language of the MMSE test. **Conclusion:** Herbal formulation based on *B. sacra* was significantly effective compared to a placebo in improving cognitive and behavioral symptoms in patients with MCI and mild-to-moderate AD.

KEYWORDS: *Alzheimer's disease, Boswellia sacra, cognition, dementia, herbal medicine*

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia that affects behavior, cognition, and function.[1] Currently, 50 million people worldwide are suffering from AD, which is expected to double every 5 years and reach 152 million by 2050.[2] Aging, genetic factors, female gender, obesity and diabetes, cardiovascular disease, history of head trauma, and environmental factors such as air pollution, diet, metals, and infections are the risk factors for this disease.[2] The exact cause of AD is unknown, and there is no definitive cure. A definitive diagnosis can be made using neurological assessment, neuroimaging evaluation such as[1] brain magnetic resonance imaging, and utilizing neuropsychological batteries such as mini-mental state examination (MMSE) and montreal cognitive

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assessment.[3] Researchers are trying to identify and validate biomarkers for diagnosing AD, such as amyloid beta in the cerebrospinal fluid.[3]

Various hypotheses have been proposed about the cause of AD, such as amyloid and tau protein.[4] Acetylcholine (ACh) is a neurotransmitter responsible for short-term memory. Therefore, cholinergic impairment in AD is also the cause of it. Various medications are used to increase the amount of ACh and inhibit the activity of the cholinesterase enzyme, including ACh precursors, nicotinic agonists, muscarinic agonists, and ACh esterase (AChE) enzyme inhibitors.[4] Medications used for the mild-to-moderate AD stages can only control the symptoms and delay their progression.

In recent years, natural products and bioactive compounds have proven effective in treating neurodegenerative diseases such as AD.[5,6] Herbs possess natural compounds such as polyphenols, terpenoids, lignans, alkaloids, and saponins that may effectively control and reduce AD progression.[7-9] These secondary metabolites have demonstrated promising and successful anti-inflammatory, AChE inhibitory, and N-methyl-D-aspartate (NMDA) receptor antagonistic effects.[10-13] Combining herbal ingredients or formulations may have advantages over single-target regulations due to their multiple target capabilities.[14]

Indian frankincense, with the scientific name *Boswellia sacra* (*Burseraceae*), has been used in multiple studies on memory enhancement. Pregnant women traditionally use this plant because of its memory-enhancing properties on their fetuses.[15,16] Lemonbalm (*Melissa officinalis L*., *Lamiaceae*) can be effective in treating dementia and forgetfulness, as well as improving behavioral symptoms in anxiety disorders, cognitive disorders, insomnia, and stress.[17-20] Cinnamon (*Cinnamomum verum J. Presl*, *Lauraceae*) possesses neuroprotective activity against Parkinson's and AD, is traditionally used in age-related brain disorders, and plays a role in multidisciplinary mechanisms.[21-23] Long pepper (*Piper longum*, *Piperaceae*) has anti-Parkinson's therapeutic activities and is used in Ayurveda and Iranian traditional medicine to delay and control dementia.[24-26] Chinese lantern or winter cherry *(Physalis alkekengi L, Solanaceae*) has anti-inflammatory, AChE inhibitory, and anti-oxidative properties.[27-29]

This study used a combined herbal formulation containing *B. sacra* (Indian frankincense or olibanum), lemon balm, cinnamon, long pepper, and winter cherry. We undertook the present study to evaluate the efficacy of this herbal formulation in improving cognitive and behavioral disorders in patients with mild cognitive impairment (MCI) and mild-to-moderate stage of AD, using a double-blind, randomized, and placebo-controlled trial design.

Methods

B. sacra resin as the main ingredient, *M. officinalis* aerial parts, *P. longum L* fruits and *C. verum J. Presl* bark, and *P. alkekengi* fruits. All plants were purchased from Tehran's market for medicinal plants and recognized by Dr. G. Amin. All voucher specimens (Number Popular market (medical) plant (PMP)-1851, 2334, 3623, 938, and 3624, respectively) have been deposited at the Herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences (TUMSs), Tehran, Iran. The capsule was prepared using olibanum 160 mg, lemon balm 14 mg, cinnamon 14 mg, long pepper 14 mg, winter cherry 14 mg, and sugar about 240 mg. According to the herbal references, the safe dose of these plants is much higher than the one used in the current formulation, so there is no concern about serious side effects.[30]

The total phenolics content of the herbal capsule was defined using the method described by Velioglu *et al*. with modifications.[31] Briefly, 200 µL (0.2 mg/mL) of methanol extract from each sample was mixed with 1.5 mL of diluted Folin–Ciocalteu reagent (0.1% V/V) in water and shaken vigorously for 5 min. After adding 1.5 mL aqueous solution of Na_2CO_3 (75 mg/mL), the solution was incubated for 2 h at room temperature, and the absorbance was measured at 760 nm. Six different concentrations (6.25–200 µg/mL) of gallic acid as a reference standard were used to obtain the trend line.

This study was a double-blinded, placebo-controlled trial from October 2021 to April 2022 undertaken on patients referred to the memory clinic of Roozbeh hospital affiliated with TUMS, and Yaadmaan clinic, referral centers for neurology and psychiatry disorders. The study protocol was approved by the Ethics Committee of TUMSs (ID No.IR.TUMS.TIPS.REC.1400.115). The study was registered in the Iranian Registry of Clinical Trials (Registration code: IRCT20210701051755N1).

Eligible participants were outpatients aged above 50 who had been diagnosed with AD based on the clinical assessment by a consultant cognitive neurologist. Laboratory tests, including thyroid function test, Vitamin B12, liver function test, blood urea nitrogen, and Creatinine, were performed to determine the treatable causes of dementia. Clinicians diagnose the disease and assess its severity based on the functional assessment staging tool (FAST), and patients who have the Stages 3, 4, and 5 on FAST, are evaluated using utilizing neuropsychological batteries, including standard Persian version tests of MMSE, and neuropsychiatric

inventory (NPI). The patients with a score of 10–30 on the MMSE test and at least 5 years of educational level with conscious consent were recruited. Patients were not admitted to the study if they had evidence of major psychiatric disorders, treatable causes of dementia or other types of dementia, severe failure of the liver (Child–Pugh Class c), renal (glomerular filtration rate, <25 ml/min), or cardiac (ejection fraction, <15%) disease, consumption of any medicine or herbal supplement with an effect on cognitive functions. The exclusion criterion was the occurrence of serious side effects or dissatisfaction with the continuation of treatment.

Based on similar studies, a sample size of 32 patients was calculated for each group.[5] The patients were randomly divided into two main groups by the random block method. One group took 500 mg herbal capsules three times daily after meals, and the other group took a placebo for 3 months. Placebo capsules contained 500 mg of maltodextrin. The appearance, smell, and color of the herbal and placebo capsules were similar. All included patients, or their caregivers signed the written informed consent form. All information was kept confidential. There was no change in the other patient's medications during the study unless necessary. None of the patients were infected with COVID-19 during the study.

Patients, associate physicians, principal investigator, and statistical analyst were blinded to the type of treatment groups. The pill-counting method assessed the patients' drug compliance during the intervention. All adverse effects reported by the patients, elicited, or observed were carefully recorded. At the end of the study, the Persian version MMSE and NPI tests were repeated.

MMSE is a widely used cognitive function test. It is used to screen cognitive decline and determine cognitive domains' impairment. It contains 30 points and asses orientation, registration, attention, working memory, recent memory language, and visual-spatial skills.[32]

FAST is a test for diagnosing the disease and determining its severity that divides the progression of the disease into seven stages. Stage 1: normal aging, Stage 2: possible MCI, Stage 3: MCI, Stage 4: mild dementia, Stage 5: moderate dementia, Stage 6: moderately dementia, and Stage 7: severe dementia. With this tool, it is possible to determine whether the changes in the patient's condition are due to Alzheimer's.[33]

NPI is an interview test based on information obtained from the patient's caregiver that assesses the neuropsychological symptoms of patients with AD and dementia disorders in the past month. In this test, ten behavioral domains and two domains of physical-nervous symptoms are evaluated: delusions, hallucinations, agitation, depression, euphoria, anxiety, indifference, disinhibition, irritability, abnormal motor behaviors, nocturnal behavior disturbances, and appetite disturbances. Behavior measurement includes the intensity and frequency of each behavior. Finally, to score in each section, it is necessary to multiply the intensity score by the number of occurrences of that symptom.[34]

Baseline characteristics of the studied patients were compared between the two groups at the beginning of the study using the Independent samples *t*-test for quantitative and Fisher's exact test for qualitative variables. The percentage of changes in the two groups was also compared through a *t*-test or Mann–Whitney *U*-test, depending on the normality of the data distributions. All analyses were conducted using IBM SPSS for windows version 26.0. A level of $P < 0.05$ was considered statistically significant.

Results

The content of total phenols was expressed by gallic acid equivalent (μg/mg extract). According to the calibration curve of different concentrations of gallic acid, the below formula was obtained [Table 1]:

$y = 0.0071x + 0.0297$ ($R^2=0.998$)

y = Mean absorbance, x = Total phenol content

This powder was standardized to contain at least 60 mg of total phenolic content based on gallic acid.

Sixty-five patients were screened and randomized for the study to the trial preparations (33 patients in the intervention and 32 patients in the placebo group). Two patients in the intervention group and three in the placebo group dropped out after 2 months because of adverse effects such as nausea, increased blood pressure, dizziness, dry mouth, and hair loss [Figure 1].

Thus, 60 patients (40 females and 20 males) finally completed the trial. These were randomly assigned to the intervention (31 patients) or placebo (29 patients) groups. The two groups were similar with respect to age ($P = 0.44$) and demographic parameters, including sex ($P = 0.17$), education ($P = 0.58$), and diagnosis ($P = 0.57$). Hence, there were no statistically significant differences regarding the baseline characteristics between the two groups. Table 2 presents the demographic characteristics of the patients.

Unlike other baseline characteristics, the two treatment groups had different MMSE (U ($N_{Intervention}$ = 31, $N_{Placebo}$ = 29) =213, $z = -3.514$, $P < 0.001$), and NPI (U ($N_{Intervention}$ = 31, $N_{Placebo}$ = 29) =316.5, $z = -1.981$, $P = 0.048$) scores at baseline.

Table 1: Total phenolic contents of herbal formulation based on *Boswellia sacra*

Sample	Absorbance (nm)			Mean absorbance (nm)	Total phenol contents (μg of gallic acid/mg herbal formulation, mean±SD)
1	0.443	0.452	0.461	0.452	59.46±0.01
2	0.486	0.465	0.444	0.471	61.31±0.02
3	0.436	0.472	0.454	0.454	59.75±0.02
4	0.449	0.471	0.427	0.451	59.06±0.02
5	0.464	0.453	0.442	0.453	59.62±0.01

SD=Standard deviation

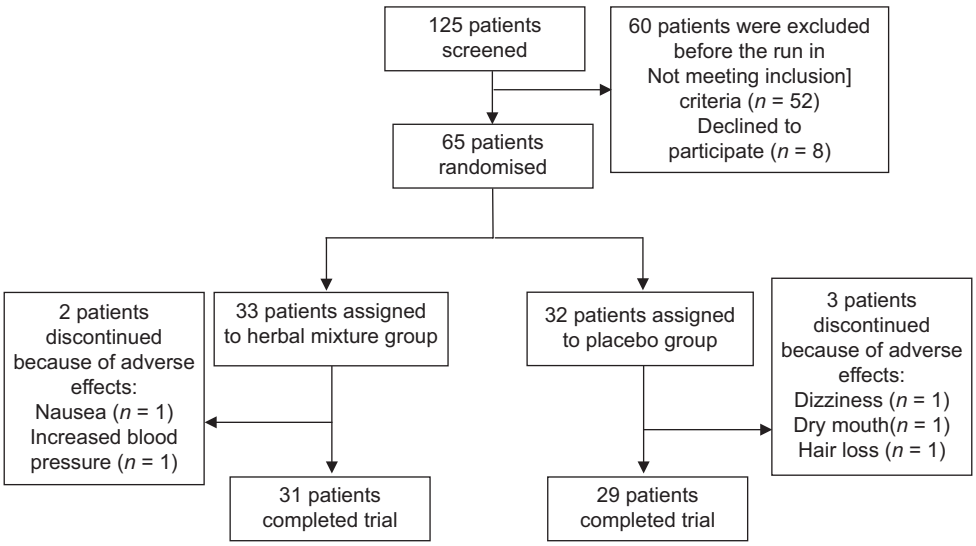

Figure 1: Patients' flow diagram

The percentage of change was calculated for each variable using the formula: 100* $(X_2\text{-}X_1)/X_1$. Then the two groups were compared using a *t*-test or *U*-test [Table 3].

There was a significant difference between the two groups regarding MMSE (U [$N_{Intervention}$ = 31, $N_{Placebo}$ = 29] =6, z = −6.56, P < 0.001), and NPI (U [$N_{Intervention}$ = 31, $N_{Placebo}$ = 29] =50.5, z = −5.93, P < 0.001).

Six types of side effects (13.3% in the intervention group and 10% in the placebo group), including headache, nausea, dizziness, dry mouth, and hair loss in the placebo group and headache, nausea, dizziness, and increased blood pressure in the intervention group were observed over the trial. The difference between the intervention and placebo in the frequency of side effects was insignificant (P = 0.870).

Discussion

AD is a neurodegenerative disease with no definitive cure. Except for Aducanumab as a curative drug for MCI or mild AD that the Food and Drug Administration has recently approved, AChE inhibitors and an NMDA glutamate receptor blocker (Memantine) are the only treatments available for AD. They are known to cause side effects, such as bradycardia, weakness and weight loss, constipation or diarrhea, and insomnia in elderly patients. Due to these complications and the belief in the effectiveness of traditional herbal medicinal, there is a great desire to use herbal medicine. Several natural products can be used alone or in combination to modify the effects and progression of AD.[8] There are very limited human studies on these herbs. To the best of our knowledge, this is the first human study that evaluated the effects of a co-administration herbal formulation based on *B. sacra* in improving cognitive and behavioral disorders in patients with MCI and mild-to-moderate stage AD. Our results demonstrated that regardless of the differences between the two diseases of MCI and AD, all our patients experienced statistically significant improvement in cognition and behavior after 3 months of treatment. The clinical evidence of these findings can be underlined by the advancements seen in the measurement of MMSE and NPI tests in the intervention group compared to the placebo. The herbal formulation had the most considerable effects on orientation, registration, working memory, delay recall, and language of the MMSE test. The reported side effects of the herbal formulation used in this study were similar to those caused by the placebo.

Table 2: Baseline demographic and clinical characteristics of the studied patients

Characteristics	Intervention group	Placebo group	*P*
Gender (male/female), *n* (%)	13/18 (21.7/30)	7/22 (11.7/36.7)	0.17
Age (years), mean±SD (range)	73.19±8.16 (55-85)	71.41±9.84 (52-88)	0.44
Patients' education levels (12 years of education/under 12 years of education), *n* (%)	22/9 (36.7/15)	18/11 (30/18.4)	0.58
Diagnosis (AD/MCI), *n* (%)	23/8 (38.3/13.3)	19/10 (31.7/16.7)	0.57

SD=Standard deviation, AD=Alzheimer'sdisease, MCI=Mild cognitive impairment

Table 3: The percentage of changes in mini-mental state examination and neuropsychiatric inventory tests among the two treatment groups

	Median (IQR)		*P*
	Intervention (*n*=31)	Placebo (*n*=29)	
MMSE (%)	11.32 (14.77)	−15.30 (13.46)	<0.001[b]
Orientation (%)	12.5 (25)	−20 (21.53)	<0.001[a]
Registration (%)	0 (0)	0 (0)	0.017[a]
Delay recall (%)	0 (100)	0 (83.33)	0.022[a]
Working memory (%)	25 (50)	−20 (40)	<0.001[a]
Language (%)	0 (7.14)	0 (18.75)	<0.001[a]
Visual-spatial (%)	0 (0)	0 (0)	1.000[a]
NPI (%)	−50 (66.68)	55.56 (172.22)	<0.001[a]

[a]Mann-Whitney *U*-test, [b]*t*-test. IQR: Interquartile range, MMSE: Mini-mental state examination, NPI: Neuropsychiatric inventory

This herbal formulation contained *B. sacra, M. officinalis, C. verum, P. longum,* and *P. alkekengi L*, and prior studies established each one had positive effects on AD. The summary of relevant studies is summarized in Table 4.

The administration of *Boswellia serrata (B. serrata)* to AD induced in rats improved the pathogenesis of AD as demonstrated by improvement in the behavioral stress tests (levels of activity and motor coordination) increased brain ACh levels and cognitive abilities.[35] The results of a study on oral administration of BBA at a daily dose of 100 mg/kg body weight for 4 weeks–24-month-old rats revealed that BBA could significantly enhance neurite outgrowth, growth of dendritic branches, increased volume of the hippocampal pyramidal layer, tubulin polymerization dynamics and also protective effect of boswellic acid against oxidative stress in the brain.[36]

An experimental study demonstrated that frankincense at a dose of 160 mg/kg body weight enhanced the power of learning at the postlearning stage, short-term memory, and long-term memory in rats.[37] It can facilitate learning and spatial memory formation in rats.[37]

Several previous studies have reported the anti-inflammatory activity of *B. serrata*.[15,38,39]

Other studies also show that B-boswellic acid (BBA) decreased levels of pro-inflammatory 5-lipoxygenase products such as 5-hydroxy eicosatetraenoic acid and leukotriene B4.[38,39]

M. officinalis extract has been shown to positively affect agitation in patients with mild-to-moderate stage of AD and severe dementia. NPI scores decreased in patients with dementia.[40] Rosmarinic acid (RA), one of the main-compound in *M. officinalis*, shows anti-inflammatory, AChE inhibitory, and antioxidant effects.[40,41] A 24-week double-blind, placebo-controlled randomized controlled trial (RCT)[2] using this extract on 23 patients with mild AD suggested that RA 500 mg daily may help prevent the deteriorating of neuropsychiatric symptoms of AD which was associated with an improvement of 0.5 points in the *M. officinalis* group and a decrease of 0.7 points in the placebo group (P = 0.012).[39] Another RCT study that evaluated the effects of *M. officinalis* extract in the treatment of patients with mild-to-moderate AD also showed improvement in cognitive functions and lower agitation.[42]

Results revealed that co-administration of *M. officinalis* and *B. serrata* improved scopolamine-induced cognitive impairment. *M. officinalis* and *B. serrata* (200 and 400 mg/kg body weight) for 4 weeks and then 30 min before scopolamine injection (0.1 mg/kg) led to improvement of memory function.[15]

Other studies also reveal that species of the *Cinnamomum* genus, such as cinnamon, contain potentially valuable agents with anti-amyloidogenic effects for the prevention and treatment of AD.[23,43] Kang *et al*. demonstrated that methanol extract from cinnamon bark efficiently reduced the production of amyloid (Aβ40), a substance derivatived from amyloid precursor protein (APP) by β-secretase and γ-secretase.[44] The current study showed that the inhibition of Aβ production is a potential therapeutic approach to AD. According to studies inhibits, the formation of toxic Ab oligomers and prevents the toxicity of Ab on neuronal PC12 cells, the reduction of plaques, inhibits the aggregation of human tau and Aβ peptides *in vitro*, and improvement in cognitive behavior are other beneficial effects of this plant on AD.[23,43]

P. longum, another component of this mixture, possessed potent antioxidant and anti-inflammatory activity.[45] It can

Table 4: A summary of studies on the effects of herbal formulation components on cognitive and behavioral symptoms

Component/dose	Year	Duration	Type of the study	Main results
B. serrate (160 mg/kg body)	2017[36]	21 days	Experimental	Enhanced the power of learning at the postlearning stage, short-term memory, and long-term memory
B. serrate (125 and 250 mg/kg/day)	2017[37]	17 days	Experimental	Anti-inflammatory activity
B. serrate (100 mg/kg/day)	2015[35]	4 weeks	Experimental	Neurite and dendritic branches growth, increased volume of the hippocampal pyramidal layer, tubulin polymerization dynamics and anti-oxidative stress effects in the brain
B. serrate (45 and 90 mg/kg/day)	2013[34]	2 weeks	Experimental	Increased ACh, decreased AChE activity, reduced Aβ plaques in the hippocampus and improved histopathology changes
M. officinalis (500 mg daily)	2020[39]	24 weeks	Double-blind placebo-controlled RCT	Positively affect agitation in patients with mild to moderate stage of AD and severe dementia and decreased NPI scores
M. officinalis (60 drops/day)	2003[41]	16 weeks	Double-blind placebo-controlled RCT	Improvement of cognitive functions and also positively affect agitation in patients with mild to moderate stage of AD
Co-administration of *M. officinalis* and *B. serrate* (200 and 400 mg/kg)	2016[15]	4 weeks	Experimental	Improvement of memory functions
C. zeylanicum (0.22 mg/ml)	2009[42]	15 h	In vitro	Inhibited the aggregation of tau protein
Methanol extract of cinnamon bark (4.20 and 50 µg/mL)	2016[43]	24 h	Experimental	Anti-amyloidogenic activity
P. longum L. fruits (50 and 100 mg/kg)	2014[45]	21 days	Experimental	Improves spatial memory impairment, reducing oxidative stress in the hippocampus

B. serrate=Boswellia serrate, *M. officinalis=Melissa officinalis*, *C. zeylanicum=Cinnamomum zeylanicum*, *P. longum=Piper longum*, Ach=Acetylcholine, AChE=Ach sterase, AD=Alzheimer'sdisease, RCT=Randomized controlled trail, NPI=Neuropsychiatric inventory

considerably control the expression of APP. According to a study, 50 and 100 mg/kg of methanolic extract of *Piper nigrum L*. fruit orally for 21 days improves spatial memory impairment caused by amyloid-beta (1–42) by reducing oxidative stress in the hippocampus of rats. Alkaloidal components are known to possess these activities.[45,46]

Studies revealed that the polysaccharide content in the *P. alkekengi* stem is a promising source of natural products, possesses good antioxidant, and AChE inhibitor activities, and may exert beneficial effects on cognitive functions.[28]

We found significant differences in the effectiveness of herbal formulation (1500 mg/day) based on *B. sacra* between placebo and intervention responders in the management of mild-to-moderate stage of AD, but it seems that the small number of patients and the relatively short period of follow-up of this study should be considered in further investigations to validate the results. In this study, we did not observe any visible interactions between components of this mixture and concomitant medications. However, as CYP2D6 and CYP3A4 metabolize AChE inhibitors, we must pay more attention to probable interactions between herbals and medications.

The limitations of the present study were the small number of patients and the relatively short follow-up period that should be considered in further investigations to validate the results. We propose an evaluation of this herbal formulation on other types of dementia syndrome and age-related cognitive impairment.

Authors' Contribution

Mahsa Panahishokouh and Mahnaz MiriMoghaddam contributed to the literature search, data collection, and writing the original manuscript. Niayesh Mohebbi, Fatemeh Mohammadian, and Mahnaz Khanavi were responsible for the study design and writing the original manuscript. Maryam Noroozian and Fatemeh Mohammadian were responsible for recruiting patients and writing the original manuscript. Niayesh Mohebbi was responsible for blinding the study and coding the capsules into groups A and B. Mahsa Panahishokouh, Maryam Noroozian, and Fatemeh Mohammadian participated in follow-up and evaluation of the patients about herbal formulation compliance and side effects. Seyed Mehrdad Savar and Hooshyar Honarmand helped in data collection and analysis, and manuscript writing. Maryam Nikoosokhan helped with herbal and placebo capsules preparation. All authors approved the final paper.

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Conflicts of interest

There are no conflicts of interest.

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