The effect of tablet containing Boswellia serrata and Melisa officinalis extract on older adults' memory: A randomized controlled trial

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ABSTRACT

Background: Memory deficits and age-related memory loss are currently two significant concerns in older adults. In Iranian herbal medicine, there are some prescriptions for memory improvement.

Objective: This study was designed to investigate the effect of tablet containing Boswellia serrata (BS) extract and Mellisa officinalis (MO) extract on memory of the older adults.

Method: This is a randomized, parallel, double-blind, placebo-controlled clinical trial that performed among 70 older adults who referred to healthcare centers of Kashan University of Medical Sciences, Iran. Subjects were randomly assigned to receive either tablets (n = 35) or placebo (n = 35) for a month (n = 30). Data were collected using a demographic questionnaire and the Wechsler Memory Scale-Revised (WMS-R). Data were analyzed using Chi-square, independent-samples *t*-tests, paired *t*-test, repeated measure ANOVA, and ANCOVA using SPSS v13.

Result: Participants' baseline characteristics were similar in the two groups. The study was completed by 53 participants. However, as the analysis was based on an intention-to treat approach, all 70 older adults were included in the final analysis. Comparison of the two groups with showed that the total scores of the WMS-R and the subscales, including auditory immediate, immediate memory, visual immediate and working memory, were increased after consumption of the containing BS and MO tablets ($p < 0.0001$).

Conclusion: The BS and MO tablet in older adults can be beneficial on improvement of memory. This is still necessary to investigate effects and durability of the tablets on older adults with memory impairments in future studies.

1. Background

According to WHO, older adults are defined as people over age 65 years (WHO, 2016). The world population is increasingly aging. The number of the older adults in the world is estimated to be 82 million by 2050 (de Rezende, Rey-Lopez, Matsudo, & do Carmo Luiz, 2014). In this group, aging can lead to health problems, such as cognitive impairments, chronic diseases, and physiological disorders (Masoudi Alavi, Safa, & Abedzadeh-Kalahroudi, 2014). The older adults are often associated with changes in the neurocognitive abilities (Canivet et al., 2015). Occurrence rate of memory deficits is approximately 21.5–71.3 per 1000 years in older adults. The prevalence of dementia in the older

adults population is about 1% to 2% per year (Eshkoor, Hamid, Mun, & Ng, 2015).

New techniques have been developed for memory enhancement and prevention from age-related memory loss (Mahboubi, Taghizadeh, Talaei, Takht Firozeh, & Tamtaji, 2016). In General, pharmacological and non-pharmacological treatments are available, especially for impairment of memory. However, they are not effective in all cases and cause side effects, especially in long-term administration. Herbal medicine is commonly used for treating diseases, such as amnesia as well as reinforcing memory (Jalili, Salahshoor, Pourmotabbed et al., 2014). Some of the most common herbs used for improving memory performance are Elaeagnus Angustifalia (Hamidpour et al., 2017), Ficus
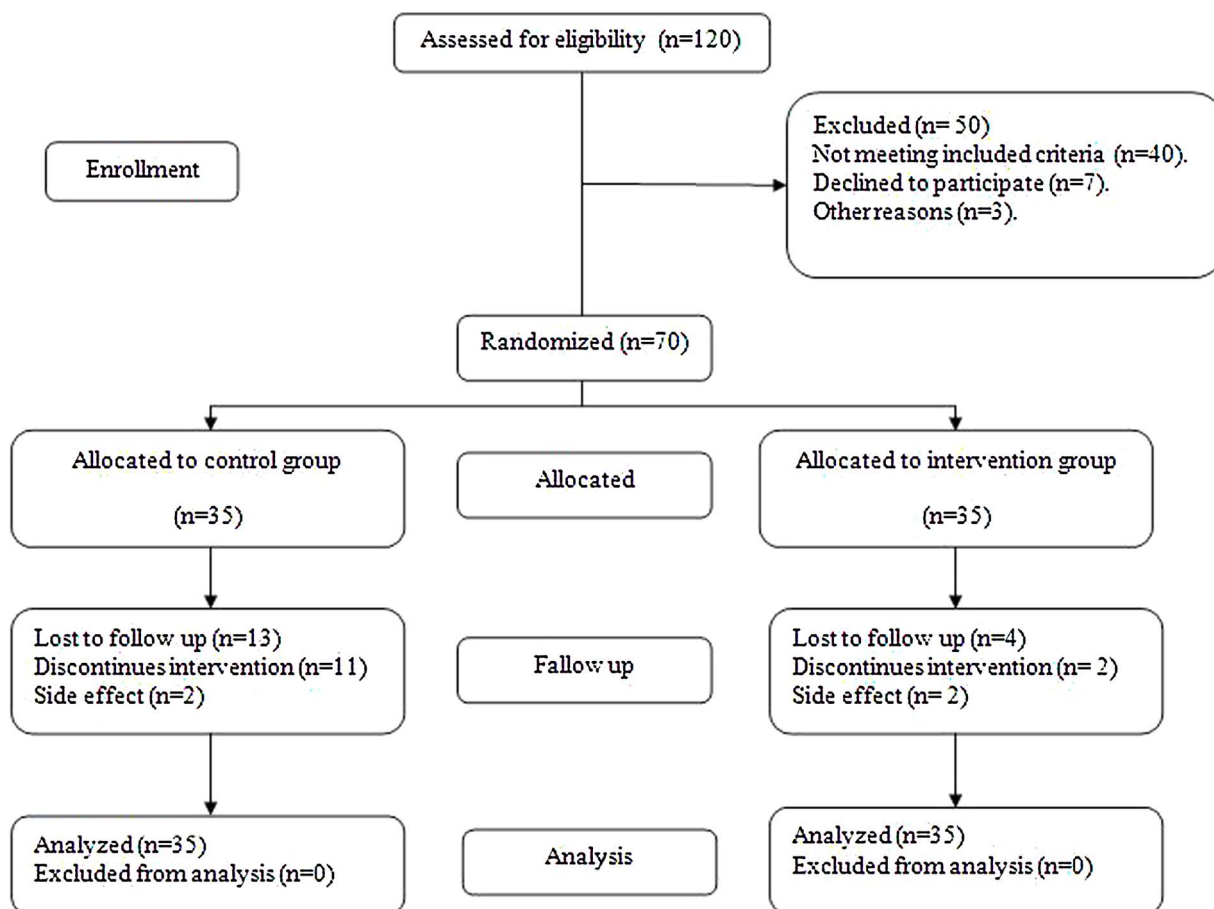
Fig. 1. Consort flow diagram of the study.

Table 1
Demographic characteri stics in intervention and control groups.[1]

	Intervention group (N = 35)	Control group (N = 35)	P[2]
Age	67.14 ± 6.28	65.62 ± 5.33	0.07
Sex			0.31
Female	23 (65.71%)	20 (57.14%)	
Male	12 (34.29%)	15 (42.86%)	
Marital status			0.35
Single	1 (2.86%)	3(8.57%)	
Married	28 (80.00%)	23 (65.71%)	
Widow	6 (17.14%)	9 (25.72%)	
Job			0.74
Self-employment	2 (5.72%)	3 (8.57%)	
Retired	10 (28.57%)	12 (34.29%)	
Homemaker	23 (65.71%)	20 (57.14%)	
Education Level			0.80
Illiterate	21(60.00%)	19(54.29%)	
Elementary	9(25.71%)	10(28.57%)	
Middle school	3 (8.57%)	5 (14.28%)	
Diploma and higher	2 (5.72%)	1 (2.86%)	

[1] Values are means ± SDs or n (%).
[2] Obtained from a chi-square test, except for age, which was obtained an Independent samples student's *t*-test.

Carica (Subash et al., 2016), Crous Sativus (Khazdair, Boskabady, Hosseini, Rezaee, & Tsatsakis, 2015), Olive oil (Lehert, Villaseca, Hogervorst, Maki, & Henderson, 2015), Ginkgo (Stackman et al., 2003) and Huperzine (Malkova, Kozikowski, & Gale, 2011). Iranian Tradi-tional Medicine recommends MO and BS for memory improvement

abilities (Mahboubi et al., 2016). In 10th century, Avicenna, the Persian physician, introduced the MO and BS for treating neurological disorder in The Canon of Medicine (The Law of Medicine) (Hosseini-Sharifabad, Kamali-Ardakani, & Hosseini-Sharifabad, 2016).

Few interventional studies have examined the effects of BS on memory. Findings from these studies indicated that memory increased after a period of BS administration (Jalili, Salahshoor, Moradi et al., 2014; Hosseini et al., 2010). BS has a botanical origin and consists of triterpenes (α- and β-boswellic acids and l upeolic acid), essential oils, and polysaccharides (Catanzaro et al., 2015). Also several studies have shown that MO might lead to improvement of memory (Ozarowski et al., 2016; Kennedy et al., 2003; Soodi, Naghdi, Hajimehdipoor, Choopani, & Sahraei, 2014). MO exhibits acetylcholine receptor ac-tivity (Akbarzadeh et al., 2015) may treat the cholinergic dysfunction in Alzheimer's disease (Kennedy et al., 2003). An earlier study showed that a joint administration of the BS and MO in animals was more ef-fective than a single BS or MO in memory improvement (Mahboubi et al., 2016). According to the authors' knowledge, there is no study on effects of joint BS and MO on human's memory. This study was con-ducted to investigate the tablet containing BS and MO on older adults' memory.

2. Methods

The present study was a randomized double-blind parallel con-trolled trial conducted from August to September 2015. The partici-pants were 70 older adults referred to healthcare centers associated with Kashan University of Medical Sciences, Kashan, Iran. For esti-mating sample size, we used the standard formula suggested for parallel clinical trials and considered the type 1 error (α) of 0.05 and type 2

Table 2

Relation between mean scores of total memory and subscales memory in two groups at the beginning of the study and at the end of the study.[1]

	at the beginning of the study			at the end of the study		
	Intervention group	Control group	P[2]	Intervention group	Control group	P[2]
auditory immediate	31.32 ± 13.74	30.63 ± 9.56	0.84	48.25 ± 12.88	34 ± 6.55	0.0001
visual immediate	49.93 ± 9.73	51.04 ± 10.59	0.69	57.25 ± 8.95	54.54 ± 15.71	0.33
immediate memory	81. 25 ± 20.91	80.77 ± 18.77	0.93	102.38 ± 20.51	85.45 ± 15.71	0.002
working memory	16.03 ± 4.72	18 ± 3.2	0.09	19.67 ± 4.44	20.36 ± 2.8	0.52
Total memory	178.54 ± 44.66	181.36 ± 37.45	0.81	227.58 ± 40.22	194.36 ± 27.61	0.002

[1] Calues are means ± SDs.
[2] Obtained from an independent samples student's t-test.

Table 3

Total memory and subscales memory at study baseline and after 4-wk intervention in elderly that received either MO & BS tablet or placebo.[1]

	Intervention group				Control group				
	Before	After	change	P[2]	Before	After	change	P[2]	P[3]
auditory immediate	31.32 ± 13.74	48.25 ± 12.88	16.93 ± 12.29	0.0001	30.63 ± 9.56	34 ± 6.55	3.36 ± 12.12	0.21	0.0001
visual immediate	49.93 ± 9.73	57.25 ± 8.95	7.32 ± 6.96	0.0001	51.04 ± 10.59	54.54 ± 15.71	3.50 ± 12.15	0.19	0.0001
immediate memory	81.25 ± 20.91	102.38 ± 20.51	21.12 ± 9.20	0.0001	80.77 ± 18.77	85.45 ± 15.71	4.68 ± 17.22	0.21	0.0001
working memory	16.03 ± 4.72	19.67 ± 4.44	3.64 ± 2.51	0.0001	18 ± 3.21	20.36 ± 2.8	2.36 ± 3.95	0.01	0.0001
Total memory	178.54 ± 44.66	227.58 ± 40.22	49.03 ± 21.31	0.0001	181.36 ± 37.45	194.36 ± 27.61	13 ± 35.72	0.11	0.0001

[1] Values are means ± SDs.
[2] Obtained from a pair t-test.
[3] Obtained from repeated measure ANOVA.

error (b) of 0.20 (power = 80%). According to evidence (Archier & Vieillescazes, 2000), we used 10 as the s_1 and 10 as s_2 as a key variable. Therefore, we needed 30 participants in each group. Considering 5 dropouts in each group, the final sample size was determined to be 35 participants per group. Inclusion criteria were (a) age 60–74 years, (b) full conscious, (c) speak pension, (d) no history of psychological disorder and Alzheimer's disease based on medical records, and (e) no history of allergy to herbal medicine. Exclusion criteria included: irregular consumption of tablets (missing two or more consecutive dosages), inaccessibility of the participants (relocation, hospitalization, and a lack of follow up) and an incidence of side effects (such as headache, nausea, vomiting and digestive problems).

2.1. Sampling

In this study, we employed multi-stage random sampling. In the first stage, Kashan city was divided into four regions: north, south, east, and west. In the second stage, one healthcare center from each region was randomly selected. Consequently, a simple random sampling method was used to reach sample size of participants in each center (n = 30).

The second author explained the study purposes, and provided information about the tablets; benefits and side effects. Then, the participants who had inclusion criteria and signed the informed consent were selected. Another researcher (psychologist) interviewed the participants in private room and completed Wechsler Memory Scale. Then eligible older adults were divided into two intervention (35 cases) and control (35 cases) groups using block random allocation. The third author performed the Block random allocation with four blocks and one code was assigned for each participant. Random assignment was performed using computer-generated random numbers.

2.2. Plant extracts and physiochemical analysis

Flowering aerial parts of MO was collected from a research farm in the Medicinal Plant Research Center of Barij (Kashan, Iran) in August 2012. The voucher specimen was identified by research institute of Forest and Rangelands, Tehran, Iran, and deposited in the Herbarium of agriculture department, Medicinal Plant Research Center of Barij,

Kashan, Iran (number 166.1). Batch Number: BS10017 (BS) was purchased from Natural Remedies Pvt. Ltd. Bangalore Karnataka, India. Rosmarinic acid of MO extract was detected by HPLC method (Wang, Provan, & Helliwell, 2004). The amount of total boswellic acids, 11-keto- boswellic acid and acetyl-11-keto -boswellic acid were determined by a calibration curve (Shah, Rathod, Suhagia, Pandya, & Parmar, 2008).

2.3. Boswellia serrata (BS) and Melissa Officinalis (MO) extract tablets

The participants received the BS and MO in the form of tablet. Tablets were produced by Barij Essence Pharmaceutical Company (Kashan, Iran). Sixty tablets containing 290 mg dried extract of MO is that had been standardized by rosmarinic acid (8.5% w/w) and 27 mg of dried extract BS that had been standardized by boswellic acid and acety l-11-keto-boswellic acids were 70, 4.67 and 1.85% w/w, respectively. Furthermore, tablets contained Avicel, corn starch, Lactose mono hydrate, and magnesium stearate adjuvant.

2.4. Intervention

The tablets and placebo were classified and coded by formulation unit of Research Center of Barij (Kashan, Iran). The placebo was prepared in the same color, shape, size, and packaging style as the tablets. The codes were considered for each package and the participants and the researchers were not aware of the content of the package at the time of the study. In the first visit, the participants received 30 tablets for 15 days. In the second visit, they received more 30 tablets. In each visit, researcher answered to the participants' questions. In the intervention group received two tablets (containing BS and MO) per day in the morning and night and the participants in the placebo group received two placebos per day for one month (n = 60). For follow-up, the participants were contacted using telephone every week by the second author. The psychologist completed the WMS-R test for two groups in the healthcare centers after a month.

2.5. Instrument

Two questioners, socio demographic characteristics, including: age, sex, marital status, job, and education level and the Wechsler Memory Scale-Revised (WMS-R), were used. Compared to the original WMS, the WMS-R has a broader normative base; includes more subscales such as Visual Span and Figural Memory.

In the WMS-R version, there are eight primary indexes, including auditory immediate (verbal), visual immediate (visual), immediate memory, auditory delayed, visual delayed, auditory reception delayed, general memory, and working memory (Franzen, Wilhelm, & Haut, 1995). In this study, four subscales were used based on education and cognitive status of the participants including, (WHO, 2016) Auditory immediate, (Logical Memory I + Visual Paired Associates I). In the auditory immediate, one short story is presented orally and the examinee is asked to retell story from memory immediately after hearing it. (de Rezende et al., 2014) Visual immediate (faces I + family picture I). In the visual, a series of five designs is shown, one at a time, each for 10 s. After presenting each design, the examinee is asked to draw the design from memory. (Masoudi Alavi et al., 2014) Immediate memory (Logical Memory I + Verbal Paired Associates I + faces I + family picture I). In the immediate memory the examiner reads 10 or 14 word pairs to the examinee. Then, the examiner reads the first word of each pair, and asks the examinee to provide the corresponding word. (Canivet et al., 2015) Working memory (letter-number sequencing + spatial span). In the working memory the examinee is briefly shown a series of abstract symbols on a page and then asked to select the symbols from an array of symbols, in the same order they were presented on the previous page.

The total score of WMS-R ranged from 0 to 455 and subscales score included: auditory immediate $0 - 73$, visual immediate $0 - 112$, immediate memory 0–185, and working memory $0 - 85$. The validity of the Persian version of the WMS-R was previously established by Orangi et al. The Cronbach's alpha of the instrument was 0.98 (Orangi, Atefvahid, & Ashayeri, 2002).

2.6. Ethical considerations

This study was approved by the Institutional Review Board and the ethics committee of Kashan University of Medical Sciences (approval number: 94013). The research objectives were explained to the participants and a written informed consent was obtained. The participants were informed about voluntary participation and the right for withdrawal at any time. They were assured that their anonymity will be protected and their personal information will be kept confidential. This study was registered at the Iranian Registry of Clinical Trials (IRCT) with registration code IRCT 2015102114086N6.

2.7. Data analysis

We used the Kolmogorov–Smirnov test to examine the normal distribution of the variables. Log transformation was used for non-normally distributed variables. The analyses were performed on the basis of an intention-to-treat approach. Missing values were controled using the Last Observation Carried Forward (LOCF) method. Descriptive statistics (mean, standard deviation, frequency, and percentage) were conducted. The categorical variables were analyzed using the chi-square test. Paired t-test was used to compare the quantitative variables with in groups. To determine the effects of BS and MO on the total memory and subscales of memory, we used One-Way Repeated Measures Analysis of Variance One-Way ANOVA to control effects of confounders. We adjusted all analyses for general characteristics to avoid potential biases. This analysis was done using the ANCOVA. The level of significance was set at 0.05. Statistical analyses were performed using SPSS version 13 (SPSS, Chicago, IL, USA).

3. Result

The total attrition rate for the intervention and control groups was 17 participants. In the intervention group, this rate was due to side effects (one digestive side effect and one allergy and flushing) and withdrawal from the study (two participants). In the control group, this rate resulted from side effects (one digestive side effect and one allergy) and withdrawal from the study (11 participants, 5 irregular consumption of 2 hospitalizations, 4 relocation and no response to phone calls). Finally, Data from 53 participants were analyzed (Fig. 1). However, as the analysis was done based on an intention-to-treat approach, the data from all participants (35 in each group) were included in the final analyses. For those who completed the trial (n = 53), the tablet counts suggested 100% adherence in both group.

The mean age in the intervention group was 67.14 ± 6.28 and in the control group was 65.62 ± 5.33. About 65.71% of the participants in the intervention group and 57.14% in the control group were female. The results indicated that there was no significant difference between the two groups in terms of the socio demographic variables, including age, sex, marital status, job, and education level ($p > 0.05$) (Table 1).

At the beginning of the study, results of the independent sample t-tests revealed that there was no significant difference between the two groups' in terms of the mean score of the total memory and the subscales of memory, auditory immediate, visual immediate, immediate memory, and working memory ($p > 0.05$). Furthermore, a significant difference was found between the two groups in terms of the auditory immediate ($p < 0.0001$), immediate memory ($p < 0.002$) and total memory ($p < 0.002$) after the intervention (Table 2).

Results of the paired t-test showed that the total memory score and its subscales were increased after the intervention ($p < 0.0001$). The results also showed a significant increase in working memory score in the control group at the end of the study (Table 3).

Differences between the two groups were not significant in terms of auditory immediate, visual immediate, immediate memory, and working memory. BS and MO administration, compared to placebo, led to a significant increase in auditory immediate (48.25 ± 12.88 vs 34 ± 6.55, p < 0.0001) and visual immediate (57.25 ± 8.95 vs 54.54 ± 15.71, p < 0.0001) scores. In addition, after the administration of BS and MO tablets, we observed a significant increase in the immediate memory (102.38 ± 20.51 vs 85.45 ± 15.71, p < 0.0001) and working memory (19.67 ± 4.44 vs 20.36 ± 2.8, p < 0.0001) scores compared to placebo. Furthermore, it resulted in a significant increase in the total memory score (227.58 ± 40.22 vs 194.36 ± 27.61, p < 0.0001) (Table 3). When we adjusted the analyses for the participants' general characteristics, no significant differences were observed in terms of age (p = 0.12), sex (p = 0.37), Marital status (p = 0.88), Job (p = 0.19) and Education Level (p = 0.11).

4. Discussion

This study showed that, BS and MO tablet improved the memory scores in the participants. To the best of our knowledge, this is the first study to examine the effects of BS and MO supplementation on memory in older adults.

With aging, the likelihood of developing memory loss increases. About 40% of older adults have age-associated memory impairment (Eshkoor et al., 2015). Cognitive impairment and Alzheimer's dementia significantly increase as the population ages (Vigil, Mizuno, Lucchesi, Valls-Comamala, & Giese, 2017). Therefore, it is important to prevent the diseases and their complications. Our study demonstrated that the BS and MO tablets for a month in participants led to a significant increase in auditory immediate and immediate memory compared to placebo. Previous studies have reported the positive effects of single MO or BS supplementation on memory in older adults; however the combined effects of BS and MO supplementation have not been assessed. In line with our study, Jalili, Salahshoor, Moradi et al. (2014)

showed that BS has positively resulted in improved learning ability. Improvement of memory after BS consumption was shown in other studies (Hosseini-Sharifabad et al., 2016; Hosseini et al., 2010; Mahmoudi et al., 2011). BS is known as a substance for improvement of memory and prevention of Alzheimer's disease (Rainer, 1996). According to pharmacokinetic studies, there are substances in BS that are associated with memory storage (Kruger et al., 2008). Other researchers reported a positive effect of MO supplementation on long-term memory (Ozarowski et al., 2016; Akbarzadeh et al., 2015; Bayat et al., 2012). Moreover, they showed that MO extract is effective in management of mild to moderate Alzheimer's disease and MO has CNS acetylcholine receptor activities, which can modulate mood and cognitive performance (Akhoondzadeh, Jalalmanesh, & Hojjati, 2014).

The findings of this study showed, the administration of BS and MO tablet improved total memory score and subscales in the participants. Our findings were in line with Mahboubi et al. (Mahboubi et al., 2016). Mahboubi et al. indicated that the memory ability to improve memory in an animal model after MO and BS intake. The mechanisms, which can explain this result is that the intake of BS supplements may affect various protein kinase activities, calcium mobilization, and signaling pathways (Mahmoudi et al., 2011). Ozarowski et al. reported that MO extract can exhibit cholinergic receptor-binding properties and inhibit acetyl cholinesterase; therefore, learning may enhance (Ozarowski et al., 2016).

Our study had limitations. The intervention was performed in a limited time

While interpreting our findings, some limitations need to be considered. The intervention in the current study was of relatively short duration. Long-term interventions may show other effects on older adult memory. In this study, the participants had no history of psychological disorders and Alzheimer's disease; therefore, generalizability of our findings to the general population of older adults is limited. Another limitation of this study was a lack of follow up for a longer period. It is recommended that in future studies follow up be considered for two, four, and six months after using of the tablets. Moreover, it is recommended that, in the future studies, researchers recruit a random sample of older adults.

Acknowledgement

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