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ORIGINAL ARTICLE

Evaluation of the effect of *Elaeagnus angustifolia* alone and combined with *Boswellia thurifera* compared with ibuprofen in patients with knee osteoarthritis: a randomized double-blind controlled clinical trial

Mansoor Karimifar[1] · **Rasool Soltani**[2] · **Valiollah Hajhashemi**[3] · **Sara Sarrafchi**[2]

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Abstract Osteoarthritis (OA) is one of the most common articular disorders. Many patients do not respond to acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), the mainstay of pharmacotherapy for knee OA. The plants *Elaeagnus angustifolia* and *Boswellia thurifera* have anti-inflammatory and analgesic properties. This study aimed to evaluate the effect of *E. angustifolia* alone and in combination with *B. thurifera* compared with ibuprofen in patients with knee osteoarthritis. In a randomized double-blind controlled clinical trial, 75 patients with knee OA were randomly and equally assigned to one of three groups Elaeagnus (n = 23), Elaeagnus/Boswellia (n = 26), and ibuprofen (n = 26) to receive the capsules of Elaeagnus, Elaeagnus/Boswellia, and ibuprofen, respectively, three times daily with meals for 4 weeks. Pain severity based on VAS (visual analog scale, 0 to 10 scale) and the scores of LPFI (Lequesne Pain and Function Index) and PGA (patient global assessment) were determined pre- and post-intervention for all patients. All interventions had significant lowering effects on VAS, LPFI, and PGA scores ($P < 0.001$ for all parameters) with no significant difference between groups in terms of effects on all evaluated parameters. Consumption of *E. angustifolia* fruit extract either alone or in combination with Boswellia oleogum resin extract could decrease pain and improve function in patients with knee osteoarthritis comparable to ibuprofen.

Keywords *Boswellia thurifera* · Clinical trial · *Elaeagnus angustifolia* · Ibuprofen · Knee osteoarthritis

✉ Rasool Soltani
soltani@pharm.mui.ac.ir

[1] Department of Rheumatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

[2] Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

[3] Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Introduction

Osteoarthritis (OA) is one of the most common articular disorders and the most common type of arthritis. It particularly affects elderly people leading to chronic disability [1, 2]. Knee OA has a high prevalence rate compared with other types of OA. It presents at earlier age groups particularly in obese women [3, 4].

Treatment of OA varies from non-pharmacologic modalities (weight loss, exercise, temperature modalities) and pharmacologic interventions, to total knee replacement [5]. The primary objective of medication is to alleviate pain [6]. Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of pharmacotherapy for knee OA [7]. However, many patients do not respond to conservative management and require further management [1]. On the other hand, NSAIDs are associated with risks of gastrointestinal, renal, and cardiovascular adverse events [8]. Therefore, search for new anti-inflammatory and analgesic medications, including herbal drugs, is mandatory.

E. angustifolia, commonly called Russian olive and commonly referred to as "Senjed" in Iran, is a plant whose fruit extract has anti-inflammatory and analgesic properties [9, 10]. Also, the plants of genus Boswellia, including *Boswellia thurifera*, have anti-inflammatory/anti-oxidant properties [11, 12]. Due to these effects, both

plants have been traditionally used for arthritic disorders in Iran. However, few clinical studies exist about their efficacy, especially in comparison to a standard therapy, in these disorders. This study aimed to evaluate the effect of *Elaeagnus angustifolia* both alone and in combination with *B. thurifera* compared with ibuprofen in patients with knee osteoarthritis.

Materials and methods

Preparation of capsules

All capsules were prepared by Barij Essence pharmaceutical company, Kashan, Iran. Each Elaeagnus capsule was prepared by 200 mg of freeze-dried aqueous extract of *E. angustifolia* fruit (equivalent to 3.5–4 mg of total phenolic compounds). Each Boswellia capsule was prepared by adding 100 mg of freeze-dried hydroalcoholic extract of *Boswellia thurifera* oleo-gum resin (containing boswellic acid 60–70% and 11-ketoboswellic acid 3%) to 100 mg of Elaeagnus extract. Each ibuprofen capsule contained 400 mg of drug.

Patient selection

Patients were selected from those referring to rheumatology clinic of Alzahra hospital of Isfahan, Iran, affiliated to Isfahan University of Medical Sciences, based on the following inclusion criteria: (1) age of 40 to 80 years, (2) knee osteoarthritis in at least one knee for at least 6 months based on ACR (American College of Rheumatology) diagnostic criteria [13, 14], (3) pain score >4 based on VAS (visual analog scale), (4) LPFI (Lequesne Pain and Function Index) >7, (5) serum CRP (C-reactive protein) <10 mg/dl and ESR (erythrocyte sedimentation rate) <20 mg/dL, (6) grade 2 or 3 of Kellgren-Lawrence scale in knee radiography obtained within the last 6 months, (7) free of liver, renal, or cardiac dysfunction, (8) no use of intra-articular glucocorticoids or hyaluronic acid preparations within the last 3 months, (9) no use of systemic glucocorticoids within the last 3 months, (10) free of all other bone and joint disorders including rheumatoid arthritis and gout, (11) free of peptic ulcer disease, (12) no knee arthroscopic procedure within the last 3 months, and (13) not being pregnant or lactating (for women).

Patients with either irregular use of capsules (less than 80% of total capsules) or no use of capsules for at least 3 days were excluded from the study.

Clinical study and interventions

This was a randomized double-blind controlled clinical trial performed in rheumatology clinic of Alzahra hospital of Isfahan, Iran from April to December 2014. The study was registered in Iranian Registry of Clinical Trials (IRCT) with the record number of IRCT2015072123282N1. Written informed consent was obtained from all participants. Patients with inclusion criteria were randomly and equally assigned to one of three groups Elaeagnus, Elaeagnus/Boswellia, and ibuprofen to receive the capsules of Elaeagnus, Elaeagnus/Boswellia, and ibuprofen, respectively, three times daily with meals for 4 weeks. Before any intervention, pain severity based on VAS (0 to 10 scale), and the scores of LPFI and PGA (patient global assessment) were determined and recorded for all patients. LPFI index consists of three subscales including pain or discomfort scale, the maximum distance of walking ability, and the function or activities of daily living (ADL). A total of 10 items should be replied by the patient with each item having a score range. The total score of LPFI ranges from 0 to 24, with higher scores presenting worse OA status. The Persian form of LPFI validated previously by Nadrian et al. [15] was used in this study. PGA was evaluated by asking the patient to assess the overall effects of the used drug on knee OA symptoms and rating the response based on the following five-point scale with 0.1 accuracy: 0 = none (ineffective), 1 = poor (some effect), 2 = fair (reasonable effect), 3 = good (satisfactory effect), and 4 = excellent (ideal response, free of pain). For patients with NSAID use, the drug was discontinued and the intervention was begun after "five NSAID half-life +2" days of the last dose. The patients were instructed to report any side effect during the use of capsules. At the end of the study, all mentioned parameters were again determined and recorded for all patients and compared to baseline values both within and between groups.

Statistical analysis

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Kolmogorov–Smirnov test was applied for determination of distribution pattern of obtained data. Chi square (χ^2) test and independent samples t-test were used for comparison of gender distribution and mean age, respectively, of two groups. Paired-samples *t* test was performed for comparison of values at the beginning and end of intervention within each group. One-way analysis of covariance (ANCOVA) test was used for comparing the mean values between the three groups. Differences with P value < 0.05 were considered as significant.

Results

During the study, a total of 167 patients were evaluated for eligibility, of whom 101 patients met the inclusion criteria and participated in the study that were assigned to the three groups (Fig. 1). Over the study period, 26 patients were excluded

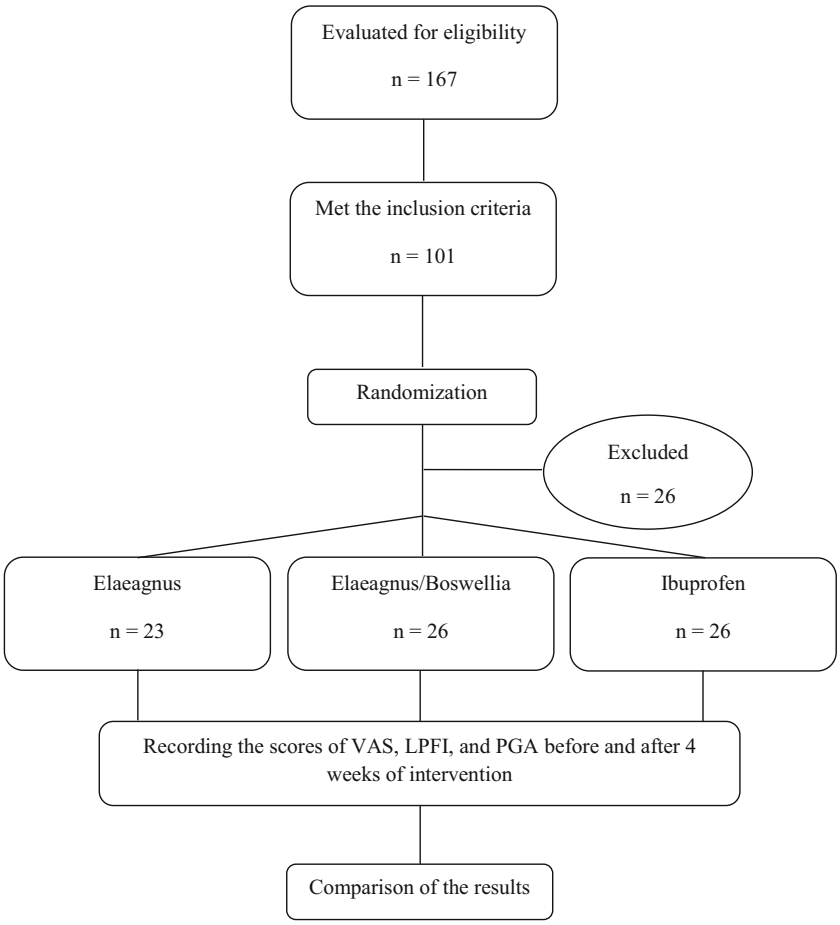

Fig. 1 Flow chart of enrollment and allocation of participants and study design

from the research due to either irregular use of capsules or no adherence to complete the study. Therefore, 75 participants completed the study including 23, 26, and 26 patients in Elaeagnus, Elaeagnus/Boswellia, and ibuprofen groups, respectively, with 91.3% (n = 21), 88.46% (n = 23), and 84.62% (n = 22), respectively, being female (P = 0.769). The mean (± SD) age of patients in the groups was 52.65 (±11.09), 52.0 (±8.74), and 52.96 (±8.57), respectively (P = 0.933).

Table 1 shows the effects of each intervention on evaluated parameters and also represents the effects comparatively between the interventions. As shown, all interventions had

Table 1 The effects of interventions on assessed parameters after 4 weeks

Parameter	Group	Baseline	Week 4	P-value* (within group)	P-value** (between groups)
VAS	*Elaeagnus* (n = 23)	7.04 ± 1.15	4.65 ± 1.84	<0.001	0.304
	Elaeagnus/Boswellia (n = 26)	7.03 ± 1.36	4.84 ± 1.96	<0.001	
	Ibuprofen (n = 26)	7.01 ± 1.25	5.30 ± 1.66	<0.001	
LPFI	*Elaeagnus* (n = 23)	12.47 ± 2.88	8.32 ± 3.25	<0.001	0.578
	Elaeagnus/Boswellia (n = 26)	12.69 ± 3.35	9.09 ± 4.18	<0.001	
	Ibuprofen (n = 26)	12.84 ± 2.73	9.34 ± 2.66	<0.001	
PGA	*Elaeagnus* (n = 23)	1.44 ± 0.62	2.38 ± 0.43	<0.001	0.202
	Elaeagnus/Boswellia (n = 26)	1.50 ± 0.68	2.17 ± 0.46	<0.001	
	Ibuprofen (n = 26)	1.79 ± 0.64	2.50 ± 0.57	<0.001	

The values are presented as Mean ± SD

VAS visual analog scale, *LPFI* Lequesne pain and function index, *PGA* patient global assessment

*paired-samples t test; **ANCOVA test

Table 2 Comparison of intervention groups in terms of assessed parameters

Parameter	Group	*Elaeagnus*	*Elaeagnus/Boswellia*	Ibuprofen
VAS	*Elaeagnus* (n = 23)	–	1.000	0.415
	Elaeagnus/Boswellia (n = 26)	1.000	–	0.835
LPFI	*Elaeagnus* (n = 23)	–	1.000	0.968
	Elaeagnus/Boswellia (n = 26)	1.000	–	1.000
PGA	*Elaeagnus* (n = 23)	–	0.515	0.278
	Elaeagnus/Boswellia (n = 26)	0.515	–	1.000

The values represent *P values* (ANCOVA test)

VAS visual analog scale, *LPFI* Lequesne pain and function index, *PGA* patient global assessment

significant lowering effects on VAS, LPFI, and PGA scores. Furthermore, there was no significant difference between groups in terms of effects on all evaluated parameters.

Table 2 shows comparison of the effects of each intervention with the other two. As shown, no significant difference was observed between groups showing equal effects of all interventions on the assessed variables.

During the study, 2, 3, and 4 patients from Elaeagnus, Elaeagnus/Boswellia, and ibuprofen groups, respectively, complained of gastrointestinal adverse effects including constipation and dyspepsia. No other side effect was reported by the patients.

Discussion

Our results showed non-inferiority of Elaeagnus fruit extract and its combination with Boswellia oleo-gum resin extract compared to ibuprofen in reduction of pain and improvement of function in knee OA patients. At the best of our knowledge, this is the second clinical study evaluating therapeutic effects of these herbal extracts compared to a NSAID in OA. In the first trial, conducted by Panahi et al., the effect of two doses of *E. angustifolia* extract (300 mg/day and 600 mg/day) compared to ibuprofen (800 mg/day) on the severity of knee OA was evaluated [16]. According to the results, both doses of *E. angustifolia* significantly reduced WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), VAS, LPFI, and PGA. Furthermore, no significant difference was observed between *E. angustifolia* and ibuprofen in terms of effects on these parameters. The authors concluded that *E. angustifolia* extract has beneficial effects comparable to ibuprofen in reducing the symptoms of knee OA. Therefore, our results are similar to the results of Panahi et al. study regarding the effects of the extract on the variables and their comparison to ibuprofen as a standard treatment for OA.

Our results are consistent to other studies showing analgesic effects of Elaeagnus and Boswellia extracts. In the study of Rabiei et al. on symptomatic knee OA patients, the combination of *E. angustifolia* and ginger extracts (200 mg) significantly reduced pain intensity according to VAS and physician global assessment compared to placebo [17]. In the study of Kimmatkar et al., consumption of 333 mg of *Boswellia serrata* extract three times daily by knee OA patients significantly reduced knee pain and increased knee flexion and walking distance compared to placebo [18]. In another study conducted by Sontakke et al., *Boswellia serrata* extract with the dose of 333 mg thrice daily resulted in significant reduction of pain, stiffness, and difficulty in performing daily activity evaluated by WOMAC [19]. Considering the effectiveness of consumed dose in our study (100 mg), it seems that combining low doses of Boswellia extract with Elaeagnus extract is equally or more effective compared to higher doses alone.

Several mechanisms have been proposed for the observed effects of these extracts. An animal study has shown inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes by aqueous extract of *E. angustifolia* similar to indomethacin [20]. This can explain comparable efficacy of Elaeagnus extract with ibuprofen, a nonselective inhibitor of COX-1 and COX-2, in our study. Also, it has been suggested that Elaeagnus extract can slow down the production of free radicals found in OA tissues, since the extract has anti-oxidant activity [21, 22] due to its flavonoid component [9, 23]. Also, as shown by Nikniaz et al. in females with knee OA, *E. angustifolia* fruit can reduce inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and matrix metalloproteinase-1 (MMP-1) and enhance anti-inflammatory cytokine interleukin-10 (IL-10) [24]. On the other hand, anti-inflammatory effects of Boswellia due to its content of boswellic acid derivatives have been shown in several studies [19, 25–28] possibly contributing to its beneficial effects in OA.

In conclusion, consumption of *E. angustifolia* fruit extract either alone or in combination with Boswellia oleo-gum resin extract could decrease pain and improve function in patients with knee osteoarthritis comparable to ibuprofen.

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Compliance with ethical standards

Disclosures None.

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