

Evaluation of the effectiveness of topical oily lotion containing frankincense extract in the treatment of knee osteoarthritis: a randomized, double-blind, placebo controlled clinical trial

Afsaneh Mohsenzadeh

Isfahan University of Medical Sciences

Mansoor Karimifar

Isfahan University of Medical Sciences

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

Isfahan University of Medical Sciences <https://orcid.org/0000-0001-9301-4732>

Valiollah Hajhashemi

Isfahan University of Medical Sciences

Research Article

Keywords: Knee Osteoarthritis, Boswellia serrata, Boswellic acid, Clinical trial

Posted Date: March 30th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1403577/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Research Notes on March 4th, 2023. See the published version at <https://doi.org/10.1186/s13104-023-06291-5>.

Abstract

Objective: Pharmacological treatments of osteoarthritis have several side effects. *Boswellia serrata* resin (frankincense) is rich in boswellic acids that have antioxidant and anti-inflammatory effects; though, their oral bioavailability is low. The aim of this study was evaluation of the clinical effectiveness of frankincense extract in the treatment of knee OA. In a randomized double-blind placebo-controlled clinical trial, eligible patients with knee OA were randomly divided into two groups of drug (33 patients) and control (37 patients), to use oily lotion of frankincense extract or placebo, respectively, on the involved knee three times daily for four weeks. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), VAS (visual analogue scale; for pain severity), and PGA (patient global assessment) scores were determined before and after intervention.

Results: For all evaluated outcome variables, there was a significant decrease from baseline in both groups ($P < 0.001$ for all). Furthermore, the end-of-intervention values for all parameters were significantly lower in drug group than placebo group ($P < 0.001$ for all), showing more effectiveness of drug compared to placebo. Topical oily lotion containing enriched extract of boswellic acids could decrease pain severity and improve the function in patients with knee OA.

Trial Registration

Trial registration number: IRCT20150721023282N14

Trial registration date: September 20, 2020

Introduction

Osteoarthritis (OA) is one of the most common degenerative and articular disorders causing negative impacts on the quality of patient's life [1, 2]. Synovial inflammation, ligaments destruction and limitation of joint ambulation occur in OA [3, 4]. The prevalence of this disease in women outweigh men between adults aged over 60 years old [5], so that it increases up to 40% in patients aged 70 years and older [6]. So, age has an important role in OA incidence as well as obesity, genetics, history of knee trauma and female gender [7].

Compared to other kinds, knee OA is the most common, involving about 85% of cases [5, 6]. The patients may experience pain and instability of joint, morning stiffness, crepitus, and reduction of daily physical activity [8]. Exercise, weight loss, and patient's education are the mainstay of OA treatment [9]. The suggested pharmacotherapy for OA based on the guidelines consists of acetaminophen, NSAIDs (non-steroidal anti-inflammatory drugs), opioids, and intra-articular injection of glucocorticoids and hyaluronic acid. Although these drugs can improve quality of patient's life and performance, knee pain and joint stiffness remain in some patients [10]. On the other hand, many adverse effects have been observed with some of the mentioned drugs, including renal and cardiovascular complications and gastrointestinal bleeding related to NSAIDs consumption [4].

Boswellia serrata is a plant from family Burseraceae with anti-inflammatory and antioxidant effects [2]. The extract of frankincense (the hardened gum-like resin obtained from *Boswellia* and also known as “Kondor” in Iran) is rich in boswellic acids, specially 3-O-acetyl-11-keto- β -boswellic acid (AKBA), which can inhibit 5-lipoxygenase enzyme as well as NF- κ B (nuclear factor kappa B) and TNF- α (tumor necrosis factor α) in many inflammatory pathways [11, 12]. Due to these effects, some *in-vivo* and clinical studies have shown that oral consumption of boswellia extract can reduce pain, swelling, and stiffness of joint in OA compared to standard treatment. However, poor absorption in aqueous intestinal environment and high first pass metabolism result in low bioavailability of boswellic acids during oral consumption[13]. Besides, in chronic inflammatory diseases, patients are usually more compliant for using topical treatments as an easier way with less side effects and drug interactions [14]. On the contrary, there is no study to show the effects of topical *Boswellia* extract on knee OA. So, this study aimed to evaluate the potential effectiveness of topical extract of *B. serrata* in relieving the symptoms in patients with knee OA.

Materials And Methods

This was a randomized, double-blind, placebo-controlled clinical trial performed in Rheumatology Clinic of Al-Zahra hospital of Isfahan, Iran, affiliated to Isfahan University of Medical Sciences (IUMS), from October 2020 to April 2021. The study was registered in Iranian Registry of Clinical Trials (IRCT) with the record number of IRCT20150721023282N14.

Preparation of oily lotions. Topical formulation of frankincense extract was prepared by Fardis pharmaceutical company, Isfahan, Iran. For preparing 100 ml of *Boswellia* lotion, 1 g of dried extract of frankincense was added to 20 ml of black seed oil, then reached to the volume with olive oil. The placebo lotion was prepared just with 20 ml of black seed oil and 80 ml of olive oil. Both types of lotion were similarly packaged in pharmaceutical tubes and labeled and a numeric code was recorded on each tube by the company.

Patient selection. Patients were selected from those referring to rheumatology clinic of Al-Zahra hospital, based on the following inclusion criteria: (1) age of 40–80 years, (2) OA of at least one knee for at least 3 months based on the diagnostic criteria of American College of Rheumatology (ACR), (3) pain score > 4 based on Visual Analogue Scale (VAS), and (4) grade 2 or 3 of Kellgren-Lawrence scale in knee radiography within the past 3 month.

The patients' exclusion criteria were: (1) use of intra-articular glucocorticoids within the past 3 months, (2) use of intra-articular sodium hyaluronate within the past 6 months, (3) use of systemic glucocorticoids (either oral or parenteral) within the past 14 days, (4) concurrent other osteoarticular disorders (e.g., rheumatoid arthritis and gout), (5) any skin disorder in the knee region, (6) any allergic reaction to the prescribed topical preparation, (7) knee arthroscopy within the past 3 months, (8) illiteracy, (9) inability to answer the questions, and (13) pregnancy or lactation (for women).

Clinical study and interventions. All included participants filled a written informed consent form. Before any intervention, the pain severity based on VAS (0 to 10 scale), and the scores of WOMAC (Western

Ontario and McMaster Universities Osteoarthritis Index) and PGA (patient global assessment) were determined and recorded for the patients according to the symptoms experienced within the past 48 hours. WOMAC index consists of three subscales including pain (5 questions), the flexibility of knee joint (2 questions), and the function or daily activities (17 questions) that a score range of every question presents the severity of the symptom. The total score of WOMAC ranges from 0 to 68, as the best and worst state for knee osteoarthritis, respectively. The Persian form of WOMAC used in this study, has been validated previously by *Nadrian et al* [15]. PGA is a visual measurement scale in the form of a colored band that ranges from white zone/point 0 (without any symptoms) to black zone/point 4 (the worst symptoms) and it was marked based on patient self-assessment. The tubes containing drug or placebo were equally and randomly given to eligible patients with the code being written on the data collection forms. Patients were asked to apply the lotion on the involved knee, three times daily for 4 weeks. Also, acetaminophen 500 mg three times a day was prescribed for all patients, as a standard treatment for OA. Furthermore, the patients were asked not to use any other drug/supplement for OA, including glucosamine, chondroitin, herbal medicines, and topical preparations during the study period. The patients were instructed to record regular use of the lotion and report any side effect during the study. As the tubes of drug and placebo lotions were fully similar, the prescribing physician (rheumatologist), the data collector, and the data analyst were all blinded to the type of intervention (drug vs. placebo) for each patient. At the end of the study, VAS, WOMAC, and PGA scores were recorded again for all patients.

The primary outcome measures were the changes of VAS, WOMAC, and PGA scores at the end of study. The secondary outcome variable was the rate of possible side effects based on the report of the patients.

Sample size calculation. The following equation was used for sample size calculation:

$$n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times 2\delta^2 / (\mu_1 - \mu_2)^2$$

Where n is the required sample size in each group; μ_1 and μ_2 are the mean of the variable in the first and second groups, respectively, according to the previous studies; δ is the standard deviation (SD); $Z_{1-\alpha/2}$ is the standard normal z-value for a significance level $\alpha = 0.05$, which is 1.96, and $Z_{1-\beta}$ is the standard normal z-value for the power of 80%, which is 0.84. According to the μ and δ values for pain scores (in WOMAC) in a previous report [16], a calculated sample size of at least 25 patients was considered for each group.

Statistical analysis. Data analysis was performed by SPSS 24.0 software (SPSS Inc., Chicago, IL, USA). Qualitative variables were compared by Chi square (χ^2) test and Fishers' exact test between the two groups. Kolmogorov–Smirnov test was used to determine distribution pattern of quantitative data. The normally and non-normally distributed data were presented as mean (SD) and median [IQR], respectively. Wilcoxon Signed Rank test and Mann-Whitney U test were applied for comparison of values at the beginning and end of intervention within each group and between the groups, respectively. P -value < 0.05 was considered as statistically significant.

Results

Patients. During the study, 90 patients who met the inclusion criteria participated in the study. The patients aged between 41 to 77 years and were divided into two groups of drug and placebo. Because of irregular consumption or usage of similar products, 20 patients were excluded from the study. So, 70 patients completed the research including 33 and 37 patients in drug and placebo groups, respectively (Fig. 1). As shown in Table 1, there was no significant difference between the groups regarding baseline demographic and clinical characteristics, including age, gender, comorbidities, and concurrent drugs.

Table 1
Baseline demographic and clinical characteristics of study patients.

Parameter	Drug group (Frankincense) (n = 33)	Control group (n = 37)	<i>P-value</i>
Age (years; mean ± SD)	59.82 ± 9.00	57.32 ± 8.18	0.229
Sex (n)			1.000
Male	4 (12.1%)	4 (10.8%)	
Female	29 (87.9%)	33 (89.2%)	
Duration of OA (month; mean [IQR])	54 [30–87]	36 [12–87]	0.158
Comorbidity (n)			0.469
Diabetes	1 (3.0%)	1 (2.7%)	
Hypertension	2 (6.1%)	4 (10.8%)	
Dyslipidemia	3 (9.1%)	1 (2.7%)	
Hypothyroidism	0 (0.00%)	3 (8.1%)	
Hyperthyroidism	1 (3.0%)	0 (0.00%)	
Migraine	2 (6.1%)	1 (2.7%)	
Hypertension + Dyslipidemia	2 (6.1%)	2 (5.4%)	
Diabetes + Dyslipidemia	1 (3.0%)	1 (2.7%)	
Hypothyroidism + Hypertension	1 (3.0%)	0 (0.00%)	
Hypothyroidism + Diabetes	0 (0.00%)	1 (2.7%)	
Hypothyroidism + Diabetes + Dyslipidemia	0 (0.00%)	2 (5.4%)	
Hypothyroidism + Diabetes + Dyslipidemia + Hypertension	0 (0.00%)	1 (2.7%)	

Parameter	Drug group (Frankincense) (n = 33)	Control group (n = 37)	<i>P-value</i>
Concurrent drugs (n)			0.367
Metformin	0 (0.00%)	1 (2.7%)	
Losartan	1 (3.0%)	1 (2.7%)	
Valsartan	0 (0.00%)	1 (2.7%)	
Aspirin	0 (0.00%)	1 (2.7%)	
Atorvastatin	3 (9.1%)	0 (0.00%)	
Levothyroxine	0 (0.00%)	2 (5.4%)	
Amlodipine	0 (0.00%)	1 (2.7%)	
Metformin + Losartan + Atorvastatin + Pantoprazole + Propranolol	2 (6.1%)	1 (2.7%)	
Losartan + Furosemide + Atorvastatin + Aspirin	1 (3.0%)	0 (0.00%)	
Metformin + Rosuvastatin + Aspirin	1 (3.0%)	0 (0.00%)	
Losartan + Aspirin	1 (3.0%)	1 (2.7%)	
Losartan + Atorvastatin + Aspirin	1 (3.0%)	0 (0.00%)	
Atorvastatin + Aspirin	0 (0.00%)	1 (2.7%)	
Metformin + Glibenclamide	1 (3.0%)	0 (0.00%)	
Losartan + Atorvastatin	0 (0.00%)	2 (5.4%)	
Metformin + Atorvastatin + Levothyroxine	0 (0.00%)	1 (2.7%)	

Efficacy evaluation. As shown in Table 2, for all evaluated outcome variables (total WOMAC score as well as its subscales, VAS score, and PGA score), there was a significant decrease from baseline in both groups ($P < 0.001$ for all). Furthermore, in contrast to the baseline values, the end-of-intervention values for all parameters were significantly lower in drug group than placebo group ($P < 0.001$ for all), showing more effectiveness of drug compared to placebo.

Table 2

Pre- and post-intervention values of parameters and their comparison between the two groups.

Parameters	Time	Group		<i>P</i> value
		Drug (Frankincense)	Placebo	
Pain severity	Baseline (week 0)	16 [13–18]	15 [10–19]	0.958 _a
	End (week 4)	4 [2-7.5]	8 [4-17.5]	0.014 _a
	<i>P</i> -value	< 0.001 _c <0.001 _c		
Flexibility	Baseline (week 0)	6 [4–7]	6 [4–8]	0.356 _a
	End (week 4)	2 [0–2]	4 [1.5-6]	0.001 _a
	<i>P</i> -value	< 0.001 _c <0.001 _c		
Function	Baseline (week 0)	46.54 ± 11.24	47.68 ± 11.55	0.68 _b
	End (week 4)	22.30 ± 15.48	36.00 ± 18.40	0.001 _b
	<i>P</i> -value	< 0.001 _d <0.001 _d		
Total score of WOMAC	Baseline (week 0)	67 [58–79]	70 [54-83.5]	0.646 _a
	End (week 4)	24 [15-36.5]	52 [25–74]	0.002 _a
	<i>P</i> -value	< 0.001 _c <0.001 _c		
VAS score	Baseline (week 0)	9 [7–10]	9 [8-9.5]	0.804 _a
	End (week 4)	4 [2.5-5]	6 [3.5-9]	0.005 _a
	<i>P</i> -value	< 0.001 _c <0.001 _c		
PGA score	Baseline (week 0)	3 [2.5-4]	3.5 [3–4]	0.918 _a
	End (week 4)	1.8 [1-2.5]	3 [1.9–3.5]	0.004 _a
	<i>P</i> -value	< 0.001 _c <0.001 _c		
<p>WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; VAS, visual analogue scale; PGA, patient global assessment.</p> <p>a. Mann-Whithney U test</p> <p>b. Independent Samples T-test</p> <p>c. Wilcoxon Signed Rank test</p> <p>d. Paired Sample T-test</p>				

Side effects. During the study, only one person in placebo group complained of itching and redness at the application site at the first days of usage; so, she was excluded from the research. No other patient reported any adverse effect during the intervention.

Discussion

In this study, the application of topical lotion of Frankincense extract could decrease pain severity and stiffness of knee and improve the patients' daily activity.

To the best of our knowledge, this is the first work evaluating *Boswellia* extract as a topical form in OA patients. Previously, several animal and human studies have shown the beneficial effects of this plant in arthritis.

An animal study demonstrated that boswellic acid could significantly suppress the increased level of lysosomal β -glucuronidase and lactate dehydrogenase enzyme releasing from neutrophils and also decreased TNF- α level in gouty arthritic mice [17].

Several clinical trials showed the effectiveness of *B. serrata* on OA. In the study of Kimmatkar et al., the effects of this plant in the reduction of pain, improvement of patients' function, and increase of walking distance and the ability of climbing the stairs were demonstrated [18]. In the study of Majeed et al., the oral use of *B. serrata* extract by OA patients could significantly decrease WOMAC and VAS score compared to placebo at the end of 4th month and also improved articular cartilage destruction based on radiography assessment[19]. However, the results of our four-week trial showed the positive effects of the extract even at a shorter duration. Similar results have been obtained in other trials of *B. serrata* extract in OA patients [20–27] which are consistent with ours. Of note, all of these works have evaluated oral form of the extract, while we applied the topical form. Therefore, it seems that topical use of frankincense extract is capable of improving OA in terms of pain severity, function, and joint flexibility, as well as patients' quality of life (as determined by PGA score).

The biological effects of *Boswellia* are mainly related to boswellic acids, of which AKBA is the most important one. This compound demonstrates anti-inflammatory and anticancer effects by selective and non-competitive inhibition of 5-lipoxygenase in the pathway of leukotriene biosynthesis [11, 22, 25] and suppressing of expression and activity of matrix 3, 10 and 12 metalloproteinases in human capillary endothelial cells [28]. Also, AKBA could inhibit the activation of transcription factor NF- κ B and TNF- α production in many inflammatory responses [12, 29, 30]. Neither animal studies nor clinical trials have demonstrated toxic manifestations due to *Boswellia* extract consumption [31, 32].

Conclusions

In conclusion, topical oily lotion containing enriched extract of boswellic acids could decrease pain severity and improve the function in patients with knee OA.

Limitations

The main limitations of our study were small sample size due to the occurrence of COVID-19 pandemic and short duration of intervention. Also, due to topical consumption of the preparations, it is possible that the patients have taken various amounts of drug and placebo. However, as the first clinical study showing the positive effects of topical frankincense in OA patients, this work could be a basis for future larger trials to introduce an effective and safe herbal treatment for these patients.

Abbreviations

OA: Osteoarthritis; NSAIDs: Non-steroidal anti-inflammatory drugs; AKBA: 3-O-acetyl-11-keto- β -boswellic acid; NF- κ B: Nuclear factor kappa B; TNF- α : Tumor necrosis factor α ; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PGA: Patient global assessment

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Isfahan university of medical science with ethics code IR.MUI.RESEARCH.REC.1399.2.33. All participants have given their written consent to participate in the study and for the publication of results.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

There is no conflict of interest.

Funding

This study was financially supported by Fardis pharmaceutical company with Grant No. 399127 From Isfahan University of Medical Sciences.

Authors' contributions

RS gave the study idea and designed it, performed the statistical analysis, and corrected the drafted manuscript. AM collected the data, followed the patients regarding the outcome measures, and drafted the manuscript. MK selected the eligible patients according to the inclusion criteria and followed them regarding the outcome measures. VH performed the statistical analysis and prepared drug and placebo preparations.

Acknowledgments

We would like to acknowledge the staff of Fardis company and Rheumatology Clinic of Al-Zahra hospital for their assistance.

References

1. Kan HS, Chan PK, Chiu KY, Yan CH, Yeung SS, Ng YL, et al. Non-surgical treatment of knee osteoarthritis. *Hong Kong Med J*. 2019. doi:10.12809/hkmj187600.
2. Umar S, Umar K, Sarwar AH, Khan A, Ahmad N, Ahmad S, et al. *Boswellia serrata* extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis. *Phytomedicine*. 2014. doi:10.1016/j.phymed.2014.02.001.
3. Sumantran VN, Joshi AK, Boddul S, Koppikar SJ, Warude D, Patwardhan B, et al. Antiarthritic activity of a standardized, multiherbal, Ayurvedic formulation containing *Boswellia serrata*: in vitro studies on knee cartilage from osteoarthritis patients. *Phytother Res*. 2011. doi:10.1002/ptr.3365.
4. D'Arcy Y, Mantyh P, Yaksh T, Donevan S, Hall J, Sadrarhami M, et al. Treating osteoarthritis pain: mechanisms of action of acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, and nerve growth factor antibodies. *Postgrad Med*. 2021. doi:10.1080/00325481.2021.1949199.
5. Primorac D, Molnar V, Rod E, Jelec Z, Cukelj F, Maticic V, et al. Knee osteoarthritis: a review of pathogenesis and state-of-the-art non-operative therapeutic considerations. *Genes (Basel)*. 2020. doi:10.3390/genes11080854.
6. Michael JW, Schluter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl Int*. 2010. doi:10.3238/arztebl.2010.0152.
7. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med*. 2018. doi:10.1136/bjsports-2016-097333.
8. Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. *Braz J Phys Ther*. 2021. doi:10.1016/j.bjpt.2020.08.004.
9. Cao P, Li Y, Tang Y, Ding C, Hunter DJ. Pharmacotherapy for knee osteoarthritis: current and emerging therapies. *Expert Opin Pharmacother*. 2020. doi:10.1080/14656566.2020.1732924.
10. Wu Y, Goh EL, Wang D, Ma S. Novel treatments for osteoarthritis: an update. *Open Access Rheumatol*. 2018. doi:10.2147/OARRR.S176666.
11. Houssen ME, Ragab A, Mesbah A, El-Samanoudy AZ, Othman G, Moustafa AF, et al. Natural anti-inflammatory products and leukotriene inhibitors as complementary therapy for bronchial asthma.

- Clin Biochem. 2010. doi:10.1016/j.clinbiochem.2010.04.061.
12. Ammon HP. Modulation of the immune system by *Boswellia serrata* extracts and boswellic acids. *Phytomedicine*. 2010. doi:10.1016/j.phymed.2010.03.003.
 13. Arden NK, Perry TA, Bannuru RR, Bruyere O, Cooper C, Haugen IK, et al. Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines. *Nat Rev Rheumatol*. 2021. doi:10.1038/s41584-020-00523-9.
 14. Meng Z, Huang R. Topical treatment of degenerative knee osteoarthritis. *Am J Med Sci*. 2018. doi:10.1016/j.amjms.2017.06.006.
 15. Nadrian H, Moghimi N, Nadrian E, Moradzadeh R, Bahmanpour K, Iranpour A, et al. Validity and reliability of the persian versions of WOMAC osteoarthritis index and Lequesne Algofunctional Index. *Clin Rheumatol*. 2012. doi:10.1007/s10067-012-1983-7.
 16. Jabbari M, Hashempur MH, Razavi SZ, Shahraki HR, Kamalinejad M, Emtiazy M. Efficacy and short-term safety of topical Dwarf Elder (*Sambucus ebulus* L.) versus diclofenac for knee osteoarthritis: A randomized, double-blind, active-controlled trial. *J Ethnopharmacol*. 2016. doi:10.1016/j.jep.2016.04.035.
 17. Sabina EP, Indu H, Rasool M. Efficacy of boswellic acid on lysosomal acid hydrolases, lipid peroxidation and anti-oxidant status in gouty arthritic mice. *Asian Pac J Trop Biomed*. 2012. doi:10.1016/S2221-1691(11)60206-2.
 18. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. *Phytomedicine*. 2003. doi:10.1078/094471103321648593.
 19. Majeed M, Majeed S, Narayanan NK, Nagabhushanam K. A pilot, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of a novel *Boswellia serrata* extract in the management of osteoarthritis of the knee. *Phytother Res*. 2019. doi:10.1002/ptr.6338.
 20. Notarnicola A, Maccagnano G, Moretti L, Pesce V, Tafuri S, Fiore A, et al. Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: Randomized trial. *Int J Immunopathol Pharmacol*. 2016. doi:10.1177/0394632015622215.
 21. Notarnicola A, Tafuri S, Fusaro L, Moretti L, Pesce V, Moretti B. The "MESACA" study: methylsulfonylmethane and boswellic acids in the treatment of gonarthrosis. *Adv Ther*. 2011. doi:10.1007/s12325-011-0068-3.
 22. Kizhakkedath R. Clinical evaluation of a formulation containing *Curcuma longa* and *Boswellia serrata* extracts in the management of knee osteoarthritis. *Mol Med Rep*. 2013. doi:10.3892/mmr.2013.1661.
 23. Haroyan A, Mukuchyan V, Mkrtchyan N, Minasyan N, Gasparyan S, Sargsyan A, et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med*. 2018. doi:10.1186/s12906-017-2062-z.

24. Vishal AA, Mishra A, Raychaudhuri SP. A double blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. *Int J Med Sci*. 2011. doi:10.7150/ijms.8.615.
25. Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, et al. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. *Arthritis Res Ther*. 2008. doi:10.1186/ar2461.
26. Sengupta K, Krishnaraju AV, Vishal AA, Mishra A, Trimurtulu G, Sarma KV, et al. Comparative efficacy and tolerability of 5-Loxin and Aflapin against osteoarthritis of the knee: a double blind, randomized, placebo controlled clinical study. *Int J Med Sci*. 2010. doi:10.7150/ijms.7.366.
27. Karimifar M, Soltani R, Hajhashemi V, Sarrafchi S. 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. *Clin Rheumatol*. 2017. doi:10.1007/s10067-017-3603-z.
28. Abdel-Tawab M, Werz O, Schubert-Zsilavec M. *Boswellia serrata*: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet*. 2011. doi:10.2165/11586800-000000000-00000.
29. Ammon HP. Modulation of the immune system by *Boswellia serrata* extracts and boswellic acids. *Phytomedicine*. 2010. doi:10.1016/j.phymed.2010.03.003.
30. Miscioscia E, Shmalberg J, Scott KC. Measurement of 3-acetyl-11-keto-beta-boswellic acid and 11-keto-beta-boswellic acid in *Boswellia serrata* supplements administered to dogs. *BMC Vet Res*. 2019. doi:10.1186/s12917-019-2021-7.
31. Abdel-Tawab M, Werz O, Schubert-Zsilavec M. *Boswellia serrata*: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet*. 2011. doi:10.2165/11586800-000000000-00000.
32. Alluri VK, Dodda S, Kilari EK, Golakoti T, Sengupta K. Toxicological assessment of a standardized *Boswellia serrata* gum resin extract. *Int J Toxicol*. 2019. doi:10.1177/1091581819858069.

Figures

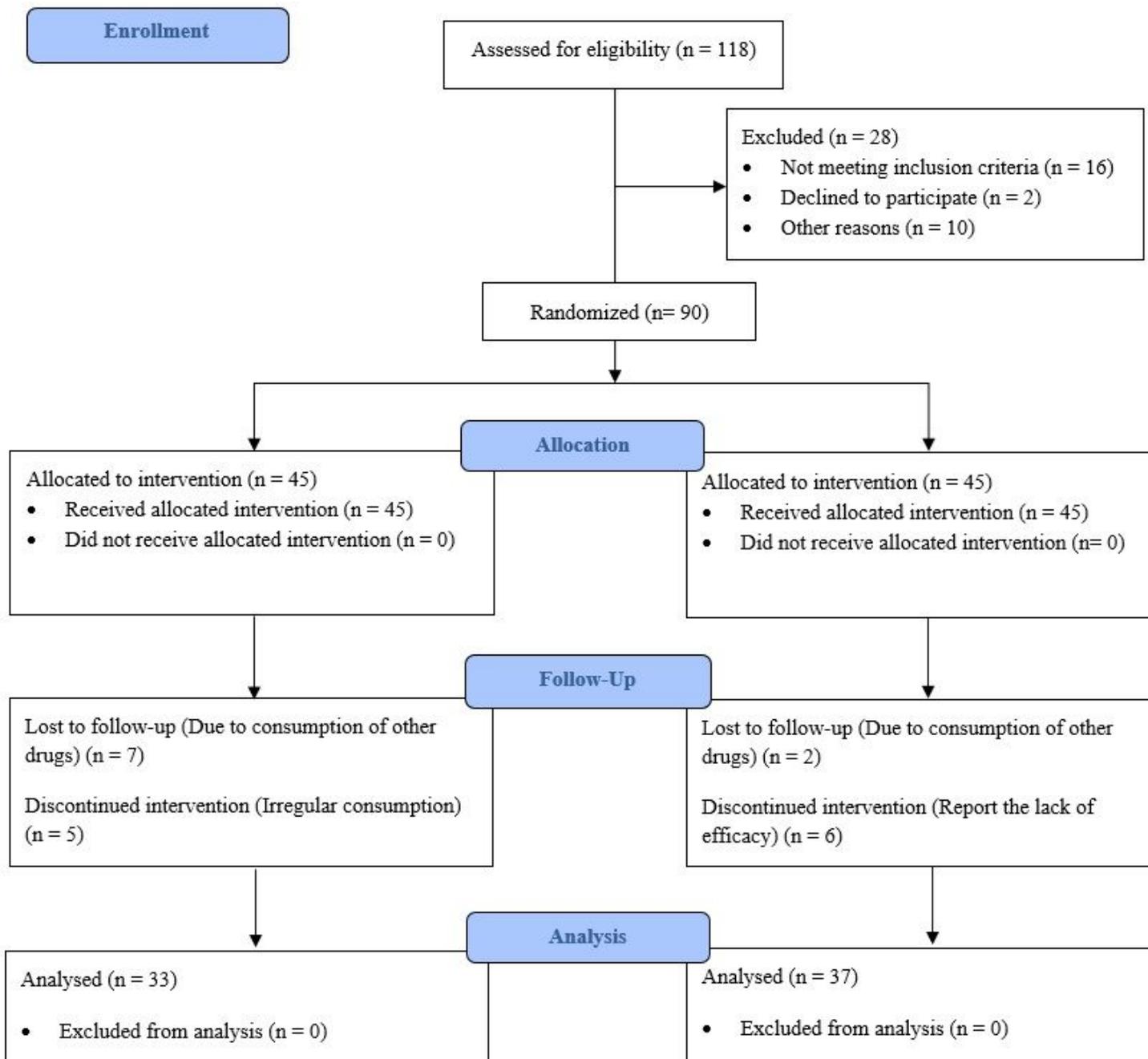


Figure 1

Flow chart of enrollment and allocation of participants and study design

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORT2010Checklist.doc](#)