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Original Research Article

Efficacy of an herbal formulation of Persian Medicine, "*Dava-e Balgham*", on knee osteoarthritis symptoms: A prospective, randomized, double-blind, placebo-controlled clinical trial

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Abstract

Objective: Knee osteoarthritis (KOA) is the most prevalent debilitating joint disorder worldwide, with limited effective and treatment options. Traditional medicines may help discover more effective and safer pharmacological treatments. This study was designed to evaluate the efficacy and safety of "*Dava-e Balgham*" (DB), a Persian Medicine (PM) herbal formula, in KOA patients.

Materials and Methods: The present trial was conducted in Shariati Hospital, Tehran, Iran, from August 2020 to June 2022. A total of 110 patients with KOA were randomly allocated to intervention or placebo (toast powder) groups. The intervention group received the *Dava-e Balgham* capsule three times daily for 8 weeks. Capsules were filled with powders of *Nigella sativa*, *Trachyspermum ammi*, *Zataria multiflora*, and *Pistacia atlantica* oleoresin. Participants were followed up to 16 weeks. The primary outcome was the severity of knee pain, while other OA symptoms, activity, sport, and quality of life were considered secondary outcomes.

Results: A total of 110 patients were enrolled, of whom, 99 completed the trial (mean age: 58 ±9.8 years). The DB formulation significantly improved KOA symptoms compared to the placebo. For the primary outcome, the between-group mean difference in KOOS Pain score change from baseline to week 8 was 15.06 points. The corresponding between-group mean differences in score change for other symptoms, activities of daily living, sport/recreation, and quality of life were 12.34, 13.66, 12.46, and 14.42 points, respectively. No considerable treatment-related adverse effects were reported.

Conclusion: The present study supports the use of the PM formula, DB, as an adjuvant treatment for KOA.

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Introduction

Knee osteoarthritis (KOA) is a chronic degenerative whole-joint disease affecting ~23% of adults ≥40 years worldwide and is a major contributor to pain, disability, and reduced quality of life. Its multifactorial pathogenesis involves interacting processes progressive hyaline cartilage loss, synovial inflammation, subchondral bone remodeling/sclerosis, ligamentous changes, and osteophyte formation within an imbalanced anabolic-catabolic joint status (Dainese et al. 2022)

Inflammation plays a pivotal role in OA progression by inducing early release of cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which activate nuclear factor κB (NF-κB), phosphatidylinositol-3 kinase (PI3K), and mitogen-activated protein kinase (MAPK) signaling pathways. These cascades upregulate inflammatory mediators and matrix-degrading enzymes (e.g., Matrix metalloproteinase-13 [MMP-13]), impair the synthesis of type II collagen and aggrecan, and disrupt cartilage homeostasis. Targeting these pathways offers disease-modifying therapeutic options, as current treatments remain largely symptomatic (Chow and Chin 2020).

Osteoarthritis (OA) has no curative treatment, and current management focuses on symptom relief. Non-steroidal anti-inflammatory drugs (NSAIDs) pose gastrointestinal, cardiovascular, and renal risks and may hinder cartilage matrix synthesis (Guan et al. 2019). Age-related pharmacokinetic changes reduce drug efficacy in older adults (Ribeiro et al. 2022), while surgical options are limited by complications and prosthesis longevity, driving interest in safer, biologically targeted complementary therapies (Organization 2013; Walker et al. 2019).

Persian Medicine (PM) as a holistic medical system emphasizes treating underlying causes and highlights functional relationships among organs, particularly the gastrointestinal tract (GIT), whose health is viewed as foundational to systemic well-being (Pasalar 2021; Pasalar et al. 2014; Shirzad et al. 2013)**.** Avicenna specifically linked GIT function to the prevention and treatment of joint disease, a view resonant with the modern gut–joint axis concept (Gleason et al. 2022; Ibn-e-sina 2005)

"*Dava-e-Balgham*" (DB) is a PM herbal formulation used to support digestion, reduce flatulence, and tonify the stomach and liver. It combines powdered seeds of *Nigella sativa L* (*N.sativa*) and *Trachyspermum ammi (L.) Sprague* (*T. ammi*), leaves of *Zataria multiflora Boiss* (*Z. multiflora*), and oleoresin of *Pistacia atlantica* Desf. (*P. atlantica*), and is cited in standard PM texts such as *Makhzan al-Advia*. (Asif et al. 2014).

Nigella sativa L. *(*Black seed*),* the Ranunculaceae family, contains thymoquinone and other bioactives compounds such as p cymene, camphene, thymol(Ghamari et al. 2023) with anti-inflammatory, antioxidant, analgesic, and chondroprotective effects(Ahmad et al. 2013; Gholamnezhad et al. 2016); preclinical and clinical studies indicate that *N. sativa* may offer therapeutic benefits in osteoarthritis (OA), demonstrated efficacy and a favorable safety profile with oral lethal dose 50 (LD_{50}) >2.4 g/kg in mice) (Bamosa 2018; Yimer et al. 2019)

Zataria multiflora Boiss. (Shirazi thyme), a thymol and carvacrol rich Lamiaceae herb (Saei-Dehkordi et al. 2010), exhibits antioxidant and anti-inflammatory effects (Khazdair et al. 2018) mainly through suppression of pro-inflammatory cytokines and enzymes. primarily mediated by thymol and carvacrol (Nazari et al. 2018)). It also shows a high safety margin, with an oral LD_{50} above 5 g/kg in mice (Mandegary et al. 2013).

Trachyspermum ammi (*Ajowan,*), a member of the Apiaceae family, provides thymol, carvacrol, p-cymene, and γ-terpinene; traditionally used for digestive disorders (Paul et al. 2011) it has shown potent anti-inflammatory, analgesic

properties comparable to morphine in experimental models(Al-Khazraji 2018; Umar et al. 2012), mainly attributed to terpenes, flavonoids, and sterols that suppress prostaglandin synthesis (Dutta et al. 2021). Toxicological evidence confirms its wide safety range (oral LD50 >3 g/kg in rat (Saraswat et al. 2021).

Pistacia atlantica oleoresin (*Saghez*), belonging to the Anacardiaceae family, has long been used for digestive and musculoskeletal disorders (Mahjoub et al. 2018), It contains phenolic acids, flavonoids, terpenoids, α-pinene, fatty acids, and sterols that exert antioxidant and anti-inflammatory effects through free-radical scavenging and modulation of nuclear factor kappa B (NF-κB), cyclooxygenase (COX), and lipoxygenase (LOX) signaling pathways (Achili et al. 2020; Rahman 2018). Preclinical and clinical studies have demonstrated reduced cartilage inflammation, enhanced tissue repair and improvements in alone or with stem cell approaches pain and stiffness in Knee OA (Khamevar et al. 2021; Tanideh et al. 2021), Moreover, the resin shows good tolerability and safety up to 5 g/kg in rats) without any adverse physiological effects(Al-Qaisi et al. 2025) .

Previous clinical trials with DB in metabolic disorders reported improvements in anthropometric and metabolic measures (weight, waist circumference, alanine aminotransferase (ALT), cholesterol, low-density lipoprotein (LDL), and fasting glucose) without adverse effects, and DB has been used clinically in metabolic management (Ardekani et al. 2011; Emtiazy et al. 2012; Hamidnia et al. 2018; Hormati et al. 2019; Tooiserkany et al. 2020). However, its oral efficacy in OA has not been evaluated. Building on the PM concept that digestive imbalance can contribute to joint disease (Tooiserkany et al. 2020), emerging evidence for the gut–joint axis(Gleason et al. 2022) and the anti-inflammatory/analgesic properties of DB constituents, we designed the present study to assess the safety and clinical effectiveness of DB for reducing pain and disability in patients with KOA.

Materials and Methods

Study design

This randomized controlled trial was conducted at the Rheumatology Clinic of Shariati Hospital, Tehran, Iran, affiliated with Tehran University of Medical Sciences (TUMS), from August 2020 to June 2022. The study protocol was approved by the Research and Development Committee and the Medical Ethics Committee of TUMS (reference number: IR.TUMS.VCR.REC.1398.600. The trial was registered at the Iranian Registry of Clinical Trials: IRCT20190807044470N1.

Participants and sampling method

Eligible participants were male and female patients aged ≥40 years (No upper age limit), with clinically diagnosed knee osteoarthritis (KOA), and without serious concomitant diseases (e.g., hypertension, cardiovascular, renal, or hepatic conditions). Diagnosis was based on American College of Rheumatology (ACR) clinical criteria (Kolasinski et al. 2020) and an average pain score of ≥40 mm on a 100-mm visual analogue scale (VAS) in the past month, confirmed by a rheumatologist.

Patients were consecutively recruited during routine clinical visits using convenience sampling, followed by random allocation. All eligible patients, were screened irrespective of visit days or times to minimize selection bias and ensure a representative sample. Exclusion criteria included pregnancy, lactation, substance abuse, allergy to the formulation components, other rheumatic or joint diseases, vascular or neurological disorders of lower limbs, recent surgery or intra-articular treatments (within 6 months), corticosteroid or anticoagulant therapy in the past 3 months, creatinine >1 mg/dl or any conditions necessitating intervention discontinuation by physician judgment. Additionally, Patients classified as having a

hot-dry temperament according to Persian medicine (Mizaj) and identified as sensitive to Dava-e-Balgham's side effects were excluded, as determined using a validated questionnaire (Mahboubi 2018; Salmannezhad et al. 2018; Zarshenas et al. 2013).

Eligible participants received a full explanation of the study procedures and provided written informed consent; they were free to withdraw at any time.

Intervention

Participants were screened through physical examination and knee radiography and received oral and written information about the study and potential side effects before providing written informed consent. Following a 2-week washout period during which, all analgesics were discontinued, eligible participants were randomly assigned to either the DB or placebo group.

The intervention group received DB capsules (one capsule three times daily, after each meal) for 8 weeks. The control group received placebo capsules containing toast powder, identical in appearance and administered on the same schedule. All participants were monitored weekly for 16 weeks, including an 8-week post-treatment follow-up period. Participants in the placebo group were assured they would receive the active treatment after trial completion.

Study medications (active, placebo, and acetaminophen as rescue medication) were dispensed by an independent assistant in identically labeled containers to maintain blinding. Allocation codes were securely documented and concealed until study completion.

Adherence was monitored using patient diaries, capsule counts, and weekly telephone reminders. Participants were instructed to return unused medication at each visit.

Rescue medicine

Considering overall cost, effectiveness, and toxicity profile, 500 mg acetaminophen tablets (Jameson et al. 2018), were provided as rescue medicine PRN (maximum of 4 g/day) to be used only during the 8-week intervention period and recorded in a patient daily diary. No analgesia was permitted during the follow-up period (weeks 8-16).

Drug and placebo preparation

Material preparation

The herbal product was prepared and standardized in the Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences. *Pistacia atlantica* oleoresin was collected from the Bastak mountains in Hormozgan. Iran. Seeds of *N. sativa*, *T. ammi*, and leaves of *Z. multiflora* were purchased from a reputable herbal store in Tehran, Iran. Scientific identification and registration of the plants were confirmed at the Herbarium Center, School of Pharmacy, TUMS, with voucher codes: *Z.multiflora* (Lamiaceae): PMP 1347, *T. ammi* L. *Sprague* (Apiaceae): PMP 2627, *N. sativa* L. (Ranunculaceae): PMP 1719, and *P. atlantica L.* (Anacardiaceae)*: PMP 1822*

Formulation and standardization

Herbs were cleaned and powdered using a mill. *N. sativa* and *T. ammi* seeds (mesh size: 40) and *Z. multiflora* leaves (mesh size: 35) were dried at room temperature in the dark for 24 hr and then sieved. *P. atlantica* gum was frozen for 24 hr before powdering. All powdered materials were stored in dry, light-protected conditions at 4°C. Capsule No 1 (DB formulation), contained a mixture of *Z. multiflora*, *N. sativa*, and *T. ammi* powders in equal amounts (85 mg each) along with *P. atlantica* gum at 0.7 parts (59.5 mg), based on turpentine content, (in a ratio of 1:1:1:0.7). Powders were filled into size "tall 0" opaque orange gelatin capsules. Capsule No. 2 contained placebo (toast powder derived from refined white bread, low in fiber and resistant starch below the minimal effective dose for prebiotic activity) (Slavin 2013) filled into

identical capsules (126 mg each). Both capsules were stored in identical plastic containers with 42 capsules per container, sealed to ensure similar odor for blinding. The botanical quantities and dosages were selected according to documented therapeutic ranges in Traditional Persian Medicine literature (Aghili Khorasani MH. In: Makhzan-ol-Adviyah [Storehouse of Medicaments]. Shams Ardakani MR). Safety and toxicity were evaluated based on prior clinical studies (Bamosa 2018; Mahmoudvand et al. 2016; Mandegary et al. 2013; Saraswat et al. 2021). All DB capsules were from a single homogeneous production batch to ensure uniformity.

Phytochemical Analysis of Dava-e-Balgham

Essential oil was obtained from the powdered formulation of T. ammi, Z. multiflora, N. sativa, and Pistacia atlantica (0.7 part) by hydrodistillation using a Clevenger-type apparatus for 4 h. The hydrodistillation process yielded approximately 2 mL of essential oil per 100 g of raw material. Volatile constituents were analyzed by GC–MS using to an Agilent 6890 GC coupled with an Agilent 5973N MS equipped with a BPX5 capillary column (30 m × 0.25 mm, 0.25 μm). Helium was used as the carrier gas (0.5 mL/min) with split injection (split ratio 1:35; injection volume 1 μL). The oven temperature was programmed from 23°C (2 min) to 240°C at 3°C/min, then to 300°C at 15°C/min (3 min). Mass spectra were recorded in EI mode (70 eV), ion source temperature 220°C, scan range 40–400 m/z. Compounds were identified by comparing retention indices and mass spectra with Adams, NIST, and Wiley libraries. Total phenolic and flavonoid contents were measured spectrophotometrically at 725 nm and 510 nm, respectively(Haydari et al. 2017; Shamekhi et al. 2017).

Microbial Quality Evaluation of Dava-e-Balgham

The microbial safety of the polyherbal formulation *Dava-e-Balgham* was evaluated according to Iranian Food and Drug Administration (IFDA) guidelines. Total aerobic microbial count (TAMC) and total yeast and mold count (TYMC) were determined using standard plate count methods. The presence of *Escherichia coli* and *Salmonella* spp. was assessed by selective enrichment and biochemical confirmation, following pharmacopeial procedures. Results were expressed as CFU/g and compared with IFDA acceptance limits.: http://www.fda.gov.ir/(Table 1).

Table 1. Microbial quality of *Dava-e-Balgham* formulation (clinical trial batch) according to IFDA criteria.

Microbial test	Acceptance criteria (IFDA)	Result
Total aerobic microbial count (TAMC)	≤ 1×10^5 CFU/g	4×10^4 CFU/g
Total yeast and mold count (TYMC)	≤ 1×10^3 CFU/g	<1×10^3 CFU/g
Bile-tolerant Gram-negative bacteria	≤ 1×10^3 CFU/g	1×10^2 CFU/g
Escherichia coli	Not detected	Not detected
Salmonella spp.	Not detected	Not detected

CFU, colony-forming units; IFDA, Iranian Food and Drug Administration: Not detected in 10 g

Assessments

Participants were evaluated at baseline and at weeks 2, 4, 8, 12, and 16 for symptom changes (adverse events, treatment efficacy, and functional outcomes). The Persian version of the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire (Roos and Lohmander 2003) and a 100-mm Visual Analogue Scale (VAS) were used. The KOOS comprises 42 items across five domains (Pain, Symptoms, Activities of Daily Living, Sports/Recreation, and Quality of Life), scored on a 0–4 Likert scale and transformed to a 0–100 scale, with higher scores indicating better outcomes (fewer symptoms), (Salavati et al. 2008).

The VAS measured pain intensity (0 = no pain, 100 = worst imaginable pain) and satisfaction (0 = completely satisfied, 100 = completely dissatisfied). Clinical evaluations were conducted by a blinded research assistant at all visits. At weeks 2, 8, and 16, a blinded physician performed physical knee examinations and recorded both physician- and patient-reported VAS satisfaction scores.

Medication use, including DB, placebo and acetaminophen, was documented at every visit. Adverse events were actively monitored and recorded throughout the study.

Radiographic assessment

The severity of KOA was graded using the Kellgren and Lawrence (KL) scale, based on tibiofemoral radiographs(Georgiev et al. 2016). The KL grading ranges from Grade 1 (doubtful joint space narrowing [JSN] and osteophyte formation) to Grade 4 (severe JSN, sclerosis, and bony deformity). Doubtful joint space narrowing (JSN) and osteophyte formation; 2) Definite osteophyte formation and possible JSN (< 50%); 3) Moderate JSN (50%), multiple osteophytes, sclerosis and possible bony deformity; and 4) Severe JSN (> 50%), sclerosis and definite bony deformity. All radiographs were independently evaluated by radiologists blinded to group allocation to minimize bias.

Sample size

Sample size was calculated using Stata version 17 and G*Power 3. A primary sample size of 90 (45 per group) was estimated to achieve 80% power, with an effect size of 0.7 and a two-sided significance level of 0.05 for mean differences (Huseini et al. 2022; Salimzadeh et al. 2017). Considering a 20% attrition rate, 110 patients (55 per group) were enrolled.

Randomization and allocation concealment

A total of 110 eligible participants were randomly assigned to two treatment groups using block randomization. Randomization lists were generated using randomly selected block permutation of size four (AABB, ABAB, ABBA, BBAA, BABA, and BAAB), with each block containing two allocations to each group. A total of 27 blocks of four and one block of two were used. The randomization sequence was generated by an independent statistician, not involved in participant recruitment or group assignment, using Randlist software (version 1.0). To account for anticipated attrition, the six possible block permutations were randomly selected to create 30 blocks. The allocation sequence was concealed from both participants and investigators. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes.

Blinding

patients, physicians, radiologists, investigators, outcome assessors and data analysts were masked to treatment allocation and study interventions. Allocation concealment was ensured by dispensing sequentially numbered, opaque, sealed containers prepared and coded by the investigational pharmacy and a blinded study assistant. The active drug and placebo were manufactured as identical hard gelatin capsules to match in size, color, weight, and odor. Capsules were packaged in identical containers, labeled only with participant-specific random codes. Original manufacturer labels were removed before dispensing, and treatment codes were stored in a secure file accessible only to an unblinded pharmacist until database lock. The randomization code was broken only after database lock.

Statistical analysis

Data were analyzed using SPSS software (version 26). Categorical variables were summarized as frequencies and percentages, and continuous variables as mean ± standard deviation (SD) for numerical data. Baseline characteristics between groups were compared using the independent samples t test for continuous variables and the chi-square test for categorical variables.

Within-group changes over time and between-group differences were evaluated using a repeated measure analysis of variance (ANOVA) model. All analyses were conducted according to the intention-to-treat (ITT) principle. A two-tailed p-value of <0.05 was considered statistically significant, and 95% confidence intervals (CI) were reported where applicable.

Results

Composition and standardization of Dava-e Balgham

Gas Chromatography–Mass Spectrometry (GC–MS) analysis identified 21 compounds, accounting for approximately 95% of the total volatile content of DB. The major constituents were thymol (36.95%), carvacrol (18.47%), trans-verbenol (9.91%), myrtenal (7.14%), ortho-cymene (5.74%), and trans-pinocarveol (4.02%), with thymol and carvacrol together accounting for nearly 50% of the total composition (Table 2).

Standardization of the DB preparation was performed based on total phenolic and flavonoid contents. Total phenolic content was 197.62 ± 8.30 mg of thymol equivalent per gram of extract, and total flavonoid content was 271.36 ± 39.95 mg of rutine equivalent per gram of extract. Measurements were carried out using a spectrophotometer at wavelengths of 725 nm (for phenols) and 510 nm (for flavonoids), following established protocols (Haydari et al. 2017; Shamekhi et al. 2017)

Table 2. Chemical composition of volatile oil components of Dava-e Balgham (identified by GC/MS analysis)

No	Compound	Retention Index(min)	Percentage %
1	α-Pinene	11.60	1.92
2	Camphene	12.49	0.16
3	Verbenene	12.72	0.56
4	ortho-Cymene	16.50	5.74
5	1.8-Cineole	16.86	0.17
6	γ-Terpinene	18.19	1.36
7	Linalool	20.41	1.59
8	trans-Pinocarveol	22.65	4.02
9	trans- Verbenol	22.91	9.91
10	Camphor	23.06	0.37
11	trans- pinocamphone	23.69	0.73
12	Terpinen-4-ol	23.61	0.44
13	Cymen-8-ol	25.09	1.68
14	Thuj-3-en-10-al	25.48	0.73
15	Myrtenal	26.14	7.14
16	trans-Carveol	26.58	0.78
17	Thymol,methyl ether	27.28	0.73
18	Carvone	27.87	0.50
19	Isobornyl formate	29.42	0.59
20	Thymol	30.06	36.95
21	Carvacrol	30.42	18.47
	Total Identified		94.54

Study flow

A total of 166 patients with knee osteoarthritis (KOA) were screened for eligibility. Of these, 56 were excluded before to randomization for the following reasons: not meeting inclusion criteria (n = 21), presence of other types of arthritis (n = 4), declined to participate (n = 16), and withdrawal before receiving DB or placebo (n = 15).

After a 2-week washout period, 110 eligible participants (mean age: 58 ± 9.8 years) were randomly allocated to the DB group (n = 55) or the placebo group (n = 55). During the intervention and follow-up period, 11 participants withdrew from the study (reasons are detailed in Figure 1). Participants who withdrew resumed their previous standard treatment.

Ultimately, 48 participants in the DB group and 51 in the placebo group completed the trial and were included in the

analysis. Overall, 86 (86.9%) were women and 13 (13.1%) were men. The CONSORT flow diagram illustrating recruitment, randomization, exclusions, and follow-up is presented in Figure 1.

Convenience sampling was used from the clinic population; no stratified sampling was applied. Although the proportion of women was higher in both groups (91.7% in the DB group and 82.2% in the placebo group), this difference was not statistically significant.

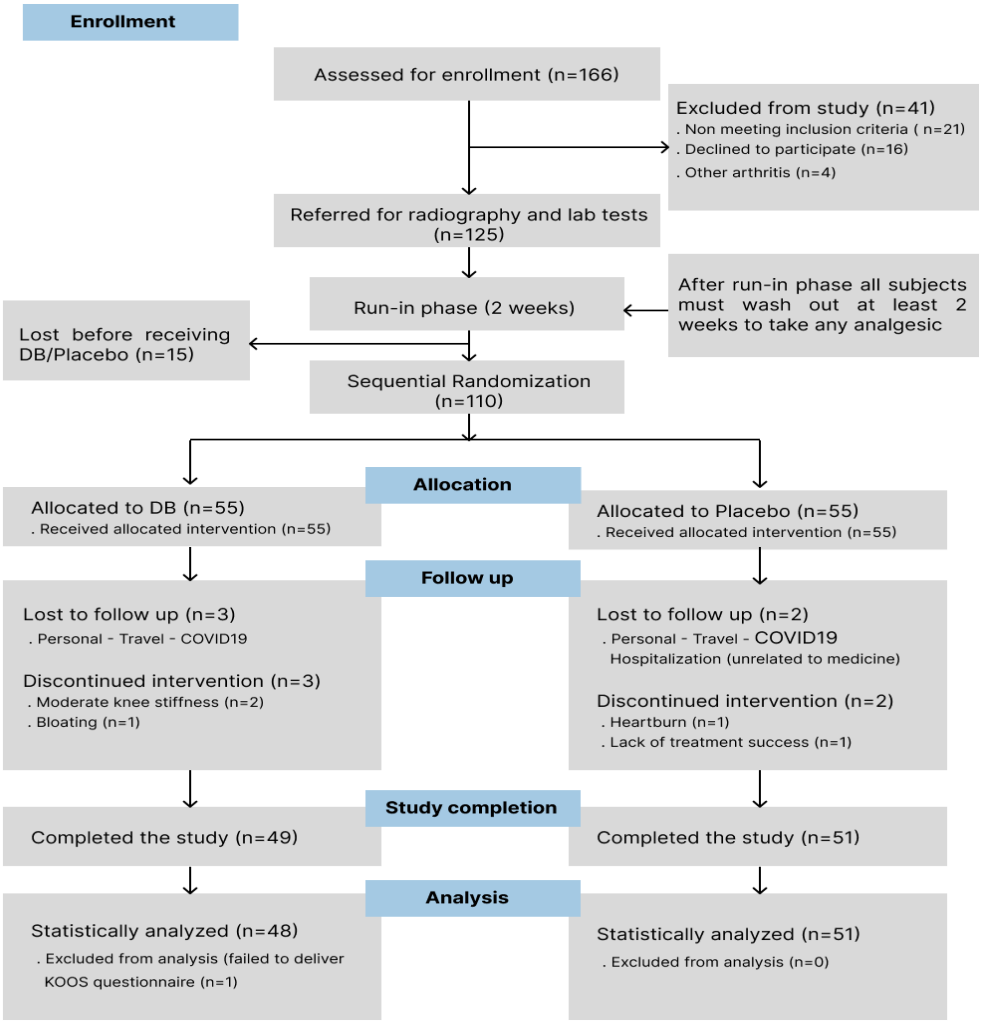

Figure 1. Flow diagram of the study (distribution of participants)

Demographic characteristics and study covariates

Baseline demographic characteristics and study covariates are presnted in Table 3. No statistically significant differences were observed between the DB and placebo groups (p>0.05). regarding age (p = 0.237), sex distribution (p=0.170), BMI (p = 0.880), baseline VAS pain scores (p = 0.137), or KOOS subscales, including Symptoms (p = 0.771), Pain (p = 0.375), Activities of Daily Living (p = 0.262), Sports and Recreation (p = 0.378), and Quality of Life (p = 0.275). Although most participants were women, the sex distribution did not differ significantly between groups.

Clinical outcomes

Figure 2 and Table 4 summarize changes in KOOS subscale and VAS pain scores during the study. At week 8, the DB group reported significantly lower VAS pain scores than the placebo group (42.66 ± 17.06 vs 61.37 ± 14.07; p<0.001), with a mean between-group difference of 2.95

(95% CI: 1.42–3.16). Both groups showed significant within-group improvements in KOOS subscale scores over time ($p<0.001$), but improvements were more pronounced in the DB group, particularly at week 8 and sustained through week 16.

Between-group comparisons at the end of the intervention revealed significant differences across all KOOS domains ($p<0.001$), especially for Pain, Activities of Daily Living, Sports/Recreation, and Quality of Life. Clinical knee examinations (crepitation, heel-to-thigh test, and flexion contracture) also differed significantly between the groups at week 8 (Table 5). Additionally, acetaminophen consumption was lower in the DB group than in the placebo (median weekly doses: 3 vs. 13, respectively).

Table 3. Baseline characteristics of the Knee osteoarthritis patients (comparison between the two study groups) (n=99)

Variables		**Dava-e-balgham (DB) group (n = 48)**	**Placebo group (n = 51)**
Age, years (Mean ± SD)		56.28 (8.68)	58.41 (10.34)
Gender, female n (%)		44 (91.7 %)	42 (82.4 %)
BMI, kg/m2 (Mean ± SD)		28.37 (3.82)	28.51 (5.16)
KOOS scores (Mean ± SD)			
Mean KOOS pain		55.79 (20.01)	52.61 (14.87)
Mean KOOS other symptoms		54.64 (19.00)	55.67 (16.20)
Mean KOOS activity of daily living		57.07 (18.73)	53.26 (14.61)
Mean KOOS sport and recreation		36.06 (18.12)	32.84 (17.84)
Mean KOOS quality of life		34.84 (18.65)	31.00 (15.91)
Dyspepsia (Intensity) Mean ± SD		8.67 (7.86)	7.76 (6.22)
Global patient assessment of pain intensity before treatment (VAS) Mean ± SD		56.17 (17.17)	60.59 (11.69)
Kellgren and Lawrence score, n (valid %)			
	1	23 (47.9 %)	21 (41.2%)
	2	21 (43.75%)	25 (49%)
	3	4 (8.4%)	5 (9.8%)
physical examination (visit 1) Mean ± SD			
Crepitus RT		1.17 (0.48)	1.14 (0.45)
Crepitus LT		1.13 (0.49)	1.16 (0.42)
Patellofemoral test RT		0.79 (0.46)	0.72 (0.45)
Patellofemoral test LT		0.72 (0.50)	0.72 (0.45)
Tibio femoral tenderness RT		0.43 (0.58)	0.20 (0.40)
Tibio femoral tenderness LT		0.49 (0.59)	0.26 (0.49)
Flexion contracture RT		0.79 (1.89)	1.02 (2.39)
Flexion contracture LT		1.09 (2.15)	1.14 (2.51)
Bony swelling RT		0.17 (0.43)	0.24 (0.48)
Bony swelling LT		0.32 (0.52)	0.28 (0.54)
Bony enlargement RT		0.85(0.42)	0.92 (0.34)
Bony enlargement LT		0.85 (0.42)	0.94 (0.37)
heel to thigh test RT		10.19 (7.62)	11.42 (7.40)
heel to thigh test LT		13.21 (8.39)	11.88 (8.04)
Alignment (Varus)		0.28 (0.45)	0.30 (0.46)
Alignment (Valgus)		0.04 (0.20)	0.06 (0.24)

KOOS, knee injury and osteoarthritis outcome score; BMI, body mass index; SD, standard deviation. Mean ± Standard deviation (SD); n (%); RT, right low extremity; LT, left low extremity; heel to thigh test, leg flexibility test; alignment (Varus), inward knee angulation test; alignment (Valgus), out ward knee angulation test

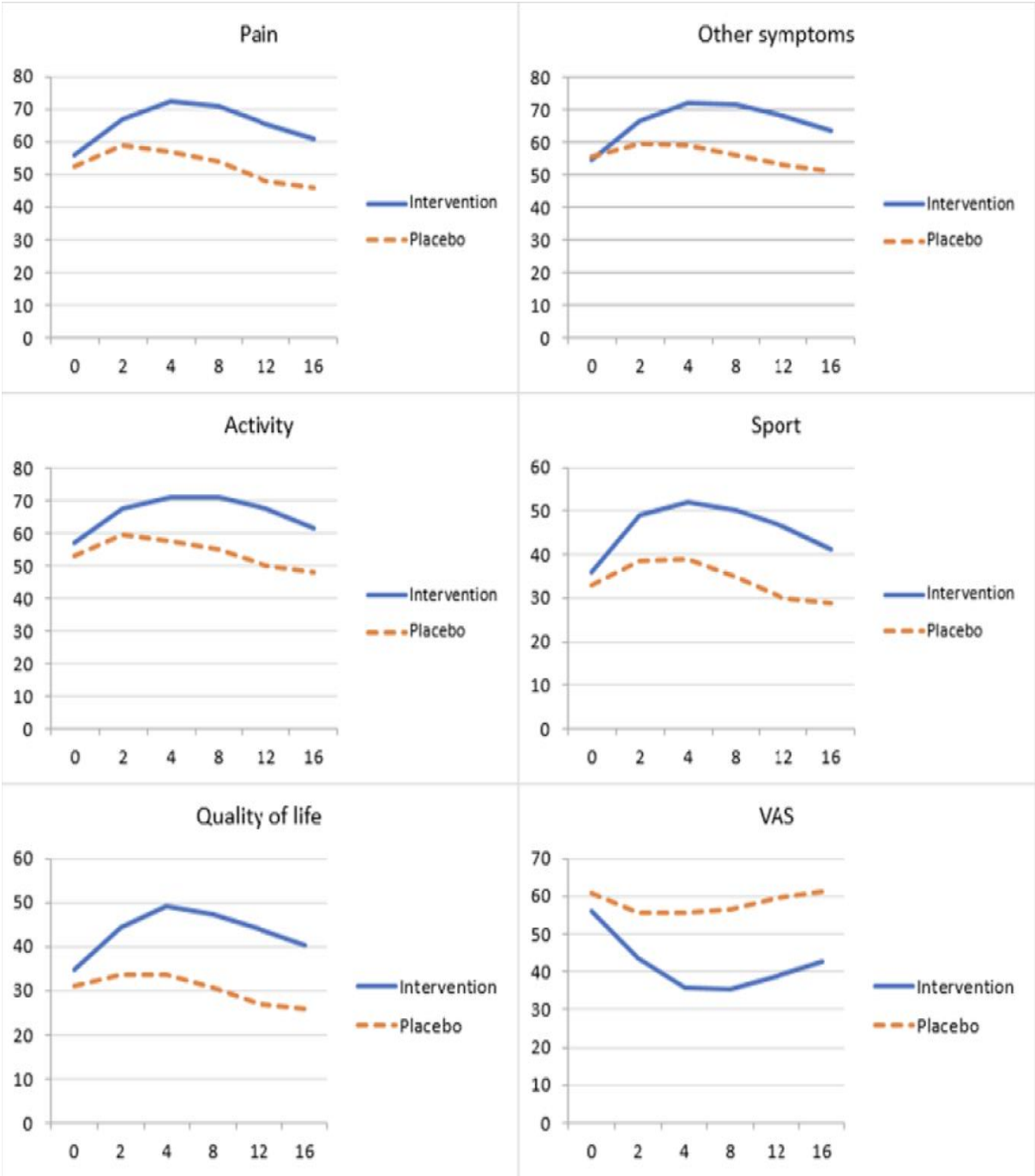

Figure 2. Change in knee injury and osteoarthritis outcome score (KOOS) profiles during the 8 weeks of intervention and two-month follow-up period in DB and placebo groups.

Table 4. Comparison of clinical outcomes of KOA patients between DB (n = 48) and Placebo (n = 51) groups, (sixteen-week changes)

KOOS scores as change from base line, mean (SD)	Group			p-value for within group difference	p-value for between group difference
	Week	Dava-e Balgham group mean (SD)	Placebo group mean (SD)		
KOOS Pain	0	55.79 (20.01)	52.61 (14.87)		
	2	66.84 (18.60)	58.55 (14.90)		
	4	72.34 (16.24)	56.70 (12.96)	< 0.001	0.002
	8	70.98 (17.43)	53.81 (13.13)		
	12	65.13 (21.03)	47.93 (14.04)		
	16	60.82 (16.71)	45.75 (14.92)		
KOOS other Symptoms	0	54.64 (19.00)	55.67 (16.20)		
	2	66.79 (17.09)	59.80 (15.38)		
	4	71.96 (16.28)	59.31 (14.81)	< 0.001	0.021
	8	71.73 (16.02)	56.09 (14.29)		
	12	68.31 (17.91)	53.01 (15.02)		
	16	63.60 (18.97)	51.26 (15.30)		
KOOS ADL	0	57.07 (18.73)	53.26 (14.61)		
	2	67.55 (16.19)	59.54 (14.82)		
	4	71.12 (17.01)	57.41 (14.43)	< 0.001	0.002
	8	71.06 (15.52)	55.16 (12.64)		
	12	67.37 (16.77)	49.88 (13.751)		
	16	61.73 (17.67)	48.07 (14.15)		
KOOS Sport/Rec	0	36.06 (18.12)	32.84 (17.84)		
	2	48.83 (17.55)	38.63 (20.03)		
	4	52.02 (16.74)	38.82 (19.17)	< 0.001	0.012
	8	50.21 (16.91)	34.80(18.411)		
	12	46.28 (18.95)	29.80 (17.43)		
	16	41.28 (18.04)	28.82 (17.57)		
KOOS QOL	0	34.84 (18.65)	31.00 (15.91)		
	2	44.41 (19.38)	33.70 (16.30)		
	4	49.07 (20.52)	33.46 (15.20)	< 0.001	0.003
	8	47.34 (20.43)	30.76 (15.10)		
	12	43.88 (17.84)	26.96 (14.92)		
	16	40.16 (17.28)	25.74 (14.82)		
VAS	0	56.17 (12.91)	60.59 (11.70)		
	2	43.40 (19.73)	55.78 (9.29)		
	4	35.64 (20.15)	55.49 (9.81)		
	8	35.21 (19.48)	56.57 (10.22)	< 0.001	0.001
	12	38.79 (17.77)	59.31 (13.31)		
	18	42.66 (17.06)	61.37 (14.07)		

KOOS, knee injury and osteoarthritis outcome score; mean ± standard deviation (SD); ADL, activities of daily living; sport/rec, sport and recreation; QOL, quality of life; VAS, visual analogue scale; global patient assessment of efficacy of treatment

Table 5. Effect of different supplementations on clinical knee examinations "*Dava-e balgham*" vs "placebo" (sixteen-week changes)

Variable	Time (weeks)	Dava-e-balgham Mean (SD)	Placebo Mean (SD)	p-Value
Crepitus (RT)	8	0.83 (0.53)	1.08 (0.35)	0.006
	16	0.88 (0.46)	1.14 (0.43)	0.012
Crepitus (LT)	8	0.91 (0.35)	1.13 (0.39)	0.007
	16	0.93 (0.42)	1.11 (0.40)	0.050
Tibiofemoral tenderness RT	8	0.13 (0.34)	0.15 (0.41)	0.844
	16	0.15 (0.36)	0.23 (0.43)	0.39
Tibiofemoral tenderness LT	8	0.17 (0.38)	0.23 (0.47)	0.536
	16	0.13(0.34)	0.23 (0.49)	0.284
Bony swelling (RT)	8	0.02 (0.15)	0.19 (0.40)	0.009
	16	0.05 (0.22)	0.29 (0.52)	0.011
Bony swelling (LT)	8	0.15 (0.42)	0.29 (0.54)	0.169
	16	0.15 (0.36)	0.26 (0.51)	0.29
Heel-to-thigh test (RT)	8	4.98 (5.02)	10.25 (6.40)	< 0.001
	16	5.51 (5.13)	9.83 (7.20)	0.004
Heel-to-thigh test (LT)	8	6.89 (6.49)	10.08 (6.58)	0.020
	16	6.36 (6.05)	10.26 (7.23)	0.014
Patellofemoral test (RT)	8	0.8 (0.40)	0.77 (0.43)	0.695
	16	0.8 (0.41)	0.66 (0.48)	0.167
Patellofemoral test (LT)	8	0.76 (0.43)	0.77 (0.43)	0.91
	16	0.75 (0.44)	0.66 (0.48)	0.385
Flexion contracture (RT)	8	0.09 (0.29)	0.73 (1.95)	0.030
	16	0.25 (0.87)	0.97 (2.24)	0.064
Flexion contracture (LT)	8	0.11 (0.32)	0.98 (2.30)	0.013
	16	0.3(0.88)	1.34 (3.33)	0.06
Alignment (Varus)	8	0.26 (0.44)	0.27 (0.45)	0.914
	16	0.23 (0.43)	0.29 (0.46)	0.595
Alignment (Valgus)	8	0.04 (0.21)	0.02 (0.15)	0.55
	16	0.05 (0.22)	0.09 (0.28)	0.543

The values are means (SD). * p-value of paired t-test, p-value <0.05 was considered as significant; RT, right; LT, left;

Safety measures and adverse events

Adverse events (AEs) were reported in 6 of 55 patients (10.9%) in the DB group and 5 of 55 patients (9.1%) in the placebo group (p = 1.00), mostly mild and transient. Treatment discontinuation due to AEs occurred in 3 DB patients (moderate knee stiffness, n=2; moderate bloating, n=1) and 1 placebo patient (mild heartburn) (p = 0.62). There were no between-group differences in specific AEs, (e.g., heartburn p = 0.62; knee stiffness p = 1.00), and no severe treatment-related AEs were reported. One hospitalization occurred in each group, both unrelated to the intervention (Figure 1).

Discussion

This study evaluated the efficacy of an 8-week treatment with a Persian medicine-based polyherbal formulation, "*Dava-e-Balgham*" (DB) comprising Zataria multiflora, Trachyspermum ammi, Nigella sativa and Pistacia atlantica in patients with knee osteoarthritis (KOA). To our knowledge, this is the first randomized controlled trial (RCT) assessing the therapeutic effects of this specific combination on KOA symptoms.

Participants were randomized to received either DB or placebo. Both groups exhibited significant within-group improvements across all five KOOS subscales by week 4. However, improvement in the DB group were more sustained. At the end of the intervention, KOOS scores in the DB group remained significantly improved better than baseline, with effects persisting throughout the 8 week follow up period, although with a mild decline. In contrast, the placebo group showed early improvements that diminished by weeks 12 and 16, with KOOS scores returning toward baseline levels. This transient response in the placebo group likely reflects non-specific trial-related effects (e.g., expectation bias

or Hawthorne effect), consistent with patterns observed in similar KOA trials (Salimzadeh et al. 2017).

GC/MS analysis of DB identified 21 volatile compounds, with thymol (36.95%) and carvacrol (18.47%) as the major constituents. These monoterpenes possess well-established anti-inflammatory, antioxidant, and analgesic properties relevant to the osteoarthritis (OA) pathophysiology (Chircov et al. 2021). Thymol reduces key inflammatory mediators (IL-1β, TNF-α, and COX-2) and exerts antioxidant effect through free radical scavenging and enhancement of endogenous defenses (Hosseinzadeh et al., 2015; Marchese et al., 2016). Carvacrol demonstrates chondroprotective activity *in vitro* and *in vivo* by inhibiting matrix metalloproteinases (MMPs) and proinflammatory cytokines involved in cartilage degradation (Hotta et al., 2010; Elbossaty, 2017).

Notably, thymol and carvacrol may act synergistically within polyherbal formulations, enhancing their pharmacological effects via multi-target mechanisms (Sharifi-Rad et al., 2018). Given their high abundance in DB, these compounds likely play a central role in the observed pain relief and functional improvements.

Many participants in the *Dava-e-balgham* (DB) group reported rapid symptom improvement often within the first week. This early onset may be attributable to the pharmacokinetic profile of Thymol and carvacrol, lipophilic low-molecular-weight monoterpenes that are rapidly absorbed from the gastrointestinal tract, with detectable plasma within 1–2 hours post-ingestion (Mason et al. 2017). Although these compounds may distribute to joint tissues, their bioavailability in synovial fluid requires further confirmation in human studies.

Supporting evidence highlights the anti-inflammatory potential of DB's phytochemicals constituents (Benmahieddine et al. 2023; Ghamari et al. 2023; Korani and Jamshidi 2020; Saei-Dehkordi et al. 2010). Bioactive metabolites in these herbs modulate inflammatory cytokines, a recognized strategy in OA management (Tripathi et al. 2017). DB is rich in flavonoids and phenolic compounds with potent antioxidant and anti-inflammatory activities, which have also been implicated in mitigating chronic inflammation associated with obesity and diabetes (Hamidnia et al. 2018; Hormati et al. 2019). Phenolic compounds scavenge free radicals, thereby attenuating oxidative stress mechanisms central to degenerative joint diseases (Paesa et al. 2025). Flavonoids from *P. atlantica* inhibit inflammatory enzymes such as MMPs partly through suppression of NF-κB signaling in chondrocytes (Tolooei and Mirzaei 2015), potentially fostering an anti-inflammatory environment conducive to chondrogenesis and tissue repair (Tanideh et al. 2021). While topical *P. atlantica* oleoresin has shown efficacy in OA symptom relief (Khamevar et al. 2021), oral administration in KOA patients had not been previously evaluated.

The analgesic and anti-inflammatory properties of *T. ammi*, both alone and in combination with *Curcuma longa*, have been validated in experimental OA models. *T. ammi* has reversed OA symptoms and even restored radiographic scores to baseline (Kellgren-Lawrence grade 0) (Khan et al. 2016), with efficacy comparable to morphine in certain settings (Al-Khazraji 2018). *Nigella sativa*, another component of DB, has demonstrated safety and efficacy in reducing pain and inflammation in OA (Huseini et al. 2022). With meta-analyses indicating reductions in malondialdehyde (MDA) and C-reactive protein (CRP) levels; Its key constituent, thymoquinone, suppresses pro-inflammatory mediators (COX-2, TNF-α, IL-1β, and IL-6) while enhancing anti-inflammatory cytokines (IL-4, IL-10) (Kavyani et al. 2023). Also, *Zataria multiflora*, rich in thymol and carvacrol,

provides additional antioxidant and anti-inflammatory benefits (Khazdair et al. 2018). Thymol, has been reported to downregulate inflammatory markers such as CRP, IL-1β, IL-6, TNF-α, and MMP-9. Together with carvacrol, it exerts strong anti-inflammatory and antioxidant effects (Chircov et al. 2021)

A key strength of this trial is the sustained symptom relief in the DB group, even after treatment cessation, contrasting with the placebo group's decline after week 4. Although the rapid onset of DB's effect is consistent with its anti-inflammatory pharmacodynamics. this prolonged benefit may reflect broader modulation of OA pathophysiology (Wang et al. 2016; Yang et al. 2023), potentially through persistent inhibition of NF-κB and COX-2 pathways (Ferraz et al. 2020; Ye and Zhou 2023), reduced gut microbiota-mediated systemic effects (Santino et al. 2017), or joint oxidative stress (Pal et al. 2023). though the latter remains hypothesis-generating and warrants further investigation.

Despite these encouraging results, several limitations should be acknowledged. The study was single-center with a prolonged recruitment period due to the COVID-19 pandemic. Radiographic assessments were not included owing to the relatively short duration. Additionally, baseline disease duration was not recorded, potentially confounding results as both early and chronic cases were enrolled. Although the placebo consisted of inert toast powder, future studies should employ metabolically inert comparators to exclude possible prebiotic effects. Finally, with 87% female participants, generalizability to male patients is limited, and sex-specific responses (e.g., hormonal influences on inflammation) merit exploration.

In conclusion, "*Dava-e-Balgham* "(DB) appears to alleviate pain, inflammation, and mobility limitations while enhancing quality of life in patients with mild to moderate KOA. its affordability, accessibility, and favorable safety profile position it as a promising complementary option to conventional therapies. Nevertheless, larger multicenter RCTs incorporating clinical, biomarker, and radiological outcomes are essential to confirm efficacy, elucidate bioavailability, and establish long-term safety.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Considerations

It was approved by the Medical Ethics Committee of Tehran University of Medical Sciences

Code of Ethics

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Authors' Contributions

Study concept and design: F.H, F N, M.A. Acquisition of data: F.H, K.K, and M.A. Analysis and interpretation of data: F.H, L.S, and M.A.Z. Drafting of the manuscript: F.H, M.A.Z, and L.S. Administrative, technical, and material support: M.M, M.A, and F.N. Study supervision: M.A and F.N

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