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Original Research Article

Clinical study to evaluate the therapeutic safety and efficacy of *Pyrethrum indicum* L. in primary knee osteoarthritis: a randomized controlled trial

Mir I. Hanief[1]*, Shameem A. Rather[2], Fouzia Farooq[3], Zarfah Fida[4], N. Z. Ahmed[1]

[1]Central Council for Research in Unani Medicine (CCRUM), New Delhi, India
[2]Regional Research Institute of Unani Medicine, Naseem Bagh, University of Kashmir, Srinagar, Jammu and Kashmir, India
[3]Department of ENT, Government Unani Medical College, Srinagar, Jammu and Kashmir, India
[4]Department of Moalajat, Institute of Asian Medical Sciences, Zakura, Srinagar, Jammu and Kashmir, India

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***Correspondence:**
Dr. Mir I. Hanief,
E-mail: dr.idreeshanief123@gmail.com

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ABSTRACT

Background: Primary knee osteoarthritis (OA) is a common degenerative joint disorder characterized by pain, stiffness, and functional limitation due to progressive cartilage degeneration and inflammation. Conventional therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), COX-inhibitors, corticosteroids etc. provide symptomatic relief but may have limited long-term efficacy and potential adverse effects. Consequently, interest in complementary and alternative medicine has increased. *Pyrethrum indicum* L. (Bozidān), traditionally used in Unani medicine for its anti-inflammatory and analgesic properties, has limited clinical evidence regarding its safety and efficacy in knee OA. The present study aimed to evaluate the therapeutic safety and efficacy of *Pyrethrum indicum* L. in participants with primary knee OA.

Methods: An open-label randomized controlled trial was conducted on 60 participants aged 40-70 years diagnosed with primary knee OA (Kellgren-Lawrence grade I and II). Participants were randomly allocated to a test group or a control group. The study received approval from the institutional ethics committee (IEC No. RRIUM-SGR/MD-2018/CT/WR/OA/BD) and was registered with the Clinical Trials Registry of India (CTRI/2021/03/032178). The test group received *Pyrethrum indicum* L. (5 grams once daily), while the control group received tablet glucosamine sulfate (1500 mg once daily) for 45 days.

Results: The test group showed significant improvement in pain, swelling, tenderness, and restriction of movement compared with the control group. A significantly greater reduction in the overall WOMAC score was also observed in the test group.

Conclusions: *Pyrethrum indicum* L. was well tolerated and demonstrated greater short-term symptomatic improvement compared with glucosamine sulfate in participants with primary knee OA.

Keywords: Knee osteoarthritis, Unani formulation, *Pyrethrum indicum* L., Glucosamine sulphate

INTRODUCTION

Degenerative joint disease, generally known as OA or wear and tear arthritis, is the leading cause of disability worldwide.[1] It is the most prevalent multifactorial musculoskeletal disorder that can affect any joint, although it's more prevalent in weight-bearing joints like hips and knees.[2-4] Knee being a complex large weight-bearing joint hence most commonly affected.[5] Knee OA accounts for nearly a quarter of all OA cases worldwide

and its prevalence rises with age and obesity.[6,7] Knee OA is defined by structural changes to articular cartilage, subchondral bone, synovia, muscles and ligaments, leading to the concept of treating OA as a disease of the whole joint.[8-10] OA has been designated a "priority disease" by the WHO.[11] Clinically this disease is characterized by pain, tenderness, decreased range of movement, crepitus, occasional effusion and variable degree of inflammation.[12] OA affects women more than men and its prevalence, incidence and severity increases after menopause.[13,14] In the Unani medicine knee OA is called Waja' ur-Rukba characterized by pain, swelling and redness with crepitus.[15] This disease usually occurs due to abnormally high levels of phlegm (Balghām) mixed with yellow bile (Safra) and blood (Dam), which when reaches to the joints leading to OA (Waja' al-Mafāṣil).[16]

The diagnosis of OA relies primarily on the clinical presentation & history and is confirmed with an X-ray.[17] The classical radiographic findings are marginal osteophyte formation, subchondral bone sclerosis and asymmetric joint space narrowing (JSN) due to loss of articular cartilage.

In the conventional system of medicine, the disease is usually treated by giving NSAIDs like salicylates, propionic acid derivatives, aryl-acetic acid derivatives, oxicam derivatives, selective cox-1 and cox-2 inhibitors and corticosteroids etc.[18] However, the potential for serious side effects, including gastrointestinal ulceration, bleeding, exacerbation of hypertension and fluid retention; concerns about their renal and cardiovascular safety particularly in older individuals with comorbidities limit their use. So, the need of the hour is to evaluate alternative mode of treatment to provide safe, efficacious and cost-effective treatment with least side effects to patients with knee OA. In Unani medicine Sūranjān (*Colchicum luteum*) is a validated drug in all forms of OA (Waja'al-Mafāṣil). According to classical literature of Unani medicine, Bozidān (*Pyrethrum indicum* L.) holds functional proximity to Sūranjān (*Colchicum luteum*) in its efficacy.[19-22] It is anti-inflammatory (Muhallil-i-Awrām), analgesic (Musakkin-i-Alam), nourishing nerves (Muqawwī Asāb), phelmagogue (Mushil-i-Balghām), detoxifies morbid humors from nerves and joints and is thus advantageous in OA.[23,24] *Pyrethrum indicum* L., a species of *Asteraceae* family, is rich in pharmacological compounds like linarin and luteolin, which have anti-inflammatory, neuroprotective and anti-oxidant properties. *Pyrethrum* genus is a good source of terpenoids, phenylpropanoids, and flavonoids.[25] It was detected by GC-MS analysis that essential oils in it mainly contain Sesquiterpenoids.[26] Most of these compounds have been isolated and purified from aqueous ethanolic extracts of *Pyrethrum* species using various chromatographic techniques, including silica gel, C18 reversed-phase column, Sephadex LH-20 chromatography, and semi-preparative HPLC.[27] Except angeloylcumambrin-B, cumambrin-A, cumambrin-B, and handelin obtained from fresh whole herb all the sesquiterpenoids have been isolated from the aerial parts of the *Pyrethrum.*[28,29] These sesquiterpenoids are known to have a great anti-inflammatory potential. Moreover, its anti-inflammatory compounds target AKT1and ALT2 in nuclear factor kB (NF-kB) signalling pathway in macrophage-mediated inflammatory response.[29] Some scientific studies have revealed that Bozidān (*Pyrethrum indicum* L.) is beneficial in alleviating the symptoms of arthritis.[20,30,31] Keeping in view the above properties of Bozidān, present study,therapeutic evaluation and safety of Bozidān (*Pyrethrum indicum L.*) in the management of primary knee OA (Waja' ur-rukba)" was conducted. The present study aimed to evaluate the therapeutic safety and efficacy of *Pyrethrum indicum* L. in participants with primary knee OA.

METHODS

An open-label randomized controlled trial was conducted in 2021 at the Regional Research Institute of Unani Medicine (RRIUM), Srinagar, Kashmir. Ethical approval for the study was obtained from the Institutional Ethics Committee of RRIUM, Srinagar (IEC No. RRIUM-SGR/MD-2018/CT/WR/OA/BD). The trial was also registered with the Clinical Trials Registry of India (CTRI) (Registration No. CTRI/2021/03/032178). Diagnosis and selection of participants was based on clinical features and radiographic examination (X-ray) of the knee joint. Participants were recruited from the outpatient (OPD) and inpatient (IPD) departments of the Regional Research Institute of Unani Medicine Hospital during a 12-month period starting from February 2021. A total of 80 participants were initially enrolled in the study. After obtaining written informed consent, eligible participants were randomly allocated into two groups (test and control) using a computer-generated randomization method. During screening, 10 participants were excluded (7 participants didn't meet inclusion criteria and 3 declined to participate). Among the remaining participants, 10 patients were lost to follow-up during the trial due to non-compliance with the study protocol (5 from the control group and 5 from the intervention group). Thus, 60 participants completed the study and were included in the final analysis. The overall flow of participants through the study is presented in Figure 1.

Sample size

The sample size for the present study was calculated based on hypothesis testing for paired differences, using an expected mean difference of 8.07 and a standard deviation of the difference (σd) of 12.76, derived from previously published clinical data on OA. With a two-tailed significance level (α) of 0.05 and statistical power of 80%, the minimum required sample size was estimated to be 20 participants per group. Considering a potential dropout rate of 30%, the sample size was adjusted to 30 participants per group. Accordingly, 30 participants were included in each group to ensure adequate statistical power.

The assumptions for sample size estimation were supported by findings from previous clinical studies on Unani interventions in knee OA, including the study by Razana and Quamri, which reported comparable variability and clinical improvement in outcome measures.[32]

However, given the relatively small sample size and short duration, the present study may be considered exploratory, and the findings should be interpreted as preliminary. Further large-scale, adequately powered randomized controlled trials are warranted to confirm these results.

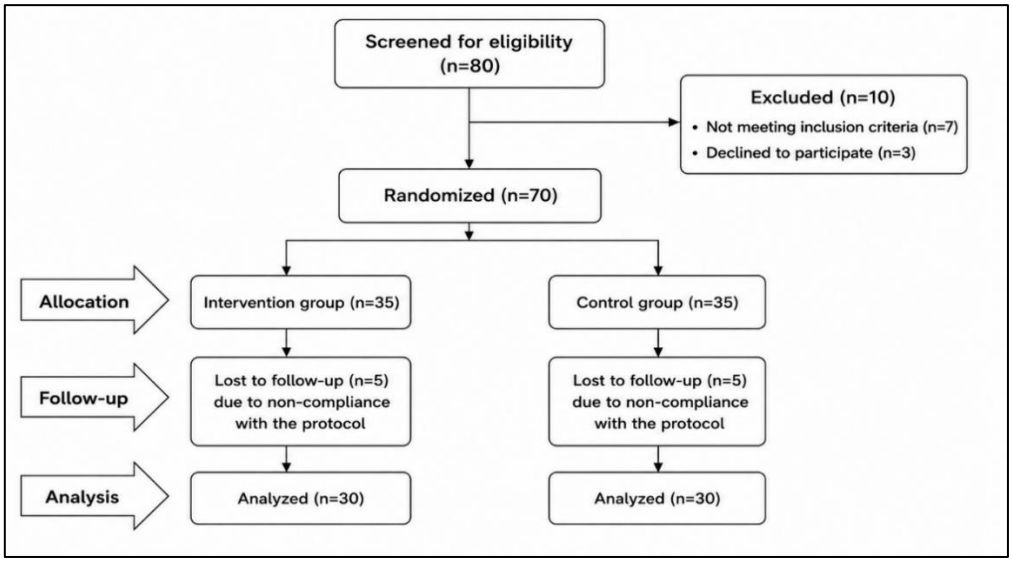


Figure 1: CONSORT flow diagram of the participants included in the trial.

Inclusion criteria

Participants of any gender, aged 40-70 years, diagnosed with primary knee OA (Kellgren-Lawrence grade 1 or 2) and willing to provide informed consent were included in the study.

Exclusion criteria

Patients with Kellgren and Lawrence grade 3 and 4 knee OA having BMI >35 kg/m^2, history of a recent knee infection/previous knee surgery, Rheumatoid arthritis and Patients with history of systemic diseases like diabetes, cardiovascular, hypertension, and impaired renal or hepatic function were excluded from study.

Intervention

Thirty (30) diagnosed participants of Primary knee OA qualifying the inclusion criteria were given the test drug Bozidān (*Pyrethrum indicum* L.) 5 grams in Safūf (powder) form once a day half an hour after breakfast with lukewarm water for a period of 45 days. Control group comprised of 30 participants in which control drug glucosamine sulfate 1500 mg was given in tablet form half an hour after breakfast with lukewarm water once a day for the same duration.

Test drug preparation and standardization

The test drug (Bozidān) which is the root of *Pyrethrum indicum* L. as depicted in Figure 2 was bought from the open market, identified and authenticated from the Centre for Biodiversity and Taxonomy, Department of Botany, University of Kashmir vide Voucher No. 4264-KASH Herbarium/2021 before the drug was processed in the Pharmacy. The drug Bozidān *(Pyrethrum indicum* L.*)* was pulverized to make fine powder and was enclosed in opaque self-locking pouches of 5 grams each.



Figure 2: Test drug *Pyrethrum indicum* L. *(Bozidān).*

Assessment of temperament (Mizāj)

The *Mizāj* (temperament) of each participant was evaluated during clinical examination according to the ten parameters (*Ajnās 'Ashara*) described in classical Unani literature.

Assessment of safety

Adverse events were recorded at each follow-up visit (0th, 15th, 30th, and 46th day) based on participant-reported symptoms and findings from clinical examination. Haematological and biochemical parameters were assessed at baseline (before treatment) and after completion of treatment to evaluate the safety of the intervention. Clinical assessment was carried out at every follow-up visit to monitor any adverse effects. Haematological investigations included haemoglobin percentage (Hb%), estimated by the cyanmethemoglobin method; total leucocyte count (TLC) and differential leucocyte count (DLC), determined using the Coulter method; and erythrocyte sedimentation rate (ESR), measured by the Westergren method. Biochemical investigations included liver function tests (LFTs), namely serum glutamic-oxaloacetic transaminase (SGOT/AST) and serum glutamic-pyruvic transaminase (SGPT/ALT), measured using the IFCC standardized method, and alkaline phosphatase (ALP), estimated by the aminomethylpropanol buffer method. Kidney function tests included blood urea estimation by the urease-glutamate dehydrogenase method and serum creatinine measurement using an enzymatic assay. All laboratory investigations were performed both before treatment (BT) and after treatment (AT).

Assessment of efficacy

Observation of demographic characteristics, age, gender, marital status and temperament (Mizaj) of the patients allocated in both the groups was assessed on day 0 of the study and hence recorded in terms of frequency and percentage. The efficacy of the test drug and control was assessed using subjective parameters (pain, swelling, tenderness, restriction of movements) and objective parameters (X-ray) and WOMAC 3.1 Likert version was used with five response levels to each item which represent different degrees of intensity i.e., none, mild, moderate, severe or extreme. The total WOMAC score ranges from 0-96, where 0 represents the best, and 96 the worst possible health status. The data of subjective parameters were recorded on baseline, 0th, 15th, 30th, and 46th day of the study. The objective parameters were assessed on the baseline and 46th day of the study. Patients were also assessed before and after study for safety parameters.

Data analysis

For the statistical analysis, data was initially compiled and entered into a spreadsheet, then exported to SPSS version 20.0 and GraphPad Prism software for processing. Continuous variables were summarized as mean±standard deviation, while categorical variables were represented by frequencies and percentages. To compare categorical variables between groups at baseline and post-intervention, the Chi-square test was applied. For within-group analysis of ordinal variables with more than two levels, the Wilcoxon signed-rank test was used. In analyzing WOMAC scores, the student's independent t-test was employed for between-group comparisons, and paired t tests were used for within-group analysis, provided the data were continuous and satisfied the normality assumption. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 80 participants were screened, out of which 60 (30 in the test group and 30 in the control group) completed the trial over 45 days. In this study it was observed that the maximum number of patients i.e., 33 (55%) were in the age group of 40-50 years and 10 (16.67%) in the age group of 50-60 years, 16 (26.67%) in the age group of 60-70 years, while as only 1 patient (1.67%) was found in the age group of 70-80 years. This data indicates that the disease is more prevalent in the 4th and 5th decades of life. Furthermore, 40 (67%) patients were females, while only 20 (33%) were males collectively in the test and control group, which mean that the disease is more prevalent in females than in males. Again 59 (98.33%) patients were married and only 1 (1.67%) was unmarried inaggregation of both the test and the control groups. It was also found that among the overall sample from both the test and control group, 52 (86.67%) patents were having phlegmatic temperament (Balghāmī Mizāj), 5 (8.33%) sanguine temperament (Damwī Mizāj), and 3 (5%) bilious temperament (Ṣafrāwī Mizāj), no case was found with Sawdāwī Mizāj (Melancholic temperament).

Knee joint pain

In the present study, we observed that there was a significant reduction in the severity of pain in both the groups after treatment with a ($p<0.0001$). However, out of 30 subjects in the test group 24 (80%) patients had no pain at the end of the study, while out of 30 subjects in case of the control group, only 11 (36.67%) had no pain at the end of the study, which clearly indicates that test drug was better in alleviating pain than in the control drug as depicted in Table 1.

Swelling

Out of 30 patients, 25 (83.33%) had no swelling in case of the test group, whereas out of 30 patients, only 9 (30%) had no swelling in the control group at the end of the study, which evidently means that the test drug was more efficacious than the control drug ($p<0.0001$) as depicted in Table 2.

Tenderness

Out of 30 patients in the test group, 26 (86.67%) has no tenderness at the end of the study, while in case of the control group, out of 30 patients, 12 (40%) patients had no tenderness at end of study, which clearly means that test drug was more advantageous in relieving tenderness compared to control drug ($p<0.0001$) (Table 3).

Restriction of movements

The 11 patients (36.67%) had no restriction of movement at the end of the study in case of the test group, whereas only 4 (13.33%) had no restriction of movement at the end of the study in control group. This evidently indicates that the test drug was better as compared to the control drug (p=0.0035) as depicted in Table 4.

X-ray knee AP/Lat

Since no radiographic change is expected over 45 days, hence Kellgren-Lawrence grades remained unchanged. According to the Kellgren-Lawrence grading system, 26 patients had Grade I and 34 patients had grade II OA at both baseline and post-treatment assessments.

WOMAC score

We observed that the WOMAC score after treatments in both the groups was significantly lower compared to what it was before treatment, which means that both treatments are effective. However, in test group, improvement was significantly better compared to control group (Table 5).

Assessment of safety

For assessment of safety; LFT (SGOT, SGPT, ALP, S. bilirubin) and KFT (blood urea and creatinine) were carried out before and after treatment. It was observed that both test and control drugs are safe with regard to assessment of safety for such duration of study (Table 6).

Table 1: Comparison between test and control group with respect to the severity of pain.

Severity of pain	Control group		Test group	
	BT	AT	BT	AT
Absent	0	11	0	24
Mild	1	19	3	6
Moderate	28	0	26	0
Severe	1	0	1	0
Total	30	30	30	30
Intra group comparison	Wilcoxon signed-rank test; p<0.0001*		Wilcoxon signed-rank test; p<0.0001*	
Inter group analysis	Chi-square=1.07, df=2, p value (BT vs BT)=0.584			
	Chi-square=11.589, df=1, p value (AT vs AT) <0.0001*			

*Denoting significance.

Table 2: Comparison between test and control group for the severity of swelling.

Severity of swelling	Control group		Test group	
	BT	AT	BT	AT
Absent	7	9	9	25
Mild	20	20	20	5
Moderate	3	1	1	0
Severe	0	0	0	0
Total	30	30	30	30
Intra group comparison	Wilcoxon signed-rank test; p=0.075		Wilcoxon signed-rank test; p<0.0001*	
Inter group analysis	Chi-square=1.25, Df=2, p (BT vs BT)=0.535			
	Chi-square=17.52, Df=2, p value (AT vs AT)<0.0001*			

*Denoting significance.

Table 3: Comparison between test and control group with respect to the severity of tenderness.

Severity of tenderness	Control group		Test group	
	BT	AT	BT	AT
Absent	0	12	0	26
Mild	1	11	5	4
Moderate	29	7	25	0
Severe	0	0	0	0
Total	30	30	30	30
Intra group comparison	Wilcoxon signed-rank test; p<0.0001*		Wilcoxon signed-rank test; p<0.0001*	
Inter group analysis	Chi-square=2.96 Df =1, p (BT vs BT) =0.085			
	Chi-square=15.424 Df =2, p (AT vs AT) ≤0.0001*			

*Denoting significance.

Table 4: Comparison between test and control group with respect to restriction of movement.

Severity status for restriction of movement	Control group		Test group	
	BT	AT	BT	AT
Absent	0	4	0	11
Mild	3	18	8	19
Moderate	27	8	22	0
Severe	0	0	0	0
Total	30	30	30	30
Intra group comparison	Wilcoxon signed-rank test; p<0.0001*		Wilcoxon signed-rank test; p<0.0001*	
Inter group analysis	Chi-square=2.78 Df=1, p (test vs control) =0.09			
	Chi-square=11.293 Df=2, p (test vs control) =0.0035*			

*Denoting significance.

Table 5: Average value of WOMAC score in test and control group before and after the treatment.

WOMAC score	BT		AT		P value
	Mean	SD	Mean	SD	
Control	38.80	3.34	23.70	7.06	<0.0001*
Test	38.60	3.25	18.10	5.98	<0.0001
(Test vs control) p=0.0017*					

*Denoting significance.

Table 6: Average value of safety parameters in test and control group before and after the treatment.

Safety parameters		Mean value in test group	Mean value in control group
Sr. Bilirubin	BT	0.6497	0.5663
	AT	0.614	0.4761
SGOT	BT	38.22	8.951
	AT	31.79	10.56
SGPT	BT	27.35	10.54
	AT	32.62	15.98
ALP	BT	114.9	48.35
	AT	104.6	26.28
Urea	BT	30.47	6.943
	AT	35.95	8.532
Creatinine	BT	0.8637	0.1634
	AT	0.9557	0.2286

DISCUSSION

There is no doubt that health care providers face plenty of challenges to deal with OA, a chronic degenerative disorder characterized by cartilage loss. The use of herbal and natural products in chronic conditions such as OA, which may require long-term treatment, is becoming more frequent to lessen the burden of side effects due to conventional medicines.[33] In this scenario the present study entitled "Therapeutic evaluation and safety of Bozidān (*Pyrethrum indicum* L.) in the management of primary knee OA (Waja' ur-rukba)" which is the first of its kind was conducted. In this study the insignificant age difference between the groups indicates that both are statistically comparable. From the results it is evident that the maximum number of patients were belonging to the age group of 40-50 years. This data suggests that the disease is more prevalent in the 5th decade of life which coincides with the study conducted by others.[34-37] This may be attributed to age-related degenerative changes in articular cartilage, cumulative mechanical stress on the knee joint, and reduced regenerative capacity of joint tissues, which contribute to the development and progression of OA.[34]An insignificant difference between the groups with respect to gender distribution indicates that both the groups have a statistically comparable male and female proportion. However, the proportion of females was found to be very high compared to males. Contemporary to our observation it has been reported that the prevalence of knee OA is higher among females than males.[37-39] Several factors can influence the higher prevalence of OA in females. Generally, women tend to engage in less physical activity, which may contribute to this condition. and often have a Bārid-ratab (cold and moist) temperament, predisposing them to knee OA. Additionally, most women experience menopause around the age of 40 to 50, and estradiol deficiency is associated with the development of OA in postmenopausal women.

After menopause, elevated levels of inflammatory markers such as IL-1, IL-6, and TNF-α in the serum and synovial fluid may further contribute to the onset and worsening of OA in women.[40] Similarly, in this study, the majority of the patients (98.33%) were married, which is in accordance with the study carried out by Heidari and others.[41]

Among the 60 patients, 52 (87.67%) patients were of phlegmatic temperament (Balghāmī Mizāj), 5(8.33%) were of sanguineous temperament (Damwī Mizāj) and 3 (5%) were of bilous temperament (Safrāwī Mizāj). This study reveals that patients with a Phlegmatic temperament are more likely to develop knee OA, which is in accordance with the writing of Unani physicians in their classical texts. In Unani medicine, Balghāmī Mizāj (phlegmatic temperament) is characterized by cold and moist qualities, which are associated with reduced metabolic activity, accumulation of Balghām, and a tendency toward joint stiffness, swelling, and impaired mobility. These features are considered to predispose individuals to disorders such as Wajaʿ al-Mafāṣil (arthritis). Classical Unani physicians have also described that joint disorders occur more frequently in individuals with Balghāmī temperament, followed by Damwī and Safrāwī, and less commonly in Sawdāwī temperament. From a modern perspective, this observation may be related to factors such as reduced metabolic activity, sedentary lifestyle, increased body weight, and low-grade inflammation, which are known contributors to OA and share similarities with traits attributed to the phlegmatic temperament.[16,42-44] However, the present study contradicts the study carried out by Ahmed et al who reported that knee OA is more prevalent in patients with bilious (Safrāwī) temperament. Although derangement in all of the four humors has been shown to cause knee OA.

The effect of both the test and control drugs was seen by calculating the mean of scores of all the subjective parameters recorded, through rigorous statistical analysis. Both intra-group and inter-group comparison was done to check the effectiveness of the test drug formulation. The severity of pain, tenderness, and restriction of movements was classified into four categories on the basis of the WOMAC scale, whereas the severity of swelling was classified into four grades on the basis of the Likert Scale.

It was observed that severity of pain reduced significantly after the treatment in both test and control groups ($p \leq 0.0001$) as depicted in Table 1. Evidently, the treatment in the test group was more effective compared to control treatment because 80% of patients had no pain after the treatment in the test group compared to 36.67% in the control group. The significant reduction in pain in the test group can be attributed to the analgesic (Musakkin-i-Alam) effect of Bozidān as mentioned in the Unani classical literature and the same has been verified in the present study.[24,44] From a modern pharmacological perspective, this effect may be related to the presence of bioactive phytoconstituents such as sesquiterpene lactones and flavonoids reported in *Pyrethrum indicum*, which have been shown to exert analgesic and anti-inflammatory effects through inhibition of cyclooxygenase (COX) pathways and modulation of inflammatory mediators.[25,27] As depicted in Table 2, we found that there exists a significant difference between the groups with respect to improvement in swelling status, after the treatment with a $p<0.0001$. Evidently, the treatment in the test group was more effective compared to control treatment as, 25 (83.3%) patients had no swelling after the treatment in the test group compared to 9 (30%) patients in the control group. As we know this disease is mainly caused by abnormal accumulation of Phlegm in the joints, which then leads to swelling. The efficacy of Bozidān in reducing the swelling may be due to its anti-inflammatory (Muḥallil-Awrām) and phlegmagogue (Mushil-i-Balghām) action, as has been already mentioned by various eminent Unani scholars in their treatise.[16,24,44] In addition, modern pharmacological studies suggest that suppression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by the phytoconstituents present in the Bozidān may contribute to the reduction of synovial inflammation and edema in osteoarthritic joints.[25,27]

In this study, we found that the severity of tenderness in both the test and control groups decreased significantly after treatment (Table 3). However, the test group treatment was more effective than the control group because 26 (86.67%) patients in the test group had no tenderness following treatment, compared to 12 (40%) patients in the control group. Since knee OA is a phlegmatic disease in which the tenderness is caused due to excess accumulation of Phlegm and yellow bile in the joint. The analgesic (Musakkin-i-Alam), phlegmagogue (Mushil-i-Balghām), and cholagogue (Mushil-i-Safra) functions of Bozidān may be responsible for relieving tenderness in the knee joint as the same has been mentioned by a corpus of Unani Physicians such as Kabir ud din in his classical book.[24] Moreover, the anti-inflammatory phytochemicals present in Bozidān may reduce inflammatory mediators and nociceptive signaling, thereby alleviating joint tenderness.[25,27]

From Table 4, it is obvious that there is a significant difference between the groups and the improvement with respect to restriction of movement is evidently better in the test group compared to the control group, as 11 (36.67%) patients in the test group had no restriction of movement compared to 4 (13.33%) patients in the control group at the end of the study. The efficacy of Bozidān in decreasing restriction of movement could be attributed to its phlegmagogue (Mushil-i-Balghām), nervine tonic (Muqawwī-i-Aṣab), and resolvent (Muḥallil) function as mentioned in the treatise of Unani, which have acknowledged the role of Bozidān in the treatment of OA.[24,44-46] From a contemporary biomedical perspective, the anti-inflammatory and antioxidant activities of plant-derived phytochemicals may reduce synovial inflammation, improve joint lubrication, and

consequently enhance functional mobility in OA.[25,27]

Among objective parameters, we had X-ray knee and WOMAC Score which were measured and recorded in the case report form at the beginning and after the accomplishment of the treatment protocol. In the current study, we observe that there was no improvement with regard to X-ray knee AP/Lat in both the groups, as 13 (43.33%) patients had grade 1 knee OA, and 17 (56.67%) patients had grade 2 knee OA in the test as well as the control group, both before and after the treatment. Since we know that knee OA is a progressive degenerative disease that primarily affects the cartilage and the cartilage takes almost 3-6 months for regeneration. Since our study was only for 45 days that could be the possible reason, that we couldn't find any change in the X-ray knee before and after the treatment. However, the WOMAC scores showed a statistically significant reduction from baseline following treatment in both groups, indicating significant improvement in clinical outcomes with both interventions. However, the magnitude of improvement was significantly greater in the test group compared with the control group.

The comparative analysis of safety parameters within the test and control group before and after the treatment (Table 5) shows no major difference which indicates both the drugs are safer for the already mentioned duration of this study.

Limitations

This study has certain limitations. It was conducted at a single center with a small number of participants, which limits how well the findings apply to a larger population. The treatment period was short and may not show long-term effects of the test drug. Similarly, we could not afford an MRI, which could have provided us with more insights at a minute level. The study also excluded patients with other health issues like diabetes and high blood pressure. Furthermore, there was no discussion of diet and lifestyle changes as part of the treatment. Key factors such as medication use and physical activity were not considered, which could affect the results. Future research should involve more centers, larger participant numbers, and longer treatment periods to better understand the test drug's safety and effectiveness for people with knee OA.

Future scope

The present study explored the use of the test drug Bozidān in the treatment of primary knee OA and found promising results in subjective and objective parameters. While the test drug was effective at the dose used in this study, further research on the efficacy of different doses and the use of adjunctive therapies may be useful in refining these findings. Additionally, increasing the sample size and extending the treatment duration beyond 45 days may improve the overall strength of the study.

CONCLUSION

The findings of this randomized controlled trial suggest that Bozidān (5 grams) produced significant improvement in clinical symptoms of primary knee OA, including pain, swelling, tenderness, restriction of movement, and WOMAC scores in participants with Kellgren-Lawrence grade 1-2 disease. Although the control group receiving glucosamine sulfate also demonstrated symptomatic improvement, the test group showed comparatively greater symptomatic benefit in several outcome measures within the study population. It should be noted that the clinical efficacy of glucosamine sulfate in knee OA remains variable and somewhat controversial across different clinical guidelines and systematic reviews; however, it was selected as the comparator in the present study because it is commonly used as a symptomatic treatment and has frequently been employed as a control intervention in clinical trials evaluating alternative or complementary therapies. No significant alterations in safety parameters were observed during the treatment period, indicating good tolerability of the intervention. However, given the relatively short treatment duration of 45 days, the results primarily reflect short-term symptomatic efficacy rather than long-term disease modification. Therefore, larger, well-designed studies with longer follow-up periods are warranted to further establish the long-term efficacy and safety of Bozidān in the management of knee OA.

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