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RESEARCH ARTICLE

Roghan Mālish 'A Topical Formulation' Attenuates Joint Pain, Down-Regulates C-Reactive Protein Level and Improves Quality of Life in Patients with Waja' al-Mafāṣil (NUMC: L-4) (Arthralgia) – A Pilot Clinical Study

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Abstract

Roghan Mālish is a cost effective topical application recommended for joint pain management. This prospective pilot study evaluated the safety, analgesic, and anti-inflammatory effect of Roghan Mālish in patients with arthralgia to validate the therapeutic claim and generate evidence for further studies. The study was conducted in patients with joint pain as chief complaint, with or without swelling and morning stiffness. The study was approved by Institutional ethic committee prior to initiation. Patients were advised to apply Roghan Mālish (2.5 mL/joint) followed by gentle massage in circular motion for 5 mins twice daily for 14 days. The efficacy was calculated from the reduction in Visual Analogue Scale (VAS), C-Reactive Protein (CRP) level and improvement in Quality of Life Scale (QOLS). Relevant pathological and biochemical indices and the observation of adverse events were used to evaluate the safety. A total number of 58 patients completed the trial with the mean age of 46.2 years and the majority (70.7%) being female. The overall therapeutic response was 93%. A significant ($P<0.05$) decrease in VAS score and CRP level, and significant improvement in QOLS was observed after treatment with Roghan Mālish. No significant difference in pathological and biochemical indices was observed before and after treatment. Roghan Mālish was well tolerated upon topical application with no any undesirable side effects. The study results indicate that the topical application of Roghan Mālish is safe and may be used successfully to treat arthralgia.

Keywords: Arthralgia, Joints Pain, Roghan Mālish, Sesame Oil, Turpentine Oil, *Waja' al-Mafāṣil*

1. Introduction

Among the most common symptoms prevailing in general population and medical practice are musculoskeletal problems. Over the age of 50, two out of every three people report musculoskeletal pain. It is one of the leading causes of disability worldwide[1,2]. Osteoarthritis among several types of arthritis is the most common cause of peripheral joint pain in adults with a prevalence of 22% to 39% in India. It is more common in women than men and the prevalence rises dramatically with age[3,4]. Though, effective treatments such as acetaminophen, NSAIDs, opiates are available in conventional system of medicine, the problem is still widely prevalent and increasing day by day. Moreover, adverse effects produced by the use of analgesics such as gastrointestinal problem, allergic reactions, headache and drowsiness, is a serious concern in the medical realm. Plants and their active metabolites are reported to have a higher rate of efficacy comparable to conventional treatment in combating many ailments including arthralgia[5]. Unani medicine offers

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various treatment regimens for joint pain and other musculoskeletal disorders. Many effective oral and topical formulations are in vogue since ages in Unani and other indigenous systems of medicine for pain management[6–9]. However, the search for a potent, cost effective and relatively safe formulation remains imperative and elusive.

Turpentine oil (*Duhn al-Batm/Roghan-e-Sanober*) obtained from live trees mainly pines by hydrodistillation of resins of pinaceae family trees, has a long history of use in Unani medicine for many ailments. Hippocrates, Dioscoride, and Galen used the oil for its properties against lung diseases and biliary lithiasis. It was also used for the treatments of blennorrhoea, cystitis, neuralgia, rheumatism, sciatica, nephritis, constipation, and mercury salivation in the past[10–12]. Modern phytotherapy revealed the intensive potential of turpenic oil including analgesic, revulsive, antiparasitic, disinfectant, balsamic, and respiratory and urinary tract infections, haemostatic, dissolving cholelithiasis, diuretic, antispasmodic, antirheumatic activities, etc[12].

Sesame oil (*Duhn al-simsim/Roghan Kunjad*) extracted from the seeds of *Sesamum indicum* L. (Family: Pedaliaceae) has a long history of medicinal and nutritional use in Unani medicine. This queen of oils is being used in many Unani formulations as a key ingredient especially in topical applications. Besides its wide medicinal and pharmaceutical applications, it checks and reduces the allergic effects of irritants in the formulation by virtue of its soothing nature and moisturizing effect[11,13]. Due to its high nutritional and therapeutic virtues, it is notably distinct from other vegetable oils. Potential health benefits of sesame include antioxidative, anticancer, anti-hypersensitive, and anti-immunoregulatory actions[14].

Roghan Mālish is a novel topical formulation (mixture of turpentine oil and sesame oil), recommended by an eminent Hakim for the management of joint pain. It is very economical, effective and traditionally being used in alleviating arthralgia and other musculoskeletal disorders in general OPD of Regional Research Institute of Unani Medicine (RRIUM), Chennai for more than four decades. However, no scientific report on the therapeutic claims of the drug is available to the best of our knowledge. Hence, this study was contemplated to evaluate the analgesic and anti-inflammatory effect and safety of Roghan Mālish, in patients with arthralgia to validate the claim and generate evidence for further studies.

2. Materials and Methods

2.1 Subject Selection

A prospective pilot clinical study was conducted at the OPD of RRIUM, Chennai during the period 2020–21 to evaluate the efficacy and safety of Roghan Mālish in patients with Waja' al-Mafāṣil (arthralgia). The study was conducted in conformity with GCP guidelines. The Institutional Ethics Committee, RRIUM, Chennai approved the study and granted ethical clearance. Before the study began, the study protocol was registered in Clinical Trial Registry-India (Registration number: CTRI/2019/10/021805). After receiving the duly signed voluntary informed consent form, participants of either gender between the ages of 18-60 years who had single or multisite peripheral joint pain with or without swelling, morning stiffness and limited motion, were recruited in the study. Patients with recent injury, wound at the affected joint, surgery on the joint within the last 6 months, patients applying any topical medicine within a week, taking intra-joint injections or corticosteroid drugs within the last three months, patients undergoing physiotherapy within last month or during study and patients with hypersensitivity or allergy to the formulation were excluded.

2.2 Details of Study Drug and Mode of Intervention

Both the oils 'Turpentine oil and Sesame oil' were procured from authorized dealers in Chennai and the formulation was prepared in a single batch by thoroughly mixing equal volume (1:1) of both the oils. The formulated oil 'Roghan Mālish' was then placed in tight air containers, each container comprising of 70 mL oil, and stored at room temperature. The duration of protocol therapy was 14 days. Roghan Mālish (1 container/week) was dispensed to the study participants with the advice to apply 2.5 ml oil over the affected joint (5 ml, if two joints are involved) with more pain (in case of multisite joint pain) and do *Dalk Layyin* (gentle massage) for 5 mins in a circular motion twice daily. The same procedure was repeated for subsequent visit. The study participants were advised to prevent over-pressure on the affected joint but change in their sports habits and limited motion was not recommended. Concomitant medication (Paracetamol 650 mg) was

allowed only to the patient with severe pain and the same was recorded in the Case Record Form (CRF). However, no case was reported to use concomitant medication during the entire study period. The study participants' temperament was evaluated at baseline and after treatment using standard, Ajnās 'Ashara-based tool developed by Central Council for Research in Unani Medicine, New Delhi, Ministry of Ayush, Government of India.

2.3 Efficacy and Safety Evaluation

Based on the improvement in the intensity of pain, swelling, and morning stiffness measured through the Visual Analogue Scale (VAS)[15,16], the efficacy of the formulated oil was evaluated. Total VAS score of each symptom was recorded at baseline and changing trend of pain, swelling, and morning stiffness was assessed using repeated measurement at subsequent visits and recorded in CRF. The level of C-Reactive Protein (CRP), a potent marker for inflammation[17], was also evaluated at baseline and after treatment with Roghan Mālish for 14 days to assess its effect on elevated levels of CRP. Quality of Life Scale (QoLS) was employed and recorded at baseline and at the end of treatment to assess the overall wellbeing of the study participants[18]. Pre-treatment and post-treatment score of individual patients was compared to assess the efficacy of the study drug. The reduction in Visual Analogue Scale (VAS) score and increment in QoLS score were used to calculate the % efficacy of Roghan Mālish.

Hemodynamic parameters, *i.e.,* pulse rate, respiratory rate, temperature, systolic, and diastolic blood pressure were observed at baseline and after 14 days of treatment and recorded in CRF. Laboratory tests were done at baseline and at the end of treatment to determine whether the formulated oil had any potential adverse effects on the levels of relevant pathological and biochemical indices. These indices include Haemoglobin (Hb), Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), Erythrocyte Sedimentation Rate (ESR), serum bilirubin, Serum Glutamic-Oxaloacetic Transaminase (SGOT/AST), Serum Glutamic-Pyruvic Transaminase (SGPT/ALT), Serum Alkaline Phosphatase (ALP), serum creatinine, serum uric acid, and blood urea. Frequency and percentage of Adverse Events (AEs), Serious Adverse Events (SAEs) reported due to study drug were recorded in CRF.

3. Statistical Analysis

The qualitative variables were expressed as frequency with percentage and quantitative variables were expressed as mean with standard deviation. Wilcoxon sign rank test was used to assess the changes in VAS scores between the baseline after 7 days and after 14 days of treatment. Also, this test was used to find out the changes in hemodynamic, CRP level, and other pathological and biochemical parameters between baseline and after treatment. All tests are two tailed and the P-value <0.05 was considered as statistical significance.

4. Results

In total, 65 patients fulfilling the inclusion criteria were enrolled in this study, however, only 58 participants completed the trial and were included in the analysis since 7 patients were lost to follow-up. The demographic data obtained in this study are illustrated in Table 1. The age distribution of patients revealed that 44.8% of them were more than 50 years old. The study populations' Mean ± SD age was found to be 46.2 ±7.1 years, and women were more likely than men to experience the problem (70.7%). The data analysis of socio-economic status revealed that 82.8% of participants were of middle economic status, whereas 17.2% were of lower economic status. Chronicity of the disease was less than 10 months in 50% of the patients enrolled in the study. The median and Inter Quartile Range (IQR) for disease duration was 10.5 (3-18) months. The percentage of study participants with *Damawī* (Sanguineous), *Balghamī* (Phlegmatic), and *Ṣafrāwī* (Bilious) temperament was 62.1%, 27.6%, and 10.3% respectively.

Figure 1 depicts the overall response of study participants to the treatment. The results revealed that 69% of study participants were relieved, 24% were partially relieved and 7% of participants showed no relief. The Mean ± SD values of the VAS score and CRP levels at baseline and after treatment are portrayed in Figure 2. The VAS score of pain, swelling and morning stiffness at baseline was recorded to be 7.6 ± 0.9, 3.3 ± 3.7 and 6.3 ± 2.8 respectively. A significant (<0.001) reduction in VAS scores was recorded after 7 days and 14 days of treatment when compared with the baseline scores. After 7 days of

Table 1. Demographic profile of Waja' al-Mafāṣil (Arthralgia) patients (n = 58)

Characteristics	Frequency (%)
Age group (years)	
<40	14 (24.1)
40-49	18 (31.0)
50-60	26 (44.8)
Mean age ± SD(years)	46.2 ± 7.1
Min-Max(years)	33 - 59
Gender (%)	
Female	41 (70.7)
Male	17 (29.3)
Socio-economic status (%)	
Lower	10 (17.2)
Middle	48 (82.8)
Chronicity (months)	
<10 (%)	29 (50.0)
10-19 (%)	17 (29.3)
20-59 (%)	8 (13.7)
>=60 (%)	4 (6.9)
Median(Inter Quartile Range) (months)	10.5 (3 - 18)
Min-Max (months)	1 - 156
Mizāj / Temperament (%)	
Damawī (Sanguineous)	36 (62.1)
Balghamī (Phlegmatic)	16 (27.6)
Ṣafrāwī (Bilious)	6 (10.3)

treatment, the Mean ± SD VAS score of pain, swelling and morning stiffness was recorded to be 5.0 ± 1.3, 2.0 ± 2.3 and 4.1 ± 2.2 respectively, whereas, after 14 days of treatment, it was found to be 2.8 ± 1.3, 1.0 ± 1.4 and 2.3 ± 1.8 respectively. A significant (<0.001) decrease in Mean ± SD of CRP level from 5.4 ± 2.8 at baseline to 3.4 ± 2.6 after 14 days of treatment was observed in this study (Figure 2).

The results revealed a statistically significant (<0.001) increase in the QoLS score after treatment with Roghan Mālish for 14 days when compared with the baseline score. The Mean ± SD value of the QoLS score at baseline and at the end of treatment was recorded as 68.9 ± 5.3 and 78.5 ± 8.4 respectively (Figure 3).

The changes observed in hemodynamic parameters between baseline and follow-ups were expressed as mean ± SD and shown in Table 2. A significant (<0.05) reduction in systolic and diastolic blood pressure was observed after 14 days of treatment when compared with the baseline value.

The data of laboratory tests obtained at baseline and the end of treatment are depicted in Table 3. The results revealed a significant (<0.05) change in the mean values of Hb% and neutrophils between the baseline and post-treatment. In all the other pathological and biochemical indices, no significant (P>0.05) difference was found between the baseline and after the treatment. No drug intolerance, AEs, or SAEs were reported during the entire study period.

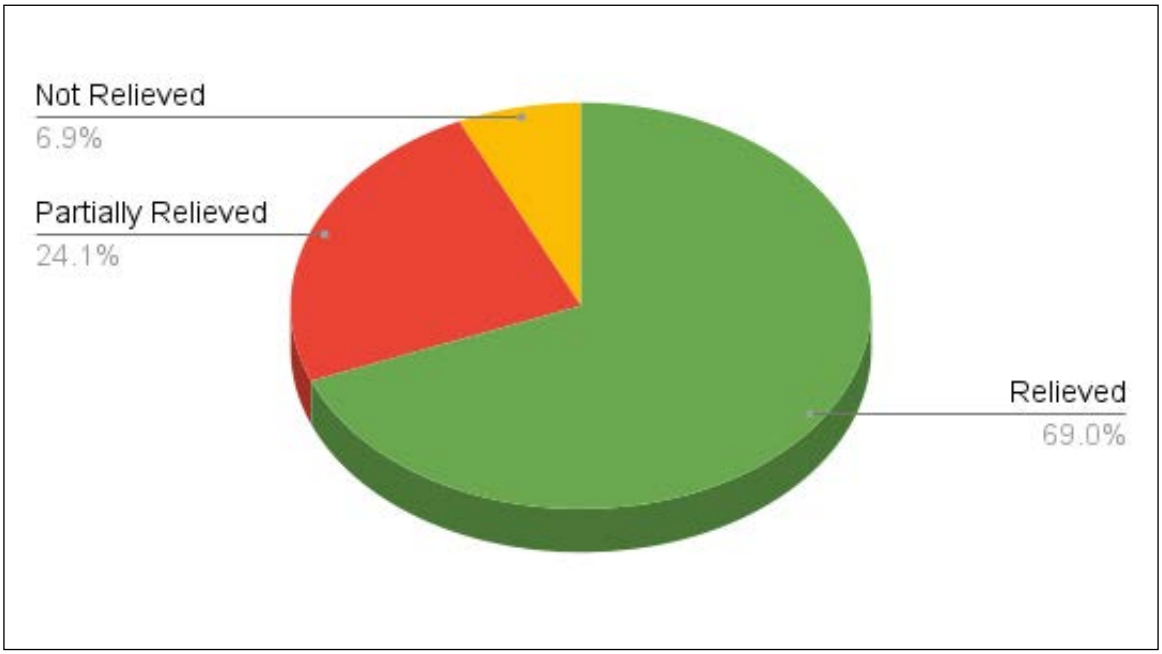
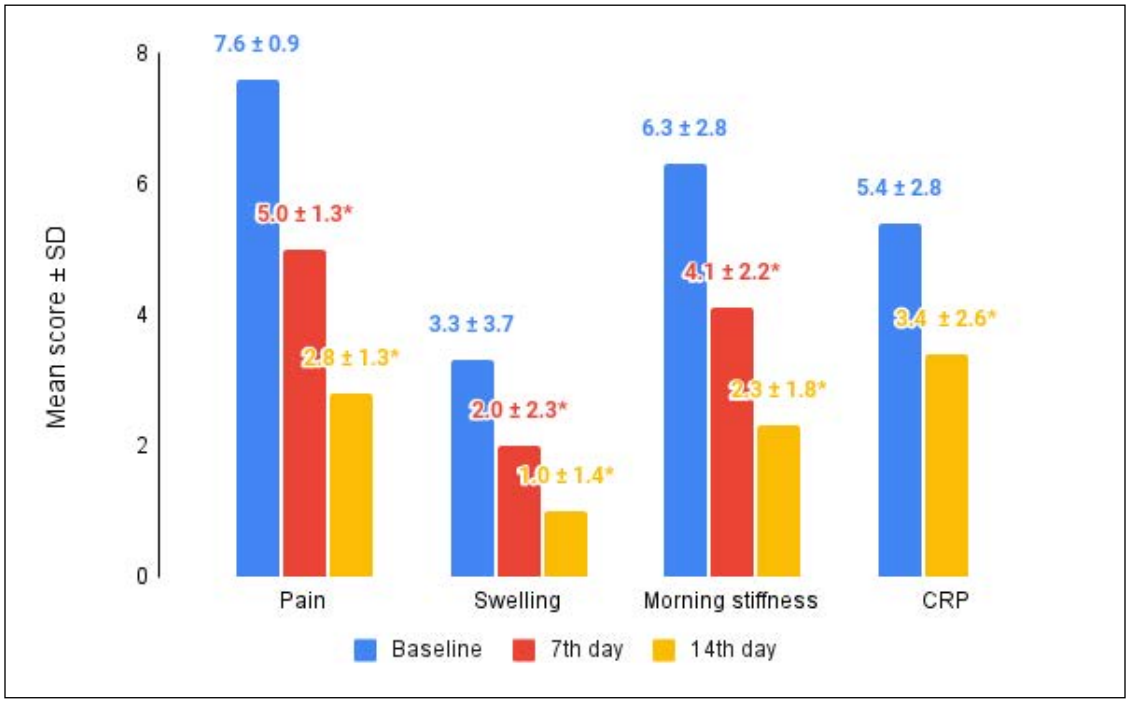
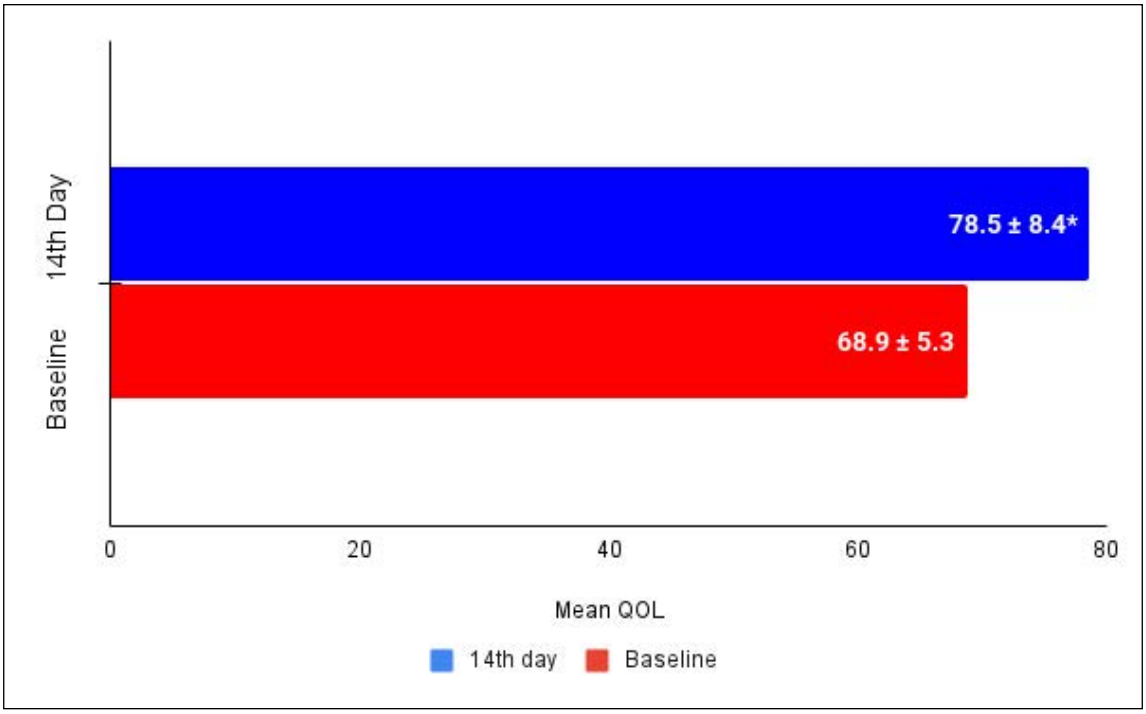


Figure 1. Response of treatment in a patient with Waja' al-Mafāṣil (arthralgia) treated with Roghan Mālish (*n* = 58).



**significant at 5% level*

Figure 2. The mean Visual Analogue Scale (VAS) score and C-reactive protein (CRP) level at baseline and after treatment in Waja' al-Mafāṣil (arthralgia) patients treated with Roghan Mālish. All values are expressed as Mean ± SD (n = 58).



**significant at 5% level*

Figure 3. The mean Quality of life scale (QOLS) score at baseline and after treatment in Waja' al-Mafāṣil (arthralgia) patients treated with Roghan Mālish. All values are expressed as Mean ± SD (n = 58).

Table 2. Hemodynamic parameter of Waja' al-Mafāṣil (Arthralgia) patients at baseline and after treatment with Roghan Mālish (*n* = 58)

Parameter	Baseline (Mean ± SD)	End of trial (Mean ± SD)	P-value
Pulse rate (beats/min)	82.8±7.8	82.5±6.5	0.601
Respiratory rate (breaths/min)	20.5±0.9	20.7±1.1	0.297
Systolic BP (mm/Hg)	118.4±16.7	113.5±12.6	0.049*
Diastolic BP (mm/Hg)	76.7±7.7	74.6±7.1	0.038*
Temperature (°F)	97.3±0.7	97.3±0.5	0.942

**significant at 5% level*

Table 3. Pathological and biochemical indices at baseline and after treatment in Waja' al-Mafāṣil (Arthralgia) patients treated with Roghan Malish (n = 58)

Parameters	Base Line (Mean ± SD)	End of trial (Mean ± SD)	P - Value
Haemoglobin (g/dL)	12.8±1.4	12.6±1.3	**0.002***
WBC (cells/mm3)	8031.6±1520.8	7724.6±1620.1	0.065
Neutrophils (%)	55.7±7.7	57.7±8.3	**0.043***
Lymphocytes (%)	37.8±7.0	35.9±7.0	0.093
Eosinophils (%)	5.2±3.3	5.0±3.9	0.265
Monocytes (%)	1.4±1.0	1.5±0.9	0.463
ESR 1 hr (mm)	26.8±17.4	26.6±16.1	0.992
ESR 2 hr (mm)	53.7±24.8	53.5±24.4	0.969
S.Bilirubin (mg/dL)	0.5±0.2	0.5±0.2	0.405
SGOT (U/L)	21.8±7.0	22.4±6.0	0.443
SGPT (U/L)	20.1±10.5	19.8±6.4	0.554
ALP (U/L)	74.8±18.5	76.7±17.8	0.370
S. Creatinine (mg/dL)	0.8±0.1	0.8±0.1	0.265
S. Urea (mg/dL)	21.4±5.9	20.2±6.2	0.540
S. Uric acid (mg/dL)	5.0±2.7	4.6±1.1	0.096

**significant at 5% level*

All values are expressed as Mean ± SD, *n* = 58, (p-value <0.05 significant). WBC represents white blood cell; ESR, erythrocyte sedimentation rate; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ALP, alkaline phosphatase.

5. Discussion

Chronic joint pain is a widely prevalent condition affecting people more than affected by all cases of diabetes, heart disease, and cancer combined. It is the most prominent cause of joint immobility and dysfunction leading to psychological distress and poor quality of life[19,20]. Chronic joint pain is more frequently associated with osteoarthritis, which negatively impacts the overall health and wellbeing, work productivity of an individual and poses undue socioeconomic implications[21]. The effectiveness of available treatment options for joint pain is limited and their long term use is precluded as they produce various side effects[20].

The present study investigated the safety and analgesic and anti-inflammatory effects of Roghan Mālish (a mixture of turpentine oil and sesame oil) in patients with arthralgia. The demographic profile of study participants demonstrated an increasing trend in the prevalence of arthralgia with the age. It was found more prevalent (44.8%) in population above the age 50 years (Table 1). The results also revealed that compared to their other counterparts,

more female and middle income group participants had joint pains. The result of the present study is in accordance with the previous reports suggesting that joint pains is more common in women and its prevalence increases greatly with advancing age[2,4,22]. The temperament of majority of patients was found to be *Damawī* (Sanguineous 62.1%), followed by *Balghamī* (Phlegmatic 27.6%), and *Ṣafrāwī* (Bilious 10.3) in this study (Table 1), which is reasonably consistent with the Unani literature, and it also affirms the fact that exorbitant *Burūdat* or *Harārat* with or without morbid materials is the dominant cause of Waja' al-Mafāṣil. As per Unani classical text, *Balgham* (phlegm) predominates in the causation of joint pain followed by *Dam* (blood) and *Ṣafrā'* (bile), whereas *Sawdā'* (black bile) is rarely involved[23]. The majority of patients with *Damawī* (Sanguineous) temperament in this study indicated that the disease was caused due to *Sū'-i-Mizāj Ḥārr* (simple hot abnormal temperament) without any involvement of morbid matter in most of the cases. The study results also confirm the phenomenon of feeblest involvement of *Sawdā'* in the causation of disease as no case reported in this study with *Sawdāwī* (Melancholic) temperament.

The pain assessment is critical in classifying the pain condition and validating the treatment effects[24,25]. Visual Analog Scale (VAS), McGill Pain Questionnaire (MPQ) and its short form (SF-MPQ), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Health Assessment Questionnaire (HAQ), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and Disease Activity Score (DAS 28) are widely used self-reporting questionnaires to quantify pain and function in patient with arthralgia[25]. The VAS scale is a valid, reliable, and frequently employed instrument in clinical setting to measure pain intensity and changes before and after treatment[15,16]. There are ample evidences supporting VAS scale as efficient tool for assessing joint pain, morning stiffness, and swelling due to its simplicity and adaptability[26,27]. The Likert scale is commonly employed for the assessment of joint tenderness and swelling[27], however, both VAS and Likert scales can alternatively be used as their responses are highly correlated and yield similar precision in osteoarthritis cases[28].

The VAS scale was employed in this study which seems to be suitable for the assessment of intensity and changing trend of joint pain, swelling, and morning stiffness before and after treatment in patient with arthralgia. The results revealed an overall therapeutic response of 93.1% in patients treated with Roghan Mālish, whereas 6.9% patients showed <30% improvement in joint pain, swelling, and morning stiffness which was considered as no relief (Figure 1). The majority of patients registered in the study were experiencing moderate to severe degree of pain and morning stiffness, and mild to moderate degree of joint swelling at baseline, which were turned to normal with minimal joint pain, stiffness and swelling after treatment. A gradual and highly significant decrease in VAS score was observed, in time dependent manner after 7 and 14 days of topical application of Roghan Mālish (Figure 2). This study also revealed a significant reduction in CRP level following topical application of Roghan Mālish for 14 days when compared with the baseline value. Though the Mean (SD) of CRP level both at baseline and after treatment was found in the normal range clinically, a significant decreasing trend can be observed post treatment (Figure 2). This observation confirms the improvement in signs and symptoms, *i.e.,* joint pain, swelling and morning stiffness assessed through VAS scale, as CRP is known to demonstrate an elevated expression during inflammatory conditions and infections, which falls with the control of underlying trigger[17]. Various reports suggest that the CRP, being an important biomarker of inflammation, can serve not only as a diagnostic tool for arthritis and other joint diseases but also as a measure of therapeutic efficacy[29].

There are numerous evidences that confirm the potential of oral herbal medications in mediating inflammatory processes, however, reports also suggest their potential in down-regulating inflammatory biomarkers upon topical application[29,30]. The findings of the present study corroborate with the previous reports as it exhibited down-regulation in elevated expression of CRP upon topical application of Roghan Mālish and alleviation of the signs and symptoms, suggesting CRP level as a potential tool in diagnosing the level of inflammatory condition and measuring the therapeutic outcome. To the best of our knowledge, this is the first prospective study to demonstrate the analgesic and anti-inflammatory effect of Roghan Mālish in patients with arthralgia, and no previous report is available to compare the effects observed in this study. However, the evidence available on turpentine oil and sesame oil supports the findings of this study, as these have exhibited potent anti-oxidant, analgesic and anti-inflammatory activities through experimental and clinical studies[5,31–35].

Quality of Life Scale (QoLS) is a valid tool with high test-retest reliability, frequently used for assessing overall well-being and evaluating health outcomes in patients with chronic conditions including osteoarthritis, rheumatoid arthritis, low back pain, and fibromyalgia. It is a 16-item tool for measuring multiple domains of quality of life, which include material and physical well-being, relationships with other people, social, community and civic activities, personal development and fulfilment, recreation, and independence, the ability to do for yourself[18]. In the present study, QOLS was employed to assess the overall well-being of a patient before and after treatment. The result revealed a significant increment in QOLS score after 14 days of treatment with Roghan Mālish when compared with the baseline score (Figure 3), suggesting a significant correlation between the changing trends in joint pain and improvement in the quality of life of patients. The study also affirms the reports suggesting chronic joint pain is the most important determinant of disease activity and the factor that negatively impacts the quality of life[21,36].

Interestingly, the observation of hemodynamic parameters in this study revealed a significant reduction in systolic and diastolic blood pressure at the end of the treatment when compared with the baseline value (Table 2). The result indicates a positive relationship between pain intensity and blood pressure and supports the report suggesting that persistent and chronic pain tend to increase blood pressure and may increase the chance of developing hypertension[37]. The safety profile of Roghan Mālish was evaluated using pertinent clinical and laboratory indices and by reporting drug intolerance, AEs, and SAEs in this study. The results of laboratory investigations revealed no significant changes in clinical and laboratory indices between the baseline and after the treatment except in Hb% and neutrophils levels. A significant decrease in Hb% and a significant increase in neutrophils level at the end of treatment was observed when compared with the baseline value (Table 3), which was clinically insignificant. The topical application of Roghan Mālish exhibited no untoward effects as no drug intolerance, AEs or SAEs were reported during the entire study period. However, it is quite possible that those who are hypersensitive to turpentine oil on the topical application may exhibit allergic reactions in the form of itching, redness, and rashes over the applied part. The result indicates that the topical application of Roghan Mālish is safe and may be used successfully to treat arthralgia. However, this study may have possible limitations. Since this preliminary study was conducted to generate evidence for further randomized controlled trial studies, no dietary restrictions or changes in the routine activities or exercise were recommended to the study subjects. The confounding factors such as diet, exercise, and other factors were not controlled in the study, which may have potentially influenced the outcome measures of the study. These limitations could be addressed in future RCT studies.

6. Conclusion

This prospective pilot clinical trial portrayed valuable information about analgesic and anti-inflammatory effects of Roghan Mālish, 'a novel topical formulation', in patients with Waja' al-Mafāṣil (arthralgia). The results obtained in this study substantiated the therapeutic claims about the formulation as it exhibited statistically significant improvement in joint pain, swelling, and morning stiffness, down-regulated the elevated expression of CRP level and improved the quality of life of the study population. The tested formulation was well tolerated with no undesirable side effects. However, it may cause allergic reactions in patients who are hypersensitive to turpentine oil. This pilot study could serve as the basis for further experimental and clinical investigations to confirm the study findings, and to complement the drug armory with equally safe and effective remedies for joint pain management.

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