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CLINICAL EVALUATION OF EFFICACY OF *MUNḍIJ* AND *MUSHIL* THERAPY IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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Keywords:

Rheumatoid Arthritis, *Munḍij* and *Mushil* therapy, Unani Medicine, *Waja' al-Mafāṣil*, Habb-e-Gul-e-Aak

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ABSTRACT: Objective: To study the anti-arthritic effect of a Unani regimen comprising of *Munḍij wa Mushil* therapy along with Habb-e-Gul-e-Aak and to propose a safe and alternative therapy for RA. **Materials and Methods:** In this clinical trial, 30 diagnosed patients of RA fulfilling the inclusion and exclusion criteria were recruited and randomly distributed into two groups A&B with 20 patients in the test and 10 in the control groups, respectively. In Group A, *Munḍij* and *Mushil* therapy was given for 21 days once in the morning and then HGA for 28 days twice a day. Patients in Group B were treated with Hydroxychloroquine (HCQ) 200 mg twice a day for 49 days. All the patients were examined clinically before the treatment and follow-up was programmed 7th day, 21st day, 28th day, 42nd day, and 49th day. The efficacy was determined on subjective parameters as well as Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Visual Analog Scale (VAS). The biochemical and hematological investigations were conducted on baseline, 21st and, 49th day. The statistical analysis was done by the Wilcoxon matched-pairs signed-ranks test, Maan-Whitney test, and Paired't test. **Results:** The improvement in both Groups at the end of treatment was statistically significant on WOMAC & VAS scales and subjective parameters. **Conclusion:** The findings demonstrated significant symptomatic relief in the patients of RA suggesting that the regimen is effective in the management of RA.

INTRODUCTION: Rheumatoid Arthritis (RA) is defined as a chronic systemic autoimmune disease that primarily affects the lining of the synovial joints resulting in its deformity and disability [1]. The prevalence of RA worldwide is about 0.8% (0.3% - 2.1%) of the total population, and in India, it is 0.5% - 0.75%. The disease is more common in women than in men (3:1) and can occur at any age but the most common age of onset is between 30 and 50 years [2].

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The exact cause of RA is still unknown but there are multiple factors (like genetic factors, environmental factors, infectious agents, *etc*.) that may play an important role in the causation and progression of the disease [2]. The clinical manifestation of RA may be articular and extra-articular. Symmetrical joint involvement is considered a typical feature of RA; the most common presentation being the involvement of the small joints of hands, wrists, and feet with pain, swelling, and stiffness on inactivity that improves with movement.

The extra-articular involvement affects the lungs, heart, muscles, blood vessels, skin, *etc*. The pathognomonic sign of RA is the symmetrical involvement and multiple joints tenderness especially in the morning with positive RF and Anti

Citrullinated Peptide Antibodies (ACPAs) [2, 3, 4, 5]. Various drugs are in use for the treatment of RA such as Disease-Modifying Anti-rheumatic Drugs (DMARDs) like methotrexate, hydroxychloroquine (HCQ), non-steroidal anti-inflammatory drugs (NSAIDs) like diclofenac, piroxicam, and corticosteroids such as prednisolone, *etc*. These drugs provide symptomatic relief but have limited effect on the arrest of the progression of the disease, and are also associated with certain side effects like gastric ulcer, perforation, renal function impairment, heart failure, stroke, *etc*. Therefore, patients suffering from a chronic musculoskeletal disorder such as RA, frequently seek alternative treatment of the disease. Unani medicine which has been practiced for hundreds of years offers effective treatment for different diseases of joints including RA. Several studies conducted in recent years have demonstrated the therapeutic potential of Unani drugs in the management of joint diseases and other musculoskeletal disorders [6, 7, 8].

Since Western Medicine lacks effective and safe anti-arthritic agents, therefore, Unani anti-arthritic drugs are studied on a priority basis. In the Unani system of medicine, RA has been attributed to be caused due to the derangement of humours specifically, *Khilṭ Balgham* (phlegm) and *Khilṭ Sawdā'* (black bile). Furthermore, people with compromised immunity are afflicted the most with the disease indicating simultaneous involvement of humors and the immune system. Therefore, the drugs having the properties of improving the quality of the *Khilṭ* (supposed to be involved in the causation of arthritis), strengthening immunity, and providing symptomatic relief are used in the management of arthritis.

The treatment of arthritis continues for a long duration, therefore the use of a drug for such a long period can result in various adverse effects. But the Unani drugs have very little liability to produce any major side effect even if used for a long duration because they are selected after taking into account the temperament of the disease and the person to whom the treatment is to be given and that too after appropriately processing to ensure safety. Several single and compound Unani drugs subjected to experimental and clinical studies have shown very promising results in various musculoskeletal disorders. For example, Buzidan **(** *Tanacetum umbelliferum***)** was demonstrated to possess significant analgesic and anti-inflammatory effects [9]. Sheer-e-Zaqoom **(***Euphorbia neriifolia***)**, was shown to produce anti-arthritic activity [10]. Suranjan Shirin (*Colchicum autumnale*), Ushba (*Smilax regilii*), and Bisfaij (*Polypodium vulgare*) possessed anti-arthritic activity; among them, Bisfaij was found to be the most effective in advanced rheumatoid arthritis with deformities [11].

Many compound Unani formulations such as Majoon Azaraqi [12], Majoon Suranjan [13], Majoon Seer Alvi Khan [14], *etc*. have been reported to produce significant anti-arthritic effects. Besides this, Unani physicians also used many non-pharmacopoeial preparations which have shown significant anti-inflammatory, analgesic, and anti-arthritic activities [15, 16]**.**

Compound formulations are mostly preferred over single drugs and prescribed more frequently by physicians in the management of arthritis as it is believed that the disease has a complex pathology so a compound drug that possesses different therapeutic attributes at a time, is considered more appropriate as it covers many aspects of complexities. Further, compound formulations are usually prepared to take into account the side effects of the drugs that are likely to arise due to their use over a relatively long period of administration. Therefore, some of the ingredients are specifically included in the compound to alleviate or minimize the toxic effects of the main drugs [17].

The characteristic symptoms of RA, and that of Unani description of *Waja'al-Mafāṣil Muzmin* [18], can be correlated with its *Muzmin* form mainly the one developed due to the impairment in *Balghami*, and/or *Sawdāwī* humors. So, the use of Unani drugs that are supposed to possess *Munḍij* (concoctive of phlegm and black bile), and *Mushil-i-Balgham* and *Sawda'* (phlegmogogue and melanogouge) effects are considered useful in its treatment. Furthermore, drugs that provide immediate relief of symptoms like pain, morning stiffness, swelling, tenderness, etc. are also likely to be useful in the management of RA. *Muhallil* (resolvent) and *Musakkin* (soothing agent) drugs are often used for this purpose.

MATERIALS & METHODS: The clinical trial was conducted on 30 diagnosed patients of RA, who visited the OPDs of departments of Ilaj Bit Tadbeer and Moalejat, Ajmal Khan Tibbiya College and Hospital, Faculty of Unani Medicine AMU, Aligarh.

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee, Ajmal Khan Tibbiya College, Faculty of Unani Medicine, Aligarh Muslim University, Aligarh [D.N0. 345/FUM dated 20.05.2019, the committee under S. No. 10].

Informed Consent Procedure: All the patients were informed about the nature of the study along with the expected benefits and drawbacks in their language. Their written voluntary consent is taken and they are given the right to withdraw themselves at any time during the protocol.

Selection Criteria: Clinically diagnosed patients of either sex aged between 20 to 60 years, with positive RA factor (screened by blood investigation) having morning stiffness, with 3 or more joints involved, having arthritis of hand joint and symmetrical involvement were included after their written informed consent. Patients of gout/osteoarthritis/rheumatic arthritis/tubercular arthritis, chronic cases of more than 10 years, with severe crippling deformity, complicated cases of RA with systemic manifestation pregnant and lactating women, those having diabetes, severe hypertension, IHD, and severe systemic diseases were excluded from the study. For the screening of cases careful history, clinical examination, and required blood investigations were carried out.

Study Design: All the enrolled cases were randomly allocated into two groups; 20 cases in test group A and 10 cases in control group B. It was an open-label clinical study hence neither clinicians nor patients were blinded to the intervention.

Intervention: In the test group, the patients were initially treated with *Munḍij* and *Mushil* therapy for 21 days. The polyherbal formulation of the following 8 drugs was given:

Ingredients Botanical Name Dose: Aftimoon *Cuscuta reflexa* 5 g, Bisfaij fustaqi *Polypodium vulgare* 5 g, Badiyan *Foenaculum vulgare* 7 g, Bekh e badiyan *Foenaculum vulgare* 7 g, Suranjan Shirin *Colchicum autumnale* 5 g, Shahitra, *Fumaria officinalis* 7 g, Chirayta, *Swertia chiraita* 7 g, Unnab *Zizyphus vulgaris* 5 (in No.).

Ingredients were provided by Dawakhana Tibbiya College and identified by the Botany Department of Aligarh Muslim University, Aligarh. Physicochemical phytochemical and safety studies were done to maintain the standard quality of ingredients of intervention.

All the ingredients were soaked in 200 ml of water at night and boiled at low flame for 10 minutes, filtered, and advised to be consumed orallyin the morning empty stomach mixed with Gulqand 15 g. After *Munḍij* and *Mushil* therapy, Habb-e-Gul-e-Aak (HGA) was given for 28 days orally twice a day (as *Muhallil* and *Musakkin* drug).

HGA is a compound pharmacopoeia formulation advised in arthritis, and other inflammatory diseases of the joints [19, 20]. Patients in Group B were treated with Hydroxychloroquine (HCQ) 200 mg twice a day orally for 49 days.

All the patients were examined clinically before the treatment and follow-ups were programmed on the 7^{th} day, 21^{st} day, 28^{th} day, 42^{nd} day, and 49^{th} day.

Assessment Parameters: The efficacy of the intervention was determined on the following parameters.

Subjective Parameters:

- Pain (number of joints involved > 4)
- Morning stiffness of joints
- Restriction of movement
- Tenderness

Subjective parameters were assessed (at baseline, 21^{st} day, and 49^{th} day of treatment) according to severity and graded as 0 = none, 1 =Mild, 2 = Moderate, 3 = Severe. Morning stiffness was assessed based on duration by an arbitrary scale with scores i.e. Grade 0 (no morning stiffness), Grade 1 (stiffness up to 30 minutes), Grade 2 (30 minutes to 1hr), and Grade 3 (>1hr).

Objective Parameters:

- Visual Analogue Score for pain (0-10)

- Western Ontario and McMaster Universities Osteoarthritis Index Score
- Erythrocyte Sedimentation Rate
- C-Reactive Protein

Assessment on VAS & WOMAC was done at baseline and 49th day of treatment. Pain, stiffness, and functional limitation were used as three subscales of WOMAC; the sum of scores for each response was calculated and analyzed. Higher scores for each subscale indicated worse pain, stiffness, or physical function. Based on the total WOMAC score obtained (out of 96), the patients were characterized as having low-risk (score ≤ 60), moderate-risk (score 60-80), and high-risk (Score ≥ 81) [21, 22]. The biochemical and hematological investigations were conducted at baseline on the 21st, and 49th day to determine the effect of the drugs, and also for the assessment of side effects if any.

Safety Parameters: For assessment of safety, investigations like a complete Haemogram, Liver and kidney Function Test, blood sugar level, and routine urine tests were done. During the intervention, clinical adverse events or unwanted effects were observed.

Withdrawal Criteria: The following were the criteria to withdraw the patient from the study.

- ✓ Right of the subject to withdraw consent at any time during the trial
- ✓ Failure to follow the protocol
- ✓ Any adverse reaction or adverse event
- ✓ Any acute systemic illness during the therapy
- ✓ Drug defaulters
- ✓ Drug intolerance
- ✓ Any subject of the test group does not respond to the treatment

Concomitant Therapy/ Rescue Medication: No concomitant therapy or rescue medication was provided or required in any case in the study.

Data Collection and Statistical Analysis: Data of all the cases were recorded on case record form and later subjected to appropriate statistical analyses. The analysis of data within the group was done by the Wilcoxon matched-pairs signed-ranks test and the intergroup comparison was done by the Maan-Whitney test. The safety parameters were analyzed using the Paired‘t’ test.

RESULTS AND OBSERVATIONS:

Physicochemical and Phytochemical Analyses and Safety Study of Test Drug:

Physicochemical Studies: The following parameters were adopted for the standardization of *Nuskha-e-Munḍij wa Mushil* (test drug) as per the W.H.O guideline. The data were based on multiple observations.

Organoleptic Description: The powder of the test drug was found to be brown in color, coarse in appearance, with a pleasant odor, and bitter.

Extractive Values: The mean percentage of successive extracts of the test drug was found to be 5.7 ± 0.153, 1.05 ± 0.150, 1.03 ± 0.174, 4.63 ± 1.867, 3.85 ± 0.318, and 14.35 ± 0.705 in different organic solvents viz. petroleum ether, diethyl ether, chloroform, acetone, alcohol, and water respectively using a Soxhlet’s apparatus.

Alcohol and Water Soluble Contents: The mean percentage of water and alcohol-soluble contents at 22°C was found to be 28.58 ± 1.114 and 9.74 ± 0.556 respectively.

Loss of Weight on Drying and Moisture Content: The mean percentage of loss of weight on drying and moisture content present in the test drug was found to be, 15.64 ± 0.014, and 7.33 ± 0.577 respectively.

Ash Values: The mean percentage of total ash, acid-insoluble ash, and water-soluble ash values in the test drug were found to be 8.57 ± 0.017, 7.43 ± 0.033, and 3.42 ± 0.088, respectively.

Determination of pH: The pH of the test drug was determined by a synchronic digital pH meter 335 equipped with a combined electrode, at 18°C and found to be 4.83 ± 0.033 in 1% aqueous solution and 4.6 ± 00 in 10% aqueous solution.

Specific Gravity: The mean value of specific gravity and refractive index of the test drug was found to be 1.0205 ± 0.819.

Viscosity: The mean value of the kinematic and dynamic viscosity of the test drug was found to be 1.4371±0.038, and 1.6235 ±0.0079, respectively.

Phytochemical Analysis:

Qualitative Analysis: The phytochemical analysis of the chemical constituents present in the test drug revealed that the test drug contained alkaloid**s,** carbohydrates, flavonoids, glycosides, proteins, phenols, sterols, saponins, tannins, and resins.

Fluorescence Analysis: Fluorescence analysis of the powdered test drug and successive extracts treated with different chemical reagents was done and a color change so appeared was observed.

Thin Layer Chromatography (TLC): TLC was carried out on already prepared plates for different successive extracts viz. petroleum ether, aqueous, and alcohol in different mobile phases, treated in different lights and iodine chamber to see the color and number of spots, and Rf values were calculated.

Safety Study:

Microbial Load: Total bacterial counts were found to be within permissible limits as the total bacterial count in the test sample did not exceed 6400 cfu/g, while the total yeast and mould count was found to be 320 cfu/g. The specific pathogen such *as E. coli*, *Salmonella*, *S. aureus*, *P. aeuginosa*, etc. was absent.

Heavy Metals: Heavy metal contamination of the test drug was within the normal limits.

Aflatoxins: Screening of the test drug for aflatoxin determination showed that aflatoxin contamination was absent in the test drug sample.

Pesticide Residue: Pesticide residue determination of the organ chlorine pesticides like DDT and Endosulfan *etc*. were not detected.

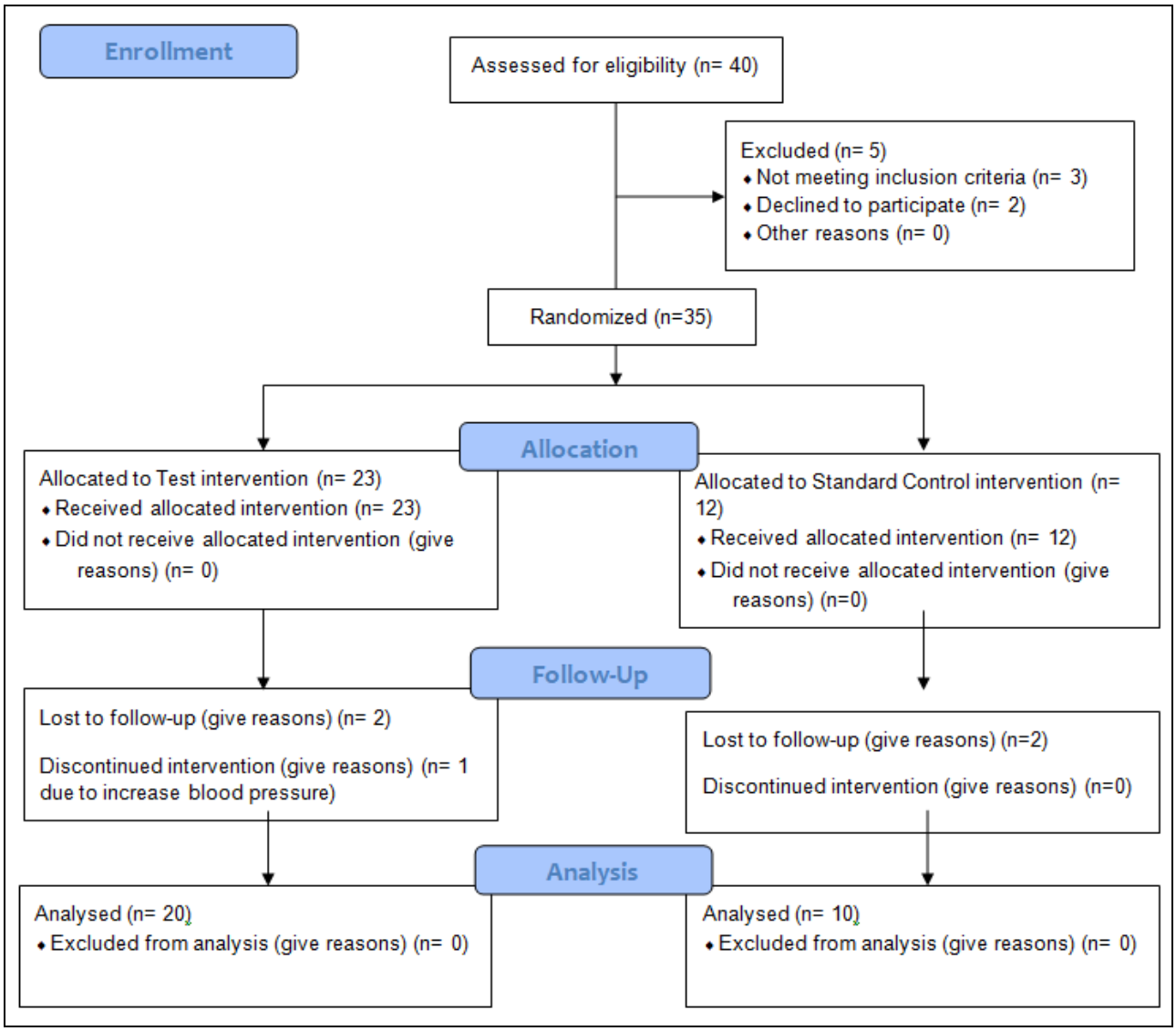

FIG. 1: CONSORT FLOW DIAGRAM

Among a total of 30 participants, 21 (70%) of the patients in the study were females, while only 9 (30%) were males with a ratio of 3:1 **Table 1**. The study also demonstrated that 21 patients (70%) belonged to the age group of 15-40 years, while 9 (30%) in the age group of 41-60 years **Table 1.**

TABLE 1: DISTRIBUTION OF PATIENTS ACCORDING TO DEMOGRAPHIC /CLINICAL DATA

S. no.	Attributes		No. In Test Group	No. In Control group	Total No. (%)
1	Age (in years)	15-40	15	6	21 (70)
		41-60	5	4	9 (30)
2	Gender	Male	7	2	9 (30)
		Female	13	8	21 (70)
3	Disease Severity	Mild	15	7	22
		Moderate	5	3	8
		Severe	0	0	0

The effects of the intervention on subjective and objective parameters are as follows;

Morning Stiffness: In Group A (test group), all 20 patients suffered morning stiffness at the baseline (mean ± S.D was 2.05 ± 0.76). After treatment, it gradually decreased and 7 patients were completely relieved to grade 0 (mean ± S.D was 1.55 ± 0.69). The improvement in Group A at the end of treatment was statistically significant (p<0.001). All the patients in Group B also had morning stiffness at the baseline (mean ± S.D was 2.2 ± 0.63), which at the end of treatment reduced to 0.8 ± 0.42, (p<0.01), which was statistically significant **Table 2.**

Tenderness: The tenderness was present in 22 (73.33%) patients. In Group A it was present in 15 (75%) patients at baseline and mean ± S.D was found 1.25 ± 0.91, which at the end of treatment reduced to 0.55 ± 0.51 showing a statistically significant reduction (p<0.01). In Group B mean ± S.D was found to be 1.5 ± 1.18 at baseline. It reduced significantly (p<0.05) to 0.6 ± 0.52 at the end of the treatment **Table 2.**

Difficulty in Movement: The difficulty in movement was present in 25 (83.33) patients. In group A at baseline mean ± S.D was 1.75 ± 0.97 and at the end of the treatment, it decreased to 0.65 ± 0.49 showing a significant result (p<0.001). In Group B at baseline mean ± S.D was 1.6 ± 1.06 and at the end of treatment, it decreased to 0.3 ± 0.48 (p<0.01), which was statistically significant **Table 2.**

Joint Pain: At baseline, all patients in Group A had joint pain (mean ± S.D was 5.1 ±1.65) that was reduced (mean ± S.D 0.8 ± 0.57) significantly (p<0.001) after the treatment. All the patients of Group B at the baseline had joint pain (with mean ± S.D 5.9 ± 1.969) that decreased to1.0 ± 0.42 (p<0.001) at the end of treatment and was statistically significant **Table 2.**

Swelling: In Group A, the swelling was present in 16 patients at baseline (mean ± S.D was 0.7 ± 0.98) which reduced (mean ± S.D was 0.1 ± 0.31) significantly (p<0.01) after the treatment **Table 2.**

In Group B, the swelling did not reduce significantly in statistical terms but the reduction was observed clinically.

WOMAC Score: In Group A, mean ± S.D of pain score (out of 20), stiffness score (out of 8), and physical function score (out of 68) before treatment were found to be 9.65 ± 4.03, 4.25 ± 1.552, and 36.95 ± 13.197 respectively, which reduced to 4 ± 2.714, 0.95 ± 0.605, and 14.65 ± 6.385 at the end of treatment. In Group A, at baseline 15 patients belonged to low-risk, and 5 patients belonged to the moderate-risk category, while at the end of treatment, all the patients belonged to the low-risk category. Similarly in Group B, 7 patients belonged to the low-risk and 3 patients belonged to the moderate-risk category at the baseline, while at the end of treatment, all the patients belonged to the low-risk category. No patients in both groups were found to be in a high-risk category. The intra and inter-group comparison of total WOMAC score (out of 96) was done at baseline and after treatment. In Group A the mean ± S.D at the baseline was found to be 50.75 ± 14.411, which reduced to 19.3 ± 6.233 after the treatment, which was found statistically significant (p<0.001). In group B the mean ± S.D at the baseline was found

to be 50 ± 14.72 which decreased to 22.4 ± 7.633 at the end of treatment (p<0.001).

VAS Score: The intra and inter-group comparison of total VAS score was done at baseline and after treatment. In Group A the mean ± S.D at the baseline was found to be 5.1 ± 1.65, which reduced significantly (p<0.001) to 1.35 ± 0.988onthe 49th day. In group B the mean ± S.D at the baseline was found to be 5.9 ± 1.969which declined to 1.2 ± 0.632 at the end of treatment (p<0.001).

TABLE 2: EFFECTS OF DRUGS ON THE SUBJECTIVE PARAMETERS IN *WAJA' AL-MAFĀṢIL* (RHEUMATOID ARTHRITIS) PATIENTS

Subjective Parameters		Group A N = 20			Group B N = 10		
		Baseline	21st Day	49th Day	Baseline	21stDay	49th Day
Morning Stiffness	Mean ± SD	2.05± 0.76	1.55± 0.69	0.7±0.57	2.2 ±0.63	1.4 ± 0.52	0.8± 0.42
(Grade)	*p-value*		0.002	< 0.001		0.008	0.002
Joint Pain	Mean ± SD	2.1±0.76	1.65±0.69	0.8±0.57	2.4± 0.63	1.7± 0.52	1.0±0.42
Swelling (Grade)	Mean ± SD	0.7±0.98	0.3±0.47	0.1±0.31	0.7±1.06	0.4±0.52	0.2±0.42
	p-value		0.016	< 0.008		0.50	0.125
Tenderness (Grade)	Mean ± SD	1.25± 0.91	0.85±0.67	0.55±0.51	1.5 ± 1.18	0.7 ± 0.67	0.6±0.52
	p-value	-	0.008	0.002	-	0.016	0.016
Restricted Movements	Mean ± SD	1.75 ±0.97	0.95±0.67	0.65 ±0.49	1.6±1.06	0.5 ±0.53	0.3±0.48
(Grade)	*p-value*	-	<0.0001	<0.0001	-	0.08	0.008

The test applied: Wilcoxon matched-pairs signed-ranks test for within-group comparison.

TABLE 3: ASSESSMENT OF WOMAC SCORE

Variables	Group A		Group B	
WOMAC Index	Baseline	49th Day	Baseline	49th Day
Pain Score (out of 20)				
Mean ± S.D	9.65 ± 4.03	4 ±2.714	11.2 ± 3.584	4.9 ± 2.846
Stiffness Score (out of 8)				
Mean ± S.D	4.25 ± 1.552	0.95 ± 0.605	5.1 ± 1.595	1.5 ± 0.972
Physical Function Score (out of 68)				
Mean ± S.D	36.95 ± 13.197	14.65 ± 6.385	33.7 ± 12.221	15.1 ± 7.078
WOMAC Index total score (out of 96)				
Mean ± S.D	50.75 ± 14.411	19.3 ± 6.233	50 ± 14.72	22.4 ± 7.633
WOMAC index score categories				
Low risk (score ≤ 60)	15	20	7	10
Moderate risk (score 60-80)	5	0	3	0
High risk (Score ≥ 81)	0	0	0	0

Test applied: Paired t-test.

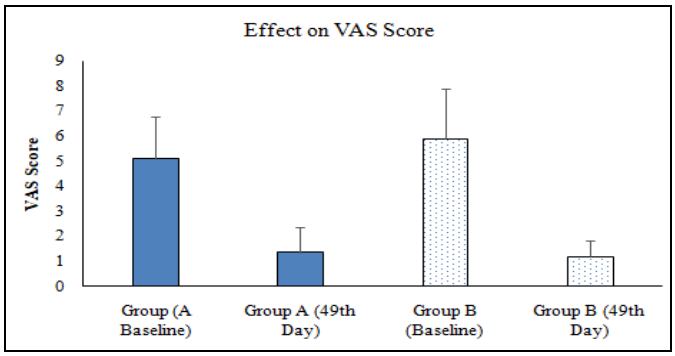

FIG. 2: EFFECT ON VAS SCORE (MEAN ± SD)

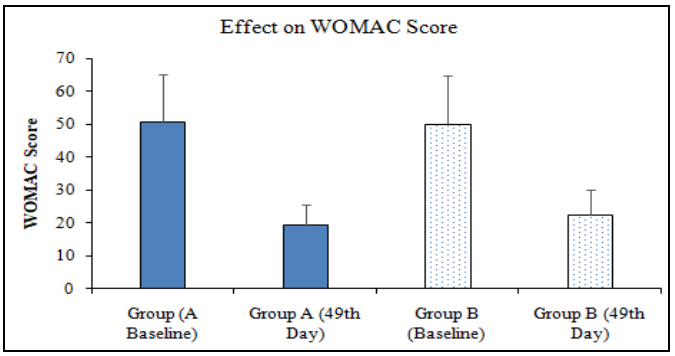

FIG. 3: EFFECT ON WOMAC SCORE

Assessment of Safety: No clinical adverse event was observed in any patient of the group that received the test drugs. Similarly, no adverse changes were found in hematological, and biochemical investigations done before and after the intervention.

DISCUSSION: The demographic findings showed that it is more prevalent in women than in men **Table 1**. A similar observation was reported by other workers [23]. Due to the overwhelming proportion of women who develop RA, some experts feel that there is a strong link between

female hormonal changes and the onset of RA symptoms [24]. Although there is no conclusive report on the higher prevalence of RA among females as compared to males however recent reports suggest that females are less likely than males to achieve remission [25]. A prevalence study with a higher number of patients from different centers will provide more clear information. The study also demonstrated a higher number of cases in the age group of 15-40 years **Table 1**. This data coincides with the study conducted by Islam *et al*. (2015)[26] and was also found in consonance with other descriptions as mentioned in the literature that RA mostly appears between the ages 30 and 50 [2]. In our study, more cases were enrolled from the mild category in the test group in comparison to the control group. This is due to the randomization and enrolment of a higher number of cases in the test group.

Physicochemical and phytochemical Analyses and safety studies of test drugs validated and authenticated their use as pharmaceutical interventions. The test drugs were found safe on the safety parameters that have been mandated by WHO concerning plant drugs and natural products. The concentration of metals, Aflatoxins, Pesticide residue, and Microbial load was found to be within the normal limits.

The *Munḍij* and *Mushil* therapy was itself found effective in treating the disease to an extent, as during the initial 21 days of therapy patients reported considerable relief. The ingredients of the test drug have pharmacological activities required for the treatment of the disease according to Unani principles. Aftimoon (*Cuscuta reflexa*) has been described to be a purgative that removes the impaired humors mainly the phlegm and, black bile, and is useful in arthritis [17]. Badiyan (*Foeniculum vulgare*) is carminative, digestive, resolvent, deobstruent, and tonic to the stomach if the digestive system is afflicted with the dominance of black bile. Its root Bekh-e-Badiyan (*Foeniculum vulgare*) is used as a concoctive and is one of the five purgatives [27], that are commonly used in Unani medicine and other traditional medicines. Bisfaij (*Polypodium vulgare*) is purgative which expels bile and phlegm [28]. It has also been reported to be effective in *Waja'al-Mafāṣil Mutasallab* (arthritis with deformities) [6, 29]. According to IbnSina, Suranjan Shirin (*Colchicum autumnale*) possesses two different components with opposite actions i.e. purgative and costive (*Mushil wa Qabiz*) at a time. Consequent upon an action of *Hararat-i-Gharizi* (innate heat), and *QuwaTabi'iyya* (natural faculties) in the body, the *Mushil* (purgative) part gets separated; which resolves and expels out the morbid matter from the body, especially the joints. Later, the costive part acts on the joint and helps in straightening out the joints by strengthening them and restoring the normalcy of function and that structure to some extent [17, 30]. It is considered to be a prototype anti-arthritic agent effective in almost all types of arthritis [31, 32]. Shahatra (*Fumaria officinalis*) is used as a purgative for black humor and bile. Unnab (*Ziziphus vulgaris*) is used to liquefy the thick humors and purify the blood [30, 31].

This formulation was aimed at removing the morbid matter that is presumed to be the main causative factor.Since *Waja'al-Mafasil* is caused due to *Ghair Tab'ee* (morbid) *Balgham* and *Sawda*, it produces *Sue Mizaj Maddi.* To bring it to equilibrium, evacuation of these types of morbid matter is necessary. Once the morbid matter is removed *Tab'ee Mizaj* is restored bringing out the normalcy. This evacuation is known as *Tanqiya* and the restoration of *Mizaje Tab'ee* is known as *Ta'deel.* The combination of these drugs has *Muhallil, Mulattif, Mufattehe Sudad, Munḍij,* and *Mushil -i-Balgham wa Sawda* effects helping to evacuate the *Madda* and relieve the symptoms of *Waja' al-Mafāṣil.*

In an experimental study, HGA has been shown to produce significant effects against acute, sub-acute, and chronic forms of inflammation but in established arthritis, its effect was more pronounced [33]. A clinical study was also done that showed HGA had relieved the symptoms of arthritis [34]. Given the reported effect and the common practice of physicians with HGA in the management of arthritis, it was included in the regimen proposed for RA in the present study. The effects of the test drug observed on major symptoms were as follows.

Morning Stiffness: Morning stiffness (that lasts more than 1 hour) is the characteristic feature of RA and differentiates it from the other types of arthritis. It affects the ability to work and the

overall quality of life, therefore, the improvement in morning stiffness following the treatment, is taken as the index of the efficacy of that particular treatment. All the patients included in this study had morning stiffness. The reason behind the morning stiffness is supposed to be the spasm of the synovial membrane and related tendons which is because of the lack of oxygen and tissue nourishment **Table 2**. Immobilization of the joints for over a period especially at night leaves the area deficient in blood and ultimately relatively cold. Swelling also plays an important role in developing ischemia by exerting mechanical pressure over microvasculature. That is why the restoration of the movements of the particular area improves the circulation and makes it relatively warm. This explains why the condition is worse in the initial hours of the morning and gets aggravated in winter.

In *Unani* medicine, the morning stiffness may be attributed to comparatively *Burudat* (coldness) of morning and night time which is favorable for the production of *Balgham*. Besides this, the patients were usually involved in different activities during the daytime leading to the production of *Hararat* (heat) which decreases the stiffness by dissolving the *Balgham*. So, the test drugs were found effective due to their *Haar Mizaj* (hot temperament) that modulates the *Burudat* (coldness) evacuates the morbid matter and improves the circulation hence thereby decreasing the morning stiffness. A clinical study conducted by Abid (2017), also indicated that HGA decreased morning stiffness due to its systemic effect i.e. anti-inflammatory [34]. Islam *et al.*, (2015) evaluated that the *Munḍij* and *Mushil* therapy can evacuate the morbid matter from the affected parts of the body and relieve the symptoms of arthritis [26]. The findings of the present study indicated that the treatment with Unani drugs significantly reduced the morning stiffness of patients with RA.

Swelling: Extravasation of fluids and cells from the bloodstream into the intercellular space leads to local swelling and effusion in and around the joints. Such abnormal accumulation of the fluid is responsible for swelling, pain, and restriction of movements. So, when the *Munḍij* and *Mushil* drugs were given they evacuated such fluid decreasing the swelling. Furthermore, joint inflammation also causes swelling which increases when the joint remains immobile for quite some time. The administration of HGA is more likely to decrease the swelling. Similar findings have been reported by Abid (2017) in respect of HGA [34]. Nafees *et al* (2015) also evaluated the anti-inflammatory effect of HGA indifferent phases of inflammation and reported that it is more effective in chronic inflammation [7]. In the present study, it was observed that the swelling is reduced more in comparison to standard drug HCQ. Suranjan and Bisfaij *etc*. were studied by Viqar (2012) and found to possess a significant anti-inflammatory effect in chemically induced RA [11]. In several other studies, Bisfaij has been reported to produce a significant anti-inflammatory effect [35]. According To Unani literature, it possesses important pharmacological effects such as *Mulattif* (making the morbid humours detachable from joints) and *Mukhrij-i-Sawda wa Balgham* (eliminator of morbid humours *Sawda* and *Balgham*), therefore, it can be used in the advanced stage of RA [6].

Tenderness: Joints show localized tendernessin RA, especially if synovitis is present. Synovitis develops due to the accumulation of some pro-inflammatory mediators in the intra-articular space. According to Unani medicine, the intra-articular pressure is raised by the accumulation of *Akhlat-e-Fasida* (Morbid Humors), which causes tenderness. *Munḍij* and *Mushil* therapy attributed to eliminating the morbid humors decreasing the pressure and relieving the tenderness has appeared to have played a role in relieving the symptoms.

Difficulty in Movement: The difficulty of movement has a direct relation with pain and swelling, as it occurs as a result of joint and tendon sheath swelling. This effusion may restrict joint motion through pain or sufficient tightness of the joint capsule. Since these features are the sequel of inflammation and as discussed earlier, the test drugs are known for their anti-inflammatory effects, therefore, they subsided the pain, and swelling resulting in improvement in the restricted movements.

Joint Pain: Pain in *Waja' al-Mafāṣil* may originate in different ways. It may be due to inflammation, due to the change of local pH, or may arise because some of the ions can stimulate nerve endings. The synovial fluid distends the joint, potentially

compressing blood vessels, and leading to the stimulation of pressure receptors in the capsule. Joint distension also compromises the transport of nutrition and oxygen from the synovium to the cartilage, and waste product from the cartilage to the synovium [5]. Anti-inflammatory analgesic drugs are used for relieving pain. Kabeeruddin (1925) mentioned that HGA has *Muhallil* (anti-inflammatory), and *Musakkin* (analgesic) activities, for which it can be used in arthritis [20].

In an experimental study, it was revealed that HGA has an analgesic effect and that its efficacy was more pronounced in established arthritis [33]. In a clinical study, HGA has been reported to have relieved pain in patients with arthritis [34]. Several studies have been conducted on the various ingredients of the drugs and found to possess analgesic effects. The ethanolic extracts of *Bambusa arundinaceae* leaves (one of the ingredients of test drug HGA) showed a dose-dependent increase in latency time and inhibition in pain sensation in both high and low doses, in a pattern similar to diclofenac sodium [36]. According to Tasleem *et al*. (2014), piperine the main constituent of *Piper nigrum* (5mg/kg), and its ethanolic extract (15 mg/kg) produced significant analgesic activity in animal studies conducted on mice and rats [37]. According to Unani medicine, pain occurs when the *Mizaj* of an organ is disturbed. In RA, *Mizaj* is supposed to deviate towards *Burudat.* The Unani regimen is given in the test group aimed to correct the perverted *Mizaj* towards normal by evacuation of morbid matter. *Munḍij wa Mushil* therapy evacuates the morbid matter that causes derangement in the local temperament and also relieves the pressure caused by its accumulation which in turn causes pain. The pain is further relieved with the effect of HGA which has a proven analgesic effect.

Three drugs of the HGA viz. *Piper nigrum*, *Calotropis procera,* and *Zingiber officinale* have been reported to possess immunomodulatory activity that promotes the maintenance of a healthy immune system [38, 39, 40]. Although the exact relationship of the immunomodulatory components of the test drugs with that of the disease cannot be established conclusively, the reported actions of the three drugs possibly had some ameliorating effect. With the above discussion, it may be concluded that the Unani treatment of RA with *Munḍij* and *Mushil* therapy for 21 days followed by the treatment with HGA for 28 days is effective, as it was found to improve the symptoms significantly as well as the quality of life in cases of rheumatoid arthritis. One of the important principles of treatment of Unani medicine i.e. *Munḍij* and *Mushil* therapy mainly for chronic ailments is validated to a great extent through the study.

The accumulation of morbid matter mainly the phlegm in the body, and the joints not only changes the temperamental status of the joints but also makes physical/structural changes in the joints causing pain, swelling, loss of movement, etc., and adversely affecting the quality of life. The absence of any adverse clinical event or adverse effect on blood investigations supports patients' safety compliance with *Munḍij* and *Mushil* therapy along with HGA in patients with RA. Two important and globally accepted scales WOMAC and VAS were used to determine the improvement induced by the test drugs and verified the hypothesis that Unani treatment comprising *Munḍij* and *Mushil* therapy along with a known antiarthritic drug is effective and safe for the treatment of RA. The effect of the Unani regimen was found to be comparable with that of the standard drug HCQ. The prescription of *Munzij* and *Mushil* therapy that was used in the present study may also be studied in other chronic diseases and the other prescriptions mentioned in classical literature and may be studied independently or in comparison with each other mentioned.

CONCLUSION: The test formulation of *Munzij* and *Mushil* drugs along with Habb-e-Gul-e-Aak is an effective regimen for the treatment of Rheumatoid Arthritis as evidenced by the improvement in WOMAC and VAS scales. This Unani treatment is safe for patients of Rheumatoid Arthritis as no untoward incident was reported during the study. *Munḍij* and *Mushil* drugs mainly produce their effect by evacuating the morbid matter and bringing back the humoural composition to the normal but some of the ingredients of *Munḍij* and *Mushil* composition also possess analgesic and anti-inflammatory effects which may be responsible for partial relief in the initial phase of treatment. HGA alone is an effective drug to manage the inflammatory diseases of joints but

when combined with *Munḍij* and *Mushil* therapy its efficacy is augmented and makes the combined therapy ideal for the patients of RA. The efficacy of *Munḍij* and *Mushil* therapy as advocated by Unani medicine in chronic diseases including RA was validated through the study. The study provides one of the earliest reports on the physicochemical and phytochemical standards of the composition of *Munḍij* and *Mushil* drugs that were used in the study. The findings will serve as the standard of quality for future studies. Although the study was conducted on a small number of patients, however, given the age-old practice of Unani physicians and few recent reports on the drugs used in the study the therapy may be generalized in a phased manner.

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