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Efficacy and safety of a Unani compound drug– *Habb-e-Asgand* in *Waja'al-Mafāsil* (Rheumatoid Arthritis) cases- A preliminary study

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Rheumatoid arthritis affects about 24.5 million people worldwide as of 2015. Modern medicine still eludes satisfactory cure for this problem. Therefore, world is looking forward for some traditional medicines in this direction. In the present work, therapeutic efficacy of a Unani compound drug *Habb-e-Asgand* has been evaluated at Regional Research Institute of Unani Medicine (RRIUM), Aligarh, during 2016-2018. A total of 68 patients were selected from the lot of patients attending outpatient department (OPD). The drug *Habb-e-Asgand* was given 2 Tablets for 84 days and results evaluated statistically by one-way analysis of variance (ANOVA) followed by Dennett's' test. The results of the present study were evaluated on clinical, biochemical, and haematological parameters have amply demonstrated that the drug *Habb-e-Asgand* is therapeutically effective in the treatment of *Waja 'al-mafasil* (rheumatoid arthritis). The study has also shown the drug non-toxic and safe. Further studies are suggested in large population.

Keywords: *Balghami* (Phlegmatic), *Damwi* (Sanguine), *Safrawi* (Bilious) and Visual analogue score (VAS), *Waja-al-Mafasil*

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Wajaul Mafasil also known as *'Gatthia'* is a chronic inflammatory disease in which joints become painful and bulging with decreased normal activity. Soo-e-Miza (Derangement of temperament) is the main etiological factor of *Waja-al Mafasil* according to Tib-e-Unani. Depending upon the madda affecting the joints, four types of diseases are commonly produced; Damawi (Sanguine), Safrawi (Bilious), Saudawi (Melancholic) and Balghami (Phleghmatic). Mostly two or more Akhlat (Humours) constitute the 'Madda', with changes in preponderance of a Khilt (Humour) in various phases of the disease[1].

Rheumatoid arthritis affected about 24.5 million people as of 2015[2]. This is between 0.5 and 1% of adults in the developed world with 5 and 50 per 100,000 people newly developing the condition each year[3]. Rheumatoid arthritis strikes during the most productive years of adulthood between the 20-40 years of age[4]. The prevalence of Rheumatoid arthritis varies between 0.3% and 1% around the globe and 0.28-0.7% in India[5]. Women are affected 2.5 times as frequently as men[6].

In the year 2016, the global burden of disease (GBD) proves that the musculoskeletal diseases accounted for the second highest contribution for the disability around the world. There are around 20-30% of people around the globe with a painful musculoskeletal condition[7]. It is a state of chronic inflammation as a result of damage of joints, disability with morning stiffness in the joints of hand, feet, knee and ankle joints. According to Unani claimed text, accumulation of 'madda' (substance) in joints, which is neither absorbed nor expelled is due to absence of *Quawwat-e-Jazibah* (power of absorption) and *Quawwat-e-dafia* (power of expulsion)[8].

Several important modern drugs are being used for rheumatoid arthritis treatment like glucocorticoids, DMARDS, NSAIDS, like cyclophosphamide, intramuscular gold, sulfasalazine and methotrexate but had side effects of stomach ulcers, GIT bleeding, kidney, liver damage and hypertension[9].

Now attention is diverted to herbal and Unani drugs due to their versatile role in the management of rheumatoid arthritis with no or negligible side effects besides being cost effective[10]. Keeping in view the

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above facts, the therapeutic efficacy and safety of a Unani compounds drugs–*Habb-e-Asgand* was evaluated on scientific lines in the present study Table 1.

Materials and Methods

This study was conducted during 2016-2018 at RRIUM, Aligarh. Unani compound drug- *Habb-e-Asgand* was procured from CCRUM, New Delhi. Sixty eight patients of 18-65 years of either sex were selected from the lot of patients attending the Out Patient Department (OPD) with signs and symptoms related to *Waja-al Mafasil*. The follow-ups for clinical parameters were done on 14th-day, 28th –day, 42th–day, 56th-day, 70th–day and 84th -day. In total 204 cases were screened, out of these 141 were registered on the basis of inclusion and exclusion criteria. 68 cases finally completed the study. The efficacy and safety of Unani compound drug-*Habb-e-Asgand* was evaluated on the demographical, biochemical and haematological parameters to combat *Waja 'al-Mafasil*.

Selection criteria

Patients were enrolled on the basis of following inclusion and exclusion criteria:

Inclusion Criteria

- Patients of either sex in the age group 18-65 years.
- Patients having *Waja'al-Mafāsil* (rheumatoid arthritis) as defined by the following ACR-Eular criteria
- Definite clinical synovitis (pain, swelling, tenderness) in at least 1 joint.
- Absence of an alternative diagnosis for the observed synovitis (arthritis).
- A total score of at least 6 from the individual scores in 2 domains:
- Number and site of involved joints (range 0-5)
- Duration of symptoms (range 0-1)

Table 1 — Composition of *Habb-e-Asgand*[26]

Traditional name	Scientific name/Chemical identity	Amount
Ajwayin Desi	*Trachyspermum ammi*	20 g
Asgand	*Withania somnifera*	40 g
Bidhara	*Argyreia speciosa*	40 g
Peepla Mool	*Piper longum*	20 g
Pipal Kalan	*Ficus religiosa*	20 g
Zanjabeel	*Zingiber officianale*	40 g
Satawar	*Asparagus racemosus*	40 g
Musli Siyah	*Curculigo orchioides*	20 g
Gur	Jaggery	50 g

Exclusion Criteria

- Rheumatoid arthritis with extra-articular manifestations, joint deformities, and advanced radiological lesions (e.g., joint subluxation and collapse).
- Obese subjects (BMI ≥30)
- History or clinical evidence of any systemic inflammatory condition other than RA that may interfere with evaluation.
- History or clinical evidence of any serious systemic illness, DM, TB, disseminated/ complicated

Herpes zoster (e.g., multi-dermatomal involvement, ophthalmic zoster, CNS involvement, post-

Herpetic neuralgia) or HIV infection that could interfere with the interpretation of data.

- Are currently receiving or have received intra-articular treatment (e.g., corticosteroids or hyaluronic acid), oral or parenteral corticosteroids, or NSAIDs within 2 weeks, DMARDs or anticipated IFN therapy within 4 weeks prior to study entry.
- Screening laboratory test values, including creatinine, blood urea nitrogen (BUN), bilirubin outside the reference range and SGOT, SGPT raised >2 times the ULN that in the opinion of the investigator, could pose an unacceptable risk to the participant.
- History of hypersensitivity to study drug or any of its ingredients.
- Pregnant and lactating women
- History of addiction (alcohol, drugs).

Ethical consideration

Written informed consent of all patients included in the study was obtained. This project was registered in Clinical Trials Registry-India (CTRI) (Ref: 2016/07/011657 (H).

Drug, dose and mode of administration

Two tablets each of (650 mg) of *Habb-e-Asgand* were given to patients twice a day after meals for a period of 84 days. The biochemical and hematological investigation were conducted on day one and at the end of the study i.e., after 84-days.

Assessment of *Mizaj* (Temperament)

Assessment of *Mizāj* (temperament) was done at baseline and at the end of treatment (Tabe 5).

Follow-up evaluation

The patients were measured clinically at every 2 weeks, i.e., at 14, 28, 42, 56, 70 and 84 days. The subjective and objective clinical observations will be recorded in the follow-up sheet.

Criteria for assessment of efficacy

To assess the response of treatment in patients of Rheumatoid Arthritis, the following parameters were used.

Subjective parameters

Joint pain

Visual analogue scale (VAS)

In this clinical study, the VAS (0-100 mm) for joint pain and the DAS28 (0-10) for clinical disease activity was used as a measure of improvement in rheumatoid arthritis to evaluate the efficacy of studied drug.

Joint pain was measured on a 0-100 mm visual analogue scale (VAS), for which horizontal VAS was used.

Visual Analogue Scale (VAS)
0 10 20 30 40 50 60 70 80 90 100 mm

No Pain | Mild Pain | Moderate Pain | Severe Pain | Very severe Pain | Worst possible Pain

- ***Joint tenderness*****:** Nil/ Mild/Moderate/Severe
  0 1 2 3
- ***Joint swelling*****:** Nil/ Mild/Moderate/Severe
  0 1 2 3
- ***Early morning stiffness (EMS)*****:** Nil / Mild / Moderate / Severe
  0 1 2 3
  0= Nil
  1=Morning stiffness of 15-30 min duration.
  2= Morning stiffness of >30 min and <60 min duration.
  3= Morning stiffness of >60 min duration
- ***Restriction of joint movement***
  0= Nil
  1= Mild >25% restriction of movement.
  2= Moderate 25 to 50% restriction of movement.
  3= Severe >50% restriction of movement.

Patient's global assessment of disease activity (on a VAS of 0-100 mm)

Visual analogue scale (VAS)
0 10 20 30 40 50 60 70 80 90 100 mm

Not Active At all | Mildly active | Moderately active | Severely active | Very severely active | Extremely active

Disease activity score in 28 joints (DAS28)[11]

An assessment of DAS involves the physician looking at the number of tender and swollen joints (out of the 28) the patient's global assessment (PGA) of disease activity on VAS (indicated by marking a 0-100 mm horizontal line between not active and extremely active). The DAS28 provides with a number between 0 and 10.

Assessment of safety

Biochemical analysis

Serum glutamate pyruvate transaminase (SGPT, E.C. 2.6.1.2) and serum glutamate oxaloacetate transaminase (SGOT, E.C. 2.6.1.1.)[12], serum alkaline phosphatase enzyme (S-ALP, EC. 3.1.3.1)[13], blood urea nitrogen (BUN)[14], serum creatinine[15], serum total bilirubin[16], uric acid[17], rheumatoid factor (RF)[18] and C-Reactive protein[19].

Haematological analysis

Haematological parameters were done[20]. It included haemoglobin (Hb), erythrocyte sedimentation rate (ESR), total leucocytes counts (TLC), red blood corpuscles (RBC) and differential leucocytes counts (DLC): polymorphs, lymphocyte and eosinophil counts.

Collection of blood serum

Blood samples were collected by puncturing the vein at each investigation. 1.0 mL of blood with ethylene diamine tetra acetic acid (EDTA) was used for various haematological parameters and another 2.0-2.5 mL of blood sample was allowed to clot and serum was separated by centrifugation, which was used for various biochemical parameters. Biochemical and haematological investigations were carried out.

Statistical analysis

Data were analyzed statistically by one-way analysis of variance (ANOVA) followed by Dennett's' test. The values were considered significant when the p-value was found less than 0.05.

Results and Discussion

Demographic study

Out of 68 patients of *Waja'al-Mafasil* (rheumatoid arthritis), 11(16.18%) were male and 57 (83.82%) female, which shows that female have higher incidence as compared to male. Hormones in both genders may play a role in either preventing or triggering the disease[21]. The patients of 46-55 years (mean age 40.82 years) of male and 36-45 years (mean age 39.86 years) age group of female are more susceptible to rheumatoid arthritis (Table 2)**.** Non-Vegetarians had more incidences 49 (72.06%) than Vegetarians 19 (27.94%) (Table 3). Middle income group had more incidences 47 (69.12%) than lower

Table 2 — Demographic data showing arrangement of *Waja'al-Mafasil* (rheumatoid arthritis) patients according to age and sex.

Age group (In years)	Number of females & %	Number of males & %	Total number & %
15-25	05 (8.77%)	01 (9.1%)	06 (8.82%)
26-35	12 (21.05%)	03 (27.27%)	15 (22.06%)
36-45	27 (47.37%)	03 (27.27%)	30 (44.12%)
46-55	11 (19.30%)	02 (18.18%)	13 (19.13%)
56-65	02 (3.51%)	02 (18.18%)	04 (5.88%)
Total, % & Mean ± SD	57 (83.82 %), 39.86 ±9.19	11 (16.18%), 40.82±13.7	68 (100.00%), 40.34 ±0.68

Table 3 — Demographic data showing arrangement of *Waja'al-Mafasil* (rheumatoid arthritis) patients according to dietary habits.

Dietary habits	Number of cases & %
Vegetarian	19, (27.94%)
Non-Vegetarian	49 (72.06%)

Table 4 — Demographic data showing arrangement of *Waja-al Mafasil* (rheumatoid arthritis) patients according to social status.

Social status	Number of cases & %
High income group	02 (2.94%)
Middle income group	47 (69.12%)
Lower income group	19 (27.94%)

income group 19 (27.94%) followed by high income group (Table 4). The incidence was found more in Balghami (Phlegmatic) patients 58 (85.29%) as compared to Safrawi (Bilious) 07 (10.3%) followed by Damwi (Sanguine) 03 (4.41%) (Table 5). Similar results had also been reported by earlier workers[22].

Clinical study

Joint pain score

When Unani compound drug- *Habb-e-Asgand* was given to the patients orally 2-Tablet (650 mg each) twice a day after meal for 84-days, a significant reduction in joint pain score 10.17 % ($p<0.05$) on 42^{th}-day, 22.3% ($p<0.0001$) 56^{th}-day, 37.7% ($p<0.0001$) 70^{th}-day and 58.04% ($p<0.0001$) 84^{th}-day had been observed and these were compared with the values of baseline and different follow-up of treatment (84^{th}-days) (Table 6). Similar observation had been reported by other authors[23,24].

Joint tenderness

A significant reduction in joint tenderness 6.41% % ($p<0.05$) on 42^{th}-day, 28.21% ($p<0.0001$) 56^{th}-day, 45.51% ($p<0.0001$) 70^{th}-day and 49.36% ($p<0.0001$) 84^{th} day had been observed, while slight reduction in joint tenderness 1.92%, 3.21%, on 14^{th} day and 28^{th} day, respectively but no significant changes had been observed and these were compared with the values of baseline and different follow-up of treatment (Table 6). Similar observation had been reported by earlier workers[23,24].

Table 5 — Data showing arrangement of patients according to temperament in *Waja-al Mafasil* (rheumatoid arthritis) patients.

Type of Temperament	Number of cases & %
Damvi (Sanguine)	03 (4.41%)
Balghami (Phlegmatic)	58 (85.29%)
Safrawi (Bilious)	07 (10.3%)
Saudawi (Melancholic)	Nil

Joint swelling

A significant reduction in joint swelling 37.95% ($p<0.01$) on 56^{th}-day, 54.82% ($p<0.0001$) 70^{th}-day, 79.52% ($p<0.0001$) 84^{th}-day had been observed, while slight reduction in joint swelling 20.48%, 18.68%, 24.1% on 14^{th}-day, 28^{th}-day and 42^{th}-day respectively but no significant changes had been observed in the earlier days of treatment; and these were compared with the values of baseline and different follow-up of treatment (Table 6). Similar intervention had been reported by other authors[23,24].

Early morning stiffness (EMS)

A significant reduction in early morning stiffness 14.55% ($p<0.05$) on 42^{th}-day, 35.15% ($p<0.0001$) 56^{th}-day, 50.91% ($p<0.0001$) 70^{th}-day, 67.27% ($p<0.0001$) and 84^{th}-day had been observed, while slight reduction in EMS 1.82% and 1.21% on 14^{th}-day and 28^{th}-day respectively but no significant changes had been observed and these were compared with the values of baseline and different follow-up of treatment (Table 6). Similar findings had been reported by other workers[23,24].

Joint s core visual analogue score (VAS)

A significant reduction in joint score VAS 23.14% ($p<0.0001$) on 56^{th}-day, 35.64% ($p<0.0001$) 70^{th}-day and 56.1% ($p<0.0001$) 84^{th}-day had been observed, while slight reduction in joint score VAS 9.91% on 42^{th}-day but no significant changes had been observed and these were compared with the values of baseline and different follow-up of treatment (Table 6). Similar results had been reported by other authors[23,24].

Total score

A significant reduction in total score 36.98% ($p<0.0001$) on 70th-day and 56.84% ($p<0.0001$) 84th-day had been observed, while slight reduction in total score 2.22%, on 28th-day but no significant changes had been observed and these were compared with the values of baseline and different follow-up of treatment (Table 6). Similar facts had been reported by other authors[23,24].

28-joint count activity score

A significant reduction in 28-joint count activity score 37.13% ($p<0.0001$) had been observed as compared with the values of baseline and 84th-day treatment (Table 7). Similar observation had been reported by earlier workers[23,24].

Biochemical Studies

Liver function tests and kidney function tests

When Unani compound drug- *Habb-e-Asgand* was given to the patients orally 2 Tablets (650 mg each) twice a day after meal for 84th-days, no significant alterations in liver function tests as well as kidney function tests had been observed. Therefore, it can be inferred that it did not induce any negative or unfavorable response. The safety of the drug is therefore conformed (Table 8).

Serum uric acid, rheumatoid factor and C-reactive protein

No significant change but slight reduction in the level of uric acid 2.55% and rheumatoid factor (R-factor) 22.74% had been observed, while a significant decrease in the level C-reactive protein 17.24% ($p<0.05$), had been observed (Table 9). Similar report had been observed by earlier authors[25].

Haematological studies

When Unani compound drug-*Habb-e-Asgand* was given to the patients orally 2 Tablets (650 mg each) twice a day after meal for 84th-days, no significant changes in the level of (Hb), (RBC), (TLC), (ESR) and (DLC) had been observed. These were compared with the values of baseline and different follow-up of treatment (Table 10).

Table 7 — Effect of *Habb-e-Asgand* in 28-joint activity score in *Waja-al Mafasil* (rheumatoid arthritis) patients. [***p<0.001 is highly significant].

28-joint count activity score	Variable, (Mean ± SD)
Baseline (1st - Day)	5.01±1.32
Post-treatment (84th –days)	3.15±0.89***

Table 6 — Effect of *Habb-e-Asgand* on symptoms in *Waja-al Mafasil* (rheumatoid arthritis) patients. [*p<0.05& **p<0.01 are significant, ***p<0.001 is highly significant and ▪p is not significant].

Treatment ↔ / Parameter	Baseline 1st -Day	1st F-up 14th Days	2nd F-up 28-Days	3rd F-up 42-Days	4th F-up 56-Days	5th F-up 70-Days	6th F-up 84-Days
Joint pain score	44.85±13.44	45.15±13.87▪	44.56±14.19▪	40.29±13.38*	34.85±12.28***	27.94±11.27***	18.82±10.58***
Joint tenderness	1.56±0.58	1.53±0.56▪	1.51±0.56▪	1.46±0.56*	1.12±0.53***	0.85±0.50***	0.79±0.59***
Joint swelling	1.66±1.83	1.32±0.63▪	1.35±0.62▪	1.26±0.59▪	1.03±0.49**	0.75±0.53***	0.34±0.51***
Early morning stiffness	1.65±0.71	1.62±0.65▪	1.63±0.62▪	1.41±0.67*	1.07±0.55***	0.81±0.50***	0.54±0.58***
Joint score (VAS)	43.09±17.3	43.24±17.23▪	42.94±17.37▪	38.82±16.71▪	32.79±15.63***	27.35±13.34***	18.97±10.97***
Total score	48.57±16.24	48.03±17.07▪	47.49±17.08▪	43.24±16.79*	43.90±16.8▪	30.22±13.43***	21.00±11.04***

Table 8 — Effect of Unani compound drug *Habb-e-Asgand* in the levels of SGPT, SGOT and serum alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine and serum bilirubin in *Waja-al Mafasil* (rheumatoid arthritis) patients. [▪p is not significant]

Parameter ↔ / Group ↕	SGPT (IU/L)	SGOT (IU/L)	Alkaline Phosphatase (IU/L)	Blood Urea Nitrogen (BUN) (mg %)	Serum Creatinine (mg %)	Biliruibin (mg %)
(Baseline) (1st-Day)	29.33±11.01	27.73± 13.86	81.38±32.95	12.1±6.40	0.91±0.17	0.69±0.21
Post-treatment (84-Days)	28.28±13.9▪	32.23±15.27▪	79.48±27.22▪	10.01±3.55▪	0.95±0.21▪	0.70±0.20▪

Table 9 — Effect of Unani compound drug Habb-e-Asgand in the levels of uric acid, R- factor and C- reactive protein in Waja'al Mafasil (rheumatoid arthritis) patients. [*p<0.05 is significant and ▪P is not significant]

ParameterGroup ↕	Uric Acid(mg %)	RF-Factor (IU/mL)	C-Reactive Protein(mg /dL)
(Baseline) (1st-Day)	4.31±1.39	13.81±16.69	18.56±10.51
Post- treatment (84-Days)	4.2±1.26▪	10.67±11.67▪	15.36±8.84*

Table 10 — Effect of Unani compound drug *Habb-e-Asgand* in the levels of haemoglobin (Hb), red blood corpuscles (RBC) counts, total leucocyte counts (TLC), erythrocyte sedimentation rate (ESR), polymorphs, lymphocytes and eosinophils counts in *Waja'al-Mafasil* (rheumatoid arthritis) patients. [▪p is not significant]

Parameter / Group	Haemoglobin (gm %)	R B C (10^6 mm^3)	T L C ($10^3/mm^3$)	ESR (mm/h)		Differential leucocyte counts (DLC)		
				1 h	2 h	Polymorphs (%)	Lymphocytes (%)	Esinophils (%)
(Baseline) (1^{st} -Day)	11.65±1.25	4.1±0.44	6.81±2.56	40.0±12.86	49.0±11.2	69.0±9.14	26.0±9.03	5.0±1.65
Post- treatment (84-Days)	11.54±1.27▪	3.99±0.45▪	6.76±2.51▪	43.0±11.33▪	51.0±8.65▪	70.0±7.36▪	25.0±7.17▪	5.0±1.68▪

Conclusion

The presently available synthetic drugs reduce inflammation in rheumatoid arthritis but produce adverse side effects. These drugs have a tendency to develop tolerance slowly and therefore the dose is increased to marked levels. Thus, there is an urgent need to identify and validate herbal drugs and their active constituents, to be used as potential therapeutic agents for treatment of rheumatoid arthritis.

On the basis of this study, it may be concluded that Unani compound drug-*Habb-e-Asgand* possesses anti-inflammatory, analgesic and anti-rheumatic activity, for which significant improvement in sign, symptoms and C-reactive protein was observed. It can also be inferred that the drug is safe as it did not induce any toxic effect, particularly on liver and kidney functions. Further studies are warranted in large group.

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Author's contributions (add)

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