Clinical Evaluation of Efficacy of a Unani Formulation in *Waja-ul-Mafasil* "Rheumatoid Arthritis

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Abstract

In the classical *Unani* texts, *Waja-ul-Mafasil* is broadly explained and well correlated with a chronic inflammatory joint disease, rheumatoid arthritis (RA). The exact aetiology of rheumatoid arthritis is still unknown and there is no curative treatment for this chronic, painful, disabling disorder. In *Unani* system of medicine, many single drugs *(Mufrad Adviyah)* as well as compound formulations *(Murakkab Adviyah)* are being prescribed since ages for the treatment of *Waja-ul-Mafasil*. Therefore, a randomized, controlled, single-blind clinical trial was conducted to evaluate the therapeutic efficacy of three *Unani* herbal drugs (*Withania somnifera*, *Piper nigrum*, and *Datura fastuosa*) in comparison to a control drug (Aspirin) in patients of *Waja-ul-Mafasil*. The study was carried out on 40 patients of *Waja-ul-Mafasil*. The symptoms and signs of the disease after 21 days of treatment showed significant improvement with no adverse effects of test drugs in comparison to control drug. The study is affirmative of the therapeutic efficacy and safety of the *Unani* test drugs combination in patients of *Waja-ul-Mafasil*. However, there is a need to carry out further study with a large sample size and with assessment of effect on specific anti-TNF antibodies to establish the possible curative treatment to tackle this global problem.

Keywords: Rheumatoid arthritis, *Wja-ul-Mafasil*, Unani Medicine, Anti-TNF antibody, TNF Antagonists

Introduction

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown aetiology characterized by a destructive and deforming polyarthritis, mainly affecting peripheral synovial joints, usually in a symmetrical pattern and a variety of non-articular manifestations (McGee *et al*., 1992; Kasper *et al*., 2005; Boon *et al*., 2006). RA is a disease of the synovium and is a condition of synovioarthritis in contrast to osteoarthritis (Dey and Dey, 2005). However, late in the disease, degenerative changes in the abnormal cartilage lead to secondary osteoarthritis in rheumatoid joint (McGee *et al*., 1992). Rheumatoid arthritis occurs worldwide in all ethnic groups and it is estimated that about 1% of the world's population is afflicted by RA (Wngaarden *et al*., 1992; Kasper *et al*., 2005; Boon *et al*., 2006; Kumar *et al*., 2006). Rheumatoid arthritis may begin at any age (McPhee *et al*., 2007) from 10 to 70 years (Kumar and Clark, 1996) but the usual age at onset is 35 to 50 years (Kasper *et al*., 2005). Over

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70% of the patients are women (Ritchie, 1990; Cree, 1997). The risk factors for RA are cigarette smoking and female gender and this susceptibility is increased post-partum and by breast feeding, positive SRF in non-RA subjects (Boon *et al*., 2006).

Rheumatoid arthritis is an autoimmune disease. Arthritis of RA is caused by immune complexes which are localized within the inflamed cartilage and activate the complement system and generate–anaphylatoxins (permeability increasing components of C3a and C5a) and chemotactic factors (C5a). These complement activation products induce emigration (anaphylatoxins) and chemotaxis (C5a) of neutrophils and monocytes which phagocytose the immune complexes and release inflammatory mediators (cytokines) and lysosomal enzymes (collagenase and elastase) which destroy the articular cartilage and synovium. The most important cytokines are *tumour necrosis factor* α *(TNF-*α*)*, *interleukin-1 (IL-1), prostaglandin-E2 (PGE2), leukotriene-B4 (LTB4), and O2 radicals* which act as mediators of joint injury (Anderson, 1987; Kumar *et al*., 2006). Immune complexes produced within the synovium and entering the circulation are responsible for the extra-articular manifestations of RA (Anderson, 1987).

Chronicity and destructive potential are characteristic features of the inflammatory response in the synovial membrane typical for RA (Anderson, 1987). Rheumatoid arthritis begins with acute inflammation of the synovium in the joints involved and the acute reaction is soon replaced by chronic inflammation (Ritchie, 1990; Russel *et al.,* 2004). Chronic synovitis is followed by neovascularization of the inflamed synovium leading to 'pannus' formation that is a hallmark of RA (Stupack *et al*., 1999). This is followed by destruction of articular cartilage, subchondral bone, and bone at the sides of the joint leading to joint damage that may be identified only months after the onset of symptoms (Bresnihan, 1999). Progressive joint damage may lead to fibrous ankylosis, bony ankylosis and subsequently deformity of the involved joint (MacSween and Whaley, 1992). Joint deformities include ulnar deviation, "Z" deformity, 'Swan Neck' deformity, Boutonnière (Button-Hole) deformity, forefoot widening, hallux valgus, and valgus deformity of the foot and knee (Weatherall *et al*., 1996; Kasper *et al*., 2005).

Rheumatoid arthritis is mentioned in classical Unani literature as *'Waja-ul-Mafasil'*. *Waja-ul-Mafasil'* is a pain or an inflammation *(Waram)* which occurs in the joints of hands and feet, knee joints and ankle joints (Majoosi, 1889; Ali, 1896; Jurjani, 1903). Shaikh Bu Ali Sina (Avicenna) (980-1036 AD) mentioned that *Waja-ul-Mafasil* is caused by phlegm *(Balgham)*, blood *(Dam)*,

yellow bile *(Safra)*, and black bile *(Sauda)* in a decreasing order of frequency, respectively. *Waja-ul-Mafasil* is commonly caused by accumulation of sticky phlegm *(Balgham-e-Lazij)* in the joints due to weakness of the joints *(Zof-e-Mafasil)* (Majoosi, 1889; Khan, 1939). *Madda* (substance) causing *Waja-ul-Mafasil* enters the joints and it neither digests nor expels from them due to lack of power of digestion *(Quwwat-e-Hazima)* and power of expulsion *(Quwwat-e-Dafia)* in the joints, respectively and thus, it is retained in the joints leading to disturbance in the metabolic activity, hence the nutrients reaching the joints are not properly utilized, instead they are converted into harmful products which induce inflammatory process. Thus, the *Waja-ul-Mafasil* is developed (Jurjani, 1903). When this *Madda* (substance) is retained in the joints for a long period, its viscosity *(Ghilzat)* and viscidity *(Luzoojat)* are increased and it becomes stone (*Tahajjur-e-Mafasil* or Osteoarthritis) and the condition is incurable (Majoosi, 1889). When the *Madda* (substance) which produces *Waja-ul-Mafasil* enters the blood and permeates the entire body system, the non-articular manifestations are developed (Majoosi, 1889; Khan, 1939).

The exact aetiology of rheumatoid arthritis is still unknown and there is no curative treatment for this chronic, painful, disabling disorder. Moreover, synthetic drugs used as anti-rheumatic and anti-inflammatory agents have serious adverse effects and even fatalities are due to iatrogenic effects of allopathic treatment–in particular, gastrointestinal bleeding related to long-term use of anti-inflammatory drugs (aspirin, non-steroidal anti-inflammatory drugs) and infections associated with chronic steroid use and treatment with cytokine antagonists (TNF antagonists) (Kumar *et al*., 2006). Classical literature of Unani system of medicine is replete with many single drugs *(Mufrad Adviyah)* as well as compound formulations *(Murakkab Adviyah)* which have been used by eminent Unani physicians for the treatment of *Waja-ul-Mafasil*, but there is no scientific validation of these classical textual claims. Hence, there was ample need to search for some Unani drugs which could be safe and effective in the treatment of *Waja-ul-Mafasil*. Therefore, the study was carried out to scientifically validate a Unani herbal compound formulation for its safety and efficacy in the treatment of *Waja-ul-Mafasil*.

Methodology

The study was designed as a randomized, controlled, single-blind clinical trial. The present study was conducted at Majeedia Hospital, New Delhi on 40 patients of *Waja-ul-Mafasil*. The patients suffering from *Waja-ul-Mafasil* were selected by adopting clinical criteria for diagnosis of rheumatoid arthritis

revised (1988) by the American Rheumatism Association (ARA). The patients of either sex in the age group of 16 to 55 years were included in the study. Inclusion criteria were morning stiffness of at least 1 hour duration, arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor, and typical radiographic changes in the hand and wrist. Patients with four or more of the above 7 features of 6 weeks or more duration were included in the clinical trial. Exclusion criteria included extra-articular manifestations, joint deformities, advanced radiological lesions, malnourished patients, pregnant women and lactating mothers. After necessary ethical clearance and written informed consent, patients were enrolled for the treatment. Laboratory investigations were conducted including Hb, TLC, DLC, platelets, ESR, serum rheumatoid factor, and X-ray of the affected joint. The investigations were repeated after treatment. The safety of trial drugs was evaluated clinically by monitoring adverse effects which were carefully sought at each follow-up. The temperament (*Mizaj*) of the patients was assessed as per the parameters described in Unani classical literature.

A total of 40 patients, 20 in each group, were randomly allocated to the test ('X') and control group ('Y'). A tri-herbal Unani formulation in the form of capsule was administered orally to all the 20 cases of test group ('X') in the dose of 2 capsules (700 mg each) thrice daily (4.2 g/d) after meals. Each capsule contained fine powder of 3 herbs: *Withania somnifera* (Asgandh)–500 mg, *Piper nigrum* (Filfil Siyah)–150 mg, and *Datura fastuosa* (Jauz-e-Masil)–50 mg. All the 20 cases in control group ('Y') were advised to take a control drug, Aspirin orally with milk in the dose of 1 g four times daily after meals. The duration of treatment was 21 days in both the test and control groups. No concomitant treatment was allowed during the study. The follow-up of all the cases was carried out at regular interval of 7 days up to 21 days on the basis of clinical history and physical examination. The observations and results obtained in both the test ('X') and control ('Y') groups were tabulated and statistically analyzed.

Results and Discussion

The highest number of cases belonged to phlegmatic temperament (*Balghami Mizaj*) in both groups (Fig. 1). This observation was in accordance with the aetiology of *Waja-ul-Mafasil* described in Unani classical texts and it shows that the persons of *Balghami Mizaj* are more prone to develop *Waja-ul-Mafasil*. The highest incidence of disease was observed in the age group of 36–45 years and in females in both groups (Figs. 2 & 3).

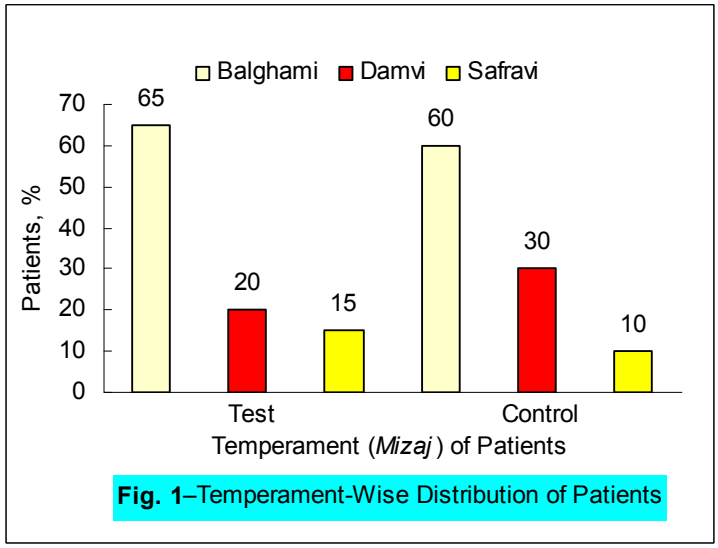

Fig. 1–Temperament-Wise Distribution of Patients

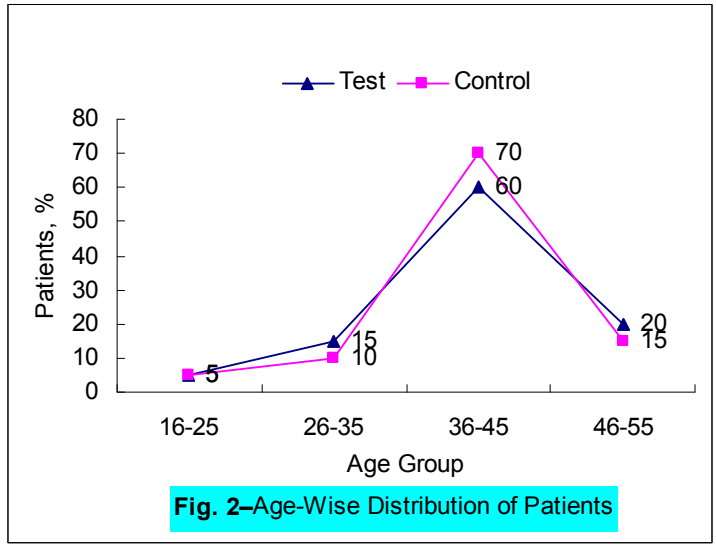

Fig. 2–Age-Wise Distribution of Patients

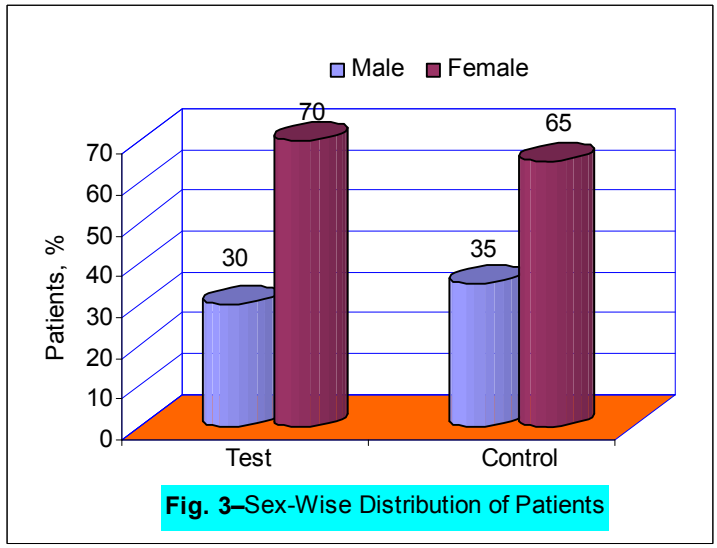

Fig. 3–Sex-Wise Distribution of Patients

A positive family history of RA was reported in 10% and 5% of patients in test and control groups respectively. The maximum numbers of patients were from urban areas in both groups. This may be due to the sedentary lifestyle among them which is a predisposing factor described in Unani classics. The highest incidence of disease was observed in winter which may be due to temperature effect (Table 1). The 25% and 30% patients were smokers in test and control groups respectively. The 60% and 65% patients were obese in test and control groups respectively. This observation indicates that the smoking and obesity may be the potential triggers of RA. The most commonly affected joints were PIP, MCP, and knee joints in both groups (Table 2).

Table-1. Distribution of Patients according to Family History of RA, Geographic Distribution and Seasonal Occurrence

Variables	Test Group ('X')		Control Group ('Y')	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
Family History–				
Positive	02	10	01	05
Negative	18	90	19	95
Area–				
Urban	14	70	12	60
Rural	06	30	08	40
Season–				
Winter	13	65	12	60
Other	07	35	08	40

After the completion of 21 days of treatment, the test drugs combination exhibited significant improvement in symptoms and signs of disease. Clinical remission based on the American College of Rheumatology (ACR) criteria, i.e. relief from joint pain was achieved in 14 cases (70%) in test group and in 12 cases (60%) in control group; relief from morning stiffness was achieved in 15 cases (75%) in test group and in 13 cases (65%) in control group; relief from joint tenderness was achieved in 16 cases (80%) in test group and in 13 cases (65%) in control group; relief from soft tissue swelling was achieved in 13 cases (65%) in test group and in 12 cases (60%) in control group (Table 3) and relief from fatigue was achieved in 14 cases (87.5%) in test group and not in any case in control group. Relief from generalized weakness was achieved in 13 cases (92.86%) in test group and in 3 cases (30%) in control group and

relief from anorexia was achieved in 13 cases (86.67%) in test group and in 2 cases (18.18%) in control group (Table 4). Erythrocyte sedimentation rate (ESR) showed significant reduction after treatment that was found to be 34.21% and 15.63% in test and control groups respectively (Table 5). Increase in haemoglobin (Hb) after treatment was recorded to be 19.67% and 2.1% in test and control groups respectively (Table 6).

Table-2. Distribution of Patients according to Predisposing Factors and Joints Involved

Variables	Test Group ('X')		Control Group ('Y')	
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)
Predisposing Factors–				
Smoking	05	25	06	30
Obesity	12	60	13	65
Joints Involved–				
PIP & MCP Joints	20	100	19	95
Knee	19	95	18	90
Wrist	17	85	16	80
MTP Joints	15	75	14	70

No adverse effects of the test drugs combination were reported by any of the patients over the treatment period and so the trial Unani drugs can be considered to be safe. The effectiveness of the trial drugs is indicative of their anti-arthritic activity. The control drug showed no effect on fatigue and its side-effects including nausea, vomiting, heartburn and dyspepsia were observed in most of the cases. The response was observed better in the early and middle stages of the disease where there were no gross structural changes in the affected joints. In cases where the structural damage had occurred, the drug was less effective in restoring the normalcy of the affected joints.

Table-3. Clinical Parameters before and after Treatment

Parameter	Day of Estimation	Number of Patients (Group-Wise)					
		Test Group ('X')			Control Group ('Y')		
		No. of Pts (N=20)	%	Response	No. of Pts (N=20)	%	Response
Joint Pain	Baseline	20	100	14 (70%)	20	100	12 (60%)
	After Treatment	06	30		08	40	

Parameter	Day of Estimation	Number of Patients (Group-Wise)					
		Test Group ('X')			Control Group ('Y')		
		No. of Pts (N=20)	%	Response	No. of Pts (N=20)	%	Response
Morning Stiffness	Baseline	20	100	15 (75%)	20	100	13 (65%)
	After Treatment	05	25		07	35	
Joint Tenderness	Baseline	20	100	16 (80%)	20	100	13 (65%)
	After Treatment	04	20		07	35	
Joint Swelling	Baseline	20	100	13 (65%)	20	100	12 (60%)
	After Treatment	07	35		08	40	

Table-4. Other Clinical Parameters before and after Treatment

Parameter	Day of Estimation	Number of Patients (Group-Wise)					
		Test Group ('X')			Control Group ('Y')		
		No. of Pts (N=20)	%	Response	No. of Pts (N=20)	%	Response
Fatigue	Baseline	16	80	14 (87.5%)	12	60	00 (0%)
	After Treatment	02	10		12	60	
Generalized Weakness	Baseline	14	70	13 (92.86%)	10	50	03 (30%)
	After Treatment	01	05		07	35	
Anorexia	Baseline	15	75	13 (86.67%)	11	55	02 (18.18%)
	After Treatment	02	10		09	45	

Table-5. Effect on ESR in both Groups

Treatment Group	Statistics			
	N	Mean ESR (mm/hr)		Reduction in ESR after Treatment (%)
		Baseline	After Treatment	
Test	20	38	25	34.21
Control	20	32	27	15.63

N= Number of Subjects

Table-6. Effect on Haemoglobin in both Groups

Treatment Group	Statistics			
	N	Mean Hb (g/dL)		Increase in Hb after Treatment (%)
		Baseline	After Treatment	
Test	20	10.78	12.9	19.67
Control	20	10.95	11.18	2.1

N= Number of Subjects

Conclusion

On the basis of above findings, it can be concluded that the trial Unani drugs are effective in the treatment of *Waja-ul-Mafasil* but chronicity of disease has the negative effect on response to therapy. The cases with early and middle stages of the disease have shown better response to treatment than cases with advanced disease. It is also observed that the trial drugs are well tolerated and have no adverse effects. The overall conclusion is that the trial Unani drugs are safe and possess potent anti-rheumatic, analgesic, and anti-inflammatory actions, which are of prime importance in the management of *Waja-ul-Mafasil*. Hence, these drugs can serve as a good alternative in the treatment of *Waja-ul-Mafasil*. However, there is a need to carry out further study with a large sample size and with assessment of effect on specific anti-TNF antibodies to establish the possible curative treatment to tackle this global problem.

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