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Clinical validation of efficacy and safety of Unani Pharmacopoeial formulations - Majoon-e-Sūranjān & Habb-e-Azaraqi in patients of Niqris (Gout)

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Abstract
Each participant was well informed about the trial and written consent was obtained before initiation of the study. Demographic data and information on the present disease condition, concomitant disease and therapy was recorded. Thorough general physical and systemic clinical examination was carried out. Signs and Symptoms pertaining to gout were recorded in CRF. The vital parameters like blood pressure, heart rate, temperature and respiratory rate were also recorded. X-Ray of affected joints was conducted and blood samples were collected for the evaluation of laboratory parameters like Haemogram, C-Reactive proteins and serum uric acid to establish and confirm inclusion criteria and other laboratory test like complete blood picture, kidney function test, liver function test and routine and microscopic examination of urine were done. All clinical and laboratory follow-up were done at every 2 weeks.

The study was carried out in a total number of 96 patients of Waja-ul-Mafasil of either sex satisfying the criteria of American Rheumatism association. All the patients received treatment with Unani Pharmacopoeial formulations - Majoon-e-Sūranjān & Habb-e-Azaraqi a period of 60 days. Out of 96 cases 75 patients completed the study, 34 patients got complete remission, 36 patients got partially remission, 05 patients showed no relief and 21 patients dropped out. No hepatotoxic and nephrotoxic side effects noticed during the course of study. The clinical and laboratory findings after treatment have shown that both drugs possessed efficacy and safety in the treatment of niqris.

Keywords: Niqris, Gout, Majoon-e-Sūranjān, Habb-e-Azaraqi, Unani medicine, Remission

Introduction

The word *'Niqris'* is derived from the Unani word "*Anqarūs*" means joint of the great toe. It usually occurs in great toe; therefore it is called *Niqris* (gout). Ibn Sina (980-1037 AD) described that pain of *Niqris* (gout) starts from fingers of the foot especially great toe but sometimes it also starts from heel and ankle joints and spread all over the foot. Ibn Nafees (1210-1288 AD) says that this pain starts from right toe and sometimes both sides simultaneously presenting redness, tenderness and swelling. Sometimes it is associated with rigor and low grade fever. Ibn Ilyas says severe pain in *Niqris* is due to constricted space of smaller joint and rich supply of nerves and fibrous ligament. It is common in male than female. Women before menopause, children and Eunuchs rarely suffer from this disease. Ibn Sina (980-1037 AD) described that the causative factor of *Niqris* is *Sū-i-Mizāj Māddi* (Derangement of Temperament) predominantly by *Dam* (Blood), *Safrā* (yellow bile), *Balgham* (Phlegm) and *Sawda* (Black Bile) other than gaseous matters but

Razi (860-925 AD) says Khilt-i-Dam may also cause Niqris other than Khilt-i-Safrā and Khilt-i-Balgham, but he opines that people of Safrāvi Mizāj (Bilious Temperament) suffer most of this disease.

Qusta Bin Luqa (820-912 AD) says that weakness in the joint and equal health and strength of other organs is an important cause of this disease (Rahman, 2007). Gout (also known as podagra when it involves the big toe) (Eggebeen, 2007) is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis- a red, tender, hot, and swollen joint. The meta-tarsophalangeal (MTP) joint at the base of the big toe is most commonly affected, accounting for approximately 50% of cases. However, it may also present as tophi, kidney stones, or urate nephropathy. The word 'gout' is derived from the Latin word gutta, meaning "a drop" (of liquid).

It is caused by elevated levels of uric acid in the blood. The uric acid crystallizes, and the crystals deposit in joints, tendons, and surrounding tissues. Long-standing elevated uric acid levels (hyperuricaemia) may result in other symptomatology, including hard, painless deposits of uric acid crystals known as tophi. Extensive tophi may lead to chronic arthritis due to bone erosion (Terkeltaub, 2010). Elevated levels of uric acid may also lead to crystals precipitating in the kidney, resulting in stone formation and subsequent urate nephropathy (Tausche *et al*. 2009) [31]. Excessive eating, sedentary life style, avoiding physical exercise, using alcohol in empty stomach, excessive coitus, prolonged indigestion, obesity, trauma, constant mental tension and bathing after meals are other causative factors of this disease. Gout affects around 1–2% of the Western population at some point in their lifetimes, and is becoming more common. Rates of gout have approximately doubled between 1990 and 2010. This rise is believed due to increasing life expectancy, changes in diet, and an increase in diseases associated with gout, such as metabolic syndrome and high blood pressure. A number of factors have been found to influence rates of gout, including age, race, and the season of the year. In men over the age of 30 and women over the age of 50, prevalence is 2%. A high level of uric acid in the blood is the underlying cause of gout. This can occur for a number of reasons, including diet, genetic predisposition, or under excretion of urate (salts of uric acid). Renal under excretion of uric acid is the primary cause of hyperuricaemia in about 90% of cases, while overproduction is the cause in less than 10%. About 10% of people with hyperuricaemia develop gout at some point in their lifetimes. The risk, however, varies depending on the degree of hyperuricaemia. When levels are between 415 and 530 µmol/l (7 and 8.9 mg/dl), the risk is 0.5% per year, while in those with a level greater than 535 µmol/l (9 mg/dL), the risk is 4.5% per year. Dietary causes account for about 12% of gout (Chen *et al*. 2008) [9], and include a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood (Terkeltaub, 2010; Weaver, 2008) [12]. Other triggers include physical trauma and surgery (Richette *et al*. 2010). Recent studies have found that other dietary factors once believed associated are, in fact, not, including the intake of purine-rich vegetables (e.g., beans, peas, lentils, and spinach) and total protein (Choi *et al*. 2004; Weaver, 2008) [32, 12]. With respect to risks related to alcohol, beer and spirits appear to have a greater risk than wine (Roddy, 2001) [33]. The consumption of coffee, vitamin C and dairy products, as well as physical fitness, appear to decrease the risk (Hak *et al*. 2008; Williams, 2008; Choi, 2010) [13, 34, 35]. This is believed partly due to their effect in reducing insulin resistance (Choi, 2010) [35]. Gout may be diagnosed and treated without further investigations in someone with hyperuricaemia and the classic podagra. However, synovial fluid analysis should be done, if the diagnosis is in doubt (Eggebeen, 2007). A definitive diagnosis of gout is based upon the identification of monosodium urate (MSU) crystals in synovial fluid or a tophus (Schlesinger, 2010) [36]. Formation of uric acid crystals in the joints is associated with gout. Under polarized light microscopy, MSU crystals have a needle-like morphology and strong negative birefringence. This test is difficult to perform, and often requires a trained observer (Schlesinger, 2007) [16]. The fluid must also be examined relatively quickly after aspiration, as temperature and pH affect their solubility, X-rays, while useful for identifying chronic gout, have little utility in acute attacks. X-Ray foot reveals soft tissue swelling at the lateral border of the foot. The typical location is the big toe joint (Richette *et al*. Hyperuricaemia is a classic feature of gout, but it occurs nearly half of the time without hyperuricaemia, and most people with raised uric acid levels never develop gout (Schlesinger, 2010; Sturrock, 2000) [36, 17].

Thus, the diagnostic utility of measuring uric acid level is limited (Schlesinger, 2010) [36]. Hyperuricaemia is defined as a plasma urate level greater than 7 mg/dL in males and 6 mg/dL in females. Other blood tests commonly performed are WBC count, electrolytes, renal function, and ESR. However, both the white blood cells and ESR may be elevated due to gout in the absence of infection.

Both lifestyle changes and medications can decrease uric acid levels. Dietary and lifestyle choices that are effective include reducing intake of food such as meat and seafood, consuming adequate vitamin-c, limiting alcohol and fructose consumption, and avoiding obesity (Chen & Schumacher, 2008) [9]. A low calorie diet in obese men decreased uric acid levels by 1.7 mg/dl (Laubscher *et al*. 2009). Vitamin C intake of 1,500 mg per day decreases the risk of gout by 45% (Choi *et al*. 2009). Coffee, but not tea, consumption is associated with a lower risk of gout (Choi *et al*. 2007). Gout may be secondary to sleep apnea via the release of purines from oxygen-starved cells. Treatment of apnea can lessen the occurrence of attacks (Abrams B, 2005).

Material and Methods

Study Design/Type

An open label, multicentric clinical study conducted.

Study Objectives

- To assess the safety of Unani Pharmacopoeial formulations *Mājūn-e-Sūranjān* & *Habb-e-Azārāqi in patients of Niqris* (Gout).
- To validate the efficacy of Unani Pharmacopoeial formulations *Mājūn- e-Sūranjān* & *Habb-e-Azārāqi in patients of Niqris* (Gout).

Selection Criteria

Inclusion Criteria (All of the following)

- Patients of either sex in the age group of 18-60.
- Serum uric acid level: normal or above normal
- Patients of gout having any of the following symptoms and signs
- Joint Pain (especially first metatarsophalangeal (MTP) joint
- Tendernes
- Swellin
- Redness

Exclusion Criteria (Any of the following)

- Other diseases involving small & large joints
- Pregnant and lactating women
- Patients having any systemic diseases such as hypertension, diabetes mellitus, Cardiovascular/ Cerebrovascular diseases, hepatic and renal disease, osteomalacia, osteoporosis
- Obesity (BMI: ≥ 30
- Patients on long term medications
- Patients taking drugs which increase serum uric acid levels (thiazide diuretics, etc.) and decrease serum calcium levels (furosemide, etc.)

Subject Selection
- Serum uric acid level: normal or above normal
- Patients of gout having any of the following symptoms and signs:
- Joint Pain (especially first metatarsophalangeal (MTP) joint)
- Tenderness
- Swelling
- Redness

Sample Size
75 cases at CRIUM, Lucknow, completed trial in all respects.

Duration of protocol therapy
8 Weeks

Duration of the study
2 Years

Study drug details
The following Unani Pharmacopoeial formulations will be used

S. No.	Study Drug	Form	Route of Administration	Dose	Frequency	Instructions
1.	Majoon-e-Sūranjān	Semisolid	Oral	5 gm.	Twice daily	Take with water after meals
2.	Habb-e-Azaraqi	Pill	Oral	1 pill	Twice daily	Take with water after meals

Composition
I. *Mājūn-e-Sūranjān*

	Name of Ingredients	Botanical Name	Quantity
1.	Suranjan Shireen	(*Merendera persica*)	500 gm
2.	Sana	(*Cassia angustifolia*)	250 gm
3.	Zanjabeel	(*Zingiber officinale*)	100 gm
4.	Zeera Siyah	(*Carum carvi*)	100 gm
5.	Filfil Daraz	(*Piper longum*)	100 gm
6.	Asaroon	(*Asarum europaeum*)	100 gm
7.	Asl Or Qand Safaid		3.5 kg

II. Habb-e-Azārāqi

	Name of Ingredients	Botanical Name	Quantity
1.	Azaraqi Mudabbar	(*Strychnos nux-vomica*)	20 gm
2.	Filfil Siyah	(*Piper nigrum*)	10 gm
3.	Filfil Daraz	(*Piper longum*)	10 gm
4.	Arq-e-Ajwayin	(*Ptycotis ajowan*)	

Follow-Up Evaluation
Clinical Follow-up
The patients will be assessed clinically at every two weeks. The subjective and objective clinical observations will be recorded in the follow-up sheet.

Re-scheduling Follow-up Visits
If any follow-up visit is missed, the visit will be rescheduled as soon as possible within an interval of +/ – one week.

Laboratory investigations
The following laboratory investigations will be done at baseline, first follow up and on completion of the protocol therapy. The laboratory findings will be recorded in the follow-up sheet.

Pathological Investigations
- CBC (Hb%, TLC, DLC, ESR)
- Urine Examination: R/M (for Urate crystals)
- Classical Examination of Bawl (Urine)

Biochemical Investigations
- Liver Function Tests (LFTs): Serum Bilirubin, SGPT, SGOT, S. Alkaline Phosphatase.
- Kidney Function Tests (KFTs): Serum Creatinine, Serum Urea, Uric Acid, CRP
- S. Calcium
- Thyroid Profile (T3, T4, TSH)
- Lipid Profile (S. Cholesterol, HDL, LDL, VLDL, & Triglycerides
- Blood Glucose (Random) will be done at the time of screening only.

Assessment of safety
1. Clinical Parameters: Adverse Events
2. Laboratory Parameters
- CBC (Hb%, TLC, DLC, ESR)
- LFT (S. Bilirubin, SGOT, SGPT, S. Alkaline phosphatase)
- KFT (S. Urea, S. Creatinine, Serum uric acid)
- Urine R/M

Assessment of efficacy
- **Clinical Parameters:** Reduction in signs and symptoms
- **Laboratory Parameters:** Reduction in serum uric acid level, ESR, & CRP
- Clinical symptoms and signs as mentioned in the CRF will be graded as follows and the scores will be recorded in the CRF.

Pain
0= No pain
1= Barely Perceptible.
2= Mild; can carry out daily activities with some trouble.
3= Moderate; cannot carry out daily activities easily.
4= Severe; bed ridden.

Tenderness
0= No tenderness
1= on palpation, Patient says it is tender, when touched.
2= on palpation, Patient says it is tender and winces.
3= on palpation, Patient says it is tender, winces and pulls back.
4= on palpation, Patient does not allow to touch

Swelling
0= No swelling.
1= Barely perceptible.
2= Mild, can be perceptible.
3= Moderate, not excessive swelling.
4= Severe, excessive swelling.

Swelling will be measured by measuring tape taking into consideration the bony landmarks around the affected joint**.**

Redness
0= No
1= Yes

Assessment of results
The overall results of the study will be recorded in terms of percentage efficacy as calculated from the reduction in the symptoms and signs.

Statistical data recording: Data recording was done on separate case record form for each subject at base line, after M. M. Therapy and at every 15 days up to three months. Active and passive complaints of patients were recorded in grades starting from "+" to "+++" at the time of Base line and at different follow up. Percentage in grading was calculated and results were assessed in terms of complete remission (more than 70%), partially remission (50% to 70%), Poor remission (less than 50%).

Results and Discussion

Temperament and response
The data showed that out of 75 cases studied maximum 27 cases had Balghami followed by 10 cases had Saudavi, 13 Safravi and 25 Damvi temperament. As per temperament and response of the formulae concerned, it is found more effective in Balghami temperament as out of 27 cases 12 cases got complete remission, 12 cases got partially remission and 03 got poor response. In Saudavi out of 10 cases, 06 cases got complete remission, 04 cases got partially remission and 00 case showed poor remission. In Safravi 13 cases, 08 got complete remission, 04 got partially remission and 01got poor remission and Damvi temperament out of 25 cases, 08 got complete remission and 16 got partially remission and 01got poor remission as presented in table-1.

Table 1: Response according to Mizaj (Temperament)

Mizaj (Temperament)	Response			Total (%)
	Complete Remission	Partially Remission	Poor Remission	
Balghami	12	12	03	27
Saudavi	06	04	00	10
Safravi	08	04	01	13
Damvi	08	16	01	25
Total (%)	34 (45.33%)	36 (48%)	05 (06.66%)	75 (100%)

Chronicity and response
Study data showed that maximum cases were having chronicity up to 02 years, out of 56 cases 29 cases got complete remission, 24 cases got partially remission and 03 cases showed poor remission followed by 10 cases having chronicity 2-4 years, 04 cases got complete remission, 06 got partially remission and 00 showed poor remission, 4-6 years, 05 cases, 6-8 years, 02 cases, 8-10 years 02 cases. As chronicity and response of the formulae concerned, it is effective in the cases having chronicity up to 04 years, above 10 years chronicity no case registered, as in Table-2.

Table 2: Response according to chronicity of the disease

Chronicity	Response			Total (%)
	Complete Remission	Partially Remission	Poor Remission	
Up to 02 year	29	24	03	56
02-04 year	04	06	00	10
04-06 year	00	04	01	05
06-08 year	01	01	00	02
08-10 year	00	01	01	02
Above 10 year	00	00	00	00
Total (%)	34 (45.33%)	36 (48%)	05 (06.66%)	75 (100%)

Sex and response
In the table-3, the study shows that this disease is common in ratio, females and males, as out of 75 cases studied 36 were female and 39 cases were males. As per response concerned, drug is somewhat equally effective in both the sexes, out of 36 females cases 12 cases got complete remission, 22 cases got partially remission and 02 cases got poor remission. While in 39 male's cases, 22 cases got complete remission, 14 cases got partial remission and 03 showed poor remission.

Table 3: Response according to sex of patients

Sex	Response			Total (%)
	Complete Remission	Partially Remission	Poor Remission	
Male	22	14	03	39
Female	12	22	02	36
Total (%)	34 (45.33%)	36 (48.00%)	05 (06.66%)	75 (100%)

Dietary habits and response
Data projected from study also shows that it is common in vegetarian than non-vegetarian approximately; out of 75 cases studied 42 cases were vegetarian and 33 non-vegetarian. As per response concerned, good response recorded in both the types of habits, out of 42 vegetarian cases 19 got complete remission, 20 cases got partial remission and 03 cases got poor remission. Likewise 33 non-vegetarian cases, 15 cases got complete remission, 16 cases got partial remission and 02 cases got poor remission as presented in table-4

Table 4: Response according to dietary habits

Dietary Habits	Response			Total (%)
	Complete Remission	Partially Remission	Poor Remission	
Vegetarian	19	20	03	42
Non- vegetarian	15	16	02	33
Total (%)	34 (45.33%)	36 (48.00%)	05 (06.66%)	75 (100%)

Social status and response
Study also shows that out of 75 cases, 31 cases from lower income group, followed by 39 cases from middle income group and only 05 cases from high income group. As per income group and response of the drug concerned, good response recorded in HIG as out of 05 cases, 03 cases got complete remission, 02 cases got partial remission. In MIG out of 39 cases studied 19 cases got complete remission, 18 cases got partial remission and 02 cases got poor remission.

In LIG group, out of 31 cases studied, 12 cases got complete remission, 16 cases got partial remission and 03 cases got poor remission Table-5.

Table 5: Response according to social status of patients

Social Status	Response			Total (%)
	Complete Remission	Partially Remission	Poor Remission	
Lower Income Group	12	16	03	31
Middle Income Group	19	18	02	39
Higher Income Group	03	02	00	05
Total (%)	34 (45.33%)	36 (48.00%)	05 (06.66%)	75 (100%)

Age and Response

In the table-6, the study shows that this is very common in the age group of 31 to 40 years as out of 75 cases studied maximum 25 cases, followed by 16 cases in the age group of 21-30 years. 11 cases were 51-60 years age group As per response is concerned, good response observed in the age group of 31-40 years as out of 25 cases belonging to this group 12 cases got complete remission, 11 cases got partial remission and 02 case got poor remission. In the age group of 21-30 years 08 cases got complete remission, 08 cases were got partial remission.

Table 6: Response according to age group of patients

Age Group (In years)	Response			Total (%)
	Complete Remission	Partially Remission	Poor Remission	
Up to 20	00	01	00	01
21-30	08	08	00	16
31-40	12	11	02	25
41-50	10	11	01	22
51-60	04	06	01	11
Total (%)	34 (45.33%)	36 (48.00%)	05 (06.66%)	75 (100%)

Laboratory investigations

On registration 75 patients completed, serum uric acid were 5.74 _+01.19 after treatment reduced 5.55 +_ 1.28 and CRP were 3.33 +_ 4.63 and after treatment become 3.85+_6.21, ESR WERE 17.71+_ 15.15 after treatment become 16.84+_ 14.72. C.R.P., normal renal and liver function test were registered. After treatment level of ESR showed downwards trend and slight change observed in S Uric acid.

Table 7: Laboratory investigations before and after treatments

Parameters	Measurement Unit	Statistics	Before Treatment	After Treatment
HB%	Gm%	Mean±SD N=75	11.83±1.68	11.90±1.64
TLC	/Cu mm	Mean±SD N=75	9553.33±924.78	9446.66±832.50
ESR	mm/1st Hour	Mean±SD N=75	17.71±15.15	16.84±14.72
Serum. Uric Acid	Mg/dl	Mean±SD N=75	5.74±1.19	5.55±1.28
C. Reactive Protein		Mean±SD N=75	3.33±4.63	3.85±6.21

Clinical signs and symptoms

Clinical signs and symptoms treated with these formulae response in the swelling change in large amount 1.85±.63 to 0.35±.48. Tenderness showed before treatment 2.08+.0.51 and after treatment become 0.81+_ 0.51. Pain showed before treatment 2.24±.54, after treatment 1.08±0.51 (Table 8).

Table 8: Clinical signs and symptoms

Tenderness	Mean±SD N=75	2.08±.051	0.81±.51
Joint Swelling	Mean±SD N=75	1.85±.63	0.35±.48
Joint Pain	Mean±SD N=75	2.24±.54	1.08±.51

Overall response

Overall response of 75 subjects completed the study, out of 75 cases, 34 cases got complete remission, 36 cases got partially remission and 05 cases got poor remission.(Table 9).

Table 9: Showing response of the drugs

	Response			
	Complete Remission	Partially Remission	Poor Remission	
Total (%)	34 (45.33)	36 (48.00)	05 (06.66)	75 (100%)

Conclusion

The study reveals that result of the Unani Pharmacopoeial formulations - Majoon-e-Sūranjān & Habb-e-Azaraqi effective, as out of 75 cases studied 34 cases got complete remission, 36 cases got partial remission and 05 cases got poor remission. The formulae reduced signs and symptoms like pain, tenderness, swelling in uniform way. During the study blood investigations of each patient for haemogram, liver function test, kidney function test, S. uric acid and C-reactive protein were done at base line, after Ist follow up

and after completion of study. There was slight increased in Hb% and marked decline ESR in well responded cases. No Toxicity and adverse effect of the drugs reported during the study. Blood investigations done to observe any hepatic or renal toxicity at baseline, I[st] follow up and after completion of study. It is observed that drug is safe and effective, has no toxic effect on liver and kidney.

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