IJBPAS, December, 2022, 11(12): 5905-5922

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

COMPARATIVE ASSESSMENT OF THE EFFICACY AND SAFETY OF HYDROALCOHOLIC EXTRACT VERSUS CRUDE FORM OF A POLYHERBAL UNANI DRUG IN PATIENTS OF HYPERURICEMIA WITH ACUTE GOUTY ARTHRITIS

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Received 26th Dec. 2021; Revised 25th Jan. 2022; Accepted 12th March 2022; Available online 1st Dec. 2022

https://doi.org/10.31032/IJBPAS/2022/11.12.6663

ABSTRACT

Background

In our previous standard controlled clinical study, a polyherbal Unani drug consisting of *Colchicum luteum*, *Aloe barbadensis*, *Carthamus tinctorious*, *Terminalia chebula* and Zanjabeel *Zingiber officinalis* in their crude forms, was tested in patients of acute gouty arthritis and found better than the standard drug allopurinol in terms of efficacy as well as safety, when administered in a dose of 6 gm per day to the patients with gout.

Objectives

To reduce the dosing load, 50% hydroalcoholic extract of this polyherbal Unani drug was tested and compared with its initial crude form for its efficacy and safety in patients of hyperuricemia with acute gouty arthritis.

Methods

A total of 40 patients aged between 18-65 years with clinical signs and symptoms of gouty arthritis with a serum uric acid more than 7 mg/dL were randomized into test and control groups to receive either hydroalcoholic extract (600 mg daily in 2 divided doses) or crude form of the polyherbal drug (6 gm daily in 3 divided doses). respectively for 6 weeks.

Results

Both hydroalcoholic extract and crude forms of Polyherbal formulation at a dose of 600 mg and 6 gm respectively (1:10) produced remarkable effects on various efficacy parameters in gouty arthritis and also reduced serum uric acid level below 6 mg/dL. The test formulation (hydroalcoholic extract) was well tolerated and no adverse/ side effects were observed during the entire period of protocol therapy in any patient in the test group, unlike control drug (crude form) which produced diarrhoea and abdominal cramps in 25% of patients.

Conclusion

Hydroalcoholic extract of polyherbal Unani drug was found better tolerated than its crude form, and the dosing load was also reduced to one-tenth of its crude form.

Keywords: Gout, Arthritis, hyperuricemia, Polyherbal, *Colchicum luteum*

INTRODUCTION

Gout, the most common type of inflammatory arthritis has been known for centuries **[1, 2]** and continues to be a health problem around the world despite the availability of therapies **[3]**. The overall prevalence of gout is 1–4% of the general population. There is a strong male predominance in western countries, where it accounts for 3–6% of men and 1–2% of women. The prevalence may increase up to 10% in some countries **[4]**.

Gout is a systemic metabolic disease that results from the deposition of monosodium urate crystals (MSU) in tissues and most often affects middle-aged to elderly men and post-menopausal women. Increased serum uric acid (SUA) above specific threshold results in the formation of uric acid crystals that can be deposited in all tissues mainly in and around the joints forming tophi. It is typically characterized by episodic acute arthritis or chronic arthritis, caused by deposition of monosodium urate monohydrate crystals in joints and connective tissue forming tophi. Nephrolithiasis may also be found as a result of MSU crystal deposition in the kidney interstitium **[4, 5]**. Gout has become progressively more common over recent years in affluent societies due to the increased prevalence of obesity and metabolic syndrome **[6]**. Increased Serum uric acid level above a specific threshold is the main factor in the pathogenesis of gout, however many people with hyperuricemia do not develop gout, or even. form uric acid crystals. Early presentation of gout is the acute joint inflammation that is relieved by NSAIDs and colchicine. Renal stones and Tophi are late presentations **[4]**. Lowering SUA levels below the deposition threshold either by dietary modification or using

serum uric acid lowering drugs is the main goal in the management of gout. This results in the dissolution of MSU crystals preventing further attacks **[7]**. Decreasing the sodium urate levels to lower than 6 mg/dl is key to preventing recurrent attacks, acute flares, and morbidity associated with chronic gout. Hyperuricemia can result from increased production of urate, decreased excretion of uric acid, or a combination of two processes **[4, 6]**. Gout is characterized by rapid onset of pain primarily in the first metatarsophalangeal joint, reaching maximum severity in 2-6 hours i.e., Podagra. There is profound tenderness and marked swelling over the affected joint with overlying red and shiny skin **[4, 5]**.

Gout in Unani Medicine

The description of Gout in the Unani system of medicine is available from the very beginning. According to Ibn-e-Hubal (1122 - 1233 A.D), the word Niqris is obtained from the term 'Anqoroos' which indicates 'the joint of great toe'. Since this disease classically affects the first metatarsophalangeal joint, hence it has been given the name 'Niqris' **[8-11]**. It was known among the Egyptians as Podagra (foot pain), typically of the big toe, as early as 2640 BC. Hippocrates (Buqrat, 460-377B.C), the father of medicine, described Niqris as "the disease of kings" due to its alliance with a rich diet and wealthy men who overindulged in food and drinks (Alcohol) **[13, 14, 18]**.

Ibn-e-Hubal (1122 - 1233 A.D), in his famous book "Kitab Al Mukhtarat Fit Tibb", said that Niqris is a type of Waja-ul-Mufasil and commonly involve both feet. According to him, Niqris especially affects the great toe joint due to which it becomes red, inflamed and painful **[8]**.

According to Masih-ul-Mulk Hakeem Ajmal Khan (1868 - 1927 A.D) "pain of all the joints of body is called Waja-ul-Mufasil and pain of great toes of feet is called Niqris **[12]**.

Etiology of Gout described in classical Unani literature comprises of Sue'mizaj maddi (Imbalance of temperament due to change in matter) **[8, 18]**, Weakness of joints, which result in accumulation of causative matter (Maddah-e-Niqris) in the joint and thus leading to the development of Niqris **[8, 9, 13, 18]**.

The important predisposing factors responsible for the development of Niqris are excessive eating, excessive drinking (Alcohol), excessive intercourse particularly just after meals, sedentary lifestyle, heredity, luxurious living, and lack of exercise **[8, 9, 11, 18, 19]**.

Gouty matter (Maddah-e-Niqris) is a by-product of liver metabolism, Niqris is one of those diseases, which is related to

hepatic and tissue metabolism (hazm-e-kabidi or hazm-e-chaharum) **[9]**.

In the Unani system of medicine, certain drugs are being used such as Majoon-e-Suranjan, Habb-e-suranjan, Safoof-e-suranjan, Habb-e-niqris, Habb-e-sibr, Majoon-e-chobchini etc for the treatment of gout **[9, 13, 18, 19]**.

In the conventional system, the treatment presently available for gout consists of NSAIDs (e.g., Indomethacin, Diclofenac, Naproxen etc), Oral colchicine, Glucocorticoids, Xanthise oxidase inhibitor (Allopurinol, Febuxostat), and Uricosuric agents (Probenecid, benzbromarone etc) **[1, 15, 16]**.

Although a large number of above said drugs are available for the treatment of gout in Modern system of medicine but recurrence of the disease and side effects of the medicine are very troublesome, which call for the development of novel drugs with similar or better efficacy and lesser toxicity than presently available drugs.

According to Modern Physiology, the excretion of uric acid takes place through urine, faeces, and perspiration **[17]**. The principle of treatment (Usool e Ilaj) of Niqris (gout) as described in classical Unani text consisted of Mudirrat (Diuretics), Mus'hilat (Purgatives) & Moariqat (Diaphoretics) **[9]**.

Keeping in view that these three categories of drugs would be helpful in the excretion of uric acid through various routes, a polyherbal formulation was developed in the form of a capsule, which consisted of five herbs in their crude form namely, Suranjan (*Colchicum luteum*), Elva (*Aloe barbadensis*), Qurtum (*Carthamus tinctorious*), Halaila Zard (*Terminalia chebula*) and Zanjabeel (*Zingiber officinalis*).

In our previous clinical study, this drug was found more effective as compared to placebo **[2]**. In another standard controlled clinical study conducted in our department, this drug was also found better than the standard drug allopurinol in terms of efficacy as well as safety, when administered in a dose of 6 gm per day to the patients with gout **[32]**.

In the present study, to reduce the dosing load, 50% hydroalcoholic extract of this polyherbal Unani drug was compared with its initial crude form for its efficacy and safety in patients of hyperuricemia with acute gouty arthritis.

MATERIALS AND METHODS

This was an open label, randomized comparative study conducted in the Department of Moalejat, Ayurvedic and Unani Tibbia College Hospital, Karol Bagh, New Delhi, India, during 2020-2021 session

Study drugs

Test drug:

The test drug was Polyherbal formulation in the form of capsule containing **50**% hydro-alcoholic extracts of five herbs namely Suranjan (*Colchicum luteum*), Elva (*Aloe barbadensis*), Qurtum (*Carthamus tinctorious*), Halaila Zard (*Terminalia chebula*) and Zanjabeel (*Zingiber officinalis)* in equal proportions. The extracts of herbs were procured from Vital Herbs, Uttam Nagar, Delhi-110059 along with their Certificate of Analysis. The identity and authenticity of the extracts were further confirmed and certified by Research Natural Product Laboratory, Department of Pharmacognosy and Phytochemistry, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi.

Comparator (Control):

The comparator was a polyherbal capsule containing the crude forms of the same five herbs i.e. Suranjan (*Colchicum luteum*), Elva (*Aloe barbadensis*), Qurtum (*Carthamus tinctorious*), Halaila Zard (*Terminalia chebula*) and Zanjabeel (*Zingiber officinalis*) in equal proportions. The crude drugs of the comparator were procured from Shamsi Dawakhana, Ballimaran, Delhi-110006. The originality and authenticity of the drugs were certified by Dr. Sunita Garg, Emeritus Scientist, CSIR- NISCAIR

Criteria for the selection of patients

Both male and female patients aged between 18-65 years with clinical signs and symptoms of gouty arthritis with a serum uric acid of more than 7 mg/dL were enrolled in the study.

Patients were excluded from the study if they were having complications like tophi nephrolithiasis etc. Patients receiving anti-gout drugs or uric acid elevating drugs e.g., Pyrazinamide, Thiazide group of diuretics/Aspirin/NSAIDs were also excluded. Other exclusion criteria were pregnant and lactating women, patients with renal or hepatic insufficiency, cardiovascular disorders/haemopoietin disorders. Patients suffering from malignancy, taking chemo and radiotherapy were also excluded.

After a thorough screening, diagnosed patients with gouty arthritis fulfilling the inclusion/ exclusion criteria were enrolled in the study. Patients were randomly allocated to test group or comparator (control) group after making them understand the study and taking their voluntary informed written consent.

Ethical consideration

The study was started after obtaining approval from **Institutional Ethics Committee**, A& U Tibbia College, Karol

Bagh, New Delhi, and getting registered in ICMR-Clinical Trial Registry India vide **CTRI No.- CTRI/2020/10/028663**, dated 30.11.2020.

Written informed consent to participate in the study was obtained from each patient and study was conducted as per to Good Clinical Practice (GCP) Guidelines.

Dosage schedule

Test group patients were given 50% hydroalcoholic extract of Unani formulation filled in a capsule of 300 mg, in a dose of one capsule twice a day orally with plain water for 42 days.

Control group patients were given powder of the crude form of same Unani polyherbal formulation filled in a capsule of 1g, in a dose of two capsules (1g each) thrice a day orally with plain water for 42 days.

Follow up

Patients of both groups followed up on weekly basis. Clinical as well as laboratory evaluation were recorded at the baseline, week 1, week 4, and week 6.

Drug compliance

Compliance with test drug/ control drug was evaluated at each follow-up visit by capsule count.

Assessment of efficacy

To assess the adequacy of treatment of gouty arthritis on patients in both groups, following subjective and objective parameters were used in the study.

Subjective parameters

- Pain (Wong Baker's Faces rating scale; with 0=doesn't hurt, 2= hurts a little, 4= hurts a little more, 6= hurts even more, 8= hurts a lot, 10= as much as the patient can imagine)
- Nausea
- Anorexia

Objective parameters

- Tenderness (0-4 point scale; with 0=no tenderness, 1=patient says it is painful, 2=patient says it is painful, winces, 3=patient pulls back, 4=patient does not allow palpation)
- Joint swelling (0-4 point scale; with 0=no swelling,1=barely perceptible, 2=mild, 3=moderate, 4=severe, bulging beyond the joint margins)
- Movement/Mobility (0-4 point scale; with 0=full voluntary movement,1=partial voluntary movement, 2=full movement when the joint is moved by the examiner, 3=partial movement when the joint is moved by the examiner, 4=no movement at all)
- Serum uric acid
- C-reactive protein
- Erythrocyte sedimentation rate

Assessment of safety

To establish the safety of drugs, the following investigations were carried out at

baseline, on 8th day and just after termination of treatment.

- Liver function test: SGOT, SGPT and S. Alkaline phosphatase
- Kidney function test: Blood urea and Serum creatinine
- Haemogram: Hb%, TLC & DLC.

Adverse event documentation

Adverse reactions in the form of loose stools, abdominal discomfort as reported by the patients were recorded in CRF and severe cases were withdrawn from the study.

Statistical analysis

After six weeks of the treatment, pre-treatment and post-treatment values of subjective and objective parameters in each group were analysed and compared to evaluate the efficacy of the treatment by applying paired student t-test. Intergroup comparison was statistically calculated by applying an unpaired student t-test.

RESULTS:

As summarised in Figure 1, a total of 87 patients having signs and symptoms of gouty arthritis were screened, 23 were excluded as they were not meeting the inclusion criteria and 12 patients refused o participate in the study. Thus, 52 patients were enrolled in the study and randomly allocated to the test group or comparator (control) group. Out of 27 patients in the test group, 07 patients were lost to follow up and 20 patients completed the study. In the control group, out of 25 registered cases, 01patient did not turn up for follow up and 04 patients discontinued the medication because of the side effect (loose stools and nausea. A total of 20 patients completed the treatment up to the end of the study (6 weeks).

Efficacy

Effect of trial drugs on serum uric acid

As shown in **Table 1 & Figure 2**, in test group, the mean values of serum uric acid decreased extremely significantly from 8.2 ± 0.85 at the baseline to 7.51 ± 0.96 on 7th day, 6.28 ± 0.93 on 28th day and 5.88 ± 1.27 at the termination of study ($t=12.34$; $p < 0.001$). While in control group, the mean values of serum uric acid reduced highly significantly from 8.12 ± 0.46 on 0 day to 7.43 ± 0.55 on 7th day, 6.36 ± 0.92 on 28th day and 5.66 ± 0.80 at the end of therapy ($t=13.35$; $p <0.001$). On applying unpaired t test in both the groups, no significant difference between the mean serum uric acid of both groups is found ($t=0.668$; $p> 0.05$).

Effects of trial drugs on CRP

The mean C-reactive protein values observed in the test group were 4.05 ± 1.90 at the baseline, 3.325 ± 1.63 on 7th day, 1.81 ± 1.20 on the 28th day, and 1.252 ± 0.75 on the 42nd day, the difference is highly significant ($t=7.36$; $p< 0.01$). On the

other hand, in the control group the mean C-reactive protein also underwent extremely significant reduction from 5.27± 1.66 on 0 day to 4.08 ± 2.85 on 7th day, 2.75 ± 2.022 on 28th day and 1.47 ± 0.633 at the end of trial (t=9.74; p < 0.001). On applying unpaired t test, the inter group difference was not statistically significant (t=1.04; p> 0.05) **(Table 2 & Figure 3)**.

Effect of trial drugs on ESR

In the test group, the mean values of E.S.R decreased significantly from 16.84± 5.31 at the baseline to 15.75 ± 3.32 on the 7th day, 12.3 ± 2.89 on 28th day, and 9.45 ± 2.89 at the termination of the study (t=5.36; p < 0.001). While in the control group, the mean values of E.S.R reduced highly significantly from 17.4 ± 4.62 on 0 day to 14.85 ± 4.43 on 7th day, 12.5 ± 4.11 on 28th day, and 9.85 ± 2.00 at the end of therapy (t= 8.38; p <0.001). On applying the unpaired t-test in both the groups, no statistically significant difference between the mean serum uric acid of both groups is found (t=0.52; p> 0.05) **(Table 3 & Figure 4)**.

Effect of trial drugs on pain (Wong Baker's Faces rating scale)

In the test group, the mean score of pain reduced from 5.9± 2.63 at the baseline to 5.7 ±3.32 on the 7th day, 2.05 ± 2.11 on the 28th day, and 1.1 ± 1.88 on the termination of treatment. While in the control group, pain reduced from 6.3 ± 2.45 on the baseline to 6 ± 3.04 on the 7th day, 3.1 ± 1.88 on the 28th day, and 1.5 ± 1.27 at the end of treatment. In the test group, Paired t-test was applied and was found to be very significant (t=8.56; p<0.001). Similarly, paired t-test was put in the control group which turned out to be extremely significant (t = 12.3; p<0.001). To see the difference between the two groups, an unpaired t-test was applied which was found to be not significant (t=0.8; p>0.05) **(Table 4 & Figure 5)**.

Effect of trial drug on tenderness

In test group, there was highly significant decrease in tenderness from 2 ± 0.85 at the baseline to 1.4 ± 0.82 on 7th day, 0.65 ± 0.67 on 28th day and 0.4 ±0.59 at the end of study (t = 8.24; p < 0.001). While in control group, the reduction in tenderness was extremely significant too from 2.4 ± 1.043 on 0 day to 1.9 ± 0.96 on 7th day, 1 ± 0.91 on 28th day and 0.6 ± 0.68 at the termination of trial (t = 9.47; p < 0.001) **(Table 5)**.

Effect of trial drugs on joint swelling

The mean joint swelling score in the test group significantly reduced from 1.8 ± 1.60 at the baseline to 1.45 ± 0.75 on the 7th day, 0.55 ± 0.75 on 28th day, and 0.3 ± 0.47 at the end of study (t=5.17; p < 0.01). Whereas, in the control group the mean joint swelling score reduced significantly

from 2.4 ± 1.26 on 0 day to 2.15 ± 1.26 on 7th day, 1.35 ± 0.98 on 28th day, and 0.7 ± 0.80 at the termination of the trial (t=7.7; p< 0.01) **(Table 6 & Figure 4)**.

Effect of trial drugs on movement restriction

The mean scores for restriction of movement significantly reduced in the test group were 1.3 ± 1.26 at the baseline, 0.95 ± 1.09 on the 7th day, 0.25 ± 0.55 on 28th day, and 0.2 ± 0.52 on 42nd day (t=4.4; p< 0.001). On the other hand, in the control group, there is a highly significant reduction in mean for restriction of movement from 1.9 ± 1.07 at the baseline to 1.5 ± 1.14 on the 7th day, 0.75 ± 0.63 on the 28th day, and 0.2 ± 0.41 at the termination of the study (t=8.09; p< 0.01) **(Table 7 & Figure 5)**.

Safety

During the study, no adverse events were reported by the patients or clinically detected by the investigator. No significant change from baseline was observed in haemoglobin, SGOT, SGPT, S. Bilirubin, B. Urea, and S. Creatinine values in both the groups (Table 8 & Table 9) Both the formulations (Crude & Extract form) were found well-tolerated as indicated by 85% drug compliance **(Table 8, 9)**.

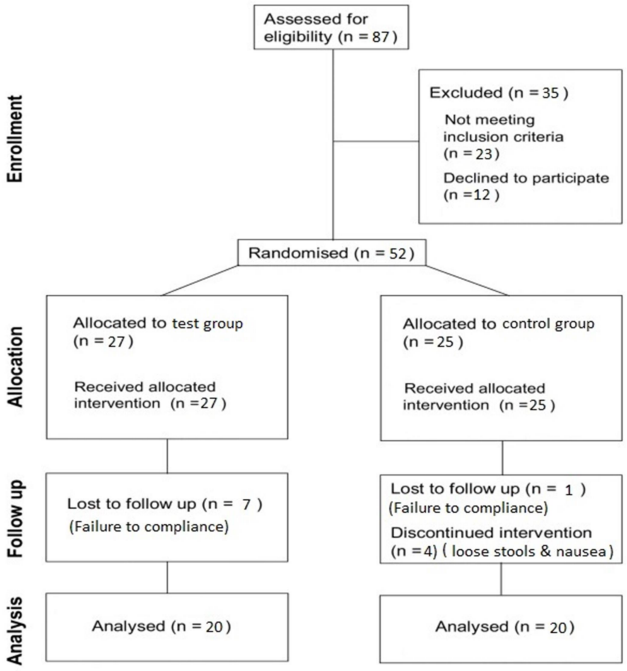

Figure 1: CONSORT (Flow chart of participation of patients in the present clinical trial

Table 1: Effect of trial drugs on serum uric acid

S. Uric acid	(Mean ± S.D.) mg/dL				p value
	0 Day	7th day	28th day	42nd Day	
Test drug	8.20±0.85	7.51 ± 0.96	6.28 ± 0.93	5.88±1.27	<0.001
Control drug	8.12±0.46	7.43 ± 0.55	6.36 ± 0.92	5.66±0.80	<0.001

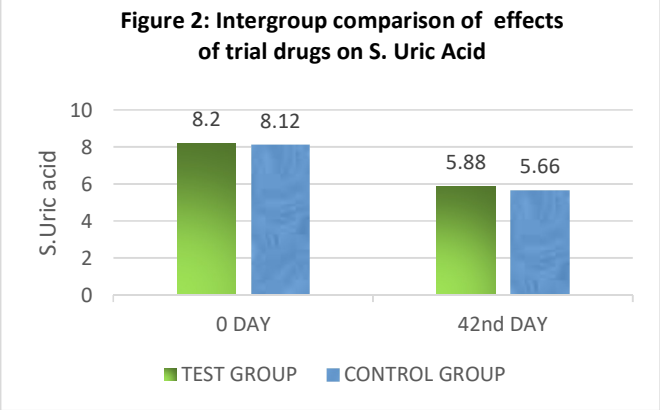

Table 2: Effect of trial drugs on CRP

C.R.P.	(Mean ± S.D.) mg/L				p value
	0 Day	7th day	28th day	42nd Day	
Test drug	4.05±1.90	3.325 ± 1.63	1.81 ± 1.20	1.25±0.75	<0.001
Control drug	5.27±1.66	4.08 ± 2.85	2.75 ± 2.022	1.87±2.01	<0.001

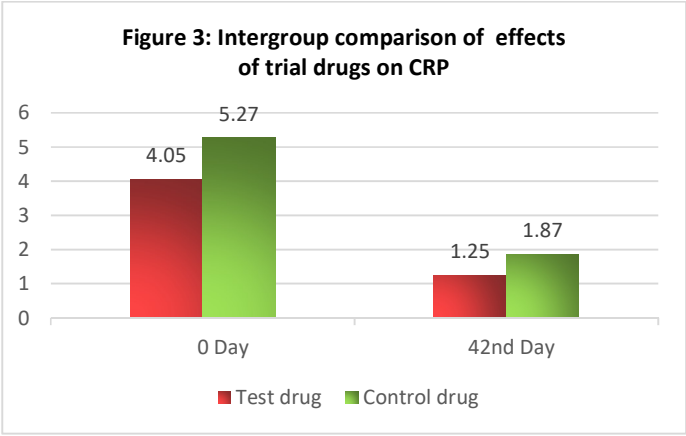

Table 3: Effect of trial drugs on ESR

ESR	(Mean ± S.D.) mm/h				p value
	0 Day	7th day	28th day	42nd Day	
Test drug	16.85±5.31	15.75 ± 3.32	12.3 ± 2.89	9.45±2.89	<0.001
Control drug	17.54±4.62	14.85 ± 4.43	12.5 ± 4.11	9.85±2.00	<0.001

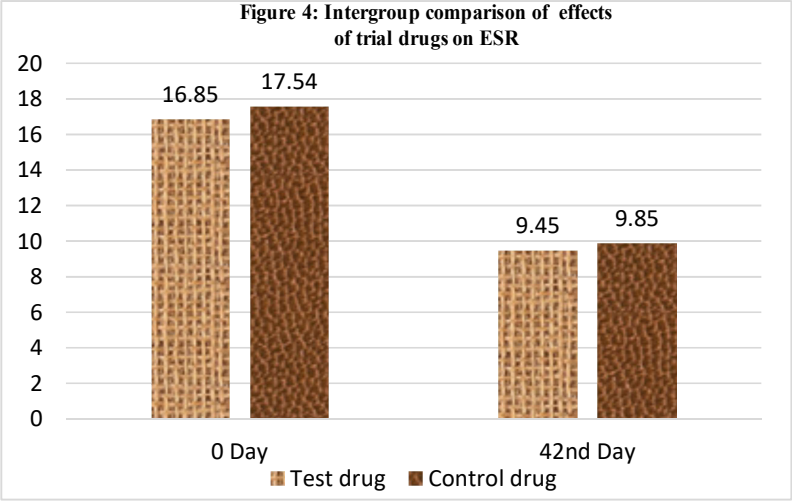

Table 4: Effect of trial drugs on pain (Wong Baker's Faces rating scale)

Pain	(Mean ± S.D.)				p value
	0 Day	7th day	8th day	42nd Day	
Test drug	5.9± 2.63	5.7 ±3.32	2.05 ± 2.11	1.1 ± 1.88	<0.001
Control drug	6.3 ± 2.45	6 ± 3.04	3.1 ± 1.88	1.5 ± 1.27	<0.001

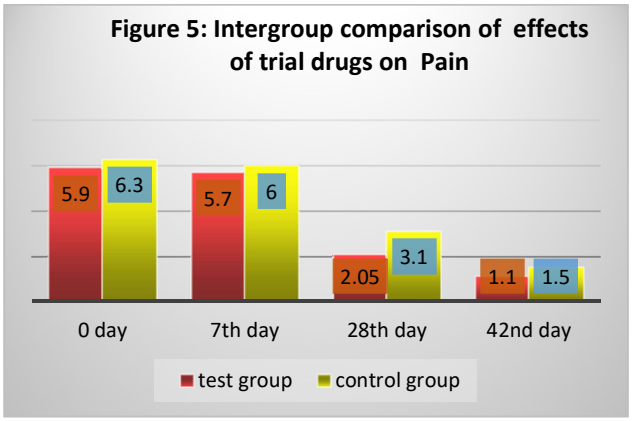

Table 5: Effect of trial drug on tenderness

Tenderness	(Mean ± S.D.)				p value
	0 Day	7th day	28th day	42nd Day	
Test drug	2 ± 0.85	1.4 ± 0.82	0.65 ± 0.67	0.4 ±0.59	<0.001
Control drug	2.4 ± 1.043	1.9 ± 0.96	1 ± 0.91	0.6 ± 0.68	<0.001

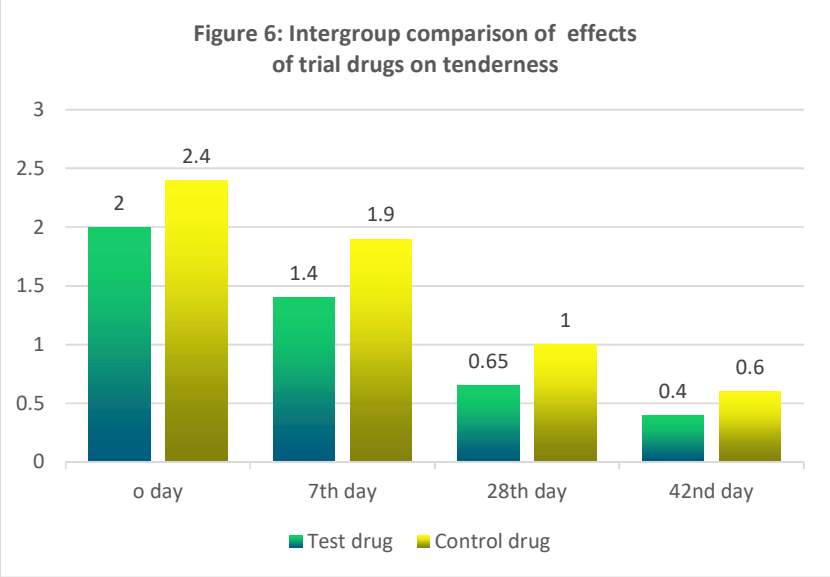

Table 6: Effect of trial drugs on joint swelling

Joint swelling	(Mean ± S.D.)				p value
	0 Day	7th day	28th day	42nd Day	
Test drug	1.8 ± 1.60	1.45 ± 0.75	0.55 ± 0.75	0.3 ± 0.47	<0.001
Control drug	2.4 ± 1.26	2.15 ± 1.26	1.35 ± 0.98	0.7 ± 0.80	<0.001

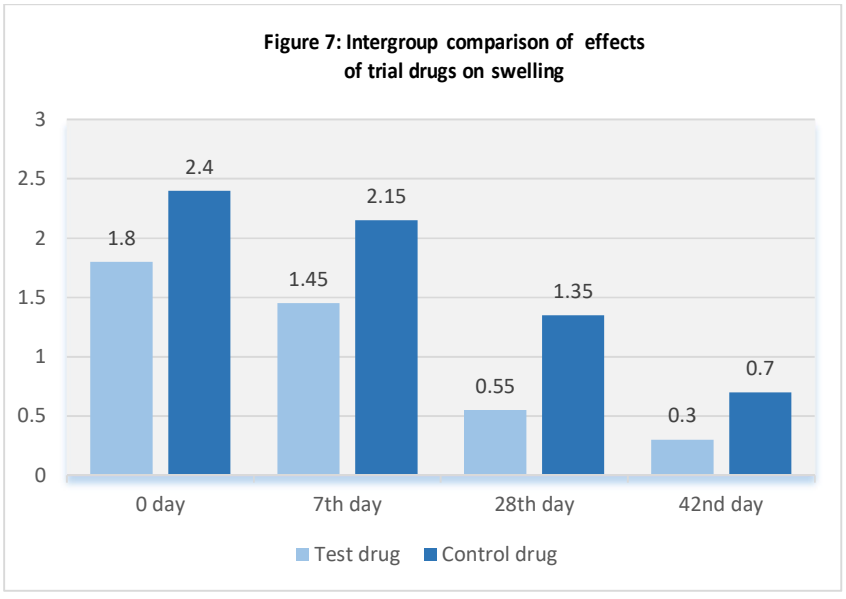

Table 7: Effect of trial drugs on movement restriction:

Movement restriction	(Mean ± S.D.)				p value
	0 Day	7th day	28th day	42nd Day	
Test drug	1.3 ± 1.26	0.95 ± 1.09	0.95 ± 1.09	0.2 ± 0.52	<0.001
Control drug	1.9 ± 1.07	1.5 ± 1.14	0.75 ± 0.63	0.2 ± 0.41	<0.001

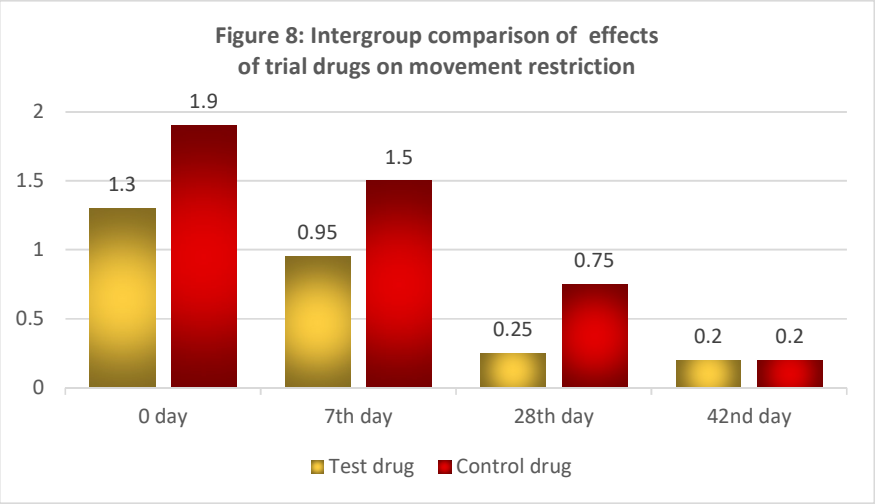

Table 8: safety assessment in test group (N=20)

Parameters		Assessments		
		0 Day	10th Day	42nd Day
Heamoglobin		13.305±0.84	13.36±0.87	13.59±0.92
RBC		4.54±0.20	4.59±0.22	4.59±0.38
TLC		8565±1327.8	8475±1366.08	8505±849.44
DLC	Neutrophils	69.56±8.29	73.15±4.62	72.23±7.34
	Lymphocytes	27.74±7.34	26.1±5.50	25.51±4.63
	Eosinophils	1.83±1.69	1.66±1.74	1.78±1.33
	Monocytes	1.66±1.49	1.72±2.17	1.64±1.40
LFT	SGOT	24.99±6.52	24.66±3.48	24.33±5.55
	SGPT	29.41±4.75	29.55±9.87	30.47±9.87
	S.Alk.Phos.	85.13±20.95	93.30±17.10	97.16±14.53
KFT	B. Urea	28.48±7.45	26.42±6.34	25.1±6.48
	S. Creatinine	0.83±0.22	0.85±0.21	0.84±0.32

TLC-Total Leucocyte Count; SGOT-Serum Glutamate Oxalate Transaminase
SGPT-Serum Glutamate Pyruvate Transaminase
***Values with plus/minus signs are expressed as Means ± S.D.**

Table 9: safety assessment in control group (N=20)

Parameters		Assessments		
		0 Day	10th Day	42nd Day
Heamoglobin		13.38±1.14	13.53±1.06	13.54±0.98
RBC		4.49±0.20	4.54±0.20	4.53±0.17
TLC		9038±1242.69	9073.5±972.43	8560±1134.80
DLC	Neutrophils	69.89±7.03	73.69±3.44	73.43±3.38
	Lymphocytes	26.08±4.69	24.08±2.87	24.76±3.97
	Eosinophils	2.52±1.88	1.1±1.24	2.95±1.24
	Monocytes	3.12±3.00	6.13±2.22	2.02±2.25
LFT	SGOT	25.70±4.83	25.21±3.87	26.23±3.44
	SGPT	30.74±7.97	28.53±2.64	28.65±4.33
	S.Alk.Phos.	92.32±20.7	97.41±16.99	99.4±12.02
KFT	B. Urea	27.48±8.04	25.46±6.73	26.24±6.9
	S. Creatinine	0.94±0.38	0.80±0.29	0.78±0.27

TLC-Total Leucocyte Count; SGOT-Serum Glutamate Oxalate Transaminase
SGPT-Serum Glutamate Pyruvate Transaminase.
***Values with plus/minus signs are expressed as Means ± S.D.**

DISCUSSION

Gout is one of the most common types of inflammatory arthritis. An acute attack of gouty arthritis is initiated by the precipitation of urate crystals in the synovial fluid resulting in the inflammatory response and the acute inflammatory cells (neutrophils) phagocytose urate crystals and release a glycoprotein which further aggravates inflammation. conventional drugs used for subsiding acute attacks or lowering serum uric acid are associated with potentially adverse effects. Moreover, these commonly used therapeutic agents often, and for various reasons, fail to achieve the desired lowering of serum urate levels to below 6.0 mg/dl. The Polyherbal Unani formulation in our previous two studies and also in the present study not only relieved various signs and symptoms of gouty arthritis but also exerted remarkable effects on lowering serum uric acid level and inflammatory markers ESR and CRP. The test drug (50% hydroalcoholic extract) in the present study was found to be better than the crude form of the Polyherbal formulation in terms of dose reduction from 6 capsules (1000 mg each) to 2 capsules (300 mg each) per day and terms of safety. The test formulation was well tolerated and no adverse/ side effects were observed during the entire period of protocol therapy unlike the crude form of the drug which produced diarrhoea and abdominal cramps in 25% of patients. However, the effect of the drugs in both the groups was almost the same in relieving signs and symptoms and also in reducing hyperuricemia, CRP and ESR.

The relief in joint pain, tenderness can be attributed to the analgesic activity of Suranjan (*Colchicum luteum*) **[20, 21]**, Elva (*Aloe barbadensis*) **[22, 23]**, and Zanjbeel (*Zingiber officinale*) **[22, 24]**. Anti-inflammatory activities of Qurtum (*Carthamus tinctorius*) **[25]**, Halaila-e-Zard (*Terminalia chebula)* **[22, 24]**, Zanjbeel (Zingiber officinale) **[22, 25, 26]** can also

be considered in decreasing pain, swelling and tenderness.

Colchicine, an active constituent of Suranjan (*Colchicum luteum*), has been proved inhibitory to the glycoprotein released by the neutrophils in acute gouty inflammation. Colchicine by binding with fibrillar protein tubulin has been found to inhibit neutrophil migration in the inflammed joint. All this explains relief in pain, swelling and tenderness because of Suranjan (*Colchicum luteum*) **[27, 28]**. The diuretic activity of Qurtum (*Carthamus tinctorius*) [29] and laxative action of Halaila-e-Zard (*Terminalia chebula*) **[30]**, and Elva (*Aloe barbadensis*) **[31]** might also help reduce monosodium urate precipitation by increased excretion of uric acid through urine and faeces respectively.

In the light of the above discussion and based on observations and results obtained in this study, large-scale, standard control, double-blind randomized clinical study is warranted to further support the efficacy and tolerability of test formulation in the treatment of gouty arthritis.

CONCLUSION

From the observations and results obtained in this study, it is concluded that Hydro-alcoholic extract and crude forms of polyherbal formulation at a dose of 600 mg and 6 gm respectively (1:10) produced remarkable effects on various efficacy parameters in gouty arthritis and also reduced serum uric acid level below 6 mg/dL. The test formulation (hydro-alcoholic extract) was well tolerated and no adverse/ side effects were observed during the entire period of protocol therapy in any patient in the test group, unlike the control drug (crude form) which produced diarrhoea and abdominal cramps in 25% of patients. Thus, the 50% hydroalcoholic extract was found better tolerated than the crude form, and the dosing load was reduced to almost one-tenth of its crude form.

ACKNOWLEDGMENTS

This article is retrieved from the MD thesis of Dr. Nasir Jamal, under the supervision of Dr. Rais ur Rahman, Head, Department of Moalejat, A & U Tibbia College, New Delhi, India. The authors wish to thank Dr. Naseem Akhtar, Associate Professor, Department of Moalejat, A & U Tibbia College, New Delhi, India, for his valuable help and suggestions during this work.

CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

FUNDING

No funding was received from any organization for conducting this study or preparation of this manuscript.

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