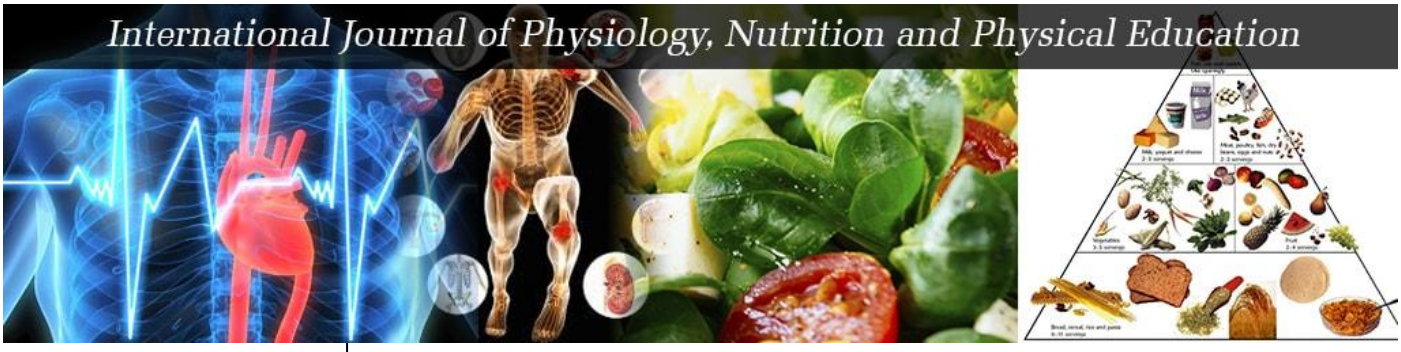

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A single-blind, randomized, placebo controlled trial to assess the efficacy and tolerability of a unani formulation in patients with acute gouty arthritis (niqris)

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Abstract
Background: The conventional drugs used for gout are full of adverse effects (hepatotoxicity, nephrotoxicity, haematological toxicity). The need of the time is to develop evidenced based safe and \cost effective hypouricemic agent which can easily counteract treatment-failure gout and minimize the suffering of the patients and improve their quality of life. A unani formulation having Colchicum luteum baker, Aloe Indica, Terminalia Chebula, Carthamus tinctorius, Zingiber Officinale, as the ingredients was selected for the clinical study on Gout and was intended to overcome the above demerits and bring to light a Unani formulation which was being used for thousands of years.
Objective: The aim of this single blind placebo control study was to evaluate the efficacy and tolerability of Unani formulation in the diagnosed patients of Gout based on scientific parameters.
Methods: Patients with acute gouty arthritis were randomised. Test group received the drug in the dose two tablets thrice in a day (5g) while the control group was given inert substance in equal dose. The subjective parameter: pain and the objective parameters: Tenderness, Movement, Health assessment Questionnaire-Disability Index, Serum uric acid, Erythrocyte Sedimentation Rate were evaluated on days 0,7,28 and 40.
Results: In test group the pain improved from 5.95 ± 1.54 at the onset of drug therapy to 4.50 ± 1.91 on the 7^{th} day, 3.30 ± 1.72 on 28^{th} day and 1.85 ± 1.98 on the termination of treatment. The improvement in tenderness proceeded from 2.0 ± 1.12 (0 day) to 1.75 ± 0.97 (7^{th} day) to 1.05 ± 0.94 (28^{th} day) and 0.60 ± 0.59 (40^{th} day).Improvement seen in restriction of movement was from 1.70 ± 0.86 (0 day) to 1.35 ± 0.59(7^{th} day) to 0.85 ± 0.67 (28^{th} day) to 0.55 ± 0.51 (40^{th} day).There was marked improvement in Health assessment Questionnaire-Disability Index since within the group difference was extremely significant ($p<0.001$) with mean value of 8 ± 4.75 at the onset of treatment and 2.85 ± 2.58 at the termination. There was drastic change in the serum levels of uric acid with a rapid decrease from 6.21 ± 1.62 on 7^{th} day to 6.27 ± 1.52 on day 28^{th} to 5.55 ± 1.57 on day 40^{th} which in all the three follow ups is extremely significant($p<0.001$). The E.S.R observed in test group was 25 ± 11.53 at 7^{th} day,25.30 ± 10.27 at 28^{th}day,22.30 ± 12.02 on 40^{th} day, not significant on all the three occasions.
Conclusion: The test drug has significant analgesic and anti-inflammatory activity. It is effective in lowering serum urate level with minimal side effects. It also minimised the suffering of the patients. However, a large scale, prospective, double blind, randomized controlled study is warranted to support the efficacy of test formulation in the treatment of gouty arthritis.

Keywords: Acute gouty arthritis, gout, hyperuricemia, Niqris

Introduction
Gouty arthritis the most common type of inflammatory joint disease which results from the deposition of monosodium urate monohydrate (MSU) crystals in and around the joints due to long standing hyperuricemia, which may be attributed to a disorder in purine metabolism or renal excretion of uric acid. An acute attack of gouty arthritis presents in the early hours of the morning as an acute monoarthritis (80-90%) [1, 2, 3] affecting the lower extremity, often the first metatarsophalangeal joint (70% of attacks are in this joint) [4, 5, 6, 7, 8, 9, 10]. The affected joint is warm, tender and swollen, and in most cases the overlying skin is erythematous. Low grade fever, general malaise and anorexia may accompany the symptoms [11, 8, 2, 9, 12]. It is a painful inflammatory disease affecting an estimated 20 million people worldwide. It is a significant

source of suffering and disability.

The pharmacologic therapy is given in the form of oral colchicine [16, 18, 29, 9], NSAID's [29, 32, 9, 34], intra articular injections of long acting steroids for acute attacks; but a number of adverse reactions have been reported with high and frequent dosing of these medicines. Recent studies indicate that the majority of gout patients under the care of physicians are not adequately managed with currently available anti-gout therapies. These gout cases have been referred to as "treatment-failure gout" and have become the primary target for quality improvement care, including new drug development [45]

Hence there is a need to develop a therapy for this disease because of the above shortcomings of modern system of medicines. So keeping in view the need of the hour, the present trial is an effort to introduce such a drug from herbal source which is least toxic, cost-effective, easily available and efficacious even in cases of "treatment-failure gout"; based on the scientific parameters.

Unani medicines and its numerous cross cultural variants offer an important perspective on the conceptualization and treatment of arthritis. According to Unani literature, Gout (niqris) is derived from the term *'Anqaroos'* which means 'the joint of the great toe'. Since this disease classically affects the First Metatarsophalangeal joint, hence the name *'Niqris*' [30, 47, 48] The line of treatment of gout as described in the classical text of Unani Medicine consists of the following groups of medicines:- (i) diuretics (ii) purgatives and (iii) diphoratic [30]. According to the modern physiology too the excretion of uric acid takes place through the faeces, urine and perspiration [29]. Based on the above observations, we can conclude that the line of treatment of gout as described in Unani Medicine is scientific and in accordance with the modern physiopathogenesis of the disease. The medicines used in the present study exhibit the following properties (i) Colchicum Iuteum baker is a specific medicine for joint pain, strengthens joints, flushes toxic substances from joints, constricts the vessels of joints, thus prevents rentry of toxic substances. According to survey of modern literature it has laxative, anti-inflammatory and diuretic properties [21, 23, 24, 25, 31, 39]. (ii)Aloe-indica is a purgative, anthelmentic, diuretic drug [23, 14, 37, 38, 40] (iii) Terminalia Chebula is a purgative, diuretic, tonic, carminative drug [15, 19, 20, 27, 28, 35, 37] (iv) Carthamus tinctorius; is a purgative, cures inflammation, diuretic [13, 27, 28, 33, 41, 42] (v) Zingiber Officinale is a stimulant, carminative. It's a corrective adjunct to purgatives for preventing nausea and griping. It is also prescribed in chronic rheumatism [14, 17, 22, 26, 33, 36, 43].

The objective of this single blind randomised placebo controlled study was to develop a safe Unani formulation based on classical line of treatment for the treatment of gout which is efficacious, least toxic and cost effective.

2. Materials and Methods

The study was carried out in A & U Tibbia College and Hospital, Department of Moalijat, Karol Bagh, New Delhi and patients were selected from OPD (Out Patient Department) and IPD (In Patient Department).

Patients with increased serum uric acid level (including patients with values higher than ¾ th that of normal range) associated with clinical features of gout; in the age group of 18-65 years irrespective of sex and fulfilling at least six of the twelve clinical, laboratory and radiographic phenomena as described by American College of Rheumatology were included. They were willing to discontinue allopurinol with a positive history of Gout, or NSAIDs for any other pain. Exclusion criteria included patients having renal insufficiency, hepatic insufficiency, cardiac disorders, pregnant women, children, elderly patients above the age of 65 years, patients receiving chemotherapy for cancer, patients receiving thiazide group of diuretics/low dose of aspirin/NSAIDs and other type of arthritis.

Diagnosis was based on clinical manifestations of the disease and elevated levels of serum uric acid. (Satisfying six of the twelve criteria as recommended by American college of rheumatology-ACR).

2.1 Study design

This was a single blind randomised placebo controlled study. Patients underwent thorough clinical examination and laboratory investigations and were included in the clinical trial after randomization. Written informed consent was obtained. For the assurance of efficacy of unani formulation, patients of gouty arthritis were divided into two groups, Group I (Test group) and Group II (Control group).Both groups contained same number of patients i.e.20 patients in Group I and 20 patients in Group II. In the Group I, the powdered drug was given in a dose of 5g thrice a day whereas placebo in a dose of 5g thrice a day for the same duration. The patients were kept under strict observation and asked to come on 7th, 28th, 40th days for the assessment of subjective and objective parameters.

2.2 Efficacy assessment

Patients were assessed for subjective and objective parameters. The subjective parameters was recorded in the form of pain (Wong-Baker's Faces rating scale) whereas the objective parameters assessed included; Tenderness (4-point likert scale), Movement (4-point likert scale), Health assessment Questionnaire-Disability Index, Serum uric acid, Erythrocyte Sedimentation Rate. The adverse reactions in the form of abdominal discomfort, loose stools as reported by the patients were recorded and severe cases were withdrawn from the study. All the patients were asked to abstain from any concomitant therapy during the entire study period of 40 days.

2.3 Tolerability assessment

To establish the safety of drugs in question, the following investigations were carried out prior, after one week and just after the termination of treatment: Liver function test – S.G.O.T, S.G.P.T. & S. Alkaline Phosphatase, Kidney function test – Blood Urea, S. Creatinine And Haemogramme – Hb%, TLC, DLC, E.S.R. Patients who reported any adverse drug reaction or drug event or failed to come for follow up or failed to consume less than 70% of drug were withdrawn from the study.

2.4 Statistical analysis

In order to find the statistical difference within the groups, Wilcoxon Signed Ranks Test was applied; and for reporting the statistical difference in between the groups i.e. control group and test group, Mann-Whitney Test was applied.

3. Results

3.1 Subject disposition

Total 46 cases were registered; out of them 23 in test group and 23 in control group. During screening 2 patients did not fulfil inclusion criteria and were thus excluded from the study; remaining 44 patients were subjected for clinical study after randomization,2 patients from test group and 2 patients

from control group did not complete the full course of treatment. Only 20 patients in test group and 20 in control group had completed the course of treatment.

3.2 Baseline characteristics

The majority of subjects were in the age group of 45-54 years i.e.16 (40%), married (87.5%) consuming no vegetarian diet i.e.85 % (34) equally distributed between both the sexes. Only 12.5 % (5) patients reported the habit of alcohol consumption in excess amount, also, as many as 32 (80%) patients out of the total 40 cases registered, reported the involvement of first metatarsophalangeal joint either in isolation or along with other joints

3.3 Efficacy Analysis

3.3.1 Pain

In control group, the mean pain score was 5.95 ± 1.50 initially, which worsened to 6.35 ± 1.23 at the end of treatment. While in test group the pain improved from 5.95 ± 1.54 at the onset to 1.85 ± 1.98 on the termination of treatment. The difference in between the group was extremely significant ($p<0.0001$). (Table:1)

3.3.2 Tenderness

There was very gradual insignificant improvement in mean tenderness in control group viz 1.50 ± 1 on 7th day, 1.55 ± 0.99 on 28th day, 1.50 ± 0.21 on termination of treatment. Whilst in test group the improvement in tenderness proceeded from 2.0 ± 1.12 (0 day) to 1.75 ± 0.97 (7th day) to 1.05 ± 0.94 (28th day) and 0.60 ± 0.59 (40th day). (Table: 2)

3.3.3 Restriction of movement

The test group showed improvement in restriction of movement was from 1.70 ± 0.86 (0 day) to 0.55 ± 0.51 (40th day). which was extremely significant ($p<0.001$) on 40th day. (Table: 3)

3.3.4 HAQ (Health Assessment Questionnaire)

In test group, there was marked improvement in HAQ since within the group difference was extremely significant ($p<0.001$) with mean value of 8 ± 4.75 at the onset of treatment and 2.85 ± 2.58 at the termination. (Table: 4)

3.3.5 Serum uric acid

In control group, the mean value of serum uric acid were 7.62 ± 1.13, 7.71 ± 1.82 on day 7th and 40th respectively which are non-significant ($p>0.05$). On the contrary, in test group there was drastic change in the serum levels of uric acid with a rapid decrease from 6.21 ± 1.62 on 7th day to 6.27 ± 1.52 on day 28th to 5.55 ± 1.57 on day 40th which in all the three follow ups is extremely significant($p<0.001$). (Table: 5)

3.3.6 Erythrocyte sedimentation rate (E.S.R.)

In control group and test groups E.S.R recorded was not significant on all the three occasions (Table: 6)

Table 1: Effect on pain in both groups

Pain	Control Group (N=20)				Test Group (N=20)			
	0 day	7th day	28th day	40th day	0 day	7th day	28th day	40th day
Mean	5.95	6.05	6.0	6.35	5.95	4.50	3.30	1.85
S.D. (±)	1.50	1.47	1.08	1.23	1.54	1.90	1.72	1.99
S.E.M. (±)	0.34	0.33	0.24	0.28	0.34	0.43	0.38	0.44
'p' value		0.62*	0.83*	0.19*		0.001***	0.0001§	<0.0001§

*p>0.05 (NS) **p<0.05(LS) ***p<0.01(MS) §p<0.001(ES) (Wilcoxon Signed Rank Test) P at 7th day (T/C) <0.01 (LS) (Mann-Whitney Test)
P at 28th day (T/C) <0.0001 (ES) (Mann-Whitney Test)

Table 2: Effect on tenderness in both groups

Tenderness	Control Group (N=20)				Test Group (N=20)			
	0 days	7th day	28th day	40th day	0 days	7th day	28th day	40th day
Mean	1.60	1.50	1.55	1.50	2	1.75	1.05	0.60
S.D. (+)	1.14	1.0	0.99	0.94	1.12	0.97	0.94	0.59
S.E.M. (+)	0.25	0.22	0.22	0.21	0.25	0.22	0.21	0.13
'p' value		0.50*	0.75*	0.56*		0.06*	<0.0001§	0.0002§

*p>0.05 (NS) **p<0.05(LS) ***p<0.01(MS) §p<0.001(ES) (Wilcoxon Signed Rank Test)
P at 7th day 0.48 (NS) (Mann-Whitney Test)
P at 28th day 0.12 (NS) (Mann-Whitney Test)
P at 40th day 0.003 (MS) (Mann-Whitney Test)

Table 3: Effect on restriction of movement in both groups

Restriction of Movement	Control Group (N=20)				Test Group (N=20)			
	0day	7th day	28th day	40th day	0day	7th day	28th day	40thday
Mean	1.40	1.45	1.45	1.65	1.70	1.35	0.85	0.55
S.D. (±)	0.59	0.60	0.60	0.74	0.86	0.59	0.67	0.51
S.E.M	0.13	0.13	0.13	0.17	0.19	0.13	0.15	0.11
'p' value		>0.99*	0.75*	0.16*		0.01***	0.0001§	<0.0001§

*p>0.05 (NS) **p<0.05(LS) ***p<0.01(MS) §p<0.001(ES) (Wilcoxon Signed Rank Test)
P at 7th day (T/C) 0.61 (NS) (Mann-Whitney Test)
P at 28th day (T/C) 0.008(NS) (Mann-Whitney Test)
P at 40th day (T/C) 0.0001 (ES) (Mann-Whitney Test)

Table 4: Effect on health assessment questionnaire (HAQ) in both groups

HAQ	Control Group (N=20)		Test Group (N=20)	
	0 day	40th day	0 day	40th day
Mean	5.75	8.35	8	2.85
S.D. (±)	1.89	2.56	4.75	2.58
S.E.M. (±)	0.42	0.57	1.06	0.58
'p' value		<0.0001§		<0.0001§

*p>0.05 (NS) **p<0.05(LS) ***p<0.01(MS) §p<0.001(ES) (Wilcoxon Signed Ranks Test)

Table 5: Effect on serum uric acid in both groups

Serum Uric Acid	Control Group (N=20)				Test Group (N=20)			
	0 day	7th day	28th day	40th day	0 day	7th day	28th day	40th day
Mean	7.81	7.62	7.62	7.71	8.04	6.21	6.27	5.55
S.D. (±)	0.91	1.13	1.14	1.18	1.98	1.62	1.52	1.57
S.E.M. (±)	0.20	0.25	0.25	0.26	0.44	0.36	0.34	0.35
'p' value		0.18*	0.49*	0.71*		<0.0001§	<0.0001§	<0.0001§

*p>0.05 (NS) **p<0.05(LS) ***p<0.01(MS) §p<0.001(ES) (Wilcoxon Signed Ranks Test)
P at 7th day (T/C) 0.0008 (ES) (Mann-Whitney Test)
P at 28th day (T/C) 0.0007 (ES) (Mann-Whitney Test)
P at 40th day (T/C) <0.0001 (ES) (Mann-Whitney Test)

Table 6: Effect on erythrocyte sedimentation rate in both groups

E.S.R.	Control Group (N=20)				Test Group (N=20)			
	0 day	7th day	28th day	40th day	0 day	7th day	28th day	40th day
Mean	28.70	29.45	29.75	30.10	26.65	25.00	25.30	22.30
S.D. (±)	11.33	11.08	10.42	11.19	10.49	11.53	10.27	12.02
S.E.M. (±)	2.533	2.48	2.33	2.5	2.35	2.58	2.29	2.69
'p' value		>0.99*	0.28*	0.39*		0.31*	0.51*	0.19*

*p>0.05 (NS) **p<0.05(LS) ***p<0.01(MS) §p<0.001(ES) (Wilcoxon Signed Ranks Test)
P at 7th day 0.29 (NS) (Mann-Whitney Test)
P at 28th day 0.27 (NS) (Mann-Whitney Test)
P at 40th day 0.02 (LS) (Mann-Whitney Test)

4. Discussion and Conclusion

Gout is one of the most common types of inflammatory joint disease; affects an estimated 1-1.5% of the world population [44]. It is characterized by hyperuricemia, which has long been attributed to a disorder in purine metabolism or renal excretion of uric acid. Although the pathophysiology of gout is well understood and clinically efficacious therapies are available, recent studies have shown that the prevalence and incidence of gout are increasing.

Medication has been a standard treatment for gout for many years. However some patients do not respond to medications and a substantial proportion of patients under the care of physicians fail to achieve adequate control of hyperuricemia or symptoms.[46] In addition to this the conventional drugs used for gout are full of adverse effects (hepatotoxicity, nephrotoxicity, hematological toxicity) Recent studies indicate that the majority of gout patients under the care of physicians are not adequately managed with currently available anti-gout therapies. These gout cases have been referred to as 'treatment-failure gout' [45].

Keeping in view the above shortcomings, it is a dire need of the time to develop evidenced based safe and cost effective hypouricemic agent which can effectively manage hyperuricemia without producing adverse reactions or hypersensitization; an agent which can easily counteract treatment-failure gout and minimize the suffering of the patients and improve their quality of life.

Unani Physicians of Unani systems have claimed to possess effective treatment for the presenting problem but most of the drugs have not been subjected for scientific evaluation. In present study therefore, a unani formulation having Colchicum luteum baker, Aloe Indica, Terminalia Chebula, Carthamus tinctorius, Zingiber Officinale as the ingredients was selected for the clinical study on Gout and was intended to overcome the above demerits and bring to light a Unani formulation which was being used for thousands of years. For this purpose, a single blind placebo control study was designed to evaluate the efficacy of Unani formulation in the diagnosed patients of Gout.

Though the demographic data was well maintained but does not reflect the very epidemiological purpose, as the sample size was very small. Hence a few of the observations in our study are not in accordance with the standard description of the disease.

In the test group the improvement in pain was observed from 24.36% on 7th day to 46.90% on the 28th day, 68.91% on termination of treatment.

Similarly the percentage improvement in tenderness as seen in the patients of test group was from 12.5 % (day 7) to 47.5 % (day 28) and 70% on termination of treatment as compared to the initiation values.

The improvement in restriction of movement was from 20.59% on 7th day, 50% on 28th day and 67.65% on the termination of treatment, which was insignificant at the end of treatment.

The improvement in HAQ in test group was 64.37% while the deterioration in control group was 45.21%, both at the end of the treatment In test group, the decrease in serum uric acid was 22.76% on 7th day, 22.015 on 28th day and 30.97% on 40th day which is extremely significant on all follow-up. The above observations show that the test drug has significant analgesic and anti-inflammatory activity. It may also be due to the decreased levels of serum uric acid (Table: 5) which consequently leads to failure of deposition of Monosodium urate crystals in the joints and thus the attack is subsided.

Although the E.S.R decreased on all the three follow-ups in

test group, but the decrease was not significant. This points out that the raised in E.S.R in the patients may be due to some other reason.

Liver function test, Kidney Function test and Haemogramme were assessed and statistical analysis yielded non-significant results ($p>0.05$), stating that the drug is neither hepatotoxic, nephrotoxic, nor has haematological toxicity.

The adverse reactions were reported in the form of slight abdominal discomfort during the first week of consuming test drug which was relieved in the subsequent week. One patient had to be withdrawn from the trial due to persistence of loose stools.

Finally it may be concluded that the test formulation used in this study is clinically significant for improving the symptomatology of gouty arthritis viz. pain, tenderness, movement. It showed significant improvement in the serum levels of Uric acid and The Quality of Life as assessed by Health assessment Questionnaire. Based on the finding of this study, a large scale, prospective, double blind, randomized controlled study is warranted to support the efficacy of test formulation in the treatment of gouty arthritis.

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