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Research Article

Clinical study to Evaluate Safety and Efficacy of *Boozidaan* (*Pyrethrum indicum*) in the management of *Niqris Muzmin* (Chronic Gout)

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Abstract

Objectives: The objectives of this study were to observe the Efficacy of unani pharmacopoeial formulation *Boozidan (Pyrethrum indicum*) for the management of *Niqris Muzmin (*Chronic gout) and to observe any concomitant and adverse effects of formulation.

Methods: This single blind, randomized and standard control clinical study was conducted between April 2021 to October 2021 for a period of 28 days. 60 patients diagnosed with chronic gout were divided into two groups, 30 Test group and 30 Control group. The test group was administered with 5g boozidaan in powder form once daily with water and the patients of control group were given tablet febuxostat 80mg once daily. Patients were followed up and improvements in subjective parameters were assessed weekly at 7th, 14th, 21st, and 29th day. Objective parameters were assessed at the baseline and at 29th day. The data obtained was subjected to statistical analysis.

Results: Both the test and control drug were effective in reducing Serum uric acid level, ESR and CRP levels. A significant improvement in subjective and objective parameters was observed in both test and control groups and no adverse effects were observed during and after the study.

However, the test drug had superior efficacy in reducing the objective parameters and it was statistically significant (p-value<0.0001).

Conclusion: Both Boozidaan and Febuxostat were safe and significantly effective in resolving the symptoms and signs of gouty arthritis and both have significant effect on reducing serum uric acid level.

Keywords: Boozidaan, Chronic gout, Niqris, Febuxostat, serum uric acid, unani medicine

1. INTRODUCTION

Niqris (Gout) is the most common inflammatory arthritis in men and in older women. It is caused by the deposition of monosodium urate monohydrate crystals in joint fluid, bones, cartilages, tendons, bursa and other tissues secondary to hyperuricemia [1,2,3,4, 5, 6]. Elevation of serum uric acid level (SU) or hyperuricemia is an essential prerequisite for the development of gout. As SU level exceeds the physiological saturation threshold of 6.8 mg/dl, urate can crystallize as MSU in and around joints[2, 7, 8, 9]. The cardinal feature and prerequisite for gout is defined as a plasma urate level >7mg/dl in males and >6 mg/dl in females[2].

It is a chronic rheumatic illness characterized by very painful recurrent acute attacks of monoarthritis which affects metatarsophalangeal joints (MTP) in over 50% of cases. Other common sites are the ankle, midfoot, knee, small joints of hand, wrist and elbow. The axial skeleton and large proximal joints are rarely involved[1, 7, 10]. The clinical picture of gout is divided into asymptomatic hyperuricemia, acute gouty arthritis, intercritical period and chronic topheceous gout[11].

Gout is the most prevalent arthritis in adults and its public health burden is increasing globally[8]. The prevalence of gout ranges from 1-4 % worldwide and its incidence ranges from 0.1 – 0.3%worldwide. Gout is more common in men than women by 3:1 to 10:1[12]. It is rare in children and premenopausal females and its mean age of onset is 40- 50 years, in women the age of incidence is post menopausal[2, 6, 13].

Annual incidence of gout is 2.68 per 1000 persons and its incidence increases globally due to poor dietary habits such as fast food, lack of exercise, increased incidence of obesity, metabolic syndrome[11].

Risk factors of gout include excessive alcohol intake, excess consumption of purine rich diet (meat, seafood, sweetened beverages), surgery, trauma, sepsis, stress, starvation, dehydration, drugs like diuretics, pyrizinamide, cyclosporine, salicylates and lead toxicity. Systemic conditions associated with high risk of gout include cardiovascular diseases (CVS), poor renal function, Diabetes mellitus (DM), menopause, psoriasis, myeloproliferative disorders and genetic factors[1,2,3,11,12 ,14,15,16]. Gout has an strong impact on individual

health and health care system [17] and is associated with functional impairment and diminished health related quality of life[18]. Patients with hyperuricemia or gout are at increased risk of developing a variety of comorbidities such as hypertension, CVS disease, DM, metabolic syndrome, chronic kidney disease and neurological disorders[14, 16, 19, 20]. Moreover, Gout is associated with excess mortality due to CVS causes[17]. Differential diagnosis of gouty arthritis includes septic arthritis, psoriatic arthritis, reactive arthritis, osteoarthritis, pseudo gout and rheumatism[1, 2]. Gout is mainly diagnosed by identification of the pathogonomic MSU crystals by joint fluid aspiration or in tophi aspirate[11]. Diagnosis is based on laboratory and radiological features. The gold standard of diagnosis is identification of characteristic MSU crystal in the synovial fluid using polarized light microscopy.

Management of gout is directed towards the treatment of acute gout, prevention of further attacks, identification and correction of factors that contribute to the disease[2, 21]. Weight reduction and reduction of urate concentration by low purine diet should be considered in the long-term management of gout[2]. Management of gout includes both pharmacological and non pharmacological approaches. Pharmacological therapies focus on Urate Lowering Therapy (ULT) and anti-inflammatory drugs. Non pharmacological therapies focus on dietary and life style changes including weight loss and exercise[3]. Management of gout includes management of flares, chronic gout and prevention of flares as well as management of comorbidities[9,11,15]. Lowering (SU) levels below the deposition threshold either by dietary modification and using ULT is the main goal in the management of gout. This results in the dissolution of MSU crystals preventing further attacks[11].

Various drugs like Colchicine, Non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroids, Probenecid and Sulfinpyrazone, and synthesis inhibitors like Allopurinol and Febuxostat are used in the management of gout[22, 23, 24]. However these medications are associated with systemic side effects like vomiting, Gastro intestinal (GI) bleeding, Hepato renal toxicity and Hypersensitivity[25]. The draw backs of all the above mentioned drugs call for the development of novel drugs with similar or better efficacy and lesser toxicity than presently available drugs.

In unani system of medicine Niqris *(Gout)* is being treated since greeco Arab periods, unani physicians claim to possess many safe and effective drugs for the management of *Niqris (*Gout) described in unani classical text books. In ancient unani literature there are description of many drugs (single and compound formulation) used to treat various types of arthritis including gout which include *Ashwagandah*a (*Withania somnifera), Halaila Zard* (*Terminalia chebula*), *Gokharu* (*Tribulus terpyrethrumrestris), Suranjanshirin (Colchium autumnale), sibrsaqotri (Aloe Barbadensis and Boozidan (Pyrethrum indicum),.*

In unani system of medicine, *Suranja*n (*colchicumluteum*) is the standard drug in the management of *Niqris (Gout).* According to classical unani literature *Boozidan (pyrethrum indicum*) holds functional approximity *to suranjan (colchicumluteum*) in its efficacy. *Boozidan (pyrethrum indicum*), having Analgesic and Anti-inflammatory action, detoxifies morbid humors from nerves and joints. That is why single unani *drug Boozidan (pyrethrum indicum*) has been selected and formulated in powder form for the treatment *of Niqris* (gout). The present study has been carried out just to evaluate the safety and efficacy *of Boozidan (pyrethrum indicum*) in the management o f *Niqris* (Gout*).*

2. MATERIALS AND METHODS

This clinical study was a single blind, randomized and standard control clinical study conducted on Sixty (60) patients to evaluate the Safety And Efficacy of *Boozidaan* (Pyrethrum Indicum) in the management of *Niqris Muzmin* (Chronic Gout) at the Regional Research Institute of Unani Medicine (RRIUM), Naseem Bagh, Srinagar J&K from April 2021 to October 2021. An inclusive protocol was framed and approval was obtained from the Institutional Ethics Committee of Regional Research Institute of Unani Medicine (RRIUM), Srinagar (IEC No: RRIUM/KU/2020-21/Tech./PB-375) dated 27.01.2021 and registered prospectively in Clinical Trials Registry (CTRI) India (CTRI/2021/03/032150).

The study started by enrolling patients from OPD/IPD of RRIUM Hospital. Every patient was questioned for detailed history of the disease. The patients were clinically examined and their hematological, biochemical and radiological investigations were carried out. Clinical symptoms, history and investigations were recorded on prescribed case report form designed for the study. A detailed history of development of present clinical symptoms like pain, joint stiffness, restriction of movements, swelling and tenderness was noted on the case report form. A thorough history of past illness regarding diabetes mellitus, hypertension, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, septic arthritis, trauma, sepsis and blood dyscrasias as well as a detailed personal history regarding excessive consumption of purine rich diet, sedentary lifestyle, excessive intercourse, alcohol consumption, drugs and smoking was taken and recorded on the case report form. A detailed occupational history, Social Status as well as family history of diabetes mellitus, hypertension, Rheumatoid arthritis and gout was also noted. Thorough general physical examination was carried out. Appearance, built, nutrition, pulse, blood pressure, respiratory rate, temperature, lymphaedenopathy, oedema, cyanosis, icterus, pallor, clubbing etc were keenly observed and recorded on the case report forms. Thorough systemic examination of respiratory system, gastro intestinal system, nervous system, cardiovascular system and urinary system was carried out to exclude the patients with severe ailments of any above mentioned systems. A thorough examination of musculoskeletal system was also carried out and recorded on case report forms. The joint involved were examined for signs of pain, swelling, erythema, tenderness, raised temperature, tophi as well as active and passive movements at the beginning of the study (0 day) and thereafter regularly during the follow up i.e. at 7th,14th day,21th and 29th day. Investigations like CBC (Hb%, TLC, DLC), ESR, LFT (Sr. Bilirubin, SGOT, SGPT, ALP), KFT (Blood Urea, Sr. Creatinine, Serum Uric Acid) and Blood Sugar (F) were performed to establish the safety & observe the effect of our drugs on renal function, liver function and blood sugar. C- reactive protein (CRP) (quantitative) and Rheumatoid Factor (qualitative) on 0th day were done to rule out the presence of rheumatoid disease.USG abdomen, Urine- routine (Microscopic) and X Ray of affected joint were also carried out on day 0^{th} (Baseline) and day 29th (after completion of the therapy). Mijaz of each patient was assessed during clinical examination on the basis of ten parameters (*Ajnās 'Ashara*) mentioned in Unani literature. Diagnosis of gout was based on classical signs and symptoms of *Niqris muzmin* (chronic Gout) with uric acid level >7mg/dl in males and >6mg/dl in females. Diagnosed patients of Chronic Gout qualifying the inclusion criteria were enrolled for clinical trial after obtaining their written consent and were randomly assigned into test and control groups. The basal clinical findings were compared with the findings observed at 7th, 14th day, 21th and 29^{th} day. The lab investigations were done before and after the treatment. The findings were

recorded on case record form. The basal clinical findings were compared with the findings. The difference if any observed was recorded in percentage and taken as the improvement caused by the respective treatment. Similarly, the basal findings of investigations were compared to the post treatment findings of the investigations and the improvement was recorded in case record form. All the observations in both groups were tabulated & statistical analysis was carried out with the help of biostatistician to known which drug is more effective clinically and in reducing the serum uric acid level. On the basis of history, clinical examination and investigations, the patients fulfilling the inclusion criteria were enrolled for the study after obtaining written voluntary consent. While those patients, who failed to fulfill the required inclusion criteria, were excluded from the study.

2.1. The selection of the subjects was made on the basis of following criteria:

a. Inclusion criteria

1) Irrespective of all genders.

2) Patients between 18-65 years of age.

3) Patients Fulfilling the criteria of American College of Rheumatology (ACR) for diagnosing gouty arthritis including clinical features, laboratory and radiological finding, having serum uric acid level>7mg/dl in males and >6mg/dl in females.

4) Patients, who are ready to sign the informed consent, follow the protocol and willing to participate in clinical study voluntarily.

b. Exclusion criteria

1) Patients below 18 and above 65 years of age.

2) Pregnant and lactating mothers.

3) Patients who fail to give consent.

4) Patients of gout associated with any systemic disorder which interfere with patient study.

5) Patients of gout associated with any severe arthritic condition such as rheumatoid arthritis, septic arthritis.

6) Patients suffering from anemia and other blood dyscrasias like leukemia, haemophilia, etc

7) Patients suffering from congenital gout.

8) Any other disease other than Gout (Gouty arthritis).

Withdrawal Criteria:

1) Failure to follow up (absence from the study for more than one month).

2) Poor compliance to the protocol such as not using drug at regular basis.

3) Any gross adverse effect. In case of possible minor adverse events such as burning, itching, swelling and redness in either group, the same was managed with appropriate drug.

2.2. Method of assessment of the disease

1. Subjective Parameters

Joint Pain
Joint Swelling
Joint stiffness
Restriction of Movements

The data of subjective parameters was recorded on , 7th, 14th and 29th day of the study.

2. Objective parameters

Serum uric acid level

CRP (quantitative) on day 0th and 29th

ESR

The objective parameters were assessed on 0th and 29th day of the study.

2.3. Availability, dosage and mode of administration of test drug & control drug

Boozidaan (Pyrethrum indicum) The drug was purchased from the local Market, identified and authenticated from centre for Biodiversity &Taxonomy, Department of Botany, University Of Kashmir, No:F(Herbarium Specimen CBT/KU)21 and Voucher Specimen No. 4265-KASH Herbarium. *Boozidaan (Pyrethrum indicum*) was prepared by grinding and pulverizing the Crude drug at Zam Zam laboratory, Rangereth Srinagar. In the form of powder (safoof), the powder form of drug was packed in the form of 5 gm sachets. Each patients of test group was advised to take 5 gms of *Boozidaan* (*Pyrethrum Indicum*) powder with water once daily after breakfast for duration of 28 days. The control drug Febuxostat was purchased from local market under the trade name of Feboxa 80mg from RANBAXY. The tablets removed from the strips and then packed in sterile air tight packets for period of seven days in order to ensure blinding. Each patients of control group was advised to take a tablet of Febuxostat 80mg with water once daily after breakfast for period of 28 days.

Follow up

The clinical assessment of all groups was carried out after every 7th day. The findings were recorded on CRF (case report form). The basal clinical findings were compared with the findings observed at 7th, 14th day, 21th and 29th day. The lab investigations were done before and after the treatment.

3. RESULTS AND OBSERVATIONS

The results of the study reveal that majority of the patients were between 40-60 years of age (53.34%), belonged to male gender (51.67%) and were muslim (100%). Majority of the patients were married (90%) belonging to middle class families (40%) having mixed dietary habits (100%) and maximum patients were from housewives group (45%) followed by businessmen (26.67%), government employees (16.67%), laborers (8%) and student (3.3%). Majority of patients in both the groups were having a balghami mizaj constituting about 60% in test group and 76.67% in control group.

3.1. Effect of drugs on subjective parameters

Joint pain:

During the course of the study it was observed that joint pain was present in all the patient of Test group and Control group before treatment. After treatment joint pain was absent in 80.0% of the patients in test group and 36.67% patients in control group. The data showing the distribution of patients according to effect on severity of joint pain in the test group and control group reveals that there exists a high significant difference before and after the treatment among both test and control groups with a p-value (<0.0001*) which means that both Unani and standard treatment is effective in resolving the severity of pain. To find out more effective drug between Test and control group, Chi Square test has been applied on the data for the difference of Test group and Control group it was found that $\chi 2 = 11.589$, df=1, P-value=<0.0001* indicating that improvement is highly significantly in test group compared to control group. (table1&2 and fig 1)

Table 1: Effect of test drug on joint pain

Distribution of patients as per severity of pain among test group as shown in Table 1						
Severity of pain	**BT**		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
Absent	0.00	0.00	24.00	80.00	24.00	40.00
Mild	3.00	10.00	6.00	20.00	9.00	15.00
Moderate	26.00	86.67	0.00	0.00	26.00	43.33
Severe	1.00	3.33	0.00	0.00	1.00	1.67
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

Table 2: Effect of control drug on joint pain

Distribution of patients as per severity of pain in control group as shown in Table 2						
Severity of pain	**BT**		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
Absent	0.00	0.00	11.00	36.67	11.00	18.33
Mild	1.00	3.33	19.00	63.33	20.00	33.33
Moderate	28.00	93.33	0.00	0.00	28.00	46.67
Severe	1.00	3.33	0.00	0.00	1.00	1.67
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

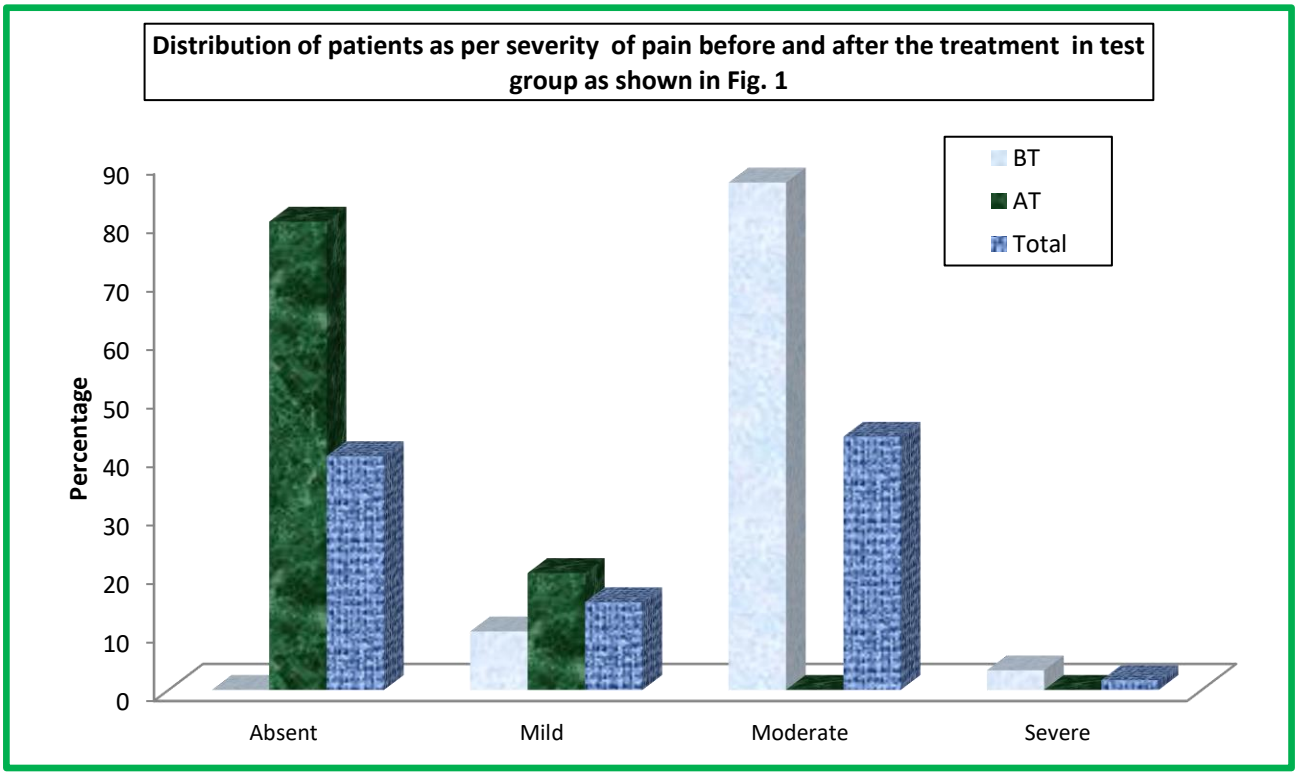

Figure 1: Effect of test drug on joint pain

Joint swelling:

During the course of the study it was observed that joint swelling was present in all the patient of Test group and Control group before treatment. After treatment joint swelling was absent in all the patients in test group and 96.67% patients in control group. The data showing the distribution of patients according to effect on severity of joint swelling in the test group and control group reveals that there exists a high significant difference before and after the treatment among both test and control groups with a p-value (<0.0001*) which means that both unani and standard treatment is effective in resolving the severity of joint swelling. To find out more effective drug between Test and control group, Chi Square test has been applied on the data for the difference of Test group and Control group it was found that $\chi 2$ =1.017, Df=1, (Fisher's Exact, P-value=1)

indicating that there is no significant difference in the efficacy of both drugs on joint swelling. Therefore, both the treatments are equally effective in resolving joint swelling. (table3&4 and fig 2)

Table 3:Effect of test drug on joint swelling

Showing severity of joint swelling before and after the treatment in test group as shown in Table 3						
	BT		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
No joint swelling	0.00	0.00	30.00	100.00	30.00	50.00
Palpable	5.00	16.67	0.00	0.00	5.00	8.33
Visible	23.00	76.67	0.00	0.00	23.00	38.33
Bulging beyond joint margins	2.00	6.67	0.00	0.00	2.00	3.33
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

Table 4: Effect of control drug on joint swelling

Distribution of patients as per severity of joint swelling before and after the treatment in control group as shown in Table 4						
	BT		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
No joint swelling	0.00	0.00	29.00	96.67	29.00	48.33
Palpable	4.00	13.33	1.00	3.33	5.00	8.33
Visible	24.00	80.00	0.00	0.00	24.00	40.00
Bulging beyond joint margins	2.00	6.67	0.00	0.00	2.00	3.33
Total	30.00	100.00	30.00	100.00	60.00	100.00

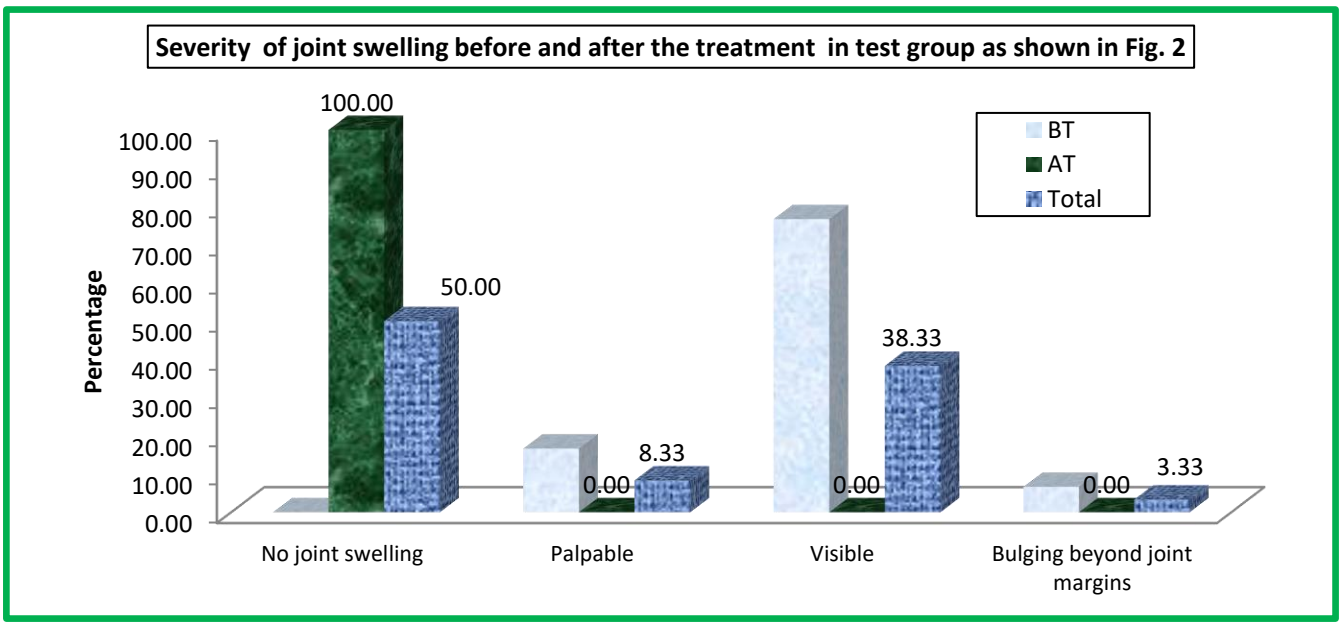

Figure 2: Effect of test drug on joint swelling

Joint stiffness:

During the course of the study it was observed that joint stiffness was present in all the patient of Test group and Control group before treatment. After treatment joint stiffness was absent in 96.67% of the patients in test group and 86.67% patients in control group. The data showing the distribution of patients according to effect on severity of joint stiffness in the test group and control group reveals that there exists a high significant difference before and after the treatment among both test and control groups with a p-value (<0.0001*) which means that both unani and standard treatment is effective in resolving the severity of joint stiffness. To find out more effective drug between Test and control group, Chi Square test has been applied on the data for the difference of Test group and Control group it was found that $\chi 2 = 1.964$, Df=1, (Fisher's Exact, P-value=0.353) indicating that there is no significant difference in the efficacy of both drugs on joint stiffness. Therefore both the treatments are equally effective in resolving joint stiffness. However, almost 97% cases had no stiffness after the treatment in test group compared to 86.67% in control group. (Table 5&6 and fig.3)

Table 5: Effect of test drug on joint stiffness

Distribution of patients as per status of stiffness before and after the treatment in test group as shown in Table 5.						
Stiffness severity	**BT**		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
No stiffness	0.00	0.00	29.00	96.67	29.00	48.33
Sometimes for (5-10) mins	1.00	3.33	1.00	3.33	2.00	3.33
Daily for (10-30 mins)	10.00	33.33	0.00	0.00	10.00	16.67
Daily for (30-60 mins)	16.00	53.33	0.00	0.00	16.00	26.67
Daily for more than 1 hr	3.00	10.00	0.00	0.00	.00	5.00
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

Table 6: Effect of control drug on joint stiffness

The distribution of patients as per status **of stiffness before and after the treatment in control group as shown in Table 6.**						
	BT		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
No stiffness	0.00	0.00	26.00	86.67	26.00	43.33
Sometimes for (5-10) mins	1.00	3.33	4.00	13.33	5.00	8.33
Daily for (10-30 mins)	8.00	26.67	0.00	0.00	8.00	13.33
Daily for (30-60 mins)	21.00	70.00	0.00	0.00	21.00	35.00
Daily for more than 1 hr	0.00	0.00	0.00	0.00	0.00	0.00
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

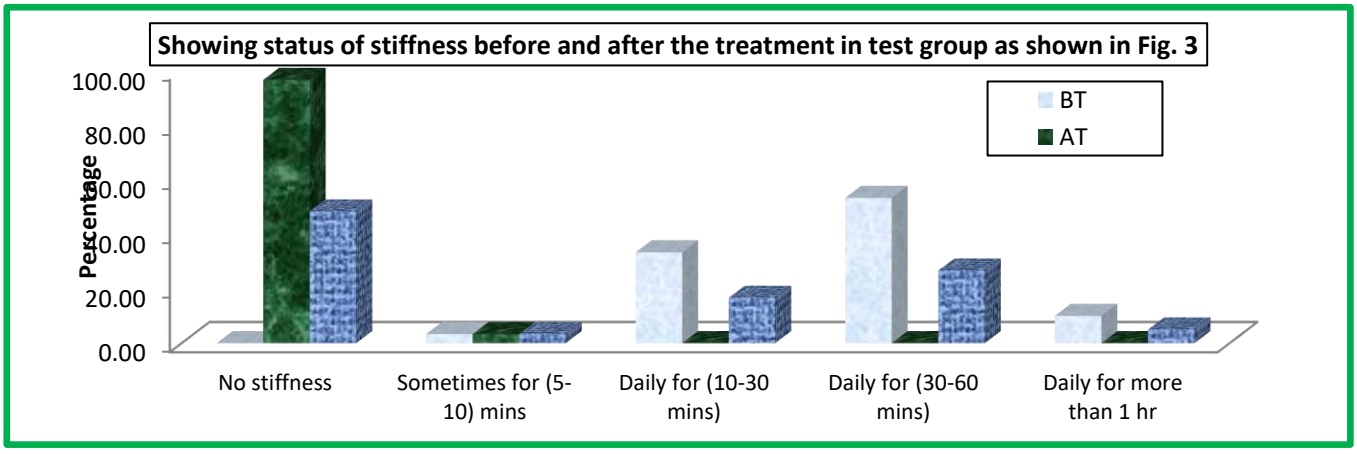

Figure 3: Effect of test drug on joint stiffness

Status of joint mobility:

During the course of the study it was observed that there was lack of Full Voluntary Movement in all the patient of Test group and Control group before treatment. After treatment Full Voluntary Movement was restored in 96.67% of the patients in test group and in all the patients in control group. The data showing the distribution of patients according to effect on status of joint mobility in the test group and control group reveals that there exists a high significant difference before and after the treatment among both test and control groups with a p-value (<0.0001*) which means that both unani and standard treatment is effective in restoring the joint mobility. To find out more effective drug between Test and control group, Chi Square test has been applied on the data for the difference of Test group and Control group it was found that $\chi 2$ = 1.017, Df=1, (Fisher's Exact, P-value=1) indicating that there is no significant difference in the efficacy of both drugs on restoring joint mobility. Therefore both the treatments are equally effective in improving the mobility of patients. (table 7&8 and fig.4)

Table 7: Effect of test drug on status of joint mobility

Status of mobility before and after the treatment in test group as shown in Table 7						
Mobility	**BT**		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
Full Voluntary Movement	0.00	0.00	29.00	96.67	29.00	48.33
Partial Voluntary Movement	3.00	10.00	1.00	3.33	4.00	6.67
Full movement if joint is moved by examiner	7.00	23.33	0.00	0.00	7.00	11.67
Partial movement if joint is moved by examiner	17.00	56.67	0.00	0.00	17.00	28.33
No movement at all	3.00	10.00	0.00	0.00	3.00	5.00
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

Table 8: Effect of control drug on status of joint mobility

Status of mobility before and after the treatment in control group as shown in Table 8.						
Mobility	**BT**		**AT**		**Total**	
	No.	%age	No.	%age	No	%age
Full Voluntary Movement	0.00	0.00	30.00	100.00	30.00	50.00
Partial Voluntary Movement	1.00	3.33	0.00	0.00	1.00	1.67
Full movement if joint is moved by examiner	12.00	40.00	0.00	0.00	12.00	20.00
Partial movement if joint is moved by examiner	17.00	56.67	0.00	0.00	17.00	28.33
No movement at all	0.00	0.00	0.00	0.00	0.00	0.00
Total	30.00	100.00	30.00	100.00	60.00	100.00
P-value=<0.0001*						

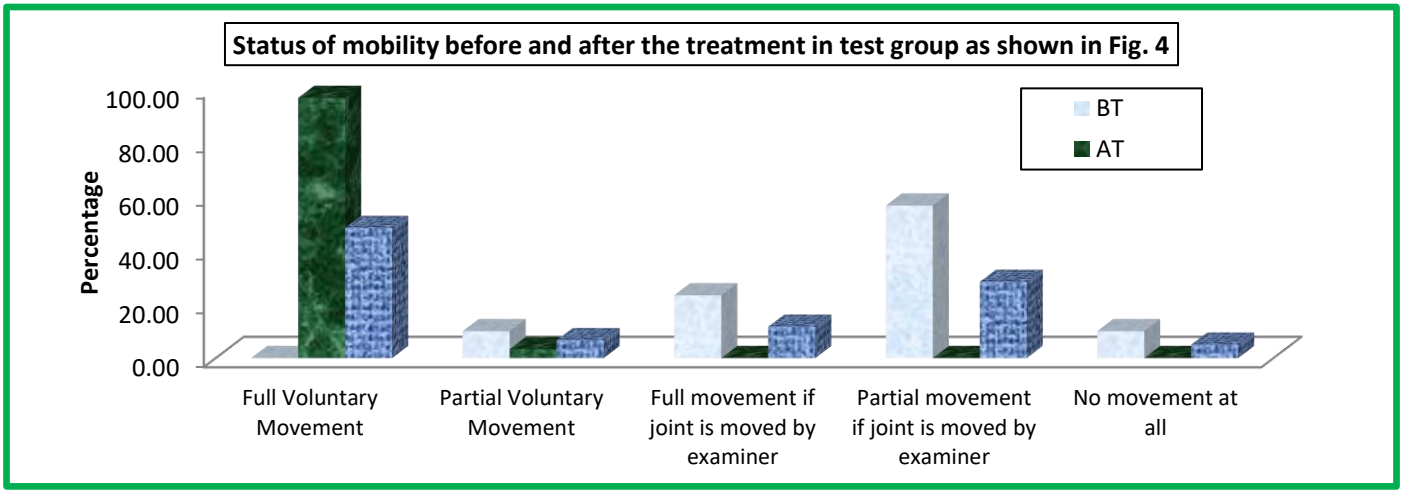

Figure 4: Effect of test drug on status of joint mobility

3.2. Effect of drugs on objective parameter (table 9&10)

Serum uric acid:

The Mean ± SD of serum uric acid before starting the treatment was 8.26±0.94 in Test group and 8.18±1.04 in control group. It got reduced to 5.33±0.30 in Test group and 6.13±0.60 in control group after treatment. The p value in Test and control group indicates that the effect of both drugs in reducing elevated serum uric acid is significant (p-value<0.0001*).

ESR:

The Mean ± SD of ESR (1st hour) before starting the treatment was 29.13±24.85 in Test group and 27.43±14.71 in control group. It got reduced to 11.26±6.22 in Test group and 8.92±5.73 in control group after treatment. The p value in Test and control group indicates that the effect of both drugs in reducing elevated ESR is significant (p-value<0.0001*).

CRP:

The Mean ± SD of CRP before starting the treatment was 8.18±2.69 in Test group and 9.03±1.86 in control group. It got reduced to 1.68±1.21 in Test group and 3.56±1.90 in control group after treatment. The p value in Test and control group indicates that the effect of both drugs in reducing elevated CRP is significant (p-value<0.0001*).

Table 9: Effect of test drug on objective parameters

Comparison **of objective parameter before and after the treatment within test group as shown in Table 9**						
Objective parameters		Mean	N	Std. Deviation	Std. Error Mean	
Sr. Uric Acid	BT	8.26	30.00	0.94	0.17	<0.0001*
	AT	5.33	30.00	0.30	0.06	
E SR (Isthr)	BT	29.13	30.00	24.85	4.54	<0.0001*
	AT	11.26	30.00	6.22	1.13	
CRP	BT	8.18	30.00	2.69	0.49	<0.0001*
	AT	1.68	30.00	1.21	0.22	

Table 10: Effect of control drug on objective parameters

Comparison **of objective parameter before and after the treatment within control group as shown in Table 10**						P-value
Objective parameters		Mean	N	Std. Deviation	Std. Error Mean	
Sr. Uric Acid	BT	8.18	30.00	1.04	0.19	<0.0001*
	AT	6.13	30.00	0.60	0.11	
ESR (Isthr)	BT	27.43	30.00	14.71	2.69	<0.0001*
	AT	8.92	30.00	5.73	1.05	
CRP	BT	9.03	30.00	1.86	0.34	<0.0001*
	AT	3.56	30.00	1.90	0.35	

3.3. Effect of drugs on safety parameters (table11 &12)

The data showing status of safety parameters before and after the treatment within test group and control group as displayed in Table 11 &12 reveals that there is an insignificant difference before and after the treatment in all the safety parameters (p-value>0.05) which means that average value of all these safety parameters was not altered during the treatment protocol of both test and control drug.

Table 11: Effect of test drug on blood safety parameters

Status of Blood safety parameters before and after the treatment within test group as shown in Table 11						P-value
		Mean	N	Std. Deviation	Std. Error Mean	
Haemoglobin percentage (Hb%)	BT	13.09	30.00	1.86	0.34	0.659
	AT	13.01	30.00	1.68	0.31	
Total leucocyte count(TLC)	BT	6.31	30.00	1.18	0.22	0.251
	AT	6.65	30.00	1.72	0.31	
Neutrophills	BT	59.80	30.00	7.97	1.45	0.169
	AT	58.23	30.00	9.04	1.65	
Lymphocytes	BT	35.94	30.00	7.46	1.36	0.233
	AT	34.74	30.00	8.26	1.51	
Eosinophills	BT	1.97	30.00	1.83	0.33	0.818
	AT	2.03	30.00	1.38	0.25	
Monocytes	BT	5.76	30.00	1.65	0.30	0.674
	AT	5.60	30.00	1.79	0.33	
Basophills	BT	.0000[a]	30.00	0.00	0.00	-
	AT	.0000[a]	30.00	0.00	0.00	
Sr Bilirubin	BT	0.78	30.00	0.35	0.06	0.017
	AT	0.69	30.00	0.33	0.06	
SGOT	BT	32.16	30.00	11.50	2.10	0.061
	AT	27.34	30.00	9.51	1.74	
SGPT	BT	29.01	30.00	19.89	3.63	0.407
	AT	25.97	30.00	7.28	1.33	
Alkaline phosphatase(ALP)	BT	112.75	30.00	27.73	5.06	0.139
	AT	103.47	30.00	31.05	5.67	
Blood Urea	BT	28.68	30.00	6.95	1.27	0.661
	AT	27.96	30.00	9.12	1.67	
BLOOD SUGAR (F)	BT	92.58	30.00	12.74	2.33	0.201
	AT	88.56	30.00	12.85	2.35	
Serum Creatinine	BT	0.97	30.00	0.27	0.05	0.074
	AT	0.87	30.00	0.21	0.04	
Weight	BT	75.33	30.00	8.71	1.59	0.592
	AT	74.97	30.00	8.97	1.63	

Table 12: Effect of control drug on blood safety parameters

Status of safety parameters before and after the treatment within control group as shown in Table 12						P-value
Safety Parameters		Mean	N	Std. Deviation	Std. Error Mean	
Haemoglobin percentage (Hb%)	BT	12.24	30.00	1.37	0.25	0.705
	AT	12.31	30.00	1.19	0.22	
Total leucocyte count (TLC)	BT	6.35	30.00	1.13	0.21	0.23
	AT	6.81	30.00	2.10	0.38	
Neutrophills	BT	56.43	30.00	7.72	1.41	0.39
	AT	57.93	30.00	8.46	1.54	
Lymphocytes	BT	36.21	30.00	7.83	1.43	0.188
	AT	34.13	30.00	8.13	1.48	
Eosinophills	BT	1.77	30.00	1.28	0.23	0.823
	AT	1.70	30.00	0.95	0.17	
Monocytes	BT	3.07	30.00	2.23	0.41	0.069
	AT	4.20	30.00	2.81	0.51	
Basophills	BT	.0000[a]	30.00	0.00	0.00	-
	AT	.0000[a]	30.00	0.00	0.00	
Sr Bilirubin	BT	0.74	30.00	0.44	0.08	0.16
	AT	0.63	30.00	0.30	0.06	
SGOT	BT	30.30	30.00	14.44	2.64	0.11
	AT	25.92	30.00	9.03	1.65	
SGPT	BT	29.12	30.00	17.14	3.13	0.762
	AT	30.05	30.00	15.37	2.81	
Alkaline phosphatase (ALP)	BT	112.53	30.00	25.63	4.68	0.071
	AT	102.77	30.00	26.67	4.87	
Blood Urea	BT	30.04	30.00	8.81	1.61	0.098
	AT	26.22	30.00	9.57	1.75	
BLOOD SUGAR (F)	BT	97.82	30.00	12.73	2.32	0.353
	AT	95.29	30.00	12.60	2.30	
Serum Creatinine	BT	0.88	30.00	0.27	0.05	0.243
	AT	0.93	30.00	0.25	0.05	
Weight	BT	71.13	30.00	8.54	1.56	0.557
	AT	70.73	30.00	9.35	1.70	

DISCUSSION

The present clinical Trial was conducted on 60 patients without any gender bias to Evaluate Safety and Efficacy *of Boozidaan (Pyrethrum Indicum*) in the management of *Niqris Muzmin* (Chronic Gout) and compare it with the efficacy of Standard drug (Febuxostat) in the management of Chronic Gout. The patients were divided into two groups- Group A, containing 30 patients (50%), were given test *drug Booziaan (Pyrethrum indicum*) while Group B, containing 30 patients, were treated with the control drug, Febuxostat 80 mg tablet.

Analysis of the data indicate that maximum number of patients were between 40-60 years of age (53.34%). Findings reveal that the disease is predominately seen in middle age group. Our observations are in accordance with the old description mentioned in classical literature and modern medical texts[26, 23, 27, 28] i.e. increased incidence and prevalence of gout with age and this may be due to deteriorating renal function in ageing population and rise in serum urate level with age. This prevalence is also supported by current medical research[29, 30, 31].

The findings clearly shows that the gout has an association with male sex and higher incidence of gout in men than women before menopause and this is due to uricosuric effect of estrogen that suppress urate levels in premenopausal women. Most of the female patients were menopausal and this prevalence is coinciding with current literature[29, 30, 31].

Although the disease has no clear-cut association with any religion. But in our study all the patients enrolled are Muslims i.e.100 % and it is mainly because of our hospital is located in Muslim populated area. Moreover, gout has an association with the intake of high purine diet which is mainly present in non vegetarian diet like meat and meat products mainly consumed by Muslims. But the earlier ascertain seems to be more relevant. The higher incidence of gout among mixed diet group is well acknowledged by unani physicians and nutrition experts in its management programme[32, 33, 34, 35.] These findings are also similar to recent literature mentioned in classical modern text book i.e. purine-rich diet (meat), used by the non-vegetarian, increased risk of gout whereas moderate intake of purine-rich vegetables do not carry the same risk[23,26,29,31,36].

In this study out of 60 patients enrolled 90% cases were married and only 10% cases were unmarried. This is accordance with *Buqrat's* saying i.e. "*A young man does not take gout unless he indulges in coitus*"[23,37, 38, 39,40,41]. However there is no scientific evidence till date to associate gout with sexual intercourse. Since gout is more common in individuals of higher age group majority of patients are married up to this age explaining why married patients predominated in our study. These findings also coincide with the current unani literature[31].

The majority of patients in our study (45%) were housewives. Similarly 26.67%, 16.67%, 8.33% and 3.33% were businessman, Govt. Employee, Labour and students, respectively. Occupation has direct and indirect association in many problems and in our observation higher incidence of gout in house wives may be due to sedentary life style. This result is coinciding with the current medical research[31]. It was found that the majority of patients (40%) belonged to middle income group followed by high income group accounting for 33.33% of patients and 26.67 % of patients belonged to lower income group. The results are consistent with the literature mentioned in the classical text book that the disease is associated with luxurious life style and affluent people are commonly affected[29,31,32,33,,34,35,42].

All the patients enrolled for the study were having mixed dietary habit. These findings are in accordance with the recent literature mentioned in classical modern text book that gout is associated with non-vegetarian purine-rich diet (meat), used by the non-vegetarians whereas moderate intake of purine-rich vegetables do not carry the same risk [23,26,29,31,43].

In the present study all the patients were non alcoholic. This does not coincide with the findings of Choi and colleagues who reported that alcohol consumption is a major triggering factor for gout. This difference could be due to the small sample size and also because of the fact that all the patients enrolled for this study were muslims who do not consume alcohol. These findings are similar with current unani research[31].

The majority of patients (68.33%) of this study were of Balghami Mizaj. Findings coincide with the description of Unani text in favour of phlegmatic association of gout but the specific reason is still not known[33, 44]. It is also hypothesized that a phlegmatic persons may be under excretors of uric acid either through intestine or kidney or both and matter is open for further study.

To assess the effect of Test and Control drug on subjective parameters the patients were assessed for various sign and symptoms (Joint pain, Joint swelling, Joint stiffness and joint mobility).

In Test group (Table1), moderate painful joint movement was present in 86.67% of patients and mild pain was present in 10% patients whereas 3.33% patients had severe pain before the treatment. After treatment pain was absent in 80% of patients and 20 % patients had only mild pain. In control group (Table 2), 93.33 % patients had moderate pain and severe pain was present in 3.33% patients where as mild pain was also present in 3.33 % patients before treatment. After treatment pain was absent in 37% of patients and the remaining 63% patients had only mild pain. There was significant but gradual improvement noted on every visit of the patient in both test and control groups. The findings of the study reveal that both test and Control drugs were significantly effective in relieving the pain associated with gout (p-value <0.0001). Moreover, daily dosing of test drug (boozidan) 5 g was superior in pain relieving efficacy to that of control drug (febuxostat 80 mg OD) and the difference was found to be statistically significant (p-value of <0.0001). The pain-relieving action is due to *Musakkin-i-Alam* (Analgesic) property of boozidan and is achieved by reducing the release of pro-inflammatory cytokines IL-6, IL-1β, histamine, serotonin, NO, TNF-α and prostaglandins E2 due to chemical constituents of Boozidan like alkaloids, iridoids, steroids, flavonoids and glycosides. This effect of *Boozidaan* is consistent with the finding of in current unani research[45, 46,47,48,49].

Visible swelling was found in 76.67% patients in test group before the treatment and it resolved completely at the end of treatment as none of the patients had any swelling after administration of *Boozidaan* (Table 3). In control group (Table 4) 80% patients had visible swelling before treatment and it resolved completely in all patients at the end of therapy. Both test and control drugs were significantly effective in resolving swelling associated with gout (p-value of <0.0001) but none of the drug was found to be superior to another (p-value of 1) in resolution of joint swelling. Resolution of swelling is due to strong *Muhallil* (Anti-inflammatory) activity *of Boozidan* exhibited by reducing nitric oxide and prostaglandin E2 production. It also inhibits the production of pro-inflammatory cytokines and suppression of TNF-*α* mediated induction of COX-2 expression indicating its anti-inflammatory property. Especially the root of pyrethrum indicum is reported to have good medicinal values in traditional system of medicine. They possess rejuvenative properties and have important therapeutic activities, in terms of analgesic, anti-inflammatory, and healing activity. This mechanism of action is supported by findings in unani research[49,50,51,52,53,54,55,56,57,58,59,60,61,62].

In test group (Table 5) 53.33% had stiffness for 30-60 mints and 33.33% patients had stiffness for 10-30 mints which was completely resolved at the end of the therapy as none of the patients reported joint stiffness after administration *of Boozidaan*. In control group (Table 6) 70% had stiffness for 30-60 mints and 27% patients had stiffness for 10-30 mints before therapy and only 13% of patients reported with joint stiffness for 5-10 mints after treatment which indicates a significant reduction in joint stiffness following treatment with control drug. Both test and control drugs were significantly effective in resolving stiffness associated with gout (p-value of <0.0001) but none of the drug was found to be superior to another (p-value of 1) in resolution of joint stiffness (table 18).It is also attributed by *Musakkin-i-Alam* (Analgesic),strong *Muhallil* (Anti-inflammatory) and muscle relaxant properties of *Boozidaan (Pyrethrum indicum*).These effects of the test

drug are consistent with the findings in recent unani literature[50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66].

In test group 57% patients had restricted movement, complete lack of mobility in 10% of patients and 23.33% had full movement if joint is moved by the examiner before treatment which was almost completely resolved after treatment as only 4% of the patients had mild limited mobility

after therapy (Table 7). In control group 56.67% had partial movement if joint is moved by the examiner and 40% had full movement if joint is moved by the examiner which was completely resolved after therapy as normal mobility was restored in all the patients after administration of the control drug (Table 8). Both the test and control drugs were highly effacious in restoring joint mobility (p-value of <0.0001) but none of the drug was found to be superior to another (p-value of 1) in this regard .This can also be explained on the basis of analgesic, anti inflammatory, healing and muscle relaxant properties of *Boozidaan (pyrethrum indicum*)[45,46,47,48,49]. One more explanation can be put forward as regards to the improvement in subjective parameters (pain, swelling, stiffness and mobility) is due to the decreased levels of serum uric acid (Table 9) which prevents the deposition of monosodium urate crystals in the joints and thus the attacks is subsided. This can be explained by the fact that Boozidaan acts as a nervine tonic, phelgmagogue (*Mushil-i-balgham*) and cholagogue*(Mushil-i-safra*) in conditions having derangement of humours like bile and phlegm in nerves and joints and is thus beneficial in gouty arthritis as it causes expulsion of humors causing the disease and it has been already described in unani literature[50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66] .

The mean values of SUA, ESR and CRP before treatment in test group were are8.26,29.13 and 8.18, respectively and the mean values of SUA, ESR and CRP after treatment were 5.33,11.26 and1.68 (Table 9). The finding revealed a significant decrease in objective parameters after treatment *with Boozidaan*. In control group the mean values of SUA, ESR and CRP before therapy were 8.18, 27.43 and 9.03 respectively and the mean values of Serum uric acid, ESR and CRP after treatment was decreased to 6.13, 8.92 and 3.56, respectively (Table10).

Both the test and control drug were effective in reducing SUA, ESR and CRP levels, however the test drug had superior efficacy in reducing the objective parameters and it was statistically significant. *Boozidaan* due to its *phlegmagogue, cholagogue*, and mild diuretic properties, facilitates the expulsion of uric acid through the intestine and kidney. As it is mentioned in our clinical text books [23,39,40,67] that seventy –five percent of uric acid is excreted in the kidney and the remaining is lost in the gut, therefore *Boozidaan* is effective in all inflammatory joint conditions due to its excretory action on uric acid and it is mainly prescribed for hyperuricaemia and gouty arthritis whether it is acute or chronic. The other important action of *Boozidaan* is its astringent and resolvent action on joints which is more or less contradictory but its purgative action on intestine, astringent and resolvent action on joints make the drug wonderful. This is why the expulsion of uric acid takes place through intestine. The root of pyrethrum indicum is reported to have good medicinal values in traditional system of medicine. They possess rejuvenative properties and have important therapeutic activities, in terms of analgesic, anti-inflammatory, and healing activity[50,51,52,62,64,65,66,68]. Its root has been used in dried form as a nervine tonic, phlegmatic (*Mushil-i-balgham*) and cholagogue*(Mushil-i-safra*) in conditions having derangement of humours like bile and phlegm in nerves and joints and is thus beneficial in osteoarthritis, gouty arthritis and neuropathy[52].

The disease Niqris is considered a disease predominantly of phlegmatic indulgence and our formulation is very much suitable to expel out excessive accumulated abnormal phlegm and

other humors responsible for such a pathognomonic state, a *Balghami* disease and occurs due to the predominance of *Balgham or Buroodat* in the body. So, the drugs with *Haar Yabis mizaj* such as *Boozidan* which possess *Munzij* and *Mus'hil-e- Balgham, Mulattif, Kasire Riyah*, *Muhallil and Mudirr-e-Bawl* properties as well as analgesic (*Musakkin-i-Alam),* Muscle relaxant (*Murkhiy-i-Azlaat),* anti-inflammatory and carminative (*Kasire Riyah)* properties by which they perform *Istifragh (*evacuation) and *Imala* (diversion) of vicid and sticky matter, removal of *excessive Buroodat and Riyah* from the joint structures.

The well-known action *of Boozidaan* i.e. the expulsion of MSU from the blood and urate crystals from joint affected make the formulation very effective to expel out urate crystals and uric acid through intestine. During the study the patients were advised to avoid purine rich diets, encourage taking plenty of water along with our medication.

During the course of the study it was found that drug has no apparent adverse effect on biochemical and hematological parameters. (table 11)

CONCLUSION

The present study evaluated the therapeutic response and safety of *Boozidan* in comparison to Febuxostat in the treatment of chronic gout and the observations and results obtained in this study revealed *that Boozidan* is safe and effective in cases of chronic gout. It was concluded that *Boozidaan (Pyrethrum indicum*) and Febuxostat both were significantly effective in resolving the symptoms and signs of chronic gout and both have significant effect on reducing serum uric acid level without any adverse effects on safety parameters. Therefore, Test drug is safe to use in case of chronic gout.

Conflict of Interest

The authors have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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