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ANTI-PYRETIC ACTIVITY OF CRUDE & DETOXIFIED LEAVES OF *MAZARYUN* (DAPHNE OLEOIDES SCHREB.) ON BREWER'S YEAST INDUCED PYREXIA IN WISTAR RATS

[1]Sayeedur Rahman*, [2]Najeeb Jahan and [3]Mohd Asad

[1]Dept. of Ilmul Advia (Pharmacology), Hayat Unani Medical College and Research Centre, Lucknow, India.

[2]Dept. of Ilmul Advia (Pharmacology), National Institute of Unani Medicine, Bangalore, India

[3]Department of Pharmacology, National Research Institute of Unani Medicine for Skin disorder, Hyderabad''

**Author for Correspondence: srghefari2@gmail.com. Mobile: +917417835686*

Abstract

Back ground: Mazaryun (Daphne oleoides Schreb.) is an anti-pyretic drug in Unani medicine used after detoxification and it is defined under fourth-degree drugs.

Objectives: To evaluate and compare the anti-pyretic activity of crude and detoxified Mazaryun in maximum and minimum doses.

Materials and Methods: Anti-pyretic activity was carried out by Brewer's yeast -induced pyrexia test. Wistar rats of either sex, weighing 150-200 gm, were divided into seven groups (I, II, IIIA, IIIB, IVA, IVB, and V) of six animals in each.

Results: Test used: ANOVA repeated measure for intra group comparison and ANOAV one way for inter group comparison with Tukey-Kramer Multiple comparison test. ***-$p<0.001$ with respect to group V positive control 60, 120 and 180 min., **-$p<0.01$ with respect to group V positive control 60 and 120 min., *-$p<0.05$ with respect to group V positive control 180 min. *+-$p<0.05$ with respect to group V positive control 180 min. #-$p>0.05$ no significant with respect to group V.

Conclusion: The study standardised the concept of detoxication in Unani medicine, as the detoxified Mazaryun showed low significant in pyrexia.

Key words: Mazaryun, Detoxification, Pyrexia, Brewer's yeast

Introduction

Fever is also known as pyrexia, is a common medical sign characterized by an elevation of body temperature over the normal range of 37°C to 39°C (98.6°F to 102.2°F) in the hypothalamic set point. Fever is one of the mammalian host's earliest health measures of illness, as well as one of the world's most common reasons for medical consultations. Fever is a natural reaction to a certain number of diseases.[1,2,3]. The physiological mechanism of thermoregulation acts to produce a balance between heat gain and heat loss [3,4,5,6,7]. According to unani concept the Humma (fever) is a state that initiates at first in the heart and then spreads along with *Rooh* (Pneuma) and *Dam* (blood) of vessels to all over the body leading to the bodily malfunctioning which is greater than that of exercise and anger [8,9]. *Humma* is caused by the *Hararat-e-Ghariba* (Foreign Heat / Unknown Heat) which starts from the heart and spreads all over the body through the blood and *Rooh* leading to disturbances in some functions of the body. If the *hararat* (heat) does not disturb the body, then it is not a Humma[8,10,11]. Humma appears in the state of health and leads to the diseased state. It may cause due to *Akhlat* and *Rooh* [9].

In Unani medicine, Mazaryun (Daphne oleoides Schreb.) is mentioned under fourth-degree drugs [12] and detoxification is recommended before use [13] as all parts of the plant are poisonous. Skin contact with the sap can cause dermatitis in some people [8]. The leaves of Mazaryun are traditionally used for the treatment of inflammatory disorders [8,14,15]. It has hot and dry temperament in fourth-degree [8,16,17]. Therefore, Unani physicians have advocated some detoxification methods before using Mazaryun for medicinal purpose [8,16,17,18]. If Mazaryun is used without detoxification it may produce severe complications; it may also lead to vomiting and/or diarrhoea [17,19]. Daphne is a genus of around 70-95 species of deciduous and evergreen shrubs in the family Thymelaeaceae, native to Asia, Europe, and North Africa. It is a small multi-branched shrub found in theWestern Himalayas. The bark contains diterpenes including mezerein and daphnetoxin (0.02%) [20,21] of which mezerein is anti-inflammatory and anti-carcinogenic [21]. Previous research studies have reported wound healing [22], antimicrobial [23] and antioxidant properties [22] of D. Oleoides Schreb., but till date no scientific study has been carried out on its crude and detoxified forms to document the comparative pharmacological effect of Mazaryun before and after detoxification. Therefore,

the present study was envisaged to evaluate the anti inflammatory activity of the crude and detoxified leaves of D. oleoides on carrageenan-induced paw edema in Wistar rats.

Material and methods

1. Animals

The study was carried out on healthy Wistar rats weighing 150e200 g of either sex. The animals were procured from a registered breeder and allowed to acclimatize for one week. They were housed in clean polypropylene cages at room temperature (25 ± 2 _C), humidity 45e55% with 12 h lighte12 h dark cycle throughout the experimental period and were provided with standard diet and water ad libitum unless stated otherwise. The animal care procedures and experimental protocol were in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA). The study was conducted after obtaining the ethical clearance by the Institutional Animal Ethics Committee (IAEC) of National Institute of Unani Medicine (NIUM), vide Reg. no. IAEC/06/17/IA/03.

2. Chemicals and reagents

All the chemicals used were of analytical grade. Paracetamol was purchased from Cipla Drug Company and Brewer's yeast from Sigma Aldrich Chemicals Pvt. Limited, Bangalore, India.

3. Plant materials and preparation of powder

The leaves of Mazaryun (D. oleoieds Schreb.) were purchased from Dr. Mohd. Afsahul Kalaam, Research Officer Unani RRIUM, Habak, Nasewmbagh Campus, Kashmir University, Srinagar, 190006, India. Acetic acid and Roghan-e-Badam (almond oil) were purchased from an authentic herbal supplier from a local market in Bangalore, India. The leaves of Mazaryun were identified by Dr. S. Noorunnisa Begum, Associate Professor, Centre for Repository of Medicinal Resources (C-RPR) at Trans Disciplinary University (TDU) 74/2, Bengalore-64, vide authentication number (FRLHT Acc. No. 5355). A voucher specimen (Ref. no. 77/IA/Res/2020) was deposited in the department of Ilmul Advia (pharmacology), drug museum, NIUM, Bangalore, for future reference. The leaves of

Mazaryun were divided into two equal parts - one part was kept crude and another partwas detoxified. The leaves selected for detoxification were kept in an earthen pot, and soaked in acetic acid for three consecutive days and nights (72 h) and the acetic acid was changed daily as mentioned in Unani classical literature [8,17]. After completion of 72 h, the Mazaryunwas taken out from acetic acid and washed with fresh water and then dried in an oven at 45 _C. Then, the dried leaves were powdered and charb (anointed) with almond oil [8,15,24]. The half crude undetoxified leaves of Mazaryun were simply ground into fine powder at the laboratory of department of Ilmul Advia, NIUM.

3.1. Dosage of the drug

The human therapeutic dose of Mazaryun mentioned in Unani classical literature is 3e5 g [17,19,25]. The dose for rats was calculated by dividing it by adult human weight of 60 kg and multiplying it with the conversion factor of 7 to accommodate the surface area of animal [26] and was found to be 0.35 mg/kg for low dose and 0.58 mg/kg for high dose. The dose of the test drug powder for each rat was dissolved in 1 ml of freshly prepared 1% CMC, daily before each administration.

4. **Brewer's yeast induced pyrexia**

This test was carried out by the method of Vogel [27]. pyrexia was induced in animals by Brewer's yeast induced pyrexia to find out activity against pyrexia. Animals were divided into 7 groups of 6 animals in each.

Group I - Animals serve as Plain control and each animal was administered with 1 ml of 1% CMC.

Group II - Animals served as standard control and were administered standard drug, Paracetamol, in the dose of 60mg/kg BW

Group IIIA - Animals were treated with low dose of crude Mazaryun, 0.35 gm/kg BW.

Group IIIB - Animals were treated with crude Mazaryun in high dose, 0.58 gm/kg BW.

Group IVA - Animal were treated with detoxified Mazaryun in the low dose, 0.35 gm/kg BW.

Group IVB - Animals were treated with detoxified Mazaryun in high dose, 0.58 gm/kg BW.

Group V - Animals served as positive control and were not treated with any drugs.

Results

The results of group analysis of mean rectal temperature revealed that there was no significant difference in mean rectal temperature of plain control (Group I) rats at '0' hr, 30, 60, 120 and 180 minutes, whereas in standard control (Group II), after 18 hr of Brewer's yeast injection, the mean rectal temperature recorded at '0' hr was 38.71±0.088 ^{0}C. After giving standard drug, Paracetamol, the temperature came down to 38.30±0.11^{0}C, 38.68±0.14^{0}C, 37.30±0.10 ^{0}C and 37.928±0.07 ^{0}C at 30, 60, 120 and 180 minutes; respectively. When the temperature at different intervals of time was compared before and after induction of pyrexia, it was found that the standard drug reduced the temperature significantly at $p<0.01$. (Table 1 , Figure 1 & 2)

In the test group (Group III), after 18hr of Brewer's yeast administration, the mean rectal temperature at '0' hr was found as 38.58±0.12 ^{0}C. After giving the crude *Mazaryun* in minimum dose (IIIA), the temperature decreased to 38.41±0.09 ^{0}C, 38.21±0.09 ^{0}C, 38.06±0.11 ^{0}C and 38.00±0.09 ^{0}C at 30, 60 120 and 180 minutes, respectively. The temperature at different interval was found that the test drug reduced the rectal temperature but not statistically significant ($p>0.05$). (Table 1 , Figure 1 & 2)

The animals of Crude *Mazaryun* in maximum dose (Group IIIB), after 18hr of Brewer'syeastadministration, showed38.55±0.14 ^{0}Cmean rectal temperature at '0' hr. After giving *Mazaryun*in maximum dose, the rectal temperature reduces to38.33±0.09 ^{0}C, 38.03±0.08 ^{0}C, 37.73±0.14 ^{0}C and 37.5±0.17 ^{0}C at 30, 60, 120, and 180 minutes, respectively. When the temperature at different interval of time was compared before and after induction of pyrexia, it was found that the test drug reduced the rectal temperature but it was not statistically significant ($p>0.05$). (Table 1 , Figure 1 & 2)

In the test group of detoxified *Mazaryun*in minimum dose (Group IVA), after 18hr of Brewer's yeast administration, the mean rectal temperature was recorded as 38.46±0.09 ^{0}Cat '0' hr. After giving detoxified *Mazaryun*in minimum dose, the temperature was found as 38.35±0.09 ^{0}C, 38.16±0.04 ^{0}C, 37.95±0.05 ^{0}C and 37.75±0.09 ^{0}C at 30, 60, 120 and180

minutes, respectively. When the temperature at different interval was compared before and after induction of pyrexia, it was found that the test drug reduced temperature but not significantly ($p>0.05$). (Table 1 , Figure 1 & 2)

In the test group detoxified *Mazaryun* in maximum dose (Group IVB), after 18 hr of Brewer's yeast administration, the mean rectal temperature at '0' hr was recorded as38.7±0.11 ^{0}C. After giving detoxified Mazaryun in maximum dose, the temperature was found as 38.20±0.13 ^{0}C, 37.98±0.06 ^{0}C, 37.66±0.10 ^{0}C and 37.56±0.12 ^{0}C at 30, 60, 120, and 180 minutes; respectively. When the temperature at different interval of time was compared before and after induction of pyrexia, it was found that the temperature reduced significantly ($p<0.05$) in maximum dose of detoxified *Mazaryun.* (Table 1 , Figure 1 & 2)

In the positive control group (Group V), after 18 hr of Brewer's yeast administration, the mean rectal temperature at '0' hr was recorded as 38.63±0.13 ^{0}Cand the temperature at 30, 60, 120, and 180 minutes was found as 38.60±0.13 ^{0}C, 38.60±0.13 ^{0}C, 38.36±0.14 ^{0}C and 38.08±0.08 ^{0}C; respectively. When the temperature at different interval of time was compared before and after induction of pyrexia, it was found that the temperature not reduced significantly. (Table 1 , Figure 1 & 2)

When the groups were compared with each other it was found that the standard drug and the detoxified *Mazaryun* at maximum dose had reduced the pyrexia at 30, 60, 120 and 180 minutes. However, other groups too reduced pyrexia but the reduction was not very significant. (Table 1 , Figure 1 & 2)

Anti pyretic effect of crude & detoxified *Mazaryun* on Brewer's yeast induced pyrexia in wistar rat model

Test used: ANOVA repeated measure for intra group comparison and ANOAV one way for inter group comparison with Tukey-Kramer Multiple comparison test.

***-$p<0.001$ with respect to group V positive control 60, 120 and 180 min., **-$p<0.01$ with respect to group V positive control 60 and 120 min., *-$p<0.05$ with respect to group V positive control 180 min. *+-$p<0.05$ with respect to group V positive control 180 min. #-$p>0.05$ no significant with respect to group V.

Table 1: Anti pyretic effect of crude & detoxified *Mazaryun* on Brewer's yeast induced pyrexia in wistar rat model.

Name of Groups	Dose, mg/kg BW	Mean ± SEM of Rectal temperature in Celsius					
		Rectal Temp. Before yeast injection	Rectal temperature in Celsius (^{0}C) after 18 hrs of Brewer's yeast injection				
			0 hr	30 min	60 mint	120 min	180 min
Group I Plain control	1 ml of 1%CMC/rat	36.9±0.09	36.89±0.08	36.91±0.10	36.88±0.08	36.83±0.07	36.8±0.07
Group II Standard Paracetamol	60 mg/kg BW	36.93±0.11	38.71±0.11	38.30±0.11#	37.68±0.14***	37.30±0.10***	37.28±0.07***
Group IIIA Crude *Mazaryun* minimum dose	0.35 gm/kg BW	36.81±0.07	38.58±0.12	38.41±0.09#	38.21±0.09#	38.06±0.11#	38.00±0.09#
Group IIIB Crude *Mazaryun* maximum dose	0.58 gm/kg BW	36.91±0.08	38.55±0.14	38.33±0.09#	38.03±0.08**	37.73±0.14**	37.50±0.17*
Group IVA Detoxified *Mazaryun* minimum dose	0.35 gm/kg BW	36.80±0.13	38.46±0.09	38.35±0.09#	38.16±0.04#	37.95±0.05#	37.75±0.09#
Group IVB Detoxified *Mazaryun* maximum dose	0.58 gm/kg BW	36.83±0.11	38.70±0.11	38.20±0.13#	37.98±0.06#	37.66±0.10#	37.56±0.12*+
Group V Positive control	No treatment	36.80±0.11	38.63±0.13	38.60±0.13	38.60±0.13	38.36±0.14	38.08±0.08

N= 6 in each group.

Figure 1. Effect of crude and detoxified *Mazaryun* and Paracetamol in Brewer's yeast induced pyrexia in wistar rats.

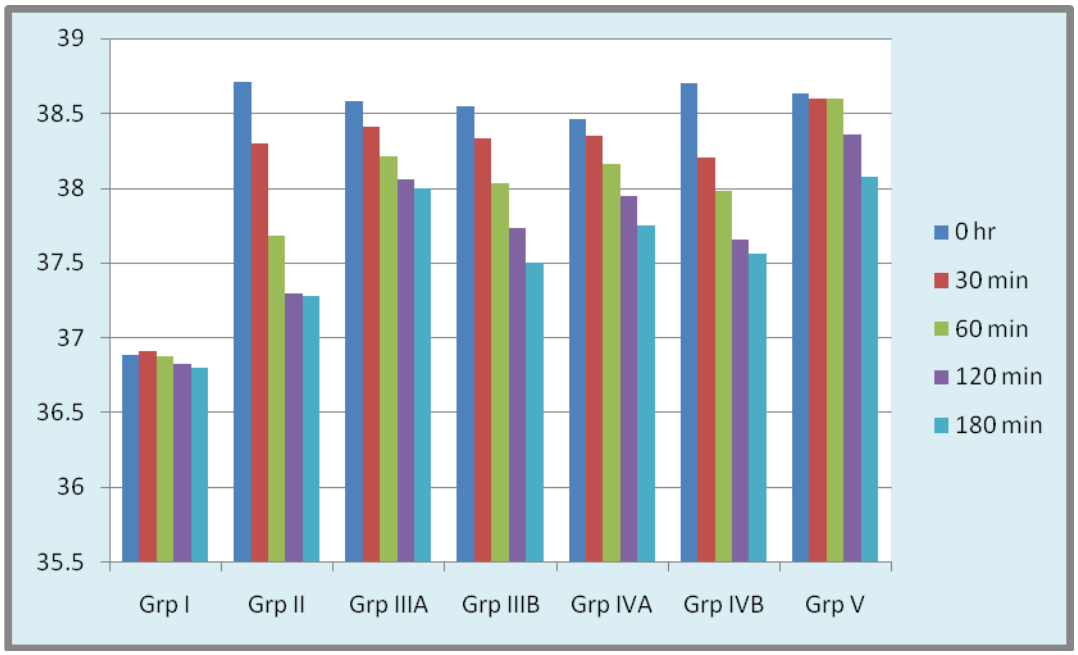
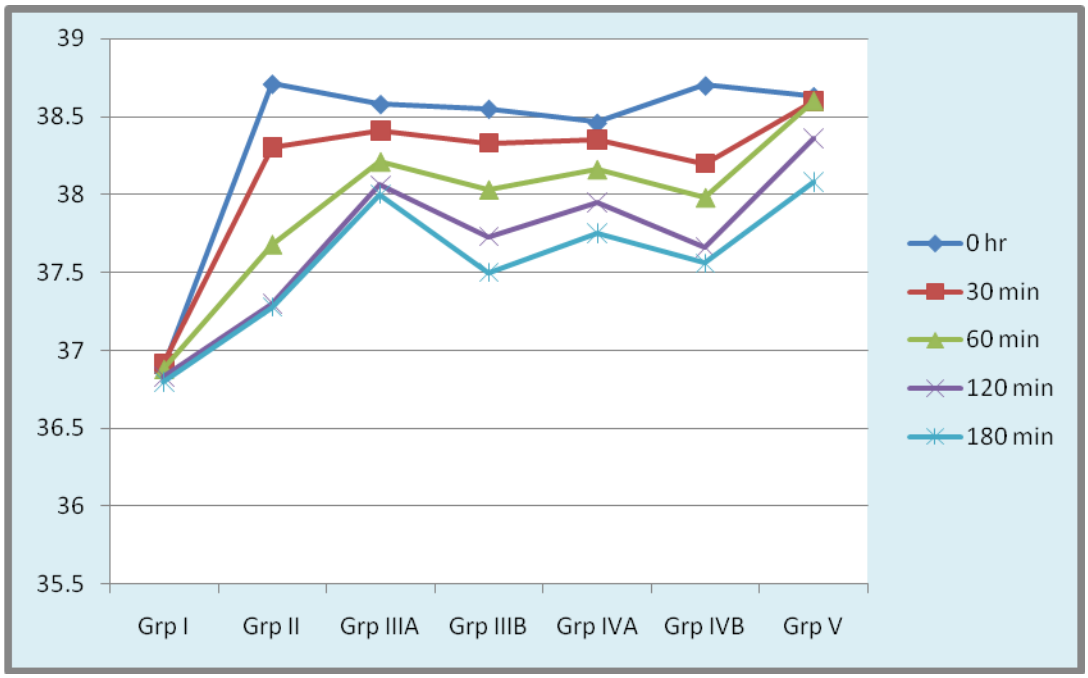


Figure 2. Changes in temperature in Brewer's yeast induced pyrexia in wistar rats of different groups.



Preparation of test Drug

Tadbeer (Detoxification) of *Mazaryun*

The leaves of *Mazaryun* were divided into two equal parts, one part for detoxification and another part to use without detoxification. The leaves, selected for detoxification were kept in an earthen pot, and soaked in acetic acid for 3 consecutive days and nights (72 hrs) and acetic acid was changed daily as mentioned in Unani classical literature. After completion of 72 hrs the *Mazaryun* was taken out from acetic acid and washed with fresh water and then dried in an oven at 45 ^{0}C. Then the dried leaves were powdered and *charb* (anointment) with almond oil [8,10,15, 20,22]. The crude leaves of *Mazaryun* were simply ground into fine powder at the Laboratory of department of Ilmul Advia, NIUM.

Discussion

Unani System of Medicine is one of the oldest traditional systems of medicines, which uses plants, minerals and animals (*Mawaleed-e-salasa)* for the treatment of a range of diseases and plays a key role in preservation of health. Therefore, in spite of the great advances observed in modern medicine in recent decades, traditional system of medicine still make an important contribution in health care system[28], and are generally considered to be safe and effective agents, but some drugs may have toxins and produce harmful effects. Such drugs are required to detoxify before use to remove the toxins or minimize their harmful effects. Sometimes, the toxic principles present in the plant drugs are also reported as their active constituents and not desirable to expel them out completely from the drugs [15,24,29,30].

Unani Medicine offers antipyretic drugs and the test drug, *Mazaryun,* is one of them. According to Unani concept this drug is categorised as 4th degree drug and need to detoxify before using it. It is mentioned in Unani literature that *Mazaryun* possess some pharmacological properties like: Purgative [8,31,32], *anti-inflammatory* [8,20,32,33], *anti-pyretic*[22], *anti-helmenthic* [33], *Mudirr(diuretic)* [33], *corrosive* [8,17],*detergent* [33,34], *and Mujaffif* [8]. This drug has been investigated for various pharmacological actions like, wound healing, antimicrobial and antioxidant, but scientific data on its anti-inflammatory and antipyretic properties is lacking. Therefore, in the present study these pharmacological properties of *Mazaryun* were selected and evaluated in animal models. The results of the study were

compared between the plain control, standard control with the minimum and maximum doses of crude & detoxified *Mazaryun* and determined the dose dependent effect, and scientifically validated the Unani concept of *Tadbeer-e-Advia.*

Fever is as an important sign of many diseases. Fever is an intricate physiologic phenomenon triggered by a number of stimulus especially infectious or aseptic stimuli due to imbalance between the heat production and heat loss. The bacterial endotoxins and other pyrogens act by inducing the enzyme cyclooxygenase which ultimately leads to biosynthesis and release of endogenous pyrogens, but the concept of fever in Unani Medicine is different from that of modern medicine. In contrast to rational medicine that considers fever a sign and not individual diseases entity, Unani Medicine considers *Humma* (fever) as a disease and classifies it in many ways. The basic classification is: *Humma-e-Ya'um, Humma Khiltia,* and *Humma-e-Diq*. When *Humma*is produced without the involvement of any humor, then it is called *Humma-e-Ya'um*. *Humma Khiltia* occurs due to qualitative or quantitative disturbance in any one or more than one humors, it is further sub divided into a number of *Humma*on the basis of humors involved. *Humma-e-Diq*is a type of fever which is also caused due to involvement of humor but the *Humma* is infiltrated in organs [17]. Apart from this basic classification of fevers in Unani medicine some other miscellaneous fevers are also mentioned according to *Kaifiyaat*, on the basis of origin. Duration, [9,35] Formation, and Continuity. Again, all these fevers have been divided into sub-types. Unani Medicine treats *Humma*on the basis of its type by using appropriate drugs recommended for the diseases that caused fever, along with symptomatic treatment.

The fever induced in the present study may be the sub-type of fever produced on the basis of origin. The fever on basis of origin is subdivided into: 1. Humma-e-Arzia (Symptomatic Fever) and 2. *Humma-e-Marzia*(Idiopathic Fever).Humma-e-Arzia (Symptomatic Fever) are produced as a symptom (arz) of many diseases, e.g. fever may result due to infections (inflammation, abscess, pneumonitis) etc [9,35]. Whereas, Humma-e-Marzia (Idiopathic Fever) is the type of fever which is produced as a disease and not as a symptom, e.g. Typhoid fever (*Humma-e-Taifoodia*) [9,35.] By the survey of Unani literature it can be assumed that the fever produced in the Brewer's yeast induced pyrexia model, can be Humma-e-Arzia as fever is produced by infecting the rats by subcutaneous injection of yeast.

In the present study, antipyretic activity of crude and detoxified *Mazaryun* was evaluated against standard and plain control groups by the Brewer's yeast induced hyperthermia animal model [27]. It is a good and a most appropriate method to study antipyretic drugs, as it is a time dependent study and evolves non-invasive method to screen antipyretic effect of a drug against pathogenic fever [27]. In this model, Wistar rats of either sex; weighing 150-200 gm were divided into five groups of six animals in each. Animals in group-I were served as plain control and each animal was administered with 1 ml of 1% CMC. In group-II, were served as standard control and administered, Paracetamol, in the dose of 60mg/kg BW, orally. Animals in group III (A &B) and IV (A &B) were treated with crude and detoxified *Mazaryun* in the minimum dose, 0.35gm/kg BW & maximum dose, 0.58gm/kg BW; after converting human dose into animal dose. And group-V, was served as positive control which was not treated by any drugs. Fever was induced by subcutaneous injection of Brewer's yeast. Rectal temperature of animals was recorded before administration of test and standard drugs, and then temperature was recorded at 30, 60,120- and 180-minutes interval.

The results of the study revealed that there was no significant difference in mean rectal temperature of plain control, Group- I rats at '0' hr, 30, 60, 120 and 180 minutes, whereas in standard control, Group II, after 18 hr of Brewer's yeast injection, the mean rectal temperature recorded at '0' hr was 38.71±0.088 ^{0}C. After giving Paracetamol, the temperature came down to 38.30±0.11^{0}C, 38.68±0.14^{0}C, 37.30±0.10 ^{0}C and 37.928±0.07 ^{0}C at 30, 60, 120 and 180 minutes; respectively. It was found that the standard drug reduced the temperature significantly at $p<0.01$. This may be because Paracetamol (acetaminophen) is part of the class of drugs known as "aniline analgesics"[36], termed a simple analgesic and an antipyretic, it inhibit COX-2 expression to reduce the elevated body temperature by inhibiting PGE2 biosynthesis [37]. In the positive control, group V, after 18 hr of Brewer's yeast administration, the mean rectal temperature at '0' hr was recorded as 38.63±0.13 ^{0}C and the temperature at 30, 60, 120, and 180 minutes was found as 38.60±0.13 ^{0}C, 38.60±0.13 ^{0}C, 38.36±0.14 ^{0}C and 38.08±0.08 ^{0}C; respectively. When the temperature at different interval of time was compared before and after induction of pyrexia, it was found that the temperature was not reduced significantly. This may be because the Brewer's yeast

induces fever by increasing synthesis of prostaglandin which ultimately increases the body temperature [38]. The fever induced by Brewer's yeast is called pathogenic fever. The subcutaneous injection of Brewer's yeast induces pyrexia by increasing synthesis of prostaglandins (PGE2), which ultimately increases body temperature.[39,40].

In the test group (Group III A), after 18hr of Brewer's yeast administration, the mean rectal temperature at '0' hr was found as 38.58±0.12 ^{0}C. After giving the crude *Mazaryun* in minimum dose, the temperature decreased to 38.41±0.09 ^{0}C, 38.21±0.09 ^{0}C, 38.06±0.11 ^{0}C and 38.00±0.09 ^{0}C at 30, 60 120 and 180 minutes, respectively. The temperature at different interval was found that the test drug reduced the rectal temperature but not statistically significant ($p>0.05$).Whereas, in Group- III B (Crude *Mazaryun* in maximum dose), the rectal temperature was reduced but not statistically significant ($p>0.05$). The results of group- IV A, detoxified *Mazaryun* in minimum dose, was also showed to reduced rectal temperature but it was statistically not significant ($p>0.05$).In the test group detoxified Mazaryun in maximum dose (Group IVB), after 18 hr of Brewer's yeast administration, the mean rectal temperature at '0' hr was recorded as 38.7±0.11 ^{0}C. After giving detoxified *Mazaryun* in maximum dose, the temperature was found as 38.20±0.13 ^{0}C, 37.98±0.06 ^{0}C, 37.66±0.10 ^{0}C and 37.56±0.12 ^{0}C at 30, 60, 120, and 180 minutes; respectively. When the temperature at different interval of time was compared before and after induction of pyrexia, it was found that the temperature reduced significantly at $p<0.05$, in maximum dose of detoxified *Mazaryun.*

Finally, when all the groups were compared with each other it was found that the standard drug and the detoxified *Mazaryun* at higher dose have reduced the pyrexia significant. However, other groups too reduced pyrexia but the reduction was not very significant.

Generally, in Unani medicine the drugs belong to *Barid* and *Ratab* [11,20] temperament are recommended for the treatment of fevers. The test drug *Mazaryun,* belongs to the hot and dry [15,20,21] temperament class of drugs, therefore, has not shown the significant antipyretic effect in the present study. The, significant antipyretic activity shown by detoxified *Mazaryun* in maximum dose may be attributed to the presence of its phytochemicals like saponins, and glycosides, tannins, as detected in quantitative chemical analysis in the

present study. Many studies reported that the steroids, tannins, and flavonoids are predominant inhibitors of PG synthetase and cyclooxygenase or lipoxygenase, this mechanism helps in inhibition pyrexia [41].

From the above discussion it can be concluded that the test drug *Mazaryun* in crude form and in minimum dose detoxified do not possesses significant anti-pyretic properties, and its detoxified maximum dose showed significant anti-pyretic affect which may be attributed to its phytochemicals.

Conclusion

The results revealed no significant antipyretic activity in maximum and minimum dose of crude *Mazaryun* and detoxified *Mazaryun* in minimum dose. The significant antipyretic activity was only shown by detoxified *Mazaryun* in maximum dose, which may be attributed to the presence of its phytochemicals like saponins, and glycosides, tannins, as detected in quantitative chemical analysis in the present study.

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