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RESEARCH ARTICLE

Validating Ethnomedicinal Claims of *Itrifal Mulayyin* in Patients With *Ṣudā'* (NUMC: A-36) (Headache Disorders) – An Open Prospective Clinical Trial

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Abstract

Background: *Ṣudā'* (Headache disorder), an incapacitating neurological disorder, negatively impacts people's quality of life, productivity, family and social life and poses huge financial constraints. *Itrifal Mulayyin*, is a widely used Unani medication for the treatment of headache disorders. **Aim:** The present study evaluates the effectiveness and safety of *Itrifal Mulayyin* in headache patients to validate its ethnomedicinal claims. **Methods:** Clinically diagnosed headache patients, who fulfilled the inclusion criteria and were willing to participate in the study were recruited after obtaining a duly signed informed consent form. The study was conducted in compliance with Good Clinical Practices (GCP) guidelines, with due approval by the Institutional Ethics Committee. Patients received 7g of *Itrifal Mulayyin*, orally once daily at bedtime for 7 days. Clinical pathology and biochemistry were done to evaluate the medication safety, alongside monitoring adverse occurrences. The Visual Analogues Scale (VAS) was used to assess the efficacy of the formulation. **Results:** Twenty of 106 recruited patients were unable to take the test, while 86 patients completed the trial. The mean age of the study population was 35.3 years and the majority of them (70.9%) were female. The overall response to treatment was found to be 85%. After 7 days of treatment with *Itrifal Mulayyin*, a statistically significant ($P<0.05$) decrease in the mean VAS score was recorded. Pathological and biochemical indices remain normal and no significant change was observed before and after treatment. Throughout the trial, no AE (adverse events) or drug intolerance were reported. **Conclusion:** The study results affirm the ethnomedicinal claims of the formulation and indicate that *Itrifal Mulayyin* may be used orally for the efficient treatment of headaches with little to no risk to medication safety.

Keywords: Headache, *Itrifal Mulayyin,* Migraine, *Ṣudā*, Unani Pharmacopoeal Formulation

1. Introduction

Ṣudā' (National Unani Morbidity Codes (NUMC): A-36; International Unani Medicine Terminologies (IUMT)-5.1.1)) (headache) is a common human complaint frequently endured in medicine and neurology[1]. Among the most prevalent and incapacitating conditions across the globe are headache disorders which impose a noticeable burden on sufferers including significant personal anguish, impaired quality of life and substantial financial strain. It also negatively impacts effectiveness at work, family life and social life as well[2].

A global estimated prevalence of 52% of active headache conditions has been reported. Tension-Type Headache (TTH) accounted for 26%, migraine accounted for 14% and headache on more than 15 days per month (H15+) accounted for 4.6%, according to reports. It has also been reported that about 15.8% of people worldwide experience a headache on a daily basis[3]. A headache can have several causes, such as a small head injury, a large brain tumour, or, more frequently, a disorder unto itself like migraine[1]. People with headaches frequently experience extremely debilitating symptoms like nausea, vomiting and hypersensitivity reactions,

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which have a detrimental effect on their day-to-day activities[4]. They may also experience fatigue, deprived sleep, poor concentration, irritability, reduced appetite and intolerance to light and noise[5].

Headaches can be classified into primary or secondary headaches. Clinical evaluations, investigations and imaging are usually normal in primary headaches which are benign. These include tension-type headaches, migraines and cluster headaches. Headaches resulting from underlying metabolic, infective, vascular, or structural causes are secondary headaches, such as headaches due to meningitis, brain tumours, or subarachnoid haemorrhage[1,6]. Among numerous conditions that occur secondarily, medication-overuse headache is considered to be the most common headache. Headache disorders, being more common in females, affect people of all ages, races, income levels and geographical areas[2,7,8]. In clinical practice, primary headaches account for about 90% of headache cases and of these, tension-type headaches followed by migraine is most common[9]. Given that they contribute significantly to the high population level of disability, dependence and poor health, tension-type headaches, migraine and medication-overuse headaches are regarded as the major public health concern[2].

Headache disorders can be acute or chronic. Recurrent or non-progressive headaches that occur daily, lasting for more than 15 days a month are labelled as Chronic Daily Headaches (CDH) and represent a primary headache[1,10]. Chronic TTH, migraine, new daily persistent headache and hemicranias continua are long-lasting primary CDH (> 4 hours duration), whereas, cluster headache and its other variants like chronic paroxysmal hemicranias are grouped under short-lasting CDH (< 4 hours)[1]. The sudden onset of a severe headache may indicate meningitis or another acute infectious cause, or it may indicate vascular involvement such as a subarachnoid bleed[10]. A few primary headaches, such as crash migraine or coital headache can also have a sudden manifestation[1].

Ṣudā‘ (NUMC: A-36; IUMT-5.1.1) or headache, as per the doctrine of Unani medicine, is defined as the pain or discomfort perceived in the structure of the head[11]. Since the brain lacks the neurons that provide pain perception (pain fibres), the pain instead comes from the tissues and structures surrounding the brain. A headache may occur due to the inflammation or irritation of the periosteum that surrounds bones, the muscles that cover the skull, the meninges covering the surface of the brain and spinal cord and the sinuses, eyes, ears, arteries, veins and nerves[11,12].

Based on the disease aetiology and pathophysiology, *Ṣudā‘* has been classified into *Ṣudā‘ Sāda* (simple headache) (IUMT-5.1.2), which is caused by the alteration in the normal *Mizāj* (temperament) of the organ; and *Ṣudā‘ Māddī* (headache due to morbid matter) (IUMT-5.1.9), which is caused by the changes in *Akhlāt* (humour) either quantitatively or qualitatively[12-14]. *Ṣudā‘* has been divided into various types based on the categories of predominant *Kayfiyat* (qualities) and *Akhlāt* (humour). Likewise, *Ṣudā‘* has been further classified into two categories, *Ṣudā‘ Aṣlī* and *Ṣudā‘ Shirkī*, based on where the aetiology of the condition originated. In the case of *Ṣudā‘ Aṣlī,* the aetiology and or pathology starts from the head or part of the head, whereas, in *Ṣudā‘ Shirkī* headache occurs as a result of pathologies of other organs such as the stomach, liver, spleen and uterus etc.) (NUMC: A-36.24; IUMT-5.1.33). Based on the site and intensity of pain, *Ṣudā‘* is classified into *Bayḍa-o-Khūdha* (circumferential headache) (NUMC: A-1; IUMT-5.1.48), in which pain affects the whole head, and *Shaqīqa* (migraine) (NUMC: A-2; IUMT-5.1.54) where the pain is localised to either half of the head[11-14].

The majority of the patients with acute headaches visit neurology or medicine clinics, but a considerable fraction of these patients express dissatisfaction with their clinic experience[15] and increasingly turn to alternative therapy options for relief[15,16]. Pharmacotherapy for headache disorders in the conventional system of medicine mostly includes analgesics, Non-Steroidal Anti-Inflammatory (NSAIDs) and triptans which are the 5HT receptor agonists and sometimes anti-emetics[15,17]. Despite being thought to be beneficial, these drugs have adverse effects that limit their therapeutic efficacy. Tiredness, paresthesias, weight loss or increase and impaired cognitive function are some common adverse effects associated with these medications[17]. They may also produce Serious Adverse Events (SAE) such as coronary spasm, myocardial infarction[18], sudden cardiac death and fatal arrhythmias[15]. Further, excessive use of analgesics and triptans may lead to CDH which is referred to as medication-overuse headache[15,19].

Unani Medicine offers a compelling approach to treating headache disorders. Principles of headache management and treatment regimen focusing on the removal of cause[11-14] have been enunciated by Unani scholars in detail. *Ṣudāʿ Sāda* (simple headache) can be treated by employing the doctrine of *Taʿdīl-i-Mizāj* (moderation of abnormal temperament), through *ʻIlāj bi'l Tadbīr* (regimenal therapy), *ʻIlāj bi'l Taghdhiya* (dietotherapy) or *ʻIlāj bi'l Dawā'* (pharmacotherapy). The principle of treatment for *Ṣudāʿ Māddī* (headache due to morbid matter) is *Nuḍj-o-Tanqiya* (concoction and evacuation of morbid material). Likewise, in the case of *Ṣudāʿ Shirkī*, removal of the cause from the organ it originates, and *Tanqiya'-i-Dimāgh* (brain cleansing) is advocated for the alleviation of the disease[12,13]. According to Unani physicians, *Talyīn-o-Ishāl* (laxation and purgation) are always beneficial while treating *Ṣudāʿ* in particular and other brain disorders in general[14]. Abundant single and compound medications have been recommended and have been in vogue for ages in Unani medicine for the treatment of headache disorders. *Itrifal Mulayyin* is one such Unani pharmacopoeial formulation, that contains ingredients which are known to possess *Munḍij* (concoctive), *Mushil* (purgative), *Munaqqī-i-Dimāgh* (brain cleanser) and *Muʿaddil* (alternative to abnormal temperament) properties, therefore has been utilised widely for the successful treatment of headache among many other conditions[20,21]. No scientific report is available to suggest its safe and effective use in headache disorders. Therefore, the present study was envisaged to validate the ethnomedicinal claims of *Itrifal Mulayyin* in patients with *Ṣudāʿ* (headache disorders).

2. Materials and Methods

2.1 Subject Selection

This prospective pilot clinical trial was carried out during the period 2018-2020, at the Regional Research Institute of Unani Medicine (RRIUM), Chennai in the Outpatient Department (OPD) setting to investigate the safety and efficacy of *Itrifal Mulayyin* in patients suffering from headache. The study was conducted in conformity with GCP guidelines, and initiated after obtaining ethical clearance from the Institutional Ethics Committee, RRIUM, Chennai (No 2-21/IEC/Tech/RRIUM/2017-18/719) and registering the study in Clinical Trial Registry-India (Registration number: Clinical Trial Registry-India (CTRI/2018/08/015450)). Patients who fulfilled the inclusion criteria and were willing to participate in the study were asked to sign a voluntary informed consent form. Patients of either gender in the age group of 18-65 years, who visited the OPD with *Ṣudāʿ* (headache) as their chief complaint, with or without associated symptoms such as *Iʿyā* (fatigue), deprived sleep, poor concentration, irritability, *Ḍuʿf al-Ishtihā'* (reduced appetite) and intolerance to light and noise, were enrolled in the study. Patients who had impaired neurological and cognitive functions, double vision, seizures, fever and neck stiffness, continuous nausea and vomiting, patients with a history of recent head injury, renal, hepatic and cardiac ailments or any other acute illness and pregnant women and lactating mothers were excluded.

2.2 Details of Study Drug and Mode of Intervention

The study medication, *Itrifal Mulayyin* containing 10 ingredients (Table 1) was made available to the study site after being manufactured in a single batch using classical methods at the Good Manufacturing Practices (GMP) certified drug manufacturing unit of the National Research Institute of Unani Medicine for Skin Disorders (NRIUMSD), Hyderabad. The study drugs were maintained at room temperature and in a safe location with suitable moisture protection. The study participants were dispensed with the study drug in a sealed plastic container, comprising 50g of *Itrifal Mulayyin,* for one week with the instructions to return the unused medication at the next visit. Patients were advised to take the study drug at a dose of 7g once daily with water at bedtime for 7 days. During the study period, no concomitant medication was allowed except rescue medication which was recorded in the Case Record Form (CRF). The patients were clinically examined at baseline and after the treatment. All the subjective and objective clinical findings were documented in the CRF. The *Mizāj* (temperament) of the patients was identified both at baseline and after treatment by employing the standard temperament assessment tool[22].

Table 1. Composition of *Itrifal Mulayyin* (Each 7g formulation contains)[20]

S. No.	Unani Name	Botanical Name	Weight
1	*Post Halaila Kabuli*	*Terminalia chebula* Retz.	100mg
2	*Post Balaila*	*Terminalia belerica* (Gaertn.) Roxb.	100mg
3	*Aamla*	*Emblica officinalis* Gaertn.	100mg
4	*Halaila Siyah*	*Terminalia chebula* Retz.	100mg
5	*Turbud*	*Ipomoea turpethum* R.Br.	100mg
6	*Badiyan*	*Foeniculum vulgare* Mill.	250mg
7	*Mastagi*	*Pistacia lentiscus* Linn	250mg
8	*Ustukhuddus*	*Lavandula stoechas* L.	250mg
9	*Saqmunia*	*Convolvulus scammonia* Linn.	250mg
10	*Revandchini*	*Rheum emodi* L.	250mg
11	*Asl/Shakar*	Honey/Sugar	5.25g

2.3 Safety and Efficacy Assessment

The medication efficacy was evaluated based on the improvement in *Sudā'* (headache) and its associated symptoms such as fatigue, deprived sleep, poor concentration, irritability, reduced appetite and intolerance to light and noise. The VAS was employed for the assessment of the intensity of pain and other associated symptoms. The total VAS score of headache and associated symptoms was documented at baseline. Repeated measurement of headache and associated symptoms was done after treatment to monitor and document the changing trend in pain intensity and severity of associated symptoms. The efficacy of the test formulation was evaluated by comparing the pre- and post-treatment VAS scores of individual patients. The reduction in VAS score was used to calculate the % efficacy of the study drug '*Itrifal Mulayyin*'. Hemodynamic parameters such as temperature, pulse rate, respiratory rate and systolic and diastolic blood pressure were measured and recorded in the CRF at baseline and after 7 days of treatment. The safety of the test drug was assessed based on the AEs or SAEs, if any, reported by the patient during the study period and by monitoring any significant change in the levels of pertinent laboratory investigations, that were performed at baseline and after treatment. These pathological and biochemical investigations include Haemoglobin (Hb%), total and differential White Blood Cell count (WBC), Erythrocyte Sedimentation Rate (ESR), urine routine and microscopic analysis, serum bilirubin, Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), serum Alkaline Phosphatase (ALP), serum creatinine, serum uric acid and serum urea.

3. Statistical Analysis

The quantitative data are expressed as mean with standard deviation, whereas, the qualitative variables as frequency with percentage. A chi-square test was employed to analyse the association between the response variable and different categorical variables. Friedman test was used to assess the mean score changes of clinical parameters. To find out the differences in the mean value of laboratory parameters between pre- and post-treatment, the Wilcoxon sign rank test was applied. P-value <0.05 was considered as statistical significance.

4. Results

In the present study, a total of 106 patients who met the inclusion criteria were registered, of which 20 patients did not visit for follow-up after treatment for various reasons. The remaining 86 patients completed the study and were included in the analysis. The demographic profile of the study population is portrayed in Table 2. The mean ± SD age of the study subjects was 35.3 ± 9.1 years. The age distribution of patients revealed that the largest proportion of patients (38.4%) were in the age group of 26 to 35 years. Women were more likely (70.9%) to experience headache than men (29.1%). The majority of patients (97.7%) were of middle socio-economic status, whereas 2.3% of patients were of lower economic status. In the study population, 81.4% of patients were married and 18.6% were unmarried. In 62% of the study population, the chronicity of the disease was found to be less than 30 months, with a median of 24 months. In the study population, 54.7% of patients had a *Damawī* (Sanguineous) temperament, whereas, patients with *Balghamī* (Phlegmatic), *Ṣafrāwī* (Bilious) and *Sawdāwī* (Melancholic) temperament were recorded to be 36%, 7% and 2.3% respectively.

The overall therapeutic response in the study participants treated with *Itrifal Mulayyin* for 7 days

Table 2. Demographic profile of patients with *Sudā'* (headache) (n=86)

Characteristics	Frequency (%)
Age group (years)	
<25	13 (15.1)
26-35	33 (38.4)
36-45	28 (32.6)
46-65	12 (14.0)
Mean age ± SD (years)	35.3 ± 9.1
Min-Max (years)	18 – 53
Gender (%)	
Female	61 (70.9)
Male	25 (29.1)
Marital Status (%)	
Married	70 (81.4)
Unmarried	16 (18.6)
Socio-Economic Status (%)	
Middle	84 (97.7)
Lower	2 (2.3)
Chronicity (months)	
<10	23 (26.7)
10-29	30 (34.9)
30-49	12 (14.0)
>=50	21 (24.4)
Median (Inter Quartile Range) (months)	24 (6 - 51)
Min-Max (months)	1 - 300 months
***Mizāj* / Temperament (%)**	
Damawī (Sanguineous)	47 (54.7)
Balghamī (Phlegmatic)	31(36.0)
Ṣafrāwī (Bilious)	6 (7.0)
Sawdāwī (Melancholic)	2 (2.3)

The data are expressed as frequency with percentage for all variables and Mean ± SD for age.

is depicted in Figure 1. The results showed that 69% of patients, in the study population who completed the study, reported feeling completely relieved, 16% of patients reported partial relief, whereas, 15% of them reported no relief. To observe the influence of gender on recovery response in different age groups of the study participants, the data of age and gender-wise recovery response was analysed and displayed in Figure 2. Similarly, the data of gender and temperament-wise recovery response was analysed to explore the possible influence of temperament in either gender and portrayed in Figure 3. The mean ± SD, median and Interquartile Range (IQR) of the VAS score recorded at baseline and after treatment are illustrated in Table 3. The baseline VAS score of headache, poor concentration, irritability, reduced appetite, fatigue, deprived sleep and intolerance to light and noise was recorded to be 8.7±1.3, 7.3±1.3, 6.7±2.3, 3.6±3.5, 6.4±2.6, 5.0±3.3, and 5.4±2.7 respectively. After 7 days of treatment with *Itrifal Mulayyin,* a significant (<0.001) decrease in VAS score was noted when compared to the baseline score. At the end of the treatment, the mean ± SD of the VAS score of headache, poor concentration, irritability, reduced appetite, fatigue, deprived sleep and intolerance to light and noise was found to be 3.4±2.6, 2.4±2.5, 2.0±2.5, 1.2±2.2, 2.5±2.6, 1.4±2.2, and 1.4±2.2 respectively (Table 3).

Table 4 shows the results of the laboratory tests that were performed at the baseline and after the treatment. The findings showed that there was a significant (<0.05) difference between the pre and post treatment mean values for S.Bilirubin, ALP, and S. Creatinine. Between

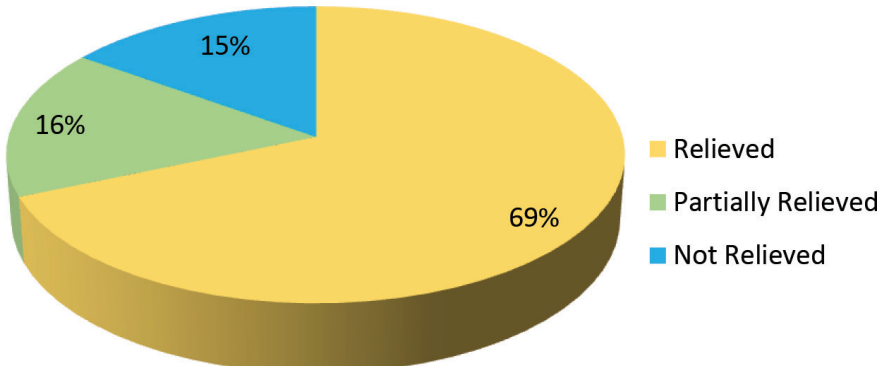


Figure 1. Treatment response in patient with *Sudā'* (headache) treated with *Itrifal Mulayyin* (n = 86).

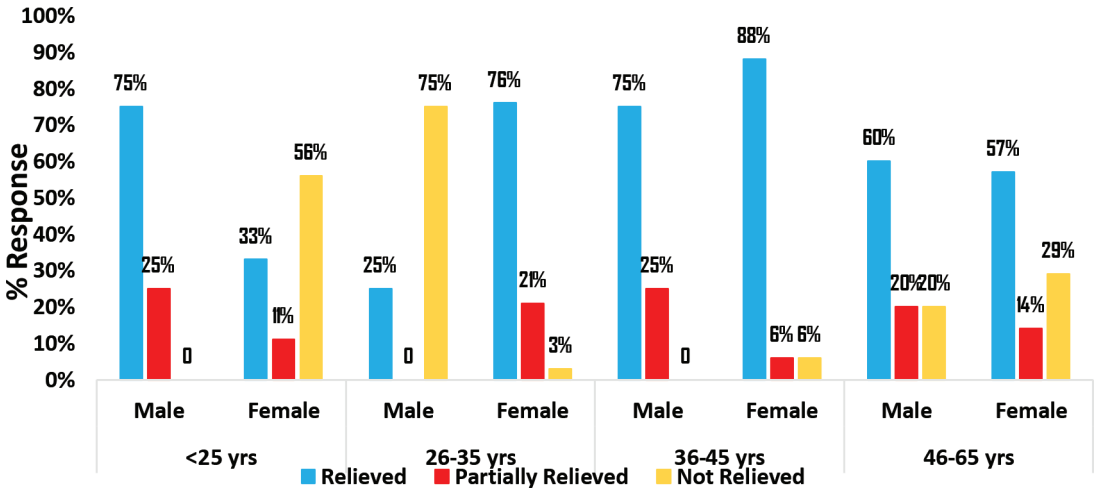


Figure 2. Age and gender-wise recovery response in patient with *Sudā'* (headache) treated with *Itrifal Mulayyin* (n = 86).

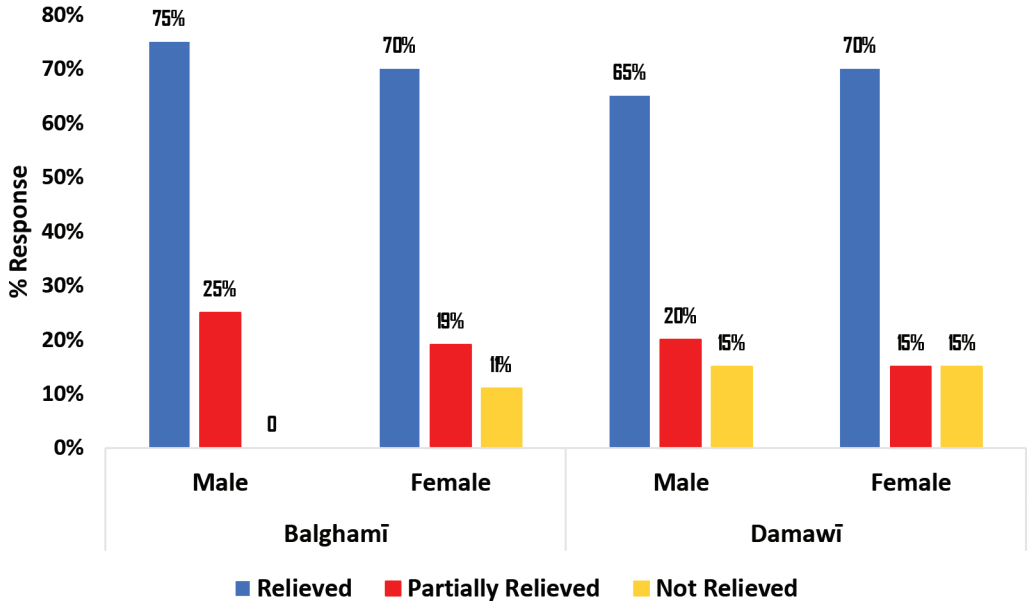


Figure 3. Gender and temperament-wise recovery response in patient with *Sudā'* (headache) treated with *Itrifal Mulayyin* (n = 86).

the baseline and post-treatment, no significant (P>0.05) difference was observed in any of the other pathological and biochemical parameters. During the entire trial period, no reports of medication intolerance, AE or SAE were made.

5. Discussion

Sudā' (headache disorders) is one of the most prevalent and debilitating neurological conditions. It has negatively impacted the livelihood of people across the world with a huge economic burden, hampered productivity, impeded family and social life, and diminished the quality of life of the individual[2]. Headache being more common in women, can affect anyone irrespective of their age, race and socio-economic conditions. According to the World Health Organization (WHO), headache is ranked in the top ten causes of disability[23]. Despite being a major public health issue, headache has been one of the most neglected problems worldwide and the inadequate responses to it in various countries have been unveiled by the WHO[24]. The therapeutic potential of current treatment options for headache disorders is limited

Table 3. The mean visual analogue scale (VAS) score of headache and associated symptoms at baseline and after treatment in *Sudā'* (headache) patients treated with *Itrifal Mulayyin* (n = 86)

Symptoms		Baseline	After Treatment	P-value
Sudā' (Headache)	Mean (SD)	8.7±1.3	3.4±2.6	<0.001*
	Median (IQR)	8.5(8-10)	2(2-5)	
Poor/Disturbed Concentration	Mean (SD)	7.3±1.3	2.4±2.5	<0.001*
	Median (IQR)	7(6-8)	2(0-4)	
Irritability	Mean (SD)	6.7±2.3	2.0±2.5	<0.001*
	Median (IQR)	7(6-8)	1(0-3)	
Ḍu'f al-Ishtihā' (Reduced Appetite)	Mean (SD)	3.6±3.5	1.2±2.2	<0.001*
	Median (IQR)	3.5(0-7)	0(0-2)	
I'yā (Fatigue)	Mean (SD)	6.4±2.6	2.5±2.6	<0.001*
	Median (IQR)	8(6-8)	2(0-4)	
Deprived Sleep	Mean (SD)	5.0±3.3	1.4±2.2	<0.001*
	Median (IQR)	6(0-8)	0(0-2)	
Intolerance to light and noise	Mean (SD)	5.4±2.7	1.4±2.2	<0.001*
	Median (IQR)	6(5-7)	0(0-2)	
Total	Mean (SD)	43.0±8.9	14.2±13.6	<0.001*
	Median (IQR)	43(37.7-50)	10(4-20)	

**Significant at 5% level*; all values are expressed as Mean ± SD, *n* = 86, (p-value <0.05 significant)

Table 4. Laboratory parameters at baseline and post-treatment in patients with *Sudā'* (headache) treated with *Itrifal Mulayyin* (n = 86).

Parameters	Baseline (mean ± SD)	After Treatment (mean ± SD)	P-value
Haemoglobin (g/dL)	12.5±2.1	12.4±2.0	0.157
WBC (cells/mm^3)	7873.3 ±1977.2	7609.3 ±2002.4	0.214
Neutrophils (%)	58.1±7.8	57.1±7.3	0.166
Lymphocytes (%)	33.8±8.1	34.8±7.4	0.152
Eosinophils (%)	6.1±4.5	6.1±4.4	0.529
Monocytes (%)	2.1±3.1	2.0±1.4	0.194
ESR 1 hr (mm)	22.1±17.5	22.0±17.8	0.558
ESR 2 hr (mm)	47.7±28.5	47.3±28.9	0.823
S. Bilirubin (mg/dL)	0.3±0.5	0.2±0.4	0.008*
AST (U/L)	17.7±5.0	17.6±5.5	0.771
ALT (U/L)	20.3±10.4	19.3±8.1	0.742
ALP (U/L)	55.2±14.4	56.7±14.8	0.016*
S. Creatinine (mg/dL)	0.9±0.3	0.8±0.4	0.039*
S. Urea (mg/dL)	16.3±5.8	16.4±5.1	0.815
S. Uric acid (mg/dL)	4.5±1.3	6.1±8.0	0.157

**Significant at 5% level*

All values are expressed as Mean ± SD, *n* = 86, (p-value <0.05 significant). WBC represents white blood cell; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase.

because of the resentment of patients with their clinic encounters and also the adverse effects associated with these medications[15].

The current study was aimed at investigating the safety profile and efficacy of *Itrifal Mulayyin,* a Unani pharmacopoeial formulation, in headache patients. The demographic representation of the population enrolled in this study showcased a rising trend in the occurrence of headaches in the early stage of adulthood. Headache was found to be more prevalent (71.4%) in the population between the age group of 26-45 years (Table 2). Additionally, a higher percentage of female and middle-class individuals experienced headaches than their counterparts. The current study's findings are consistent with the previous data indicating that headaches are more common in women and frequently prevalent in adults[2,7,8]. The majority of patients in this study had a *Damawī* temperament (54.7%), followed by *Balghamī* (36%), *Ṣafrāwī* (7%) and *Sawdāwī* (2.3%) temperament. These results are in agreement with the Unani doctrine and support the theory that inordinate *Harārat* (heat) or *Burūdat* (coldness), with or without morbid matters, is the primary cause of *Sudā'*[12,25]. According to Rāzī (Rhazes, 865–925 CE), severe headache is mainly caused due to *Harārat* or *Burūdat,* whereas *Yabūsat* (dryness) is rarely involved in the

causation of headache[25]. It is also stated that the headache caused by *Yabūsat* will always be of low intensity[12]. As per the Unani literature, a person with a phlegmatic temperament does not have a headache, unless it is accompanied by intense *Harārat* or *Burūdat*[25]. In the present study, those with a phlegmatic temperament were the second most frequently affected population with headaches. It suggests that the headache in this population might have resulted from an exacerbation of normal *Burūdat* (coldness) of the *Balgham* (phlegm).

The effects of headache disorders are primarily linked to problems with emotions, energy and tiredness, pain, diminished physical and mental health, disturbed concentration, problem-solving, and reduced physical and social activity and participation[26]. Fatigue, irritability, poor concentration, reduced appetite, deprived sleep, and intolerance to light and noise are the frequent symptoms accompanied by pain in headache disorders[5]. The intensity of pain in headache disorders or other pains is a key variable, as evaluation of pain duration and frequency only provides partial information[27]. Therefore, its assessment using valid and reliable tools is crucial in monitoring the changing trend in pain and confirming the therapeutic effects of the medication[22]. Among several patient-reported outcomes and other assessments, Migraine Disability Assessment Scale (MIDAS), the six-item Headache Impact Test (HIT-6) and the Migraine-Specific Quality of Life Questionnaire (MSQ) are frequently employed tools in headache disorders, although they are specifically designed for migraine and not for other headache disorders[26]. The International Classification of Headache Disorders, 2nd edition (ICHD-II) offers diagnostic criteria for all types of headaches using a Verbal Rating Scale (VRS)[28]. This scale is easy to use and has been used in migraine drug trials. However, it has limitations such as portraying unequal steps between categories as it has no ratio scale properties, less clinical relevance and sensitivity to change. Additionally, the VRS's ordinal characteristics only allow non-parametric statistical methods to be applied[27].

The VAS has been shown to have advantages over VRS[29]. It is a validated and widely used pain measurement method that visualises pain intensity on a 10cm horizontal line[30]. It has been found to exhibit ratio scale characteristics and ordinarily, it produces symmetrically distributed continuous numerical data[31]. It provides accurate, reliable information, is sensitive to intensity changes, is simple to use and can assess different pain dimensions, pain-related effects and generalisability[27]. It is suitable for monitoring both experimental and clinical pain[31]. Therefore, in the current study, VAS was utilised to record the intensity of pain and other associated symptoms before treatment and after 7 days of treatment with *Itrifal Mulayyin*, and the response to the treatment was calculated based on the reduction in VAS score. The study results figured an adequate therapeutic response to the tested formulation in 85% of the study population, whereas, 15% population showed inadequate response, less than 30% improvement in VAS score (Figure 1). At baseline, the majority of the study population reported a mild to moderate decrease in appetite, difficulty falling and staying asleep, sensitivity to light and noise and moderate to severe pain, fatigue, irritability and disturbed concentration. However, all these symptoms were significantly improved after treatment. Upon 7 days of treatment with *Itrifal Mulayyin*, a highly significant reduction in the VAS score for headache and other related symptoms was noted (Table 3).

The data on age and gender-specific recovery response was analysed in this study to explore if there is any possible influence of gender on recovery response across the various age groups of the study population. The data revealed significantly lower recovery response in adolescent girls (<25 years of age) and females at the menopausal age (between 46-65 years) when compared to other age groups (Figure 2). This might have been influenced by the drop or changes in the sex hormone levels, especially estrogen, in adolescent girls and menopausal women, as puberty and menopause have been known to be closely associated with primary headaches[32]. A strong menstrual association have been discerned in about 70% of females with their headaches, and menstruation-related headaches are known to be more intense, prolonged and more resistant to medications[33]. A significantly lower recovery response was also observed in the male population in the age group between 26-35 years (Figure 2). This low recovery response might have resulted due to psychosocial burden, occupational stress, dissatisfaction with the job, shift work, workplace injustice and poor leadership styles, as these are major risk factors associated with headaches in office workers[34]. Pharmacotherapy alone

may not be sufficient enough to cope with psychosocial and occupational stress-associated headaches and it may require much more comprehensive strategies and non-pharmacotherapeutic approaches such as psychological treatments along with pharmacotherapy[35]. To explore the possible impact of temperament on recovery response, the data of temperament-wise recovery response in either gender was also examined in this study. The data revealed a slight difference in recovery response between the *Balghamī* and *Damawī* groups of the study population. In the *Balghamī* group, an overall therapeutic response in male and female patients was recorded to be 100% and 89% respectively, whereas, in the *Damawī* group it was found to be 85% in both male and female patients (Figure 3). Despite a minor difference in recovery response between the *Balghamī* and *Damawī* groups of the study population, no discernible impact of temperament on recovery response can be inferred from the observations.

The present study portrayed a significant potential of *Itrifal Mulayyin* in relieving headache and its associated symptoms. As per Unani classical texts, the majority of the formulation ingredients have distinguishing characteristics in treating nervous system disorders. These ingredients are known to have implicit capabilities to address headache causes and underlying pathologies. The ingredients of the formulation act by their *Muʿaddil* (alternative to abnormal temperament), *Mulayyin* (laxative), *Munḍij-o-Mushil* (concoctive and purgative), *Munaqqī-i-Dimāgh* (brain cleansing), *Muqawwī-i-Dimāgh* (brain tonic) and *Muqawwī-i-Miʿda* (stomachic) properties, thereby arrest causative factors, reverse pathological changes and relieve headache[36,37]. These drugs have been reported to exhibit diverse pharmacological activities including anti-inflammatory, analgesic and Central Nervous System (CNS) depressant, antispasmodic, antipsychotic, antidepressant, anxiolytic, nootropic, oestrogenic, antioxidant, immunomodulatory, neuroprotective, nephroprotective, cardioprotective and gastroprotective activities among several others[38-44]. *Ustukhuddus* (*L. stoechas* L.), one of the important components of *Itrifal Mulayyin,* is a highly valued drug, employed frequently in Unani medicine for treating neurological disorders besides several other afflictions[45]. The inhalation of its essential oil resulted in a significant reduction in the severity of headaches in migraineurs. The results of the placebo-controlled clinical trial indicated lavender essential oil as a safe and effective therapy option for acute migraine management[46]. These observations suggest that the combinatorial effects of these ingredients may have produced a synergistic impact on the medication.

The evaluation of the safety profile of the tested formulation in this study was carried out by employing relevant pathological and biochemical investigations and by documenting medication intolerance, AEs, and SAEs. The findings of the laboratory investigations displayed no significant differences in pathological and biochemical indices between the pre-and post-treatment values, except S. Bilirubin, ALP, and S. Creatinine levels. Following the intervention, there was a statistically significant decrease in the levels of S. Bilirubin and S. Creatinine; nevertheless, a noteworthy rise in ALP levels was noted in comparison to the baseline values, although these changes were deemed clinically insignificant. There were no complaints of drug intolerance, AE, or serious adverse reactions to the oral administration of *Itrifal Mulayyin* during the whole study period. The findings of the study indicate that *Itrifal Mulayyin* may be taken orally for the efficient treatment of headaches and related symptoms with little to no risk to medication safety.

6. Conclusion

The current study exemplified valuable insights into the safe and effective use of *Itrifal Mulayyin* in patients with headache disorders. The study results indicated an encouraging response to treatment suggesting the potential of the formulation in headache disorders and affirming its ethno-therapeutic claims. Following 7 days of treatment with the test formulation, a statistically significant improvement was recorded in the mean VAS score of headache and related signs and symptoms. Further, no evidence of drug intolerance, untoward effects, AEs or SAEs were recorded during the whole study period. Nonetheless, the present study features preliminary data regarding the safety and efficacy of Unani formulation '*Itrifal Mulayyin*' in headache patients. To affirm the current study findings, and to explore the long-term sustainability of the medication potential, a detailed human intervention trial with larger sample size, standard control, and a longer duration of protocol therapy is highly crucial.

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