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Editorial

Unani Medicine is one of the oldest and time-tested traditional medical systems practiced as a recognized system of medicine in India and various other countries. It has the largest and well-developed infrastructure for practice, education and research in India. The Central Council for Research in Unani Medicine (CCRUM) is the apex government organization entrusted with the mandate of conducting research and development in Unani Medicine in the country. Over the last four decades of its existence, the CCRUM has been busy in conducting scientific research and generating evidences for validation of safety and efficacy of medicines which are in medical practice for centuries. The objective has been to explore the rationale behind the principles of treatment, therapeutics and philosophies adopted by the system and convince the modern scientific world in the contemporary rational language. Through its four key research programmes, namely literary research, survey and cultivation of medicinal plants, drug standardization and clinical research, the CCRUM has been making concerted efforts and contributing significantly to the cause of research and development in Unani Medicine. Vitiligo, sinusitis, filariasis, eczema, malaria, infective hepatitis and asthma are some of the conditions where Unani therapies have earned recognition due to the scientific studies conducted by the CCRUM. This has earned the CCRUM well-deserved recognition in the contemporary scientific fraternity and acceptability among diverse populations.

Started in 2006, the Hippocratic Journal of Unani Medicine (HJUM) has played a crucial role in the propagation and dissemination of research in the system amongst the scientific community. Along with studies on fundamental and applied aspects of Unani Medicine, the journal publishes recent advances in other related sciences and traditional medicines as well as different streams of medical sciences, which have bearing on validation and scientific interpretation of various concepts and strengths of Unani Medicine.

This issue of the HJUM covers seven review and research papers. The first paper presents literature review of *Safūf Dhayābīṭus Dūlābī*, a polyherbal formulation used for the management of *Dhayābīṭus Ḥārr* (diabetes mellitus). In the second paper, the authors have attempted to present an evidence-based and comprehensive review of important Unani cardiotonic drugs used as part of cardio therapy in Unani Medicine. The third paper is a review of phytochemistry, pharmacological actions and uses of Bel (*Aegle marmelos* (L.) Corrêa) with special reference of Unani Medicine. The fourth paper details standardization studies of *Marham Ḥinā*, a popular Unani ointment, involving physico-chemical analysis which included estimation of soluble extractive value, total ash, acid insoluble ash, acid value, iodine value, bulk density, saponifiable and unsaponifiable matter, chromatographic studies like TLC and HPTLC, and WHO parameters viz. microbial contamination, pesticide residue, aflatoxins and heavy metal estimation. The fifth paper is based on a preclinical research conducted to evaluate sub-chronic (90–day) toxicity of *Dawā' al-Kurkum* and its extract in rats indicating that the drug does not have any toxic effects in animals at the evaluated dose. In the sixth paper, the authors have discussed data of a demographic study of dermatophytic infection among the patients attending Skin OPD at AKTC Hospital, AMU, Aligarh. The seventh and last paper of the issue is a research article on a clinical trial conducted on the patients of Ḍu'f al-Ishtihā' (anorexia) to assess the safety and efficacy of Unani pharmacopoeial formulation *Jawārish 'Ūd Shīrīn*.

We hope that the papers would be helpful in furtherance of the cause of research and development in Unani Medicine. We sincerely acknowledge the contributions of authors and reviewers in bringing out this publication.

Prof. Asim Ali Khan
Editor-in-Chief

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Safūf Dhayābīṭus Dūlābī, a polyherbal formulation for the management of *Dhayābīṭus Ḥārr* (diabetes mellitus): A review

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Abstract

Among herbal medicines, Unani medicines are quite popular among diabetics as a sole or adjunct therapy. A considerable proportion of diabetics use Unani medicines along with conventional medicine and their use is sufficiently effective and safe in controlling the glucose level in cases of diabetes. The number of people with diabetes is growing worldwide at an alarming rate and it is one of the fastest growing health challenges of the 21st century. The chronic hyperglycemia associated with diabetes mellitus leads to cardiovascular disease, macro- and micro-vascular complications. Resistance to the conventional treatment and increase in complications communicate to have alternative treatment for controlling hyperglycemia and reducing its complications. According to the concept of Unani Medicine, *Dhayābīṭus Ḥārr* (diabetes mellitus) is due to *Ḍ'uf-i Gurda* (weakness of kidney), *Ittisā'-i Gurda wa Majrā'-i Bawl* (dilatation of kidney and urinary tract), *Burūdat-i Badan*, *Jigar wa Gurda* (cold derangement in temperament), *Sū'-i Mizāj Ḥārr Gurda* (hot derangement in the temperament of the kidney), *Sū'-i Mizāj Bārid Gurda* (cold derangement in the temperament of the kidney). A large number of drugs, single and compound formulations, have been mentioned in the context of the treatment of *Dhayābīṭus Ḥārr. Safūf Dhayābīṭus Dūlābī* is one of the poly-herbal Unani pharmacopoeial formulations used in diabetes mellitus, widely prescribed for *Dhayābīṭus Ṣādiq* (diabetes mellitus) and *Ḍu'f al-Kulya* (weakness of the kidney). The β-sitosterol, a phytosterol reported in all the ingredients of *Safūf Dhayābīṭus Dūlābī* exhibits hypo-lipidemic, anti-cancer, immuno-modulatory and anti-diabetic properties. It has also been proved to be effective in experimental studies as an anti-diabetic formulation.

Keywords: *Dhayābīṭus Ḥārr*, *Safūf Dhayābīṭus Dūlābī*, Anti-diabetic, Unani Medicine

Introduction

Diabetes mellitus (*Dhayābīṭus Ḥārr*) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of diabetes mellitus or DM exist and are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system (Kasper *et al*., 2008; Porth *et al*., 2010; Nogueira *et al*., 2013; Souto *et al*., 2011).

The word 'diabetes' is derived from the Greek word '*Dhayābīṭus*', which means 'to run through' or 'siphon' which is characterized by hyperglycemia, glycosuria, increase appetite, excessive thirst, and gradual loss of body weight. In Unani Medicine, diabetes has been mentioned with different names like *Dhayābīṭus*, *Dūlābiyya* (water wheel), *Diasquemus*, *Qarāmis*, *Zalq al-Majārī*, *Salas al-Bawl*, *Zalq al-Kulya*, *Dawwāriyya* (symptoms repeated in cyclic order), *Mu'aṭṭisha* (thirst producing), '*Atsha*, *Parkār*, *Parkāriyya*, etc. The description of *Dhayābīṭus* is mentioned in most of the Unani classical literature like *al-Qānūn fi'l-Ṭibb*, *Kitāb al-Ḥāwī fi'l-Ṭibb*, *Kāmil al-Ṣanā'a*, etc. According to Unani concept *Dhayābīṭus Ḥārr* (diabetes mellitus) is due to *Ḍ'uf-i Gurda* (weakness of the kidney), *Ittisā'-i Gurda wa Majrā'-i Bawl* (dilatation of the kidney and urinary tract), *Burūdat-i Badan*, *Jigar wa Gurda* (cold derangement in temperament), *Sū'-i Mizāj Ḥārr Gurda* (hot derangement in the temperament of the

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kidney), *Sū'-i Mizāj Bārid Gurda* (cold derangement in the temperament of the kidney) (Razi, 1999; Ibn Sina, 2010; Jurjani, 1996; Zuhr, 1986; Majusi, 1889).

International Diabetes Federation (IDF) has declared that diabetes is one of the fastest-growing health challenges of the 21st century; with the number of adults living with diabetes has more than tripled over the past 20 years. Type 2 DM is a significant cause of premature mortality and morbidity related to cardiovascular disease, macrovascular complications, and microvascular complications in older adults and increases the risk of early death. The IDF estimates that approximately 4.2 million adults will die as a result of diabetes and its complications in 2019. This is equivalent to one death every eight seconds (IDF, 2019).

Globally, the prevalence of diabetes mellitus by the IDF was estimated to be 463 million (9.3% of adults 20-79 years) in 2019; by 2030 this will rise to 578 million (10.2%) & by 2045 to 700 million (10.9%). The proportion of people with type 2 diabetes is increasing in most countries. India alone has 77 million and China has 116.4 million. 1 in 2 (231.9 million) people with diabetes were undiagnosed. The prevalence in urban areas is 10.8% and 7.2% in rural areas; about 79% of people with diabetes live in low and middle-income countries. Annual global diabetes-related health expenditure is estimated to be USD 760 billion in 2019 and will exceed USD 825 billion by 2030 and USD 845 billion by 2045 (Indian Diabetic Federation, 2019; Saeedi *et al*., 2019).

Diabetes remains a challenge for the treating physicians; despite all the advances in modern medicine, pharmacotherapy, treating devices, and preventive measures, there is no satisfactory effective therapy yet available to cure diabetes mellitus. Now, attention is diverted to herbal formulations due to its versatile role without side effects, especially in treating Type-II diabetes or NIDDM (Asima & Chandra, 2001; Gopalakrishnan & Solomon, 1992). In the Unani system of medicine, diabetes mellitus has been treated since the Greco-Arab period and this system claims to possess several cost-effective and safe compounds and single drugs that can be used in the management of diabetes mellitus. Among the compound formulations, *Safūf Dhayābīṭus Dūlābī* is a well-known Unani pharmacopoeial compound preparation mentioned in various *Qarābadīn* (pharmacopoeias and formularies) mainly based on different medicinal plants used to treat diabetes since ancient times and is widely prescribed for *Dhayābīṭus Ṣādiq* (diabetes mellitus) and *Ḍ'uf-i-Kulya* (weakness of the kidney) (MHFW, 1993; MHFW, 2000). The β-sitosterol, a phytosterol reported in all the ingredients of *Safūf Dhayābīṭus Dūlābī* exhibits hypolipidemic, cholesterol-lowering, anti-cancer, immunomodulatory and anti-diabetic properties (Shailjan *et al*., 2012).

Prescription

According to *Qarābādīn-i-A'ẓam-o-Akmal* (Khan, YNM), the original preparation of *Safūf Dhayābīṭus Dūlābī* contained eight ingredients, viz. *Post-i-Andrūn-i-Darakht-i-Guler* (Ficus racemosa L.), *Gil-i-Armanī* (Bole Armenian), *Gulnār Fārsī* (*Punica granatum* L.), *Dāna Anār Shīrīn* (*Punica granatum* L.), *Maghz Tukhm-i-Anbā* (*Mangifera indica* L.), *Āmla* (*Phyllanthus emblica* L.), *Kishnīz Khushk* (*Coriandrum sativum* L.) and *Qand Safaid* (Sugar). However, there are certain variations in the weight and number of ingredients of the compound in other Unani formulations. The formula for the preparation of *Safūf Dhayābīṭus Dūlābī* in the National Formulary of Unani Medicine (NFUM) (Urdu) (1993) contains all the ingredients except *Qand Safaid* (Sugar).

According to the National Formulary of Unani Medicine (1993), the formula composition of *Safūf Dhayābīṭus Dūlābī* (Table 1) includes six medicinal herbs along with *Gil-i-Armanī* (a type of soil used in many Unani preparations). However, there is certainly variation regarding the *Qand Safaid* (Sugar), as it has been deleted from the original text (MHFW, 1993). Whereas in *Qarābādīn-i-Aʿẓam-o-Akmal* (Khan, YNM), all the ingredients are the same as that of NFUM except Qand Safaid (sugar) which is included in it. The formulation under study has been taken from NFUM because of its wide acceptability among the physicians who prescribe it in their routine practice to manage diabetes and the conditions associated with it. According to different Unani *Qarābadīn* (pharmacopoeias), *Safūf Dhayābīṭus Dūlābī* is used as an anti-diabetic medication but more scientific studies and clinical trials are needed on this compound formulation to ensure its scientific validation.

Table 1: Formula of preparation of *Safūf Dhayābīṭus Dūlābī* according to the NFUM, Part-I

S. No.	Ingredient	Part used	Botanical/Scientific Name	Quantity
1	*Post-i-Andrūn-i-Darakht-i-Guler*	Stem bark	*Ficus racemosa* L.	30 g
2	*Gil-i-Armanī*	Silicate of alumina, magnesia, and oxide of iron	Bole Armenian	10 g
3	*Gulnār Fārsī*	Flower	*Punica granatum* L.	10 g
4	*Dāna Anār Shīrīn*	Seed	*Punica granatum* L.	10 g
5	*Maghz Tukhm-i-Anbā*	Seed	*Mangifera indica* L.	10 g
6	*Āmla*	Fruit pericarp	*Phyllanthus emblica* L.	10 g
7	*Kishnīz Khushk*	Fruit	*Coriandrum sativum* L.	10 g

Method of preparation

Preparation of *Safūf Dhayābīṭus Dūlābī*: The bark of *Ficus racemosa* L. and the kernel of *Mangifera indica* L. were cleaned from the earthy material, washed with running tap water, and dried in shade. Each ingredient of *Safūf Dhayābīṭus Dūlābī* was ground separately in electric grinder and passed through no. 80 mesh sieve. Then these powdered ingredients were weighed separately in the ratio mentioned in NFUM and mixed rigorously in an electric kitchen mixer to get homogenous powder.

Dosage and administration: 3 to 6 g with water orally.

Pharmacological action: *Muqawwī-i-Kulya* (nephrotonic)

Therapeutic uses

- *Dhayābīṭus Ṣādiq* (diabetes mellitus)
- *Ḍuʿf al-Kulya* (weakness of the kidney)

Physiochemical standards of *Safūf Dhayābīṭus Dūlābī*

Organoleptic parameters like appearance, colour, odour, and taste were used to confirm uniformity in the visual identity of raw materials and finished products. The results are tabulated in Table 2 (Bijauliya *et al*., 2017).

Table 2: Organoleptic characters of *Safūf Dhayābīṭus Dūlābī*

Parameters	*Safūf Dhayābīṭus Dūlābī*
Colour	Reddish brown
Odour	Specific odour
Taste	Tasteless

The physicochemical study included the determination of loss of weight on drying, ash value, and solubility (Table 3) (Jenkins *et al*., 1967; Anonymous., 1968; Afaq *et al*., 1994).

Table 3: Physicochemical study of *Safūf Dhayābīṭus Dūlābī*

S. No.	Parameters	Results
1.	Loss on drying at 105 ℃ (% w/w)	8.77
2.	Total ash (% in w/w)	18.38
3.	Acid insoluble ash (% in w/w)	5.32
4.	Alcohol soluble extractive (% in w/w)	15.45
5.	Water soluble extractive (% in w/w)	20.98

Pre-clinical studies

Hussain *et al*. (2020) evaluated anti-diabetic activity of *Safūf Dhayābīṭus Dūlābī* in streptozotocin-induced diabetic rats. Diabetes was induced using streptozotocin at a dose of 55mg/kg i.p. The study was carried out for 8 weeks. On treatment with *Safūf Dhayābīṭus Dūlābī* 200 mg/kg and 400 mg/kg, the drug effectively showed increased body weight of diabetic rats when compared with the disease control group. It was also observed that the blood glucose levels and HbA1c levels were reduced in *Safūf Dhayābīṭus Dūlābī* 200 mg/kg and 400 mg/kg treated groups when compared with the disease control. A liver function test was performed in the study to evaluate the safety profile of *Safūf Dhayābīṭus Dūlābī*. On treatment with *Safūf Dhayābīṭus Dūlābī* at 200 mg/kg and 400 mg/kg, the drug effectively decreased alkaline phosphatase, SGPT, SGOT, and total bilirubin when compared with the disease control group, thus suggesting that *Safūf Dhayābīṭus Dūlābī* possesses anti-diabetic activity.

Shailajan *et al*. (2012) evaluated phytoconstituents of *Safūf Dhayābīṭus Dūlābī* and documented standard operating procedures (SOP) for the preparation of *Safūf Dhayābīṭus Dūlābī* as per NFUM. *Safūf Dhayābīṭus Dūlābī* was found to be enriched with essential oils, tannins, glycosides, flavonoids and alkaloids and presence of the major secondary metabolites in *Safūf Dhayābīṭus Dūlābī* may attribute to its therapeutic efficacy and assure its traditional use. The β-sitosterol content in *Safūf Dhayābīṭus Dūlābī* and its ingredients was estimated for the first time using HPTLC, fingerprint pattern of *Safūf Dhayābīṭus Dūlābī* and its ingredients.

Brief description of ingredients of *Safūf Dhayābīṭus Dūlābī*: (Ghani, 2011; Usmani, 2008; Kabiruddin, 1951; Nadhkarni, 1982; Haleem, 2009)

S. N.	Ingredient (Botanical name)	Parts Used	Dosage	Temperament	Action & Uses	Therapeutic Uses	Pharmacological Studies
1.	*Post-i-Andrūn-i-Darakht-i-Guler* (*Ficus racemosa* L.)	Stem bark	5-7 g Milk: 10 ml	Hot & wet	*Taghdhiya-i-Badan* (Nutrition) *Mufarriḥ* (Exhilarant) *Munaffith-i-Balgham* (Expectorant) *Munḍij* (Concoctive) *Muḥallil* (Resolvent) *Mufajjir-i-Awram* (Ruptures matured sewlling) *Mubarrid* (Refrigerant) *Musakhkhin* (Calorific) *Qābiḍ-wa-Ḥābis* (Astringent) *Ḥābis-i-Ishāl* (Anti-diarrheal)	*Aaitshak* (Syphilis) *Ishāl* (Diarrhoea) *Su'āl* (Cough) *Dama* (Asthma) *Dhayābīṭus* (Diabetes) Ḥummā-i-Diq (Tuberculosis) *Bawāsīr* (Hemorrhoids)	Hypoglycemic Hepatoprotective Hypolipidemic Anti-carcinogenic Antioxidant Probable radioprotector Wound healing Anti-bacterial activity Anti-fungal activity Anti-diarrhoeal activity Anti-diuretic Anti-inflammatory Anthelmintic Antifertility activity Analgesic Larvicidal Antitussive Anticholinesterase Antipyretic (Paarakh, 2009)
2.	*Gil-i-Armanī* (Bole Armenian)	Silicate of alumina, magnesia and oxide of iron	1-7 g	Cold & dry 2^0	*Qābiḍ* (Astringent) *Mujaffif* (Desiccative) *Mundamil-i-Qurūḥ* (Wound healing) *Mugarrī* (Glutinous)	*Dhayābīṭus* (Diabetes) *Nafth-al-Dam* (Hemoptysis) *Nazf al-Dam* (Hemorrhage)	Antidiabetic Antidyslipidemic Hepatoprotective activity (Ali, 2015)

					Muffarriḥ wa Muqawwī-i-Qalb (Cardiac exhilarant and tonic) *Ḥabis-i-Dam* (Haemostatic) *Nafth al-Dam* (Haemoptysis) *Nazf al-Dam* (Haemorrhage) *Dāfi'-i-Ḥummayāt Wabā'iya* (Anti-epidemic fever) *Dāf-i-Ṭā'ūn* (Anti-plague) *Rādi'-i-Mawād* (Divertive) *Dāfi'-i-Ta'affun* (Anti-septic) *Ḥābis-i-Ishāl* (Anti-diarrhea) *Dāfi'-i-Su'āl* (Anti-tussive) *Sozish-i-Bawl* (Burning micturition) (Ali & Hamiduddin, 2015)	*Su'āl* (Cough) *Ḍu'f-i-Qalb* (Cardiac weakness) *Qulā'* (Stomatitis) *Qarḥa* (Ulcer) *Ḥummayāt-i-Wabā'iya* (Epedemic fever) *Ḍīq al-Nafas* (Bronchial asthma) (Ali & Hamiduddin, 2015)	
3.	*Gulnār Farsī* (*Punica granatum* L.)	Flower	5-10 g	Cold & dry 2^0 Cold 2^0 & dry 2^0 Cold 3^0 & dry 3^0	*Qābiḍ* (Astringent) *Mujafif* (Desiccative) *Hābis al-Dam* (Haemostatic) *Rādi'* (Divertive)	*Dhayābīṭus* (Diabetes) *Dusūmat-i-Dam* (Dyslipidemia) *Qurūḥ 'Asīrat al-Indimāl* (Non-healing ulcers)	Antidiabetic Antidyslipidemic Hepatoprotective Antioxidant Wound healing

					Muqawwī-i-Asnān wa Litha (Teeth and gums tonic) *Muqawwī-i-Aʿḍāʾ Raʾīsa* (Vital organs tonic) *Mudammil* (Cicatrizing) *Qātil-i-Dīdān Amʿāʾ* (Anti-helminthic)	*Qurūḥ Miʿdī* (Peptic ulcer) *Istisqāʾ Ziqqi* (Ascites) *Waja' al-Mafāṣil* (Osteo-arthritis) *Ḍuʿf-i-Qalb* (Weakness of heart) *Ḍuʿf-i-Jigar* (Hepatic insufficiency) *Ishāl* (Diarrhoea)	Hemostyptic Immunomodulator Anticancer activities DPP4 inhibitors Antimicrobial activity (Jurenka, 2008)
4.	*Dāna Anār Shīrīn* (*Punica granatum* L.)	Seed	2–5 g	Cold & dry 2^0 Moderate Cold & wet 1^0	*Muqawwī-i-Qalb-o-Jigar* (Cardiac and liver tonic) *Mulayyin-i-Ṣadr-o-Ḥalaq* (Laxative to thorax and throat) *Mudirr-i-Bawl Khafīf* (Mild diuretic) *ʿUṭāsh Mufriṭ* (Polydipsia) *Qābiḍ* (Constipative)	*Dhayābīṭus* (Diabetes) *Faqr al-Dam* (Anemia) *Iltihāb-i-Lawzatayn* (Tonsillitis) *Ḍuʿf-i-Kabid* (Weakness of liver)	Antidiabetic Hypolipidemic (Arun & Singh, 2012)
5.	*Maghz Tukhm-i-Anbā* (*Mangifera indica* L.)	Seeds	3 g	Ripe: Hot & wet Unripe: Cold & wet & dry	*Ḥabis-i-Ishāl* (Anti-diarrheal) *Muqawwī-i-Miʿda* (Stomachic) *Salas al-Bawl* (Incontinence of urine) (Shah *et al*., 2010)	*Nazf al-Dam* (Hemorrhages) *Bawāsīr Dāmiya* (Bleeding hemorrhoids) *Dama* (Asthma) *Suʿāl* (Cough) *Qātil-i-Dīdān-i-Amʿāʾ* (Anti-helminthic) *Ishāl Muzmin* (Chronic diarrhea) *Zaḥīr* (Dysentery)	Antidiabetic Antidiarrheal Anti-inflammatory Antimicrobial Analgesic Anti-inflammatory (Shah *et al*., 2010)

						Nafth al-Dam (Haemoptysis) *Qarḥa Dihan* (Aphthous ulcer) *Saylān al-Raḥim* (Leucorrhoea) *Istiḥāḍa* (Menorrhagia) *Qay'* (Vomiting) (Shah *et al*., 2010)	
6.	*Āmla* (*Phyllanthus emblica* L.)	Dry and fresh fruit, leaves, root, bark, flower, fruit Seed	10.5 g 5–10 g 6 g	Cold 2^0 & dry 4^0 Cold 2^0 & dry 3^0 Cold & dry	*Mulayyin* (Laxative) *Mudirr-i-Bawl* (Diuretic) *Jālī* (Detergent) *Qābiḍ* (Constipative) *Mubarrid* (Cooling) *Kāsir-i-Riyāḥ* (Carminative) *Māni'-i-Qay'* (Antiemetic) *Dāfi'-i-Khafaqān* (Anti-palpitation) *Dāfi'-i-Ḥummā* (Antipyretic) *Muḥarrik-i-Bāh* (Sexual stimulant) *Muqawwī-i-Bāh* (Aphrodisiac) *Mulaṭṭif* (Demulcent) *Muqawwī 'Ām* (General tonic) *Muwllid-i-Manī* (Semen producing)	*Khafqān* (Palpitation) *Bawl fi'l-Firāsh* (Nocturnal enuresis) *Bayāḍ-i-Chashm* (Opacity) *Bawāsīr* (Piles) *Kathrat-i-Lu'āb* (Excessive salivation) *Saylān al-Raḥim* (Leucorrhoea) *Qay'* (Vomiting) *Ṣar'* (Epilepsy) *Nazf al-Dam* (Haemorrhage) *Sūzāk* (Gonorrhoea) *Bāl Khora* (Alopecia) *Ḥurqat al-Bawl* (Burning micturition) *Nisyān* (Amnesia) *Āshob-i-Chashm* (Conjunctivitis) *Ḥumūḍat-i-Mi'dī* (Hyperacidity)	Antidiabetic Antioxidant Hypolipidemic Gastroprotective Hepatoprotective Immunomodulating activity Antidiarrheal Antitussive Anti-pyretic and analgesic activity Antimicrobial Antitumor Adaptogenic Antiproliferative Apoptotic Antiulcerogenic Wound healing (Masihuddin *et al.*, 2019)

					Muqawwī-i-Baṣar (Vision improving) *Muqawwī-ī-Dimāgh* (Brain tonic) *Muqawwī-i-Litha* (Gum tonic) *Muqawwī-i-Jigar* (Liver tonic) *Musakkin-ī-ʿAṭash* (Relieving excessive thirst) *Ḥābis-i-Ishāl* (Anti-diarrhoeal) *Mufarriḥ wa Muqawwī-i-Qalb* (Cardiac exhilarant and tonic) *Muṣaffī-i-Dam* (Blood purifier) *Muqawwī-i-Miʿda* (Stomachic) *Musawwid-i-Shaʿr* (Hair blackening) *Mushtahī* (Appetizer) *Ḥabis-o-Qābiḍ* (Astringent) *Taqwiyat-i-Ḥāfiẓa* (Memory tonic) *Ḍuʿf Amʿā'* (Weakness of intestine)	*Suʿāl* (Cough) *Sūʿ-i-Haḍm* (Indigestion) *Qābḍ* (Constipation) *ʿUṭāsh* (Excessive thirst) *Ḍuʿf-i-Qalb-o-Dimāgh* (Weakness of the heart and brain) *Dāʿal-Ḥayya* (Hair fall) *Nazf al-Dam* (Haemorrhage) *Ishāl* (Diarrhoea) *Surkh Bāda* (Erysipelas) *Naksīr* (Epistaxis) *Shabkorī* (Night blindness) *Zaḥīr* (Dysentery) *Faqr al-Dam* (Anaemia) *Mālankhūliya wa Sawdāwī Amrāḍ* (Melancholia and black bile disorders) *Fālij* (Paralysis) *Ḍūʿf-i-Ishtihāʾ* (Lack of appetite) *Yaraqān* (Jaundice) *Kathrat-i-Luʿāb* (Excessive salivation) *Laqwa* (Facial paralysis) *Juzām* (Leprosy)	

7.	*Kishnīz Khushk* (*Coriandrum sativum* L.)	Whole plant and fruit	5-7 g	Cold 2^0 dry 2^0 or *Murakkab al-Quwā*	*Munawwim* (Hypnotic) *Musakkin* (Sedative) *Musakkin-i-Alam wa Ḥarārat* (Sedative for pain and heat) *Mubarrid* (Refrigerant) *Muḥallil-i-Waram* (Resolvent) *Māniʿ/Dāfiʿ-Tabkhīr* (Anti-flatulence) *Muffriḥ-i-Qalb* (Exhilarant) *Muffriḥ-i-Dimāgh* *Muqawwī-i-Qalb* (Tonic to heart) *Muqawwī-i-Miʿda* (Tonic to stomach) *Mudirr-i-Bawl* (Diuretic) *Kāsir-i-Riyāḥ* (Carminative) *Mushtahī* (Appetizer) *Qābiḍ* (Astringent) *Dāfiʿ-i-Khafqan wa Waswās* (Relives palpitation and hallucination) *Ḥābis* (Styptic)	*Sahr* (Insomnia) *Ṣudāʿ* (Headache) *Duwār* (Vertigo) *Ḍuʿf-i-Qalb* (Weakness of heart) *Ḍuʿf-i-Miʿda* (Weakness of stomach) *Ḍuʿf-i-Dimagh* (Brain weakness) *Nafakh-i-Shikam* (Flatulence) *Ḥumūḍat Miʿdī* (Hyperacidity) *Ishāl* (Diarrhoea) *Tabkhīr* (Flatulence) *Kathrat-i-Shahwat* (Increase libido) *Khafaqān* (Palpitation) *Shiddat-i-ʿAṭash* (Thirst) *Qulāʿ* (Stomatitis) *Dard-i-Ḥalaq* (Pain in throat) *Suʿāl-i-Aṭfāl* (Cough) *Dama* (Asthma)	Antidiabetic Antioxidant Hepatoprotective Antibacterial Antifungal Sedative Anthelmintic hypnotic Activity Anticonvulsant Diuretic Hypolipidaemic Anti-cancer Anti-anxiety Anti-protozoal Gastric mucosal protective Post-coital antifertility Antimutagenic (Yasir *et al*., 2019)

Shailajan *et al*. (2012) also evaluated the acute toxicity of *Safūf Dhayābīṭus Dūlābī* on healthy mice; no significant changes in body weight, food intake, and water intake of the animals were observed compared to animals of the control group and no mortality was recorded. Thus, at the doses empirically used in traditional medicine, the formulation, at least its aqueous slurry (2.0g/kg body weight of animals), could be considered with a wide margin of safety for oral use.

Conclusion

With the above discussion, the inference may be drawn that *Safūf Dhayābīṭus Dūlābī* is one of the best Unani formulations with a lot of health benefits. It has been proven to be beneficial in many diseases especially in the treatment of diabetes mellitus. However, more scientific studies and clinical trials are needed on this compound formulation to ensure its scientific validation for clinical use in patients in general.

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ज़यीबीतुस हार्र (मधुमेह) के उपचार के लिए पॉली हर्बल मिश्रण *सफूफ़–ए–ज़यीबीतुस दूलाबी* – एक समीक्षा

ग़ौसिया तबस्सुम, नजमुद्दीन अहमद सिद्दीक़ी*, आसमा आबिद, मो. एहसान फ़ारूक़ी और अमीर आज़म

सारांश

मधुमेह रोगियों में प्रमुख या सहायक चिकित्सा के रूप में हर्बल औषधियों में यूनानी औषधियां काफी लोकप्रिय हैं। मधुमेह रोगियों की बड़ी संख्या पारंपरिक चिकित्सा के साथ–साथ यूनानी औषधियों का उपयोग करती है और इनका उपयोग मधुमेह रोगियों में ग्लूकोज के स्तर को नियंत्रित करने के लिए काफी प्रभावशाली और सुरक्षित है। विश्वभर में मधुमेह के रोगियों की संख्या में अत्यधिक वृद्धि हो रही है जोकि 21वीं सदी की सबसे तेजी से बढ़ती स्वास्थ्य चुनौतियों में से एक है। मधुमेह से जुड़ी दीर्घकालिक हाईपरग्लाइसिमिया हृदय वाहिनी रोग, मैक्रो तथा माइक्रोवस्कुलर जटिलताओं का कारण बनती है। पारंपरिक उपचार का प्रतिरोध और जटिलताओं में वृद्धि का तकाज़ा है कि हाईपरग्लासिमिया को नियंत्रित और इसकी जटिलताओं को कम करने के लिए वैकल्पिक उपचार पर ध्यान केन्द्रित किया जाए। यूनानी चिकित्सा की अवधारणा के अनुसार *ज़ोफ़–ए गुर्दा* (गुर्दे की कमज़ोरी), *इत्तिसा–ए गुर्दा व मजरा–ए बॉल* (गुर्दे और मूत्र पथ का फैलना), *बुरूदत–ए बदन, जिगर व गुर्दा* (मिजाज़ की सर्दी), *सू–ए मिज़ाज हार्र गुर्दा* (गुर्दे के मिज़ाज की गर्माहट), *सू–ए मिज़ाज बारिद गुर्दा* (गुर्दे के मिज़ाज की सर्दी) के कारण *ज़यीबीतुस हार्र* होता है। *ज़यीबीतुस हार्र* के उपचार के संदर्भ में बहुसंख्यक औषधियों और यौगिक मिश्रणों का उल्लेख किया गया है। *सफूफ़–ए–ज़यीबीतुस दूलाबी* मधुमेह के उपचार में उपयोग होने वाले पॉली हर्बल मिश्रणों में से एक है जो व्यापक रूप से *ज़यीबीतुस सादिक़* (मधुमेह) और *ज़ोफ़ अल–कुल्या* (गुर्दों में कमज़ोरी) के लिए बताई जाती है। *सफूफ़–ए–ज़यीबीतुस दूलाबी* के सभी अवयवों में मौजूद फाइटोस्टेरॉल, β-सीटोस्ट्रॉल में हाइपोलिपिडेमिक, कैंसररोधी, इम्यूनो–मॉड्यूलेटरी और मधुमेहरोधी गुण होते हैं। *सफूफ़–ए–ज़यीबीतुस दूलाबी* मधुमेहरोधी मिश्रण के रूप में प्रयोगात्मक अध्ययनों में भी प्रभावशाली साबित हुई है।

शब्दकुंजी: *ज़यीबीतुस हार्र, सफूफ़–ए–ज़यीबीतुस दूलाबी,* मधुमेहरोधी, यूनानी चिकित्सा

An evidence-based review of important Unani cardiotonic drugs used as part of cardio therapy in Unani Medicine

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Abstract

Cardiovascular diseases (CVDs) are the leading cause of global mortality and a major contributor to disability. This paper reviews the magnitude of the total cardiovascular disease burden as well as the role of important Unani cardiotonics mentioned in the Unani classical literature. Ethnobotanical classical texts of Unani Medicine were explored for the understanding of Unani drugs specific as cardiotonic. Databases including PubMed, Scopus, ScienceDirect, and Google Scholar were used to find scientific studies. Unani cardiac treatment and strategies aid in the prevention, management, and monitoring of cardiovascular disease by minimizing the disease incidence, morbidity, and death. The active biomolecules present in Unani cardiotonics include triterpenoids, cardiac glycosides, diosgenin, oligomeric procyanidins, isoflavones, catechin, and quercetin, among others. Numerous studies of cardiotonic drugs have demonstrated a variety of mechanisms, including positive inotropic and negative chronotropic effects, increased coronary blood flow, and inhibition of enzymes such as angiotensin converting enzyme (ACE) and phosphodiesterase, and so on. There is a plethora of literature about Unani cardiotonic drugs, but there is a scarcity of scientific explanations of how they work. We have attempted to give scientific evidence in the present paper that may be used to support and validate the application of Unani cardiotonics. Hence, an urgent need is required to focus on utilizing existing traditional safe and cost-effective Unani therapies and interventions for better health outcomes.

Keywords: Cardiotonics, Unani Medicne, Biomolecules, Cardiovascular diseases

1. Introduction

The world is going through an epidemiological shift and is on the verge of a cardiovascular disease epidemic. Cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year, and accounts for 32% of all deaths worldwide (WHO, 2021). CVDs are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. For millennia, medicinal plants have been used to treat angina pectoris, congestive heart failure, systolic hypertension, arrhythmia, and venous insufficiency in individuals from ancient to current times. The recent rise in the popularity of natural products and alternative medicine has reignited interest in traditional therapies used in the treatment of CVDs. The anti-oxidative, anti-hypercholesterolemic, anti-ischemic, and platelet aggregation inhibitory effects of the various herbs help reduce the risk of CVD (Naveed *et al*., 2020). According to cause-specific mortality data, cardiovascular disease is already a major cause of death. According to demographic estimates, as life expectancy rises and the age structure of the rising population shifts, cardiovascular disease mortality will skyrocket. In metropolitan areas, coronary risk factors are already prevalent, and immediate action is required to prevent further increases as socioeconomic development progresses (Reddy, 1993).

1.1. Current epidemiology and trends

Cardiovascular diseases include ischemic heart disease, stroke, heart failure, peripheral arterial disease and a variety of other cardiac and vascular illnesses which are the

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significant contributor to poor quality of life. The World Bank and the World Health Organization initiated the GBD (Global Burden of Disease) Study in 1991 to look at the global, regional, and national burden of CVD. In 2017, CVD claimed the lives of 17.8 million people in the world, resulting in 330 million years of life lost and 35.6 million years of disability (Mensah *et al*., 2019). The GBD provides data on incidence, prevalence, case fatality, mortality, and health risks for 204 countries and territories from 1990 to 2019. Prevalent cases of total CVD nearly doubled from 271 million (95% uncertainty interval [UI]: 257 to 285 million) in 1990 to 523 million (95% UI: 497 to 550 million) in 2019, and the number of deaths steadily increased from 12.1 million (95% UI: 11.4 to 12.6 million) in 1990 to 18.6 million (95% UI: 17.1 to 19.7 million). The disability-adjusted life years (DALYs) and years of life lost also increased significantly, and years lived with disability doubled from 17.7 million (95% UI: 12.9 to 22.5 million) to 34.4 million (95% UI:24.9 to 43.6 million). The total number of DALYs due to ischaemic heart diseases has risen reaching 182 million (95% UI: 170 to 194 million), 9.14 million (95% UI: 8.40 to 9.74 million) deaths in the year 2019, and 197 million (95% UI: 178 to 220 million) prevalent cases of ischaemic heart disease in 2019. The total number of DALYs due to stroke has also risen steadily, reaching 143 million (95% UI: 133 to 153 million) DALYs, 6.55 million (95% UI: 6.00 to 7.02 million) deaths in the year 2019, and 101 million (95% UI: 93.2 to 111 million) prevalent stroke cases in 2019 (Roth *et al*., 2020). In South Asia, cardiovascular disease is responsible for 27% of deaths. Ischemic heart disease is the main cause of mortality in India, Pakistan, Nepal, and Sri Lanka, while stroke is the leading cause in Bangladesh, despite the inadequate quality and breadth of data. In contrast to most other regions, South Asia has seen a rise in the number of age-standardised years of life lost due to cardiovascular disease. This is partly due to the fact that cardiovascular disease is more prevalent in South Asia than in high-income countries. Furthermore, acute myocardial infarction strikes South Asians six years earlier than Europeans, owing to the development of risk factors earlier. In South Asia, case fatality rates are greater, especially among younger adults, resulting in more years of life lost. Because more than half of the population lives in poverty, the impact of early cardiovascular disease deaths is significantly greater in South Asia than elsewhere (Misra *et al*., 2017).

1.2. Concept and mechanism of action of cardiotonics in conventional system

Cardiotonics are drugs that improve the efficiency and contraction of the heart muscle, resulting in increased blood flow to all body tissues. They increase the force with which the heart muscle (myocardium) contracts and the mechanism is known as positive inotropic action. When the force of contraction of the myocardium is increased, the amount of blood leaving the left ventricle at the time of each contraction is increased. When the amount of blood leaving the left ventricle increases, cardiac output (the amount of blood leaving the left ventricle with each contraction) is also increased (Subhash *et al*., 2015). They actually work by altering cardiac output or blood supply to certain segments of the circulatory system. The cardioprotective plants contain a variety of bioactive compounds, including diosgenin, isoflavones, sulforaphane, carotene, and quercetin, which have been proved to enhance cardio protection. They are not only used for the management of disease condition but also to maintain proper health (Shah *et al*., 2019).

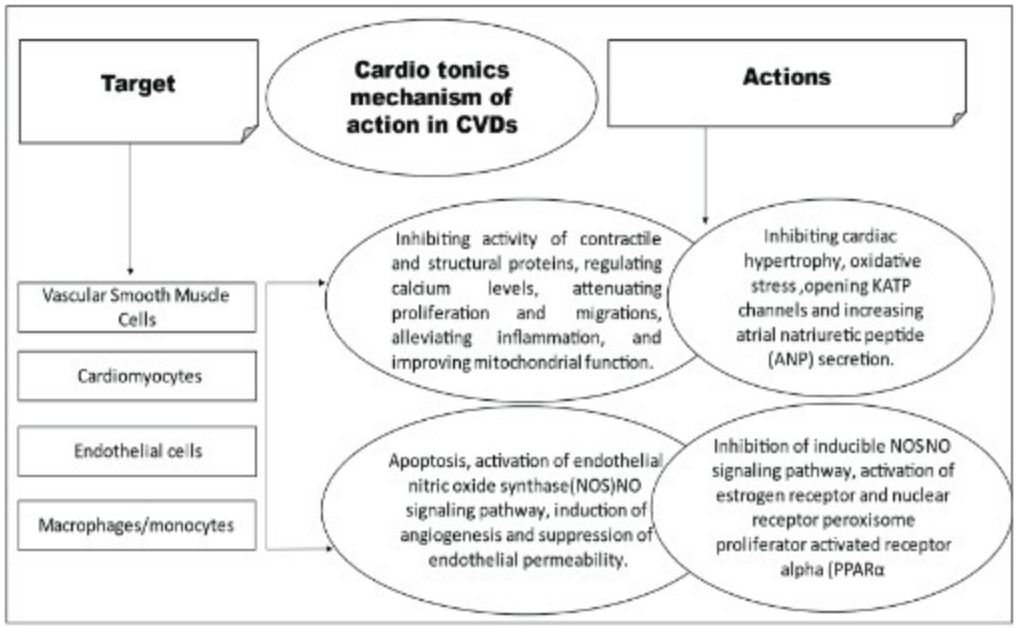

Figure 1: Targets and actions of cardiotonic drugs during the pathogenesis of CVDs

1.3. Concept of traditional and Unani cardiotonics

Many of our earliest therapeutic remedies were made from plants or plant extracts that had been given to sick people (e.g., quinine from cinchona tree bark for treating malaria in the mid-1600s and digitalis from the foxglove plant in the mid-1700s for the treatment of heart failure, to name a few). Some of these early treatments were undoubtedly successful, and with the passage of time, significant advances in the field of phytochemical study were made (Subhash *et al.*, 2015). The applicability of Unani drugs has grown globally in recent years due to the safety and efficacy of Unani drugs and the incorporation of current scientific methodologies to accurately validate traditional drugs. Unani medical research strives to develop new pharmaceuticals and validate existing Unani remedies using modern research techniques and technology while keeping the system's traditional characteristics. According to the Unani holistic approach to health and disease, the patient's complete being and lifestyle are considered when diagnosing and providing appropriate treatment (Anonymous, 2020). In Unani Medicine, drugs acting as tonic for the heart are known as *Muqawwiyāt-i-Qalb* and have been referenced in classical literature by ancient renowned Unani physicians (Ghani, YNM). Ibn Sina (980-1037 A.D.), a distinguished Unani scientist who wrote *al-Qānūn fi'l-Ṭibb* (The Canon of Medicine), left a treatise on 63 cardiac drugs called *Kitāb al-Adviyāt al-Qalbiya*. As far as cardiac care in Unani Medicine is concerned, Unani drugs act either by their temperament (*Mizāj*) or by their essence (*Ṣūrat Naw'iyya*) and they are responsible for the modification of cardiac output to certain parts of circulatory system (Hameed, 1983). There are three types of drugs mentioned in the treatise: plant origin (the most prevalent), mineral origin, and animal origin. The majority of them are plant-based medications (spices, flowers, fruits, and vegetables), such as *Dār Chīnī* (*Cinnamomum zeylanicum* Blume.), *Jā'iphal* (*Myristica fragrans* Houtt.), *Tejpāt* (*Cinnamomum tamala* Buch.-Ham.), *Pūdīna* (*Mentha spicata* L.), *Za'frān* (*Crocus sativus* L.), *Adrak* (*Zingiber officinale* Roscoe.), *Lahsun* (*Allium sativum* L.), *Kishnīz* (*Coriandrum sativum* L.), *Saunf* (*Foeniculum vulgare* L.), *Ajwāyin* (*Trachyspermum ammi* L.), *Zīra* (*Cuminum cyminum* L.), *Bādranjboya* (*Melissa officinalis* L.), *Tulsī*

(*Ocimum sanctum* L.), *Gul-i-Surkh* (*Rosa damascena* Mill.), *Gul-i-Nilofar* (*Nymphaea lotus* L.), *Gul-i-Gurhal* (*Hibsicus Rosa Sinensis* L.). *Yāqūt* (Ruby), *Lājward* (Lazurite), *Gil-i-Armanī* (Armenian Bole), *Momiyā'ī* (Asphaltum), *Ṭilā* (Gold), *Fiḍḍa* (Silver), *Zahr Mohra* (Bezoar stone) are mineral origins. *Lu'lu'* (Pearl), *Marjān* (Coral), *Abresham* (Silk cocoon), *Busad* (Coral roots), *'Asal* (Honey), *Mushk* (Musk), *Amber* (Ambergris), *Zardī Bauyḍa'-i-Murgh* (Hen's egg) are examples of animal origin. Compound preparations acting as cardiotonics are *Khamīra Abresham 'Ūd Maṣṭagī Wālā, Khamīra Abresham Sāda, Khamīra Abresham Shīra 'Unnāb Wālā, Khamīra Ga'uzabāṉ 'Ambarī, Khamīra Ga'uzabān 'Ambarī Jadwār 'Ūd Ṣalīb Wālā, Khamīra Ga'uzabān 'Ambarī Jawāhar Wālā, Khamīra Ga'uzabān Sādā, Khamīra Khāṣ, Khamīra Marwārīd Zahr Mohra, Sharbat Ṣandal, Mufarriḥ Yāqūtī, 'Araq Ilā'ichī, Dawā' al-Misk, etc.* (Ansari, 2014). *Dawā' al-Misk* is a variety of *Ma'jūn* whose major constituents are musk and valuable stones. It's made by combining powdered drugs with sugar in a base, then adding musk and precious stones soaked in rose water. The medication acts as tonic and is used to treat cardiac problems (Anonymous, 2012). Unani drugs are still often used for cardiotonic purposes, particularly because they are enriched with cardiac glycosides. Cardiac glycosides are secondary chemicals found in a variety of plant species that have a cardiotonic effect. Their mechanism is based on the blockage of the heart's sodium potassium ATPase, with a positive inotropic effect (Botelho *et al*., 2019).

Given the rising prevalence of heart disorders, a detailed scrutiny of cardiac drugs is presented in this paper. On the basis of modern research methods, an attempt has been made to appraise the value of the cardiotonic drugs indicated especially by Ibn Sina (Avicenna). In this review, key cardiotonic drugs prescribed by Avicenna have been investigated pharmacologically/chemically using modern scientific approaches.

2. Methodology

The work was conducted at Hakim Ajmal Khan Institute for Literary & Historical Research in Unani Medicine, New Delhi. The data collected were manuscripts of Unani Medicine such as *al-Qānūn fi'l-Ṭibb*, *Khazā'in al-Adviya*, *Makhzan al-Adviya*, *Muhīt-i-A'ẓam*, *al-Jāmi' li-Mufradāt al-Adviya wa'l-Aghdhiya*, etc. Relevant studies concerning various pharmacological activities of cardiotonics were searched through electronic search using PubMed, Google Scholar, Scopus, Cochrane Library and Web of Science without time limit. According to the inclusion and exclusion criteria, the studies were chosen. The review covered randomised trials, *in-vivo* and *in-vitro* cardiotonic drug research. Conference abstracts, letters to editors, dissertations, non-English language, oral presentations, and papers published before 1990 were all excluded. Keywords used for the search were 'cardiotonic', 'herbal', 'Unani', 'cardiovascular diseases', etc. The plant name has been checked and confirmed with http://www.theplantlist.org. The accurate illustration of the Unani terminologies was taken from Standard Unani Medical Terminology published by the Central Council for Research in Unani Medicine in collaboration with the World Health Organization.

3. Result and Discussion

Medicinal plants have been utilised to restore the body's homeostatic balance for centuries. Despite the significant improvements in modern medicine over the last few decades, Unani medications continue to play an essential role in healthcare because of its better efficacy and safety. In the treatment of chronic ailments such as asthma,

arthritis, mental, cardiac, liver, and digestive disorders, Unani Medicine is unrivalled. The drugs given to the patient are well-suited to his or her temperament, hastening healing and lowering the chance of adverse drug reactions. People are increasingly turning to Unani Medicine in the present day due to its fewer side effects and holistic approach (Anonymous, 2020). Herbal medicine has made many contributions to drug preparations today including ephedrine from *Ephedra sinica* (ma-huang), digitoxin from *Digitalis purpurea* (foxglove), salicin (the source of aspirin) from *Salix alba* (willow bark), and reserpine from *Rauwolfia serpentina* (snakeroot), to name just a few. Some common plant sources of cardiac glycosides include *Adonis microcarpa* and *Adonis vernalis* (adonis), *Apocynum cannabinum* (black Indian hemp), *Asclepias curassavica* (red headed cotton bush), *Asclepias friticosa* (balloon cotton), *Calotropis procera* (king's crown), *Carissa spectabilis* (wintersweet), *Cerebra manghas* (sea mango), *Cheiranthus cheiri* (wallflower), *Convallaria majalis* (lily of the valley, convallaria), *Cryptostegia grandiflora* (rubber vine), *Helleborus niger* (black hellebore), *Helleborus viridus*, *Nerium oleander* (oleander), *Plumeria rubra* (frangipani), *Selenicerus grandiflorus* (cactus grandiflorus), *Strophanthus hispidus* and *Strophanthus kombe* (strophanus), *Thevetia peruviana* (yellow oleander), and *Urginea maritima* (squill). Even the venom glands of the animal Bufo marinus (cane toad) contain cardiac glycosides (Botelho *et al*., 2019). The cardio-protective properties of the various herbs are possibly due to their anti-oxidative, anti-hypercholesterolemic, anti-ischemic activities, and inhibition of platelet aggregation that reduce the risk of cardiovascular diseases (Naveed *et al*., 2020). There are plentiful researches that support the pharmacological properties of Unani medicinal plants when utilised in cardiac dysfunction. The findings of one study on *Punica granatum* flower (Unani anti-diabetic and cardioprotective herb) revealed that *Punica granatum* flower extract reduced up-regulated cardiac mRNA expression of ET-1, ETA, inhibitor-kappa B beta and c-jun, and normalized the down-regulated mRNA expression of inhibitor-kappa B alpha in Zucker diabetic fatty rats. In vitro, *Punica granatum* flower extract and its components oleanolic acid, ursolic acid, and gallic acid inhibited lipopolysaccharide-induced NF-kappa B activation in macrophages resulting in diminished cardiac fibrosis in Zucker diabetic fatty rats, at least in part, by modulating cardiac ET-1 and NF-kappa B signalling (Huang *et al*., 2005).

Important Unani cardiotonic drugs

Since the dawn of civilization, Unani plants have been employed, and several derivatives (such as aspirin, digitalis and reserpine) have become mainstays of pharmacology. In patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia, Unani cardiotonic drugs have been used. Some of the important Unani cardiotonic drugs are as follows:

***Ga'uzabān* (*Borago officinalis* L.)**

Cardiotonic plant-based drug belonging to the family Boraginaceae is a perennial, hirsute herb and consists of dried leaf and stem portion (Anonymous, 2008). Ibn Sina characterizes it as having a strong quality of exhilarating and strengthening the heart, which is supported by its power of eliminating their atrabilious matter, purifying the pneuma and blood in the heart (Hameed, 1983).

Dose: 3-5 g (Anonymous, 2008)

Temperament (*Mizāj*): Hot and dry in first degree (Anonymous, 2008)

Part used: Leaves, seeds (Anonymous, 2008)

Chemicals present: γ-linolenic acid, flavonoids, anthocyanins, tannin and sugars. Metabolites identified in the leaf extracts include m-Geranyl-p-hydroxybenzoic acid, Caffeoyl shikimate acid, Syringaldehyde, p-Hydroxyphenyl lactic acid, Sinapic acid hexoside, Lithospheric acid B, Quercetin-3-O-glucoside (Iso quercetin), Dihydroferulic acid, β-Sitosterol Luteolin 7-O-glucoside, Quercetin-3-O-rhamnoside (Quercetin), Catechin-7-O-glucoside, Oleuropein Apigenin 8-C-glucoside (Vitexin) Apigenin 6-C-glucoside (isovitexin), 3,4-Dimethoxycinnamic acid Caffeic acid, Luteolin 7,3′,4′-trimethyl ether, Kaempferol 3,7,4′-trimethyl ether, Coumaroyl hydroxyagmatine, Naringenin O-hexosides, 4-Hydroxybenzoic acid glucoside (Zemmouri *et al*., 2014).

***Abresham* (Silk-pod /Bombyx Mori)**

It is heart-toning, shining in appearance and an animal origin drug (Ibn Baitar, 1987). Raw silk-pod is considered better and used after being decocted till it becomes colourless. It is worth noting that most of the drugs mentioned by Ibn Sina as cardiotonics are not in use as raw, but are used as ingredients in compound formulations, e.g. *Khamīra Abresham Ḥākīm Arshad Wālā* is a famous Unani compound formulation which has *Abresham* as its main ingredient. This drug has been found to have a good anti-hypercholesterolemic and antiarrhythmic activity (Hameed, 1983).

Dose: 3.5 g (Khan, 2013a)

Temperament (*Mizāj*): Hot and dry (Ibn Baitar, 1987)

Part used: Silk pod

Chemicals present: Fibroin and sericin (proteins constituting silk) (Satoshi, 2009)

***Amlaj* (*Emblica officinalis* L.)**

It's a popular cardiotonic fruit from the Euphorbiaceae family that helps in palpitation and other heart problems (Khan, 2013a). Its root, bark, leaf, flower, fruit, and seed are all used in Ayurvedic and Unani medicinal formulations to enhance cardiovascular health (Gantait *et al*., 2021). It is included among tonic and astringent drugs and is specific as a tonic and exhilarant for the heart (Hameed, 1983).

Dose: 10.5 g (Khan, 2013a)

Temperament (*Mizāj*): Cold and dry (Khan, 2013a)

Part used: Fruit

Chemicals present: Vitamin C, β-carotene, calcium, phosphorus, protein, fat, carbohydrate, and emblicanin-A, emblicanin-B, tannins, gallic acid, pyrogallol, and pectin (Gantait *et al*., 2021)

***Bādranjboya* (*Melissa officinalis* L.)**

The cardiotonic herb, belonging to the family Lamiaceae, consists of dried leaves and found in hilly areas (Anonymous, 2007a). It possesses wonderful property of exhilarating as well as strengthening the heart. This property is helped by its fragrance,

refinement, the power of opening up and astringence. Alongside, it is useful for all internal viscera (Hameed, 1983).

Dose: 5-7 g (Anonymous, 2007a)

Temperament (*Mizāj*): Hot and dry in the second degree (Hameed, 1983)

Part used: Leaves

Chemicals present: Geranial, neral, citronellal, linalool, geraniol, geranyl acetate, eugenol glucoside, rosmarinic acid, cynaroside, naringenin, cosmosiin, rhamnocitrin, isoquercitrin, ursolic acid, coumaric acid (Zarshenas *et al*., 2016)

***Nilofar* (*Nymphaea lotus* L.)**

The cardiotonic aquatic herb, generally found in tanks and ponds and warmer regions, belongs to the family Nymphaeaceae and consists of dried flowers (Anonymous, 2007b). The fragrance of the drug, which suits the pneuma, strengthens the pneuma in the heart (Hameed, 1983).

Dose: 5-7 g (Anonymous, 2007b)

Temperament (*Mizāj*): Cold and dry

Part used: Flowers

Chemicals present: Glycoside nymphalin, proanthocyanins, phenols, tannins, flavanols, flavonoids, saponins, alkaloids and steroids (Anthony *et al*., 2013)

***Za'frān* (*Crocus sativus* L.)**

It is considered as excellent cardiotonic drug and is a bulbous, perennial, yellowish style and trifid stigma, belonging to the family Iridaceae. It is dark red or reddish-brown in colour, cornucopia shaped with taste aromatic, and bitter (Anonymous, 2009). It has astringent and dissolving power which is invariably followed by strong strengthening property for the pneuma and its exhilaration because it produces illumination and expansion as well as stability. Its strong fragrance helps in the aforementioned properties (Hameed, 1983).

Dose: 25–50 mg (Anonymous, 2009)

Temperament (*Mizāj*): Hot in the second and dry in the first degree (Hameed, 1983)

Part used: Dried style and stigma

Chemicals present: Safranal, crocin, picrocrocin (Alemzadeh, 2018)

***Sumbul al-Ṭīb* (*Nardostachys jatamansi* (D.Don) DC.)**

Belonging to the family Caprifoliaceae, this cardiotonic herb is dried rhizome dark brown in colour, cylindrical, with reddish brown fibre with taste highly aromatic, acrid, and slightly bitter (Anonymous, 2007c). It possesses antiarrhythmic, anticonvulsant and hypotensive actions that ultimately strengthen the heart (Hameed, 1983).

Dose: 3–5 g (Anonymous, 2007c)

Temperament (*Mizāj*): hot and dry (Khan, 2013a)

Part used: Root

Chemicals present: Sesquiterpenes such as lignans and neolignans (Singh *et al*., 2020)

***Tamar Hindī* (*Tamarindus indica* L.)**

This cardiotonic fruit belonging to the family Leguminosae is reddish brown in colour and taste ranges from sweet and sour to a tangy and tart flavour. It is found in almost all parts of the world (Ghani, YNM). Tamarind has been demonstrated to strengthen the heart in those with hot temperaments, particularly in bilious people. The coldness of it tempts the senses while the purgative qualities of it helps in purification (Hameed, 1983).

Dose: 3–5 g (Ghani, YNM)

Temperament (*Mizāj*): Cold and dry in the second degree (Hameed, 1983)

Part used: Fruit

Chemicals present: Phenolic compounds like catenin, procyanidin B2, epicatechin, tartaric acid, mucilage, pectin, arabinose, xylose, galactose, glucose, uronic acid and triterpene (Kuru, 2014)

***Dār Chīnī* (*Cinnamomum zeylanicum* Blumes.)**

Belonging to Lauraceae family, this cardiotonic herb is made up of the dried inner bark devoid of cork and cortex and is a medium-sized evergreen tree (Anonymous, 2007c). According to Ibn Sina, it has a strong attenuating and exhilarating effect, which is aided by the aroma (Hameed, 1983).

Dose: 1–2 g (Anonymous, 2007c)

Temperament (*Mizāj*): Hot in the second and dry in the first degree (Hameed, 1983)

Part used: Bark

Chemicals present: (E)-cinnamaldehyde (71.50%), linalool (7.00%), β-caryophyllene (6.40%), eucalyptol (5.40%), and eugenol (4.60%), tannin and mucilage (Behrooz *et al*., 2020)

***Ṣandal Surkh* (*Pterocarpus santalinus* L.)**

It is a medium sized, deciduous cardiotonic tree, belonging to the family Fabaceae and consists of heart wood. It is deep blood-red to dark purplish-red or dull black in colour, hard, but can be easily split and odourless with taste, slightly astringent (Anonymous, 2008). *Ṣandal* has the property of exhilarating and strengthening the heart, and is helped by its fragrance, astringency and rarefying power (Hameed, 1983).

Dose: 1–4 g (Anonymous, 2008)

Temperament (*Mizāj*): Cold and dry (Anonymous, 2008)

Part used: Wood

Chemicals present: Santalin A and B, savinin, calocedrin, pterolinus K and L, and pterostilbene (Bulle *et al*., 2016)

***Ṣandal Safed* (*Santalum album* L.)**

It is a cardiotonic evergreen, semi parasitic tree, belonging to the family Santalaceae and consists of dried heart wood. Yellowish-brown to pale-reddish orange in colour, hard but can be easily split and odour persistently aromatic with taste slightly bitter (Anonymous, 2009). It has the property of exhilarating and strengthening the heart (Hameed, 1983).

Dose: 3–6 g (Anonymous, 2009)

Temperament (*Mizāj*): As for white *Ṣandal*, it is extremely cold, being in the second degree, and is less in dryness than red *Ṣandal*, which is also in the second degree (Hameed, 1983).

Part used: Wood

Chemicals present: Santalol (90% or more), is a mix of two primary sesquiterpene alcohols (C15H24O) viz., α-santalol (bp-166-167oC) and β-santalol (bp-177-178oC). Alpha form is more predominately present in the sandalwood oil. Sandalwood oil includes tannins, terpenes, resins, and waxes such as hydrocarbons- santene (C9H14), nortricyclo-ekasantalene (C11H18), α- and β-santalenes (C15H24), alcohols-santenol (C9H16O), teresantalol (C10H16O), aldehydes- nor-tricyclo-kasantalal (C11H16O) and the α-and β- santalic acids, (C15H22O2) and teresantalic acids (C10H14O2) (Arshiya, 2018).

***ʿAmbar* (Ambergris)**

Ambergris is animal origin drug with a strong fragrance. It is the pathological secretion of the intestine sperm whale Physeter macrocephalus syn. Physeter catodon belonging to the family Physeteridae. Ibn Rushd mentioned the medicinal uses of ambergris as a tonic to the heart, brain, stomach and senses (Suleiman, 2020). Ibn Sina has opined that it has a strong property to strengthen and exhilarate the heart simultaneously. Thus, it is tonic for the pneuma in all parts of the body (Hameed, 1983).

Dose: 416-832 mg (Khan, 2013b).

Temperament (*Mizāj*): Hot and dry in the second degree (Hameed, 1983)

Part used: Ambergris

Chemicals present: Ambrein C30H52O, 1-ambra-8, 13, 18- triene, is the major constituent (up to 97%). (Suleiman, 2020)

***Kishnīz* (*Coriandrum sativum* L.)**

It is a dried ripe fruit, belonging to the family Umbelliferae and is an important cardiotonic herb. The drug-producing plant is a slender, glabrous, branching, annual vine with a characteristic aromatic odour when rubbed and peppery and distinct in taste (Anonymous, 2007c). The drug has the ability to strengthen the heart, especially in people with a hot temperament, and its smell and astringency aid in its categorization as a stimulant and corrective (Hameed, 1983).

Dose: 5–7 g (Anonymous, 2007c)

Temperament (*Mizāj*): Cold in the second degree and dry in the third (Hameed, 1983)

Part used: Seeds

Chemicals present: Linalool (58.0–80.3%), g-terpinene (0.3%–11.2%), a-pinene (0.2%–10.9%), p-cymene (0.1%–8.1%), camphor (3.0%–5.1%) and geranyl acetate (0.2%–5.4%), Benzofuran,2,3-dihydro (15.4%), hexadecanoic acid, methyl ester (10.32%) 2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2h-1-benzofuran (9.35%), 2-methyoxy-4-vinylphenol (8.8%) 2,3,5,6-tetrafluroanisole (8.62%), 2,6-dimethyl-3- aminobenzoquinone (6.81%) dodecanoic acid (5%), Decanal (19.09%), trans-2-decenal (17.54%), 2-decen-1-ol (12.33%) and cyclodecane (12.15%), cis-2-dodecena (10.72%), Dodecanal (4.1%), dodecan-1-ol (3.13%) (Mandal, 2015).

***Sa'd Kūfī* (*Cyperus rotundus* L.)**

It is a perennial plant with strong odour and peppery taste belonging to the family Cyperaceae (Ghani, YNM). It is a vital cardiotonic drug and its action resembles aromatic drugs having astringent and rarefying power (Hameed, 1983).

Dose: 3–9 g (Ghani, YNM)

Temperament (Mizāj): Hot and dry in the second degree (Hameed, 1983)

Part used: Root

Chemicals present: *C. rotundus* contains many secondary metabolites such as sesquiterpenes (with diverse skeletons such as patchoulane, rotundane, eudesmane, guaiane, cadinane and caryophyllene types), quinones, flavonoids (visnagin, khellin, ammiol, isorhamnetin, and tricin), saponins, alkaloids, phenolic acids (salicylic acid, protocatechuic acid, caffeic acid and pcoumaric acid), coumarins, steroids (steroidal glycoside, sitosterol-(6'-hentriacontanoyl)-β-d galacto pyranoside) and essential oil (Bajpay *et al*., 2018).

***Ṭabāshīr* (*Bambusa arundinacea* (Retz.) Willd.)**

It is a noteworthy cardiotonic drug which consists of thorny glabrous hard shining bamboo and belongs to the family Poaceae (Anonymous, 2006). Bamboo manna has the property of strengthening and exhilarating the heart and is useful in case of tachycardia and syncope in which its astringency helps it (Hameed, 1983).

Dose: 3.5–7 g (Ghani, YNM)

Temperament (*Mizāj*): Hot and dry in the second degree (Hameed, 1983)

Part used: Root, Bamboo manna, leaf

Chemicals present: SiO2, Al2O3, Fe2O3, CaO, MgO, TiO2, K2O, P2O5, Si / Al. It is mainly composed of Silicic acid (Sio2) up to 96.9%, traces of iron, alum, alkalis and 1% organic matter. Silica 90.5 %, potash 1.1 %, alumina 0.4% and iron peroxide 0.9%. Protein, predominantly glutelin contains lysine and methionine; betaine, choline, proteolytic enzymes, diastatic and emulsifying enzyme, nuclease and urease (Aisha *et al*., 2019).

Table 1: Scientific evidences of cited Unani cardiotonic drugs

S. No.	Botanical name	Unani name	Method/Model used/Assay	Results	Reference
1.	*Borago officinalis* L.	*Ga'uzabān*	In vivo study: Diet-induced obesity rat model & BSO	↑serum HDL-cholesterol intensity & down-regulation Cebpa (Adipogenesis linked gene) in BSO	Navarro-Herrera *et al*., 2018
2.	Bombyx Mori	*Abresham*	In vivo study: DOX-induced cardiotoxicity in adult male Wistar albino rats; UPLC-MS, amino acid profiling by HPLC method &HPLC-FLD)	Protects against oxidative stress; LP; reverted apoptotic markers (caspase-3 & TNF-α), cardiac markers (CK-MB & LDH actions) & IL-6	Khan *et al*., 2014a
3.	*Emblica officinalis* L.	*Amlaj*	In vivo study: ISP-induced cardiotoxicity in rats & E. *officinalis* (100, 250 & 500 mg/kg) or vehicle (normal saline) for 30 days	↓Antioxidant enzymes, SOD, catalase, GP, MIME, CPK-MB, LD, glutathione & ↑ TBA	Ojha *et al*., 2012
4.	*Nymphaea lotus* L.	*Nilofar*	In vivo study: Male Wistar rats (five groups): control; L-NAME (10 mg/kg); L-NAME & losartan (10 mg/kg); L-NAME & N. lotus (75 mg/kg and 200 mg/kg) for 8 weeks,	Protects from L-NAME-induced tissular oxidative damages & ↑vasodilator factors	Mireille *et al*., 2016
5.	*Melissa officinalis* L.	*Bādranjboya*	In vivo study: IIN heart injury in male Sprague-Dawley rats against MOE- (25, 50 and 100 mg/kg)	Improved ischemia/reperfusion (I/R); ↓infarct size; ventricular tachycardia, & ventricular ectopic; ST segment changes and QTc shortening;	Sedighi *et al*., 2019

				↑ SOD activity ↓ serum cardiac troponin I (CTnI, LDH& MDA levels	
6.	*Crocus sativus* L.	*Za'frān*	In vivo study: ISO-induced MI in Wistar rats; ISO (85 mg/kg, 24 hr interval, SC) & saffron extract (20, 40, 80 & 160 mg/kg/day IP)	↓ serum LDH, CK-MB, myocardial LP & oxidative stress	Mehdizadeh *et al*., 2013
7.	*Nardostachys jatamansi* (D. Don) DC.)	*Sumbul al-Ṭīb*	In vivo study: Dox (2.5mg/ Kg IP) induced cardiotoxicity in adult male Wistar rats; CNT (NS), TOX (no treatment); MEJ (JAT1, 250 mg/ kg/day); (JAT2, 500 mg/kg/day) & STD,50mg/kg/ day)	↓Serum CK-MB, LDH & HMG-CoA, levels, and tissue MDA	Singh *et al*., 2020
8.	*Tamarindus indicus* L.	*Tamar Hindī*	In vitro study: Langendorff's heart perfusion; In vivo study: Dox (1.5 mg/ kg,IP) induced cardiotoxicity in rats; TIEE (200 mg/kg, p.o) & (400 mg/kg, p.o); Digoxin (100 µg/ kg, po) for seven days	TIEE (60 µg/ mL) showed cardiotonic effect in vitro by ↑ contraction force, heart rate &cardiac output. In vivo: TIEE ↓ QT & RR interval in ECG, serum enzyme levels (LDH, CPK)	Haroon *et al*., 2021
9.	*Cinmamomum zeylanicum* Blume.	*Dār Chīnī*	In vivo study: Adult male Sprague–Dawley rats induced ischemia and reperfusion; *C. zeylanicum* bark extract (50, 100 &200 mg/kg, IG) 14 days before ischemia	Normalize ST segment & QTc changes, ↓R-wave amplitude, ↑heart rate, serum SD, GP, ↓serum cardiac troponin I, LD& MDA	Sedighi *et al*., 2018

10.	*Pterocarpus santalinus* L.	*Ṣandal Surkh*	In vivo study: Streptozotocin-induced diabetic adult male Wistar rats	↓LP; tissue, organ mass & cholesterol levels; TBARS; ↑antioxidants, SOD, CAT, GP & GT	Halim, 2011
11.	*Santalum album* L.	*Ṣandal Safed*	In vivo study: Dox induced cardiomyopathy in adult male Wistar rats	↓IL-6 and TNF-α in serum whereas caspase-3 in cardiac tissue; ↓MDA, LDH, CK-MB levels	Khan *et al*., 2014b
12.	Ambergris	*ʿAmbār*	In vivo study: Ambrein (50-200 mg/kg) administered to the normotensive anaesthetized rats	Ambrein (100 mg/kg) block the effects of adrenaline, nor adrenaline, isoprenaline, acetylcholine, HR &BP ↑ Ca channels &β−adrenergic receptors in the heart.	Raza *et al*., 1999
13.	*Coriandrum sativum* L.	*Kishnīz*	In vivo study: ISP-induced heart failure (HF) in Wistar rats.	Improved LV-functions, hemodynamic outcomes & baroreflex sensitivity; ↓LP, lipid profile, & downregulation expression of endothelin receptors	Dhyani *et al*., 2020
14.	*Cyperus rotundus* L.	*Saʿd Kūfī*	In vivo study: Isoprenaline ((85mg/kg, s.c.)-induced MI in Wistar rats with ethanolic extract of *Cyperus rotundus* L. (250 and 500 mg/kg body wt., oral)	Improved serum ALT, AST, (CK-MB) &LD (P <0.0001)	Khwaja *et al*., 2016

15.	*Bambusa arundinacea* [(Retz.) Willd.]	*Ṭabāshīr*	In vivo study: Phenylephrine-tempted vasoconstriction in thoracic aortas of hyperlipidaemic rats & triterpenoid-rich EBS	Triterpenoid tempted ↓ serum total cholesterol &total triglyceride levels, friedelin induces vasodilator effect	Jiao *et al*., 2007

UPLC-MS: Ultra Performance Liquid Chromatography-Mass Spectrometry; FLD: fluorescence detector; IIN: ischemia-induced; BSO: borage seed oil; ISP: isoproterenol; GP: glutathione peroxidise; MIME: myocyte-injury-specific marker enzymes; CPK-MB: Creatine phosphokinase-MB; TBA: thiobarbituric acid; L-NAME: N (ω)-nitro-L-arginine methyl ester (L-NAME); MI: myocardial infarction; MEJ: Methanolic extract of jatamansi; SD: superoxide dismutase; CK-MB: creatine kinase-myoglobulin; EBS: extract from bamboo shavings; NS: Normal saline; DOX: Doxorubicin; CK-MB: creatine kinase-MB; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin -6; LDH: lactate dehydrogenase; CNT: Control; TOX: toxicant; STD: standard desferrioxamine ; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; MDA: melondialdehyde level; TIEE: ethanol extract of leaves of Tamarindus indica; IG: intragastric; TBARS : Thiobarbituric Acid Reactive Substance; CAT: Catalase ; GT: gluthathione transferase; LV: left ventricular; LP: lipid peroxidation; ↑: Increased; ↓: Decreased

4. Conclusion and Future Prospects

The therapeutic and preventative potential of Unani cardiotonics for the therapy of cardiovascular illnesses has been discussed in this article. Phytoconstituents appear to have a wide range of cardioprotective properties, which they appear to exert through decreasing particular factors, blocking important enzymes, and scavenging oxygen-free radicals. The evidence presented in this study strongly suggests that Unani cardiotonics represent a source of emerging medicines for the prevention and treatment of cardiovascular diseases. As a result, using natural herbs to generate more effective and safe medications is a promising strategy to prevent and cure cardiovascular problems. The Unani medical system recommends a number of cardiac tonic drugs that have been referenced in classical literature by notable Unani physicians from the past. In conclusion, the medications identified by Ibn Sina as cardiotonic require a thorough pharmacological and clinical examination using modern research methods. Unani drugs' active ingredients should also be separated for structural and elucidation purposes. It is possible that these molecules, if they are significant in character, will open up new frontiers for synthetic chemists and lead to the development of more helpful medications as synthetic analogues. The quest to describe cardiotonic Unani medications will aid in the research of the Unani system spectrum, resulting in better healthcare outcomes. However, scientific evidence on their safety and efficacy is inconsistent, and very few were subjected to the same rigorous evaluation methods and standards as modern pharmaceuticals and documentation for clinical studies is also essential for standardizing the evaluation of Unani medicinal plants. As an alternative to conventional treatment approaches, medicinal plant screening should be carried out to investigate specific plant constituents with therapeutic potential against cardiovascular illnesses. Furthermore, the characterisation of specific isolated chemicals from potent cardiotonic medicinal plants could be extremely useful in innovative drug design and development for the treatment of cardiovascular diseases. Future studies

should concentrate on well-designed clinical trials, in-depth mechanistic studies, and investigations into herb side effects and drug interactions. Unani drug studies on generating novel drugs with efficacy and safety are a viable strategy to prevent and treat individuals with cardiovascular ailments. Collaboration with mainstream/conventional medicine may be promoted in order to improve the research quality.

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यूनानी चिकित्सा में कार्डियो थैरेपी में उपयोग की जाने वाली महत्वपूर्ण यूनानी कार्डियोटोनिक औषधियों की साक्ष्य–आधारित समीक्षा

शबनम अन्जुम आरा*, शाहीन अख़लाक़, मोहम्मद फज़ील, बिलाल अहमद, मेराजुल हक़, उसामा अकरम, अहमद सईद और आसिम अली ख़ान

सारांश

हृदय रोग विश्व स्तर पर मृत्यु और विकलांगता का एक प्रमुख कारण है। इस शोधपत्र में हृदय रोग भार के आकलन के साथ–साथ यूनानी क्लासिकल साहित्य में उल्लिखित महत्वपूर्ण यूनानी कार्डियोटोनिक औषधियों की भूमिका की समीक्षा की गई है। कार्डियोटोनिक के रूप में विशिष्ट यूनानी औषधियों को समझने के लिए एथनोबॉटनिकल क्लासिकल ग्रंथों की खोज की गई। पबमेड, स्कोपस, साइंसडायरेक्ट और गूगल स्कोलर, आदि डाटाबेस को खंगाला गया। वैज्ञानिक अध्ययनों की खोज के लिए यूनानी हृदय रोग उपचार और रणनीतियां रोग की व्यापकता, रुग्णता और मृत्युदर को कम करके हृदय रोग की रोकथाम, उपचार और देखरेख में सहायता करती हैं। यूनानी काडिर्योटोनिक औषधियों में मौजूद सक्रिय जैविक अणुओं में ट्राइटरपेनॉइड्स, कार्डियक ग्लाइकोसाइड्स, डायोसजेनिन, ऑलिगोमेरिक प्रोसायनिडिन्स, आइसोफ्लेवोन्स, कैटेचिन और क्वेसेटिन शामिल है। कार्डियोटोनिक औषधियों पर हुए अनेक अध्ययनों ने सकारात्मक इनोट्रोपिक और नकारात्मक कोनोट्रोपिक प्रभावों, कोरोनरी रक्त प्रवाह में वृद्धि और एजियोटेंसिन कनवर्टिंग एंजाइम (एसीई) और फॉस्फोडिएस्टरेज़ जैसे एंजाइमों के निषेध सहित विभिन्न तंत्रों को दर्शाया है। यूनानी कार्डियोटोनिक औषधियों के बारे में बहुतायत साहित्य है परन्तु ये कैसे कार्य करते हैं इसके वैज्ञानिक स्पष्टीकरण की कमी है। हमने इस शोध पत्र में वैज्ञानिक साक्ष्य देने का प्रयास किया है जिसको यूनानी कार्डियोटोनिक्स के उपयोग के प्रोत्साहन और वैधीकरण के लिए उपयोग किया जा सकता है। अतः बेहतर स्वास्थ्य परिणामों के लिए मौजूदा पारंपरिक सुरक्षित और लागत प्रभावी यूनानी उपचारों और उपायों के उपयोग पर ध्यान केन्द्रित करने की तत्काल आवश्यकता है।

शब्दकुंजीः कार्डियोटोनिक, यूनानी चिकित्सा, जैविक अणु, हृदय रोग

Phytochemistry, pharmacological actions and uses of *Bel* (*Aegle Marmelos*) with special reference of Unani Medicine: A comprehensive review

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Abstract

Traditional herbal medicines are naturally occurring plant-derived substances that have been utilized as medicines to treat the illness for thousands of years. *Aegle marmelos* (L.) Corrêa, commonly known as wood apple or Bel/Bilva belongs to Rutaceae family. It is a potential herb that has been used for various ailments since ancient times. It is a moderate sized deciduous tree that has great mythological significance for Hindus. *Bel* (*Aegle marmelos* (L.) Corrêa) is the most widely used medicine in Unani and other systems of medicine for the treatment of diarrhoea and dysentery. Besides, it is also used for abdominal disorders, peptic ulcer, nervine disorders, gonorrhoea, heart disorders, dog bite, jaundice, snake bite and many more. Various investigations have been carried out on different parts of *Aegle marmelos* (L.) Corrêa from which different types of phytochemical compounds are isolated that belong to alkaloids, terpenoids, vitamins, coumarins, tannins, carbohydrates, flavonoids, fatty acids, essential oils and some other miscellaneous compounds. The plant also possesses various pharmacological activities such as antioxidant, antibacterial, antifungal, antidiarrheal, antidiabetic, antiproliferative, cytoprotective, hepatoprotective, antifertility, analgesic, antiarthritic, antihyperlipidemic, cardioprotective, radioprotective, anticancer, anti-ulcer, immunomodulatory and wound healing properties. The current review article focuses on the complete profile of *Bel* (*Aegle marmelos* (L.) Corrêa) in terms of Unani Medicine.

Keywords: Unani Medicine, *Bel*, *Aegle marmelos*, Antidiarrheal

Introduction

From time to time, the researchers have focused more on detecting the ability of various drugs to treat the disease and maintain general health (Haider *et al*., 2012). Herbal medicines are unique gift of the nature. Herbs and plants have been utilised as a natural source of medicinal compounds since thousands of years (Kumar *et al*., 2011). Many plants and plant-derived products are used by humans for treatment and relief from various physical and mental illnesses. These plants are used in traditional Unani, Ayurveda, Siddha, Chinese and Tibetan medicines (Balunus & Kinghorn, 2005). According to the World Health Organization, about four billion people, 80% of the world's population, presently use herbs for some aspect of primary care due to their natural origin and minimal side effects (Nejad *et al*., 2013). India has a rich heritage of traditional knowledge and is home to many important health care systems like Unani, Ayurveda, and Siddha. In India, it has been estimated that the proportion of medicinal plants in relation to the existing flora is higher than any other country (Shiva, 1998; Kala *et al*., 2006).

Herbal drugs are obtained as whole or part of it from plants such as root, stem, leaf, bark, fruit, flowers and seeds. Herbal plants play an important role in traditional health care system as well as in international herbal and pharmaceutical markets and the medicinal value of these plants lies in some chemical substances that produce a definite physiological action on human body (Tilburt & Kaptchuk, 2008; Pieters & Vlitinck, 2005).

A large number of herbal medicines are mentioned in Unani Medicine, and *Bel* (*Aegle marmelos* (L.) Corrêa) is one of them. *Aegle marmelos* (L.) Corrêa is a native plant of India, commonly known as wood apple or Bel/Bilva, and belongs to Rutaceae family. It

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is also known as Bengal quince, Indian quince, holy fruit, and golden apple. This herb has great medicinal, spiritual and religious significance. The tree is generally considered as sacred tree as its leaves are offerings to the Hindu Gods like Lord Shiva that's why it is also called Shivadurme, the tree of Shiva. According to Hindu mythology, the tree is another form of Lord Kailashnath. Traditionally, *Aegle marmelos* (L.) Corrêa is used in the treatment of diarrhoea and dysentery. *Bel* fruits are also used as dietary product and the pulp of fruit is used to prepare delicacies like murabba, puddings and juice. The Bel fruit has lots of pharmacological activities such as antibacterial, antimicrobial, antidiarrheal, gastroprotective, anti-ulcerative colitis, hepatoprotective, anti-diabetic, cardioprotective, free radical scavenging, antioxidant, etc. (Anonymous, 1948; Maity *et al*., 2009; Purohit & Vyas, 2004; Chaudhry *et al*., 2017). In this review, an attempt has been made to explore pharmacological actions, pharmacological activities and uses of *Aegle marmelos* (L.) Corrêa with the reference to Unani Medicine.

Fig. 1: Ripe fruit of *Aegle marmelos* (L.) Corrêa

Fig. 2: Leaves of *Aegle marmelos* (L.) Corrêa

Fig. 3: Unripe fruit of *Aegle marmelos* (L.) Corrêa

Habitat and distribution

Aegle marmelos (L.) Corrêa is a slow-growing, medium sized sharp tree, about 12 to 15 meter in height with short trunk. *Aegle marmelos* (L.) Corrêa is a subtropical plant, has its origin from Eastern Ghats and Central India. It is native to India and grows well in hilly and plain areas. *Aegle marmelos* (L.) Corrêa is a widely distributed plant and found in India, Ceylon, Pakistan, Nepal, Sri Lanka, China, Myanmar, Bangladesh, Burma, Thailand, Tibet, Indonesia, Malaysia, Vietnam, Laos, Cambodia, and Philippines. In India, it is found in Uttar Pradesh, Bihar, Chhattisgarh, Madhya Pradesh, Uttarakhand and Jharkhand (Dhankhar *et al*., 2011; Bhar *et al*., 2019).

Table 1: Taxonomy of *Aegle marmelos* (L.) Corrêa (ITIS, Accessed on September 20, 2020)

Kingdom	Plantae
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta
Superdivision	Embrophyta
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Magnoliopsida
Superorder	Rosanae
Order	Sapindales
Family	Rutaceae
Genus	Aegle
Species	*Aegle marmelos* (L.) Corrêa

Table 2: Vernacular names (Anonymous, 2007; Kritikar & Basu, 2012; Anonymous, 1999)

Language	Name
Latin	*Aegle marmelos* (L.) Corrêa
English	Wood/Stone apple, Bengal quince, Indian quince
Urdu	Bel
Arabic	Safarjal Hindi
Persian	Safarjal Hindi, Shul
Hindi	Bel, Bel, Siriphal, Sirphal
Telugu	Maredu
Sanskrit	Shreephal, Bilva, Bilwa, Shivadruma, Shivapala
Bengali	Bel
Tamil	Vilva Maram, Vilva Pazham, Kuvalum
Marathi	Kaveeth
Kannada	Bilpatra, Kumbala, Malura
Gujrati	Bil, Bili, Bilvaphal
Malyalam	Marredy
Vietnamese	Mbau Nau, Trai Mam
Thai	Mapin, Matum, Tum
French	Oranger du Malabar
Nepali	Bel, Gudu
Burmese	Ohshit, opesheet
Indonesian	Mojo tree
Javanese	Modjo
Portuguese	Marmelos

Cultivars

There are no standardized names for *Aegle marmelos* (L.) Corrêa cultivar so the names are based on location where these are found. The weight of fruit varies in different cultivars and the shapes and sizes are also different in different cultivars such as spherical, oblong, cylindrical, pear shaped and flat. The percentages of peel, seeds and contents of other fibres also varry. In India, the plant is widely cultivated particularly in Uttar Pradesh and Bihar in which four cultivars Kagzi Etawah, Sewan Large, Mirzapuri, and Deoria Large have been found to be superior and excellent in taste and other qualities (Pandey *et al*., 2013; Srivastava & Singh, 2004).

Morphological description of Aegle marmelos (L.) Corrêa

Macroscopic

The *Bel* tree is armed with straight sharp axillary thorns which are 2.5 cm long and the leaflets are ovate or ovate-lanceolate about 5-10 cm long and 2.5-6.3 cm wide. Its bark is thick, soft, flaking and spreading. Branches are spiny, and the lower ones are drooping. The flowers are greenish white in colour, occur in clusters of 4 to 7 along the young branchlets, have 4 recurved, fleshy petals, green outside, yellowish inside and 50 or more greenish-yellow stamens and having sweet scented fragrance. New foliage is glossy and pinkish-maroon in colour. Its leaves are trifoliate, having round base and pointed tip. Young leaves are light green and matured leaves are dark green in colour. Mature leaf emits a disagreeable odour when bruised. The fruits are round, pyriform oval, or oblong and has a hard-outer jacket with a diameter of 5-20 cm. It is greyish green when unripe and after ripening it turns into yellowish brown colour. It contains upto 20 orange pulp inside. There are 8 to 15 segments in the pulp of fruit in which seeds are embedded. The pulp is yellow, soft, pasty, sweet, resinous and fragrant. The seeds are small, about 1 cm long, hard, flattened-oblong, and bearing woolly hairs (Anonymous, 2007; Kritikar & Basu, 2012; Dhankhar *et al*., 2011; Patel *et al*., 2012).

Microscopic

Transverse section (T.S.) of *Aegle marmelos* (L.) Corrêa leaves shows groups of fibres with calcium oxalate crystals and also exhibits outer and inner epidermis covered with striated cuticle. It contains numerous covering trichomes and shows paracytic stomata, more in number on the upper epidermis and lesser in the lower epidermis. A multi-layered strip of collenchyma appears between the lower epidermis and upper epidermis, midrib compose of xylem and phloem which arranged in an arc. Palisade cells and spongy parenchyma are also visible (Siddique *et al*., 2010).

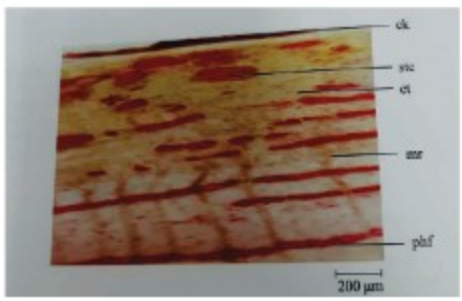

Fig. 4: Microscopy of *Aegle marmelos* (L.) Corrêa stem bark
(*ck-cork, stc- stone cells, ct- cortex, mr- medullary rays, phf- phloem fibers)

T.S. of *Aegle marmelos* (L.) Corrêa stem bark shows outermost multi-layered cork, wider cortex embedded with groups of stone cells, phelloderm is parenchymatous, scattered with groups of sclereids and fibres associated with idioblast. It contains prismatic crystals of calcium oxalate, wider phloem and shows uni to triseriate wavy medullary rays running parallel in the inner zone (Tandon & Sharma, 2010).

***Bel* (*Aegle marmelos* (L.) Corrêa) in Unani Medicine**

Parts used: Fruit (both ripe & unripe), root bark, leaves, rind of the ripe fruit and flowers (Nadkarni, 1976; Anonymous, 2006).

Temperament (*Mizāj*): Ripe fruit – Hot 1° & Dry 2° (Gani, 1998; Nabi, 2007). Unripe fruit – Cold 1° & Dry 2° (Gani, 1998). Cold 2° & Dry 3° (Khan, 2012).

Dose: Leaves juice – 5 *Tola* (1 tola=12 g); Powder (*Safūf*) – 2-3 Masha (1 *Masha*=1 g); Decoction (*Joshānda*) or infusion (*Khīsānda*) – 3-5 g (Tariq, 2010).

Side effects: It causes haemorrhoids (Gani, 1998; Nabi, 2007; Tariq, 2010).

Correctives: Sugar, Yogurt (Khan, 2012; Tariq, 2010).

Substitute: *Sumāq* (Rhus coriaria L.), *Shūra* (Potassium nitrate) (Khan, 2012).

Compound formulations: *Sharbat Belgirī*, *Murabba Belgirī*, *Safūfe Tiryāq-i-Ishāl*, *Safūf Zaḥīr*, *ʿAraq Belgirī Sāda*, *Jawārish Zanjabīl* (Anonymous, 2007; Tariq, 2010).

Phytochemistry of *Bel* (*Aegle marmelos* (L.) Corrêa)

Various phytoconstituents like alkaloids, (Agelin, aegelenine, marmeline, dictamine, fragrine, halfordino), coumarins (Marmelosin, marmesin, imperatorin, marmin, scopoletin, umbelliferone, psoralen, marmelide), tannins (Skimmianine), polysaccharides (Galactose, arabinose, uronic acid and L-rhamanose), cardiac glycosides, terpenoids (α-Phellandrene, β-Phellandrene, p-cymene, limonene), flavonoids (Rutin, flavone, flavan-3-ols, flavone glycosides), phenylpropanoids (hydroxycoumarins, phenylpropenes, lignans), steroids, carbohydrates, fat have been isolated and identified from different parts of the tree out of which major chemical constituent is marmelosin (furocoumarin). A small amount of ascorbic acid, sitosterol, crude fibres, α-amyrin, carotenoids, and crude proteins is also present (Kokate & Purohit, 2012; Sivraj & Balakrishan, 2011; Manandhar *et al*., 2017). In a research, some amount of valencic acid, praealtin D, trans-cinnamic acid, 4-methoxy benzoic acid, betulunic acid, montanin and rutaretin have also been found in *Aegle marmelos* (L.) Corrêa (Ali & Pervez, 2004). Seed oil consists palmitic acid (15.6%), stearic acid (8.3%), and linoleic acid (28.7%). Apart from these, 12.5% of an unusual fatty acid, ricinoleic acid along with other normal fatty acids have also been found in seed oil. *Bel* tree also possesses some of the minerals such as phosphorus, potassium, calcium, magnesium and iron (Mujeeb *et al*., 2014).

Pharmacological actions in Unani Medicine

Ripe fruit: *Qābiḍ* (astringent), *Ḥābis al-Dam* (haemostatic), *Hāḍim* (digestive), *Muqawwī-i-Qalb* (cardiotonic), *Muqawwī-i-Dimāgh* (brain tonic), *Muqawwī-i-Miʿda* (stomachic), *Muqawwī-i-Jigar* (liver tonic), *Mushtahī* (appetizer), *Kāsir-i-Riyāḥ/ Muḥallil-i-Riyāḥ* (carminative), *Muḥallil-i-Waram* (anti-inflammatory) (Gani, 1998; Nabi, 2007; Khan, 2012; Anonymous, 2010).

Table 3: Different types of phytochemical compounds isolated from different parts of *Aegle marmelos* (L.) Corrêa- (Maity *et al*., 2009; Farooq, 2005).

S. No.	Plant part	Phytoconstituents
1	Leaf	Skimmianine, Aeglin, Rutin, Y-sitosterol, β-sitosterol, Flavone, Lupeol, Cineol, Citral, Glycoside, O-isopentenyl, Halfordiol, Marmeline, Citronellal, Cuminaldehyde phenylethyl cinnamamides, Eugenol, Marmesinin, α-Phellandrene, p-cymene
2	Fruit	Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tannin
3	Bark	Skimmianine Fagarine, Marmin
4	Root	Psoralen, Xanthotoxin, Scopoletin, Tembamide
5	Seed	Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cymene, Cuminaldehyde.

Unripe fruit: *Qābiḍ* (astringent), *Mugharrī* (stimulant), *Mullaṭṭif* (demulcent), *Ḥābis al-Dam* (haemostatic), *Mushtahī* (appetizer), *Hāḍim* (digestive), *Muqawwī-i-Qalb* (cardiotonic), *Kāsir-i-Riyāḥ/Muḥallil-i-Riyāḥ* (carminative) (Gani, 1998; Nabi, 2007; Khan, 2012; Anonymous, 2010).

Leaves: *Mullayyin* (laxative), *Qābiḍ* (astringent), *Hāḍim* (digestive), *Dāfiʿ-i-Bukhār* (febrifuge), *Munaffith-i-Balgham* (expectorant) (Gani, 1998; Nabi, 2007; Khan, 2012; Anonymous, 2010; Anonymous, 2009).

Root: *Muqawwī-i-Qalb* (cardiotonic), *Dāfiʿ-i-Bukhār* (febrifuge), *Qābiḍ* (astringent), *Hāḍim* (digestive)

Therapeutic uses

Fruit: *Ishāl Muzmin* (chronic diarrhoea), *Zaḥīr Muzmin* (chronic dysentery), *Waram al-Litha* (gingivitis), *Ḍuʿf al-Haḍm* (delayed digestion), *Qayʾ* (vomiting), *Taqṭīr al-Bawl* (dribbling of urine), *Dīdān al-Amʿāʾ* (worms infestation), *Wajaʿ al-Miʿda* (Stomachache), *Sill* (tuberculosis), *Waram al-Kabid* (hepatitis), *Bawāsīr* (haemorrhoids), *Fasād al-Haḍm* (dyspepsia) (Kritikar & Basu, 2012; Gani, 1998; Khan, 2012).

Root: Snake poison, *Ghathayān* (nausea), *Ishāl* (diarrhoea) (Kritikar & Basu, 2012; Gani, 1998; Khan, 2012).

Bark: *Ḥummā Dāʾira* (intermittent fever), *Khafaqān* (palpitation), *Qayʾ* (vomiting), Snake poison (Kritikar & Basu, 2012; Gani, 1998; Khan, 2012; Tariq, 2010).

Leaves: *Ḥummā* (fever), *Suʿāl* (dry cough), *Nazla* (cold), *Zukām* (catarrh), *Ḍīq al-Nafas* (asthma), *Suzāk* (gonorrhea), *Ḍuʿf al-Baṣar* (asthenopia/amblyopia), *Bawāsīr* (haemorrhoids), *Yaraqān* (jaundice), *Dhayābīṭus* (diabetes), *Waqr* (deafness) (Kritikar & Basu, 2012; Gani, 1998; Khan, 2012; Tariq, 2010; Anonymous, 2009).

***Bel* fruit as a dietary agent**

Ripe fruits of *Bel* have been used as a dietary agent. The sweet aromatic fruit pulp is very nutritious and beating the seeded pulp together with milk and sugar makes a

popular drink called *Sharbat* in India. Mature but still unripe fruits are made into jam with addition of sugar, citric acid and preservatives. The pulp is also converted into marmalade, *Murabba* or syrup, which are used as food material (eaten with Indian bread) as well as therapeutic agent. In Indonesia, the pulp of the fully ripe fruit is consumed for breakfast either by cutting or breaking open the soft fruits and eating the pulp of fruit dressed with palm sugar. In Thailand, dried pieces of the fruits are packed as tea bags either whole or pulverized. They may also be preserved in syrup and used as dessert or for preparing cakes. The fruit pulp is used to make a firm jelly alone or combined with guava to modify the astringent flavour. The pulp is also pickled (Anonymous, 1948; Purohit & Vyas, 2004; Baliga *et al*., 2011).

General uses

Every part of *Bel* tree is utilized for various purposes. The wood takes good polish and is suitable for home construction, cart construction, carving, pestles, agricultural implements, tool handles, combs, etc. The wood is used for building productive gas plants and is also useful for making small household articles and animal sheds. Leaves and twigs are used as fodder and twigs are also used as tooth brushes or chew-sticks. The yellow dye is useful in calico printing, which is obtained from unripe rind. The pulp of the fruit combines with lime to form a strong cement, which is used to construct wells. The pulp has detergent properties and is often used as an alternative to laundry soap. The dried fruits, after separating the pulp from the rind, are used as boxes to keep valuable medicines, sacred ashes and snuff balls. Gum which is obtained from stem acts as a good adhesive and often used for book binding. The tree has been identified as suitable windbreaker or wind barrier (Purohit & Vyas, 2004; Dastur, 1968).

Traditional uses

Bel (*Aegle marmelos* (L.) Corrêa) is one of the most important tree species, whose various parts are widely used in the Traditional Indian System of Medicine. Among different parts, fruits are used to cure maximum number of ailments. The medicine is prepared in the form of pills, powder and paste. It is considered as an important medicine in Unani and Ayurveda for the treatment of chronic diarrhoea and dysentery and is an important ingredient in the preparation of *Dasamula* (ten roots) and *Chyavanprash*, which is used for recovering the loss of appetite. Apart from these, it is used to treat jaundice, constipation, stomach-ache, inflammations, abdominal discomfort, acidity, burning sensation, intestinal ulcer, indigestion, dyspepsia, nausea, vomiting, fever, eye disorders, smallpox, spermatorrhoea, leucoderma, thyroid disorders and mental illness. It also provides relief from cough, cold, asthma, bronchitis, influenza and other similar respiratory tract disorders. *Bel* (*Aegle marmelos* (L.) Corrêa) has been used as a herbal medicine for the management of diabetes mellitus in Ayurvedic, Unani and Siddha systems of medicine in India, Bangladesh and Sri Lanka (Kala, 2006; Neeraj *et al*., 2017; Kar *et al*., 2003).

The pulp of unripe fruit mixed with milk and sugar cures urogenital disorders. Unripe fruit pulp mixed with boiled rice water is taken twice a day to cure vomiting during pregnancy. Young leaves are eaten and said to cause sterility or even abortion. Leaves are used as mild laxative and also employed in asthmatic complaints, ophthalmia and other eye infections. The decoction of root bark is useful in intermittent fevers, fish poison, remedy for heart palpitation and melancholia. Extract of *Bel* root, *Piyāz* (*Allium cepa* L.) and *Haldī* (*Curcuma domestica* L.) mixed in equal proportion is put

into the ears to relieve earache and ear secretions. Half roasted pulp of unripe fruit mixed with sugar is essential for the treatment of dysentery and abscess. *Bel* is also useful for controlling haemorrhoids as the dose involves the intake of a combination of dried and powdered *Bel* leaves, dried ginger, carom seeds, and black pepper mixed in a glass of buttermilk or lukewarm water (Kritikar & Basu, 2012; Kala, 2006; Dutta *et al*., 2014; Upadhyay, 2015).

Table 4: Pharmacological studies

Pharmacological activities	Part used / solvent extract	Effects
Antimicrobial activity	Aqueous, petroleum ether and ethanol extract of the leaves and fruit	Inhibitory activity against Escherichia coli, Streptococcus pneumoniae, Salmonella typhi, Klebsiella pneumoniae and Proteus vulgaris. The ethanolic extract showed activity against Penicillium chrysogenum, petroleum ether and aqueous extract showed activity against Fusarium oxysporum (Sivaraj *et al*., 2011). The decoction of the fruit has good antifungal and antibacterial activity against Aspergillus niger, Aspergillus fumigatus, Candida albicans and Staphylococcus aureus (Gheisari *et al*., 2011).
Antidiarrheal activity	Ethanolic and aqueous extract of fruit	The aqueous extract exhibited inhibitory activity against giardia and rotavirus by affecting the production of cholera toxin and binding of both labile toxin and cholera toxin to ganglioside monosialic acid receptor (Brijesh *et al*., 2009). The ethanolic extract showed good activity against Shigella boydii, S. sonnei and S. flexneri, moderate against S. dysenteriae (Joshi *et al*., 2009).
Antioxidant activity	Alcoholic and aqueous extracts of fruit pulp	Both the extracts showed good antioxidant power with IC50 value ranges from 37.11±3.50 to 158.99±59.46µg/ml for aqueous extract and 35.02±8.10 to 283.06 ±135.80µg/ml for alcoholic extract. It might be due to inactivation of free radicals or complex forming with metal ions or combination thereof (Rajan *et al*., 2011).
Anthelmintic activity against earthworm	Aqueous and ethanolic extracts of leaves and pulp	Both the extracts produced paralysis as well as death of worms and showed dose dependent wormicide activity as compared to the control group. Most potent activity was observed at the dose of 20 mg/ml (Wagh *et al*., 2017; Singh *et al*., 2012).
Antidiabetic activity	Aqueous, petroleum ether, benzene, chloroform and methanol extract of leaves and callus	All the extracts reduced the blood sugar level in streptozotocin-induced diabetic rabbits by acting as an anti-hyperglycaemic agent. The extracts may act, through certain mechanism, to improve the receptor-responsiveness to insulin causing increased sugar uptake by the tissue. Among the various extracts, methanol extract produced the maximum reduction of blood sugar level (Arumugam *et al*., 2008).

Anti-ulcer activity	Aqueous and methanolic extract of leaves	Both the extracts showed significant reduction in ulcer index along with the reduction in gastric volume and free acidity on indomethacin induced ulcer models in rats (Madhu *et al*., 2012; Shenoyet *et al*., 2012).
Anti-cancer activity	Methanol and acetone extract of leaves	Both the extracts exhibited anticancer activity on MDA-MB-231 cells with IC50 values of 79.62 and 61.79µg/ml and HEP-2 cells with IC50 values of >100 and 47.08µg/ml respectively by sparing normal Vero cells (Seemaisamy *et al*., 2019).
Hepatoprotective activity	Ethanolic and aqueous extract of leaves and pulp	Both the extracts showed significant hepatoprotective effect in carbon tetrachloride (CCl4) induced hepatic damage in mice/rats by lowering the levels of enzyme like SGPT, SGOT, ALP, bilirubin, total cholesterol, triglycerides, low density lipoprotein, very low-density lipoprotein, and increase in the level of high-density lipoprotein (Sumitha & Thirunalasundar, 2011).
Nephroprotective activity	Aqueous extract of leaves	The extract showed dose dependent nephroprotective activity in cisplatin-induced nephrotoxic rats with reducing the elevated MDA (malondialdehyde) level, serum urea, creatinine, TNF-α, IL-1β levels and increased GSH (glutathione) level (Hassan *et al*., 2020).
Anti-microfilarial activity against Brugia malayi microfilariae	Methanolic extract of leaves	Methanolic extract of leaves at 100 ng/ml concentration showed complete loss of motility of microfilariae after 48 hr of incubation (Sahare *et al*., 2008).
Cardioprotective effect	Aqueous, ethanolic and petroleum ether extracts of leaf, stem and root	Among the various extracts, aqueous extract of leaf exhibited significant cardioprotective effect with improved biochemical parameters and reversed isoproterenol-induced myocardial infarction in rats (Ramachandra *et al*., 2012).
Radioprotective effect	Ethanolic extract of leaves	The extract reduced the frequency of MPCE and MNCE along with inhibition of a radiation-induced decline in the PCE/NCE ratio exposed to different doses of gamma-radiation in bone marrow of mice (Jagetia *et al*., 2007).
Anti-inflammatory activity	Ethanolic extract of leaf	The extract showed significant anti-inflammatory activity at a dose of 400 mg/kg in carrageenan-induced rat paw edema. It might be due to the inhibition of release of mediators like histamine, serotonin and prostaglandins (George *et al*., 2016).
Antiarthritic activity	Aqueous, petroleum ether, methanol, chloroform and ethyl acetate extracts of unripe fruit	The extracts showed dose dependent antiarthritic activity at 50, 100 and 200 µg/ml dose level by bovine serum protein denaturation and egg albumin protein denaturation method (Sivakumar *et al*., 2020).

Analgesic activity	Aqueous extract of stem bark	The extract showed dose dependent analgesic activity in tail-flick test (centrally acting analgesics) and acetic acid-induced writhing method (peripherally acting analgesics) in rats and mice respectively (Ghodki *et al*., 2016).
Antipyretic activity	Ethanolic and aqueous extracts of leaves	Both the extracts showed antipyretic activity at the dose of 200 and 400 mg/kg on Brewer's yeast-induced pyrexia and produced significant reduction in elevated rectal temperature of rats in a dose-dependent manner (Vyas *et al*., 2011).
Antimalarial activity	Methanolic extract of leaves	The extract exhibited promising antimalarial activity against 3D7 strain of Plasmodium falciparum (Kamaraj *et al*., 2012).
Antifertility activity	Methanolic extract of bark	The extract showed dose and duration dependent antifertility activity in male Wistar rats with reducing reproductive organ weight and serum testosterone levels along with reduction in sperm density, motility, viability and sperm acrosomal integrity (Agrawal *et al*., 2012).
Antihyperlipidemic /Hypolipidemic activity	Aqueous, ethanol and chloroform extracts of leaves	The extracts showed dose dependent antihyperlipidemic or hypolipidemic activity with significant decreases in TC, TG, LDL and VLDL along with an increase in HDL level (Kumar *et al*., 2018; Bhuvaneswari & Sasikumar, 2013).
Neuroprotective effects	Ethanolic extract of leaves	The extract showed protective efficacy against CdSO4 induced neurotoxicity in BALB/c mice, and significantly reversed increased lipid peroxidation and attenuated the decreased enzymatic and non-enzymatic markers (Seth *et al*., 2018).
Anti-anxiety activity	Methanolic extract of leaves	The extract showed dose dependent anxiolytic activity in Elevated plus maze (EPM) and Actophotometer (locomotor activity) models of rats with increased open arm activity by increase in time spent and number of entries into open arms and significant decrease in locomotor activity (Halemani *et al*., 2015).
Anti-convulsant activity	Ethanolic extract of leaves	The extract exhibited dose dependent anticonvulsant activity that showed significant increase in the onset time and decrease the duration of tonic-clonic convulsions in PTZ induced model along with decreasing the duration of extensor in MES induced seizures (Bhatti *et al*., 2013).
Anti-proliferative activity	Ethanol, hexane, petroleum ether and chloroform extracts of leaves	Among the different extracts, ethanol extract exhibited significant antiproliferative activity that showed maximum inhibition in colon and breast carcinoma cell line at the dose of 100 µg/ml (Bhatti *et al*., 2013).

Table 5: Physicochemical standards of *Bel* (*Aegle marmelos* (L.) Corrêa) (Pande *et al*., 2018)

S. No.	Parameters	% Value (w/w)
1	Loss on drying	92
2	Total ash	5.75
3	Water soluble ash	5.16
4	Acid insoluble ash	0.16
5	Sulphated ash	6.66
6	Petroleum ether soluble extractive value	11.67
7	Toluene soluble extractive value	14.05
8	Ethyl acetate soluble extractive value	16.66
9	Methanol soluble extractive value	11.78
10	Water soluble extractive value	34.07

Toxicity studies

For acute oral toxicity, ethanolic extract of dried pulp of Aegle marmelos (L.) Corrêa was screened at the doses of 550 and 1250 mg/kg bw in Swiss albino mice. At these concentrations, there was no sign of toxicity. Moreover, there was no change in the behavioural and physiological activity during the study period i.e., 14 days. From the above data, it can be concluded that LD50 of the mentioned extract is more than 1250 mg/kg/bw (Atul *et al*., 2012).

Conclusion

This comprehensive review article emphasizes and elaborates the complete knowledge of *Aegle marmelos* (L.) Corrêa as it is considered very potent and effective drug which has been used as single and compound formulation in Unani Medicine since ages. It is a plant origin drug used for variety of ailments. Though, *Aegle marmelos* (L.) Corrêa has various medicinal applications, but there is a need to explore more medicinal values at molecular level. Further studies should be conducted to elucidate its mechanism of action in different diseases and may play a very important role in modern medicine.

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यूनानी चिकित्सा के विशेष सन्दर्भ में *बेल (एगल मार्मेलोस)* के पादप रसायन और औषधीय कार्य एवं उपयोगः एक व्यापक समीक्षा

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सारांश

पारंपरिक हर्बल औषधियां प्राकृतिक रूप से उगने वाले पौधों से प्राप्त पदार्थ हैं जो औषधियों के रूप में हज़ारों वर्षों से रोगों के उपचार के लिए उपयोग किए जाते रहे हैं। *एगल मार्मेलोस* (एल.) कोरिया, जिसे आमतौर पर वूड एप्पल या बेल/बिल्वा के नाम से जाना जाता है, रूटासी प्रजाति से संबंधित है। यह एक सशक्त जड़ी–बूटी है जिसका उपयोग प्राचीन काल से विभिन्न रोगों के उपचार के लिए किया जाता है। यह एक मध्यम आकार का पर्णपाती वृक्ष होता है जिसका हिन्दुओं में बहुत पौराणिक महत्व है। *बेल (एगल मार्मेलोस)* (एल.) कोरिया) यूनानी एवं अन्य चिकित्सा पद्धतियों में दस्त और पेचिश के उपचार के लिए व्यापक रूप से उपयोग की जाती है। इसके अलावा इसका उपयोग पेट के विकार, पेप्टिक अल्सर, तंत्रिका विकार, प्रमेह, हृदय विकार, कुत्ते के काटने, पीलिया, सांप के काटने और कई अन्य रोगों के लिए भी किया जाता है। *एगल मार्मेलोस* (एल.) कोरिया के विभिन्न भागों पर बहुत से अध्ययन किए गए जिनके परिणामस्वरूप इसमें से विभिन्न प्रकार के पादप रसायन यौगिकों को अलग किया गया है जो एल्कालॉइड, टेरपेनॉइडस, विटामिन्स, कौमारिन, टैनिन, कार्बोहाड्रेट, फ्लेवोनॉइड्स, फैटी एसिड, ऐसेन्शियल ऑयल और कुछ अन्य विविध यौगिकों से संबंधित हैं। पौधे में विभिन्न औषधीय गतिविधियां होती हैं जैसे– ऑक्सीकरणरोधी, जीवाणुरोधी, फंगसरोधी, अतिसारोधी, मधुमेहरोधी, प्रजननशीलरोधी, साइटोप्रोटेक्टिव, हेपैटोप्रोटेक्टिव, उर्वरतारोधी, एनाल्जेसिक, गठियारोधी, एंटीहाइपरलिपिडेमिक, कार्डियोप्रोटेक्टिव, रेडियोप्रोटेक्टिव, कैंसररोधी, अल्सररोधी, इम्यूनोमॉड्यूलेटरी और घाव भरने वाले गुण। वर्तमान समीक्षा पत्र यूनानी चिकित्सा के सन्दर्भ में *बेल (एगल मार्मेलोस)* (एल.) कोरिया) का पूर्ण विवरण प्रस्तुत करता है।

शब्दकुंजीः यूनानी चिकित्सा, *बेल, एगल मार्मेलोस,* अतिसाररोधी

Standardization of *Marham Ḥinā* – A popular Unani ointment

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Abstract

Marham Ḥinā is a Unani medicine widely used in the treatment of skin conditions like acne, pruritus, furuncles, burns, etc. The drug is prepared using herbal ingredients in a base of beeswax and petroleum jelly. Standardization of the formulation was carried out to ensure its quality, efficacy, safety and reproducibility. The finished product was subjected to physico-chemical analysis which included estimation of soluble extractive value, total ash, acid insoluble ash, acid value, iodine value, bulk density, saponifiable and unsaponifiable matter, chromatographic studies like TLC and HPTLC, and WHO parameters, viz. microbial contamination, pesticide residue, aflatoxins and heavy metal estimation. The data evolved in the present work will help in fixing the pharmacopoeial standards of *Marham Ḥinā* and laying down the SOP for its preparation.

Keywords: SOP, TLC, HPTLC, Heavy metal, Aflatoxin, *Marham Ḥinā*

Introduction

The increasing global interest in traditional system of medicine has renewed the attention of scientists towards the necessity of producing effective and safe medicinal drugs. Hence, there is a need of sufficient scientific data to promote acceptance of such traditional medicinal products amongst the masses. Unani Medicine, which is one of the oldest traditional systems of medicine, is a rich storehouse of specialized dosage forms or formulations. *Marham* (ointment), an important preparation of Unani Medicine, is generally used as a topical applicant for cuts, abrasions, pains, etc. (Anonymous, 2011). A *Marham* may act on the skin or is absorbed through the skin for systemic action. Plant products or minerals form the core ingredient of *Marham* which may vary from formulation to formulation.

For the present study, an important Unani formulation *Marham Ḥinā* was selected and standardized. The main ingredients of *Marham Ḥinā* are Rowghan-i-Ḥinā (oil of Lawsonia inermis L.) (Anonymous, 2011) and *Kāfūr* (*Cinnamomum camphora* (L.) J.Presl.) (Anonymous, 1990).

Ḥinā leaves have been used since centuries as an herbal dye for coloring hair and skin tattoos (Anonymous, 2007). In Unani classical literature, *Ḥinā* leaves and oil prepared from the leaves are claimed to possess *Muḥallil-i-Waram* (anti-inflammatory) and *Musakkin-i-Alam* (analgesic) properties. *Kāfūr* is said to possess *Dāfiʿ-i-Taʿaffun* (antiseptic) action along with *Musakkin-i-Alam* (analgesic) properties. The other ingredients of the formulation, i.e. *Satt-i-Ajwāʾin* (extract of *Ptychotis ajowan* DC.) and *Satt-i-Pudīna* (extract of *Mentha spicata* L.) are also used externally in skin diseases like acne because of their *Jālī* (detergent) and antiseptic actions (Kabiruddun, YNM). *Marham Ḥinā* (Table 1) which is a combination of all of the above mentioned ingredients has *Dāfiʿ-i-ʿUfūnat* (antiseptic), *Musakkin Maqāmī* (local sedative), *Dāfiʿ-i-Sozish* (anti-irritant) and *Dāfiʿ-i-Waram* (anti-inflammatory) properties. It is used in skin diseases like pruritus, acne, furuncles, ringworm, burns, local irritation, etc. (Anonymous, 2011). The formulation has been listed in the National Formulary of Unani Medicine, Part-VI and is a part of the formulations of Dawakhana Tibbia College, Aligarh. The present work is an attempt to scientifically evaluate the Unani compound formulation *Marham Ḥinā* for laying down pharmacopoeial standards and subject it to analytical parameters and TLC studies which have not been reported so far.

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Materials And Methods

Raw materials

Marham Ḥinā was prepared according to the formulation described in National Formulary of Unani Medicine, Part-VI which has been derived from the classical book 'Pocket Ilmul Advia' published by Dawakhana Tibbia College, Aligarh. All the ingredients listed in Table 1 were procured from local raw drug dealer and were of pharmacopoeial quality.

Preparation of Marham

Rowghan Ḥinā was heated in a pan. Beeswax and vaseline were added followed by *Kāfūr*, *Satt-i-Pudīna* and *Satt-i-Ajwā'in*. All the ingredients were stirred to obtain a homogenized mixture. The mixture was allowed to cool and then transferred to a sterile container (Fig. 1).

Analytical parameters

The homogenized mixture obtained was subjected to analytical studies in triplicates to check the quality, identity, and purity of the ointment. Physico-chemical studies like petroleum ether (60–80°), soluble extractive, ash value, acid insoluble ash, bulk density (Anonymous, 1987; WHO, 1998), acid value, iodine value, saponification value and unsaponified matter (Anonymous, 1986) were determined as per the standard methods. The presence of microbial load, aflatoxins, pesticide residues (AOAC, 2000) and heavy metals (Sahito *et al*., 2001) were also studied as per the WHO guidelines.

Preparation of extracts for TLC/HPTLC

The chloroform extract was prepared by refluxing 2 g of the drug sample with 40 ml chloroform for about 20 minutes and filtered through Whatman no. 1 filter. Another sample of the drug (2 g) was shaken vigorously with 40 ml ethanol in a separating funnel until an emulsion was formed. The emulsion was left undisturbed for 4–5 hours which separates the ethanol layer. The ethanol layer was collected in a beaker to obtain ethanol extract. Both the extracts were used for the TLC/HPTLC finger printing by employing DESAGA AS30 automatic sample applicator on aluminum TLC plate pre-coated with silica gel 60 F254 (E. Merck). The chromatograms were developed using the solvent system Toluene: Ethyl acetate in the ratio 9:1 for both the extracts. The plate was dried at room temperature and observed the spots under UV-254 and UV-366. Further the plate was dipped in 1% Vanillin-Sulphuric acid reagent and heated at 105 °C till coloured spots appeared (Wagner *et al*., 1984; Sethi, 1996; Stahl, 1996).

Observation

The drug *Marham Ḥinā* is a semi solid compound preparation with yellowish brown color and agreeable characteristic odour. The drug did not show any filth, fungus or objectionable matter when the sample was spread on a petri dish (Fig. 1).

Results and Discussion

The present study is an attempt to ascertain the pahrmacopoeial standards for the standardization of *Marham Ḥinā*. The results observed for the physiochemical data, presence of microbial load, aflatoxins, pesticide residue, heavy metals, TLC and HPTLC finger printing are shown in Table 2, 3, 4, 5, 6 and 7 respectively.

The drug shows more than 90% solubility in petroleum ether (60–80°), which is attributed to the oily nature of the drug. The ash value recorded was less than 1%, stipulating that the drug is free from siliceous matter. Acid insoluble ash was found only in traces. Saponification value (around 165) indicates the presence of substantial amount of fatty acid in the drug. The unsaponifiable matter recorded was very low. Low acid value (13–15) indicates less number of free acids. The iodine value (around 76–78) and moderate bulk density (0.8) confirm the semi solid nature and high degree of unsaturation in the drug.

The drug did not show any presence of aflatoxins (Table 4), microbes and pesticide residues (Table 5). The heavy metals detected were also within the permissible limits (Table 6).

HPTLC profile

Chromatogram of ethanol extract shows one spot under UV 254 nm at Rf 0.57 (green). Under UV 366 nm, one florescent spot is observed at Rf 0.38 (blue). After derivatization, the chromatogram shows under visible light 05 major spots at Rf 0.30 (violet), 0.34 (pink), 0.44 (pink), 0.56 (red) & 0.61 (peach) (Table 7, Fig. 2). Similarly, chromatogram of chloroform extract shows one major spot under UV 254 nm at Rf 0.56 (green). Under UV 366 nm, one florescent spot is observed at Rf 0.36 (blue). After derivatization, the chromatogram shows under visible light 05 major spots at Rf 0.30 (violet), 0.34 (pink), 0.43 (pink), 0.55 (red) & 0.61 (peach) (Table 7, Fig. 2).

Conclusion

The present study holds high significance in the identification and development of SOP for the compound Unani formulation, *Marham Ḥinā*. The study also ensures the authenticity, quality and efficiency of the medicine and renders it as safe for topical application.

Acknowledgement

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Table 1: Formulation composition

S. No.	Ingredients	Botanical/English Name	Part Used
1.	*Rowghan-i-Ḥinā*	*Lawsonia inermis* L.	Oil
2.	*Kāfūr Khāliṣ*	*Cinnamomum camphora* (L.) J.Presl	Natural camphor
3.	*Satt-i-Pudīna*	*Mentha sp.* L.	Menthol
4.	*Satt-i-Ajwā'in*	*Ptychotis ajowan* DC.	Thymol
5.	*Mom Khāliṣ*	Bees wax	Solid wax
6.	*Vaseline Safaid*	White petroleum jelly	Semi solid jelly

Table 2: Physico-chemical parameters

S. No.	Parameters	Batch-1	Batch-2	Batch-3
1.	Pet. ether (60-80o) soluble extractive (% w/v)	90.40	90.50	90.80
2.	Total ash (%)	0.22	0.23	0.24
3.	Acid insoluble ash (%)	0.050	0.078	traces
4.	Acid value	13.41	14.35	15.04
5.	Iodine value	76.18	77.46	78.57
6.	Saponification value	166.27	165.43	163.89
7.	Un-Saponifiable matter	12.45	12.83	13.11
8.	Bulk density	0.8324	0.8371	0.8416

Table 3: Microbial loads

S. No.	Parameter Analysed	Results	Permissible Limits
1.	Total bacterial load	23 x 10*3 cfu/g	Not more than 10*5/g
2.	Total fungal count	15 x 10*2cfu/g	Not more than 10*3/g
3.	Enterobacteriaceae	Absent	-
4.	E.coli	Absent	-
5.	Salmonella sp.	Absent	-
6.	Staphylococcus aureus	Absent	-

Table 4: Aflatoxins level

S. No.	Parameter Analysed	Results	Permissible Limits
1.	B-1	Nil	Not more than 0.5 ppm
2.	B-2	Nil	Not more than 0.1 ppm
3.	G-1	Nil	Not more than 0.5 ppm
4.	G-2	Nil	Not more than 0.1 ppm

Table 5: Pesticide residue

S. No.	Parameter Analysed	Results	Permissible Limits
1.	Chlorpyriphos	Not detected	0.20 mg/kg
2.	DDT	Not detected	1.00 mg/kg
3.	Endosulfan	Not detected	3.00 mg/kg
4.	Malathon	Not detected	1.00 mg/kg
5.	Parathion	Not detected	0.50 mg/kg

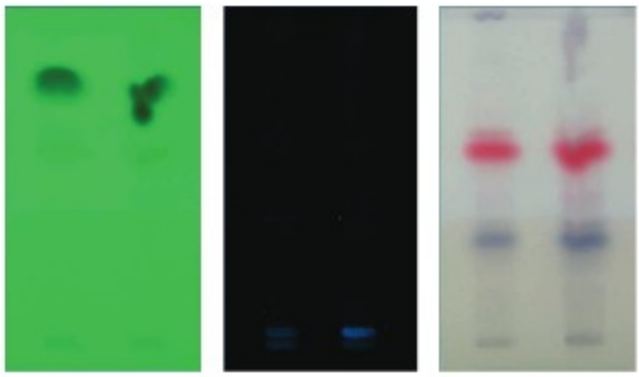
Table 6: Heavy metals

S. No.	Parameter Analysed	Results	Permissible Limits
1.	Arsenic	Not detected	Not more than 3.0 ppm
2.	Cadmium	Not detected	Not more than 0.3 ppm
3.	Mercury	Not detected	Not more than 1.0 ppm
4.	Lead	Not detected	Not more than10 ppm

Table 7: Thin layer chromatography

	Solvent system	Spray/ Reagent treatment	No. of spots	R_f value with color
Ethanol extract	Toluene: ethylacetate 9:1	Dipped in 1% vanillin sulphuric acid	5	0.30-violet
				0.34- pink
				0.44-pink
				0.56-red
				0.61-peach
	Solvent system	**Spray/ Reagent treatment**	**No. of spots**	**R_f value with color**
Chloro-form extract	Toluene: ethylacetate 9:1	Dipped in 1% vanillin sulphuric acid	5	0.30-violet
				0.34- pink
				0.44-pink
				0.56-red
				0.61-peach

Figure 1: *Marham Ḥinā*



A- Ethanol extract; B- Chloroform extract

Figure 2: TLC of *Marham Ḥinā*

मरहम हिना – एक लोकप्रिय यूनानी मरहम का मानकीकरण

फ़राह अहमद, असमा सत्तार ख़ान, अख़लाक़ मुस्तफ़ा, शोएब अहमद अन्सारी, अनस इक़बाल अल्वी, असमा मिर्ज़ा, उमर हुसैन और आर. पी. मीना

सारांश

मरहम हिना एक यूनानी औषधि है जो मुहांसे, अत्यधिक खुजली, फोड़े–फुन्सी, जलन इत्यादि त्वाचा विकारों में व्यापक रूप से उपयोग की जाती है। यह औषधि मधुमोम और पेट्रोलियम जेली में हर्बल अवयवों का उपयोग करके तैयार की जाती है। मिश्रण की गुणवत्ता, प्रभावकारिता, सुरक्षा और पुनरुत्पादकता सुनिश्चित करने के लिए इसका मानकीकरण किया गया। तैयार उत्पाद का भौतिक–रासायनिक विश्लेषण किया गया जिसमें घुलनशील निष्कर्षण मात्रा, कुल राख, एसिड अघुलनशील राख, एसिड मात्रा, आयोडीन मात्रा, थोक घनत्व और साबुनीकरण तथा असाबुनीकरण पदार्थ का आकलन, वर्णलेखी अध्ययन जैसे टीएलसी और एचपीटीएलसी और डब्ल्यूएचओ मापदंड अर्थात् माइक्रोबियल सम्मिश्रण, कीटनाशक अवशेष, एफ्लाटॉक्सिन और भारी धातु आकलन शामिल थे। वर्तमान कार्य में प्रस्तुत डाटा से मरहम हिना के भेषजकोशीय मानक को ठीक करने और इसकी तैयारी के लिए एसओपी निर्धारित करने में सहायता मिलेगी।

शब्दकुंजी: एसओपी, टीएलसी, एचपीटीएलसी, भारी धातु, एफ्लाटॉक्सिन, *मरहम हिना*

Sub-chronic toxicity studies of *Dawā' al-Kurkum* and its extract in experimental rats

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Abstract

Objective: The objective of the present study was to evaluate sub-chronic (90–day) toxicity of *Dawā' al-Kurkum* and its extract in rats.

Methods: The sub-chronic toxicity of *Dawā' al-Kurkum* and its extract was studied by feeding the extract at 250, 500 and 1000 mg/kg bw daily to rats as per OECD guidelines 408. After 90-day feeding, biochemical and oxidative parameters of treated rats were compared with control animals. Histopathology of all the major organs was also studied.

Results: In the sub-chronic toxicity study, no mortality or clinical signs of toxicity were observed in any of the animals. The repeated administration of *Dawā' al-Kurkum* and its extract for 90 days in rats at the maximum dose level body weight did not induce any observable toxic effects, when compared to its control animals. The biochemical and oxidative profile of treated rats was similar to control animals and difference was non-significant. The histopathology of major organs of all the control and treated animals was normal.

Conclusion: The present study indicates that *Dawā' al-Kurkum* and its extract do not have any toxic effects in animals at the dose evaluated as evidenced by sub-chronic toxicity studies in rats.

Keywords: OECD 408, Toxicity, *Dawā' al-Kurkum*

1. Introduction

Unani medicines have been utilized to cure a variety of diseases since ancient times. Despite the significant improvements in modern medicine over the last few decades, Unani medications continue to play a major role in the health-care system. The rising interest in adopting alternative treatments is important because many allopathic medicines have side effects, which can be life threatening in some cases (Wal *et al*., 2011). As a result of the restrictions and hazards associated with conventional therapy, many patients and practitioners are seeking alternatives. Herbs and herb-derived medications have long been utilised in Ayurveda and Unani systems to prevent and treat a variety of ailments. Despite the fact that these medications are widely used to treat a variety of diseases, little is known regarding their toxicity and safety. Unani medications must meet numerous criteria such as safety, efficacy, and quality when examined using modern scientific instruments in order to get widespread acceptance in the worldwide community. Validating traditional remedies for safe therapeutic use is therefore critical. Despite the fact that there are over a thousand Unani medications approved for clinical use, their use is restricted due to the lack of knowledge about their safety and toxicity. Toxicology research is thus critical for the global survival of herbal mixtures (Dar *et al*., 2015). Safety evaluation studies provide the essential experimental data and information on a drug's scientific data and safety measures, allowing practitioners to prescribe it. If the formulations' safety and toxicity profiles are determined, they will have a higher chance of competing with modern medications and being accepted by international regulatory agencies (Wal *et al*., 2011).

Dawā' al-Kurkum, a polyherbal composition used in Unani Medicine, is useful in situations of liver dysfunction, anorexia, ascites, and abdominal pain. This polyherbal

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is made up of *Nardostachys jatamansi*, *Commiphora myrrha*, *Cinnamomum cassia*, *Saussurea lappa*, *Cymbopogon shoenanthus*, *Cinnamomum zylenicum*, *Crocus sativa* with ethyl alcohol and *Saccharum officinarum* (Gulati *et al*., 2019; Hafeez *et al*., 2018).

The goal of this study was to determine the toxicity of *Dawā' al-Kurkum* and its extract according to OECD (Organization for Economic Co-operation and Development) guidelines in order to support its safety for human usage.

2. Materials and Methods

2.1. Drugs and chemicals

The polyherbal Unani drug *Dawā' al-Kurkum* was formulated by the Central Research Institute of Unani Medicine (CRIUM), Hyderabad. Other routine chemicals were procured from SRL, New Delhi. Biochemical kits were purchased from ERBA Diagnostics Mannheim Gmbh.

2.2. Animals

Wistar rats of either gender (180–250 g) were used for the study. The animals were maintained in the Vallabhbhai Patel Chest Institute, University of Delhi, at a constant temperature (25 ± 2°C) under standard laboratory conditions. The animals had free access to food and water and care of animals was taken as per the guidelines of CPCSEA for the use of animals in scientific research with approval of the Institutional Animal Ethics Committee (IAEC) (Registration number VPCI/IAEC/2017/13).

2.3. Investigational drug

The standardized drug, *Dawā' al-Kurkum*, was prepared and provided by the Central Research Institute of Unani Medicine (CRIUM), Hyderabad, Ministry of Ayush, Govt. of India with a batch No. 3-1/2018-19/CRIUM. This polyherbal formulation is composed of 9 herbs as mentioned above. The formulation is well-documented in standard Unani literature (National Formulary of Unani Medicine, 2006) and is certified to have been prepared as per traditional classical Unani text by the CRIUM.

The 50% hydroalcoholic extract was prepared by mixing 100 g of *Dawā' al-Kurkum* with 100 ml ethanol (99% alcohol) + 100 ml distilled water. The mixture was boiled for 9 h, filtered and the filtrate was heated till the volume was reduced to half. The extract was used for further comparative studies with *Dawā' al-Kurkum*.

2.4. Sub-chronic (90–day repeated dose) toxicity study

This study was conducted as per OECD guidelines for testing of chemicals (No. 408). Thirty rats (both sex) were divided into five groups. The animals were acclimatized for seven days before the commencement of dosing. Group 1 served as healthy control; Group 2 received *Dawā' al-Kurkum* (DK) (250 mg/kg); Group 3 received *Dawā' al-Kurkum* (500 mg/kg, orally); Group 4 and 5 animals were administered hydroalcoholic extract (HA) at the dose of 500 and 1000 mg/kg orally, respectively. All the drugs were administered for 90 days. On 91st day, the animals were anesthetized and blood was collected by cardiac puncture, centrifuged and stored at -80ºC. After blood collection, the animals were sacrificed and their livers were collected for histopathological studies and estimation of biochemical and oxidative stress parameters. As per approval of the IAEC, total 30 animals were included in the experimental study.

2.5. Biochemical estimations

The markers of liver function, i.e. serum alanine aminotransferase, serum aspartate aminotransferase and serum alkaline phosphatase were estimated by using Kinetic method of International Federation of Clinical Chemistry. The serum bilirubin and total protein were estimated by end point assay as per the instruction of the Kit Manufacture's manual.

2.6. Estimation of MDA levels

Malondialdehyde (MDA), the oxidative stress marker of lipid peroxidation in biomedical research, was measured spectrophotometrically as 2-thiobarbituric acid-reactive substance (TBARS) in supernatant of liver homogenate (). 0.1 ml of homogenate supernatant was added to 0.2 ml of sodium dodecyl sulfate (8.1%), 1.5 ml of acetic acid (20%) and 1.5 ml of 2-thiobarbituric acid (0.8%). The total mixture was finally made up to 4.0 ml with distilled water and vortexed. The samples were incubated for 1 h at 95°C and cooled with tap water. 1.0 ml of distilled water and 5.0 ml of mixture of butanol-pyridine 15:1 (v/v) were added to the sample and shaken for 10 min and centrifuged for 10 min at 4000 rpm. Butanol-pyridine layer is measured spectrophotometrically at 532 nm. 1, 1, 3, 3-tetramethoxypropane (TMP) was used as the standard for comparative purpose (Satoh, 1978).

2.7. Assay of reduced glutathione (GSH) levels

Glutathione (GSH) levels were measured by method described by Ellman (Ellman, 1959). This assay is based on the enzymatic recycling in which glutathione was sequentially oxidized by DTNB and reduced by NADPH in the presence of glutathione reductase. An equal amount of sample was mixed with 10% trichloroacetic acid and centrifuged to separate the proteins. To 0.1 ml of this homogenate supernatant, 2 ml of phosphate buffer (pH 8.4), 0.5 ml of 5'5-dithiobis (2-nitrobenzoic acid) and 0.4 ml of double distilled water was added. The mixture was vortexed and absorbance was read at 412 nm within 15 min. The measured reduced glutathione is expressed as µmol/mg protein.

2.8. Nitrates and nitrites (NOx) assay

NOx concentrations were measured by using the Griess reaction as described by Tracey *et al*. (Tracey *et al*., 1995). 6 µl of homogenate supernatant was mixed with 44 µl of distilled water, 20 µl of 310 mM phosphate buffer (pH 7.5) and 10 µl each of 0.86 mM NADPH, 0.11 mM flavin adenine dinucleotide (FAD) and 10 µl Nitrate reductase (1 U/ml) in individual wells of a 96-well plate. The plate was thereafter incubated for 1 h at room temperature in the dark. 200 µl of Griess reagent [1:1 mixture of 1% sulfanilamide (1% solution with 5% orthophosphoric acid) and 0.1% N(1-naphthyl) ethylenediamine (NEDA) (1% solution with distilled water)] was added to each well and the plate was incubated for an additional 10 min at room temperature. Absorbance was measured at 540 nm using a microplate reader. The method of Lowry *et al*. (Lowry *et al*., 1959) was used to estimate total protein and concentration of total nitrate and nitrite (NOx) in liver homogenates was expressed as nM/ mg protein.

2.9. Histopathological examination

The livers collected from all the rats after completion of respective drug treatments

were subjected to histopathological examination. The microscopic examination was done by a pathologist using hematoxylin and eosin staining in a blinded fashion.

2.10. Statistical analysis

The results are expressed as mean ± standard error of the mean. Using Graph Pad Prism software the data was analyzed by one-way analysis of variance (ANOVA) followed by Tukey test used for analysis. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on body and organ weight in sub-chronic toxicity (90-day)

The mean body weight was recorded in all groups at 0 and 91st day and organ weight was recorded on 91st day after various drug treatments. The results showed no-significant change in body weight in all treatment groups of both *Dawā' al-Kurkum* (250 and 500 mg/kg) and 50% hydro-alcoholic extract of *Dawā' al-Kurkum* (500 and 1000mg/kg) and no-significant change in organ weight. No animals died during the study period in any of the treated as well as control group. The results are shown in Table 1 and 2.

Table 1: Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on body weight in sub-chronic toxicity study

Treatment	Initial body weight (g)	Final body weight (g)	% change in body weight
Control	186.0 ± 5.78	241.0 ± 7.96	22.82
DK 250	194.0 ± 7.31	236.0 ± 5.78	17.79
DK 500	192.0 ± 8.74	210.0 ± 22.97	8.57
HA 500	214.0 ± 12.19	257.0 ± 16.25	16.73
HA 1000	223.0 ± 17.29	267.0 ± 15.46	16.47

The values are expressed as mean ± SEM; DK-*Dawā' al-Kurkum*; Initial and final body weight was measured on 0 and 91st day of treatment.

Table 2: Effects of *Dawā' al-Kurkum* and hydro-alcoholic extract on organ weight in sub-chronic toxicity study

Treatment	Liver	Heart	Stomach	Lung	Spleen	Kidney	Ovaries/ Testes
Control	8.66 ± 0.81	1.137 ± 0.100	2.865 ± 0.081	1.908 ± 0.071	1.058 ± 0.047	1.732 ± 0.062	0.780 ± 0.018
DK250	8.16 ± 0.47	1.065 ± 0.082	2.775 ± 0.182	1.895 ± 0.064	1.057 ± 0.061	1.803 ± 0.055	0.735 ± 0.025
DK500	8.45 ± 1.09	1.128 ± 0.129	2.855 ± 0.139	1.870 ± 0.056	0.986 ± 0.057	1.760 ± 0.057	0.798 ± 0.016

Treatment	Liver	Heart	Stomach	Lung	Spleen	Kidney	Ovaries/ Testes
HA500	7.96 ± 0.83	1.118 ± 0.054	2.947 ± 0.138	1.928 ± 0.052	1.015 ± 0.049	1.815 ± 0.067	1.202 ± 0.047
HA1000	8.31 ± 0.67	1.155 ± 0.096	2.962 ± 0.083	1.855 ± 0.085	1.022 ± 0.067	1.752 ± 0.071	1.208 ± 0.064

All values are expressed as Mean ± SEM.

3.2. Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on liver function test (LFT) in sub-chronic toxicity (90-day)

In control group, vehicle was given for 90 days. In Group 2 and 3 treated with *Dawā' al-Kurkum* at doses 250 and 500 mg/kg respectively for 90 days, no-significant difference in parameters like SGOT, SGPT, ALP, total bilirubin, direct bilirubin and total protein was observed when compared with control group. Similarly, no-significant difference was observed in the levels of serum SGOT, SGPT, ALP, total bilirubin, direct bilirubin and total protein of group 4 and 5 treated with 50% hydro-alcoholic extract of *Dawā' al-Kurkum* (500 and 1000 mg/kg) when compared with control group. The results are shown in Table 3, 4.

Table 3: Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on SGOT, SGPT and ALP in sub-chronic toxicity

Treatment	SGOT(IU/L)	SGPT (IU/L)	ALP(IU/L)
Control	164.4 ± 11.31	49.06 ± 10.46	91.60 ± 17.13
Dk250	157.1 ± 4.42	52.54 ± 3.632	88.29 ± 9.45
Dk500	159.3 ± 11.17	51.77 ± 4.64	93.12 ± 7.56
HA500	155.8 ± 10.59	47.70 ± 3.19	95.41 ± 5.30
HA1000	165.0 ± 12.94	54.65 ± 3.94	96.64 ± 6.94

The values are expressed as mean ± SEM. The data were analyzed using one way ANOVA followed by Tukey test.

Table 4: Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on total bilirubin, direct bilirubin and total protein in sub-chronic toxicity

Treatment	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	Total protein (g/dl)
Control	0.73 ± 0.32	0.91 ± 0.09	5.70 ± 0.35
DK250	0.75 ± 0.07	0.87 ± 0.08	5.33 ± 0.24
DK500	0.71 ± 0.20	0.90 ± 0.24	5.77 ± 0.57
HA500	0.71 ± 0.18	0.84 ± 0.17	5.32 ± 0.36
HA1000	0.76 ± 0.19	0.88 ± 0.17	5.85 ± 0.39

The values are expressed as mean ± SEM. The data were analyzed using one way ANOVA followed by Tukey test.

3.4. Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on oxidative stress parameters in sub-chronic toxicity (90 day)

In control group, vehicle was given for 90 days. In Group 2 and 3 treated with *Dawā' al-Kurkum* at doses 250 and 500mg/kg respectively for 90 days, no-significant difference was observed when compared with control group like homogenate supernatant NOx, MDA and GSH. Similarly, in Group 4 and 5 treatment with 50% hydro-alcoholic extract of *Dawā' al-Kurkum* (500 and 1000mg/kg) no-significant difference was seen when compared with control group in the levels of NOx in homogenate supernatant, MDA and GSH. The results are shown in Table 5.

Table 5: Effects of *Dawā' al-Kurkum* and its hydro-alcoholic extract on oxidative stress parameters in sub chronic toxicity

Treatment	NOx (nmol/mg) protein	MDA (nmol/mg) protein	GSH (µmol/mg) protein
Control	0.188 ± 0.007	1.074 ± 0.070	1.883 ± 0.8084
DK250	0.175 ± 0.010	1.027 ± 0.057	1.915 ± 0.5314
DK500	0.176 ± 0.009	1.057 ± 0.121	1.915 ± 0.4258
HA500	0.181 ± 0.008	1.042 ± 0.086	1.927 ± 0.4539
HA1000	0.178 ± 0.011	1.052 ± 0.091	1.803 ± 0.6594

The values are expressed as mean ± SEM. The data were analyzed using one way ANOVA followed by Tukey test.

3.5. Histopathological examination

After a 90-day dosage period, all the animals (treatment and control) were sacrificed and gross pathological findings were assessed. When the animals in the medium and high dose groups were compared to their control counterparts, there were no significant histopathological changes (Figure 1–5).

1. Control

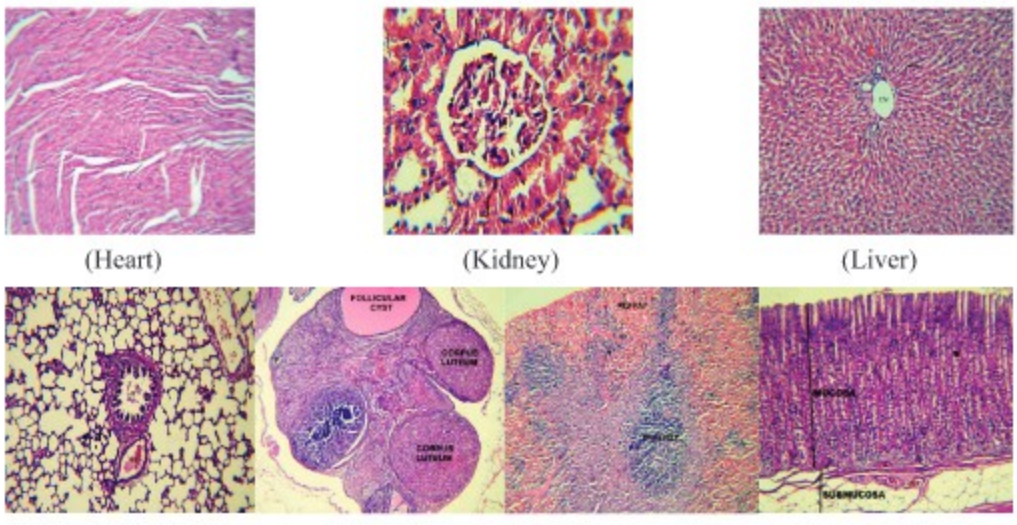
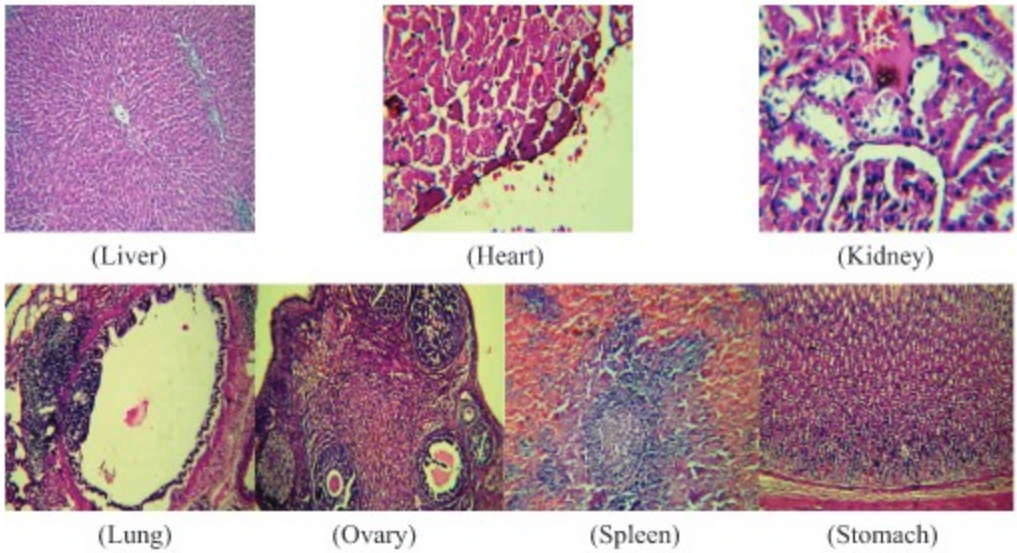


Fig. 1: Histopathological sections of major organs in 90-day repeated dose toxicity study

2. DK 250

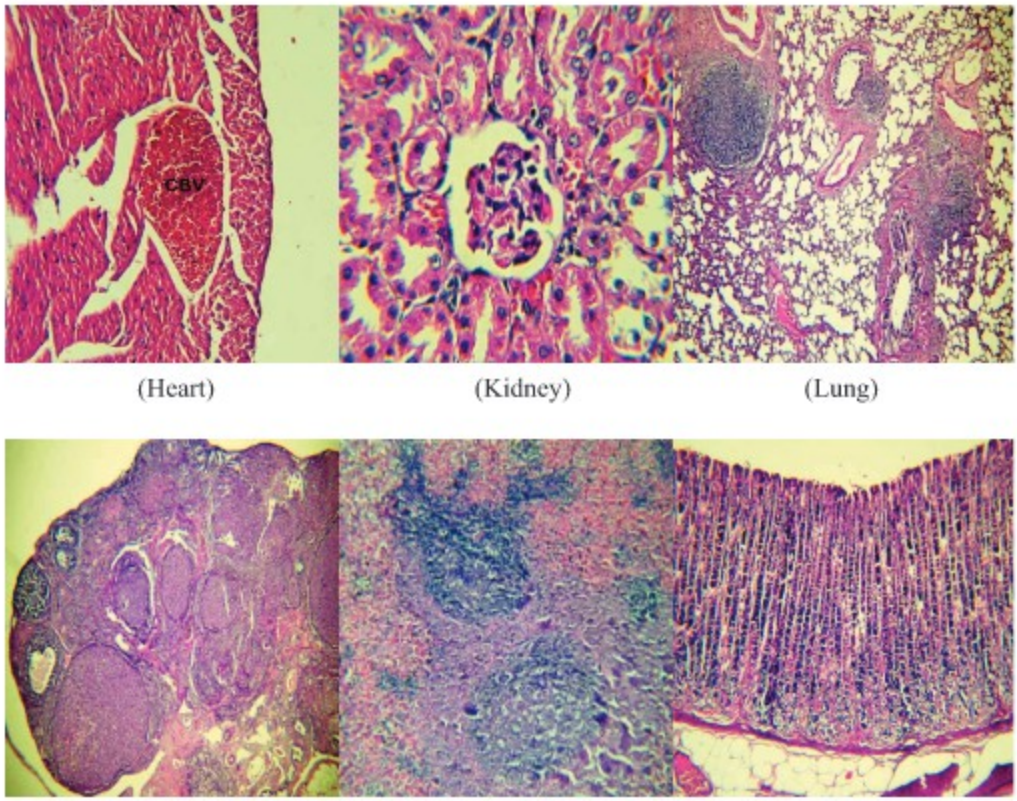


(Liver) (Heart) (Kidney)

(Lung) (Ovary) (Spleen) (Stomach)

Fig. 2: Histopathological sections of major organs in 90-day repeated dose toxicity study

3. DK 500



(Heart) (Kidney) (Lung)

(Ovary) (Spleen) (Stomach)

Fig. 3: Histopathological sections of major organs in 90-day repeated dose toxicity study

4. HA 500

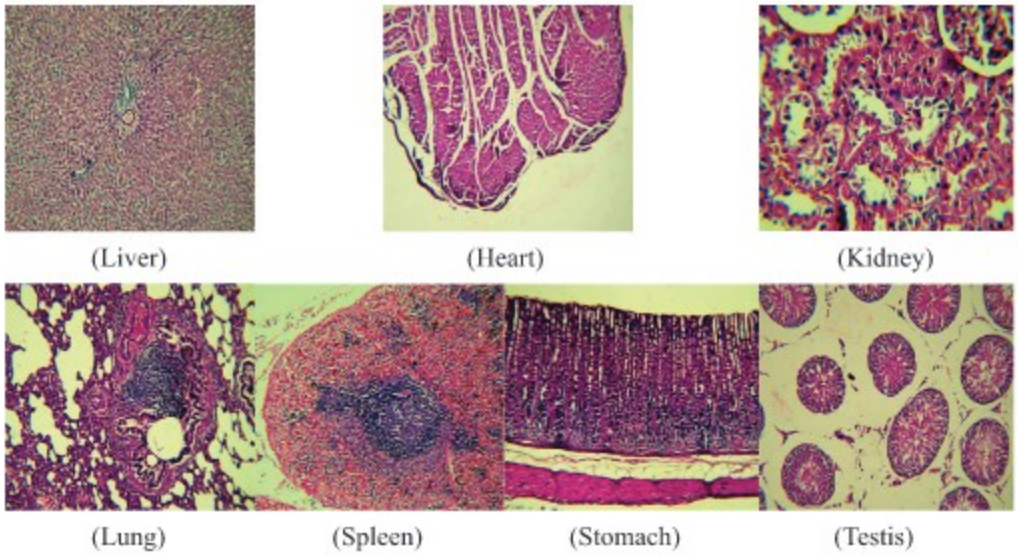


Fig. 4: Histopathological sections of major organs in 90-day repeated dose toxicity study

5. HA 1000

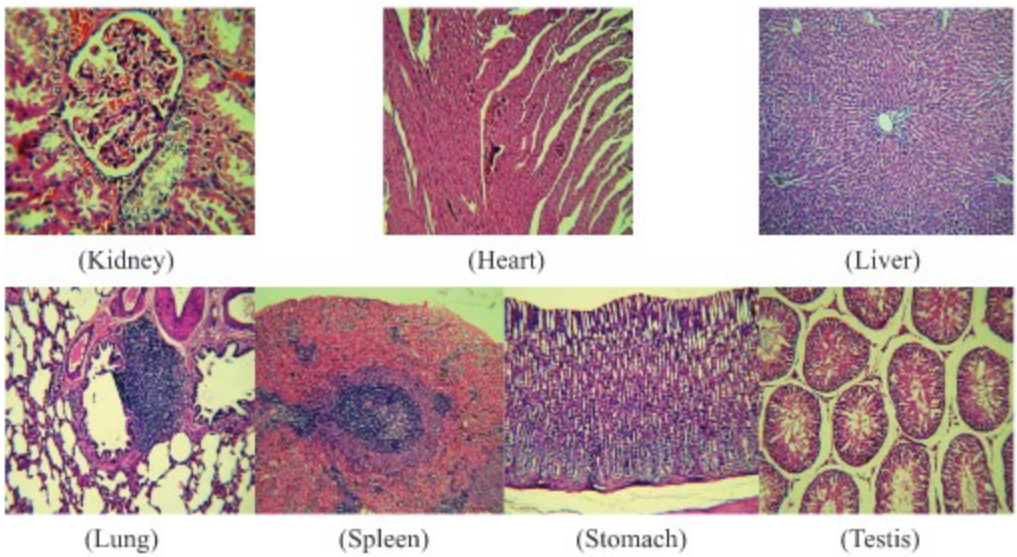


Fig 5: Histopathological sections of major organs in 90-day repeated dose toxicity study

4. Discussion

According to the WHO, about 70%–80% of the world population uses alternative medicines, largely from herbal sources, for basic health care (Hariharan *et al*., 2012) particularly in developing and/or developed countries where traditional or modern pharmaceuticals are widely used (Ogbonnia *et al*., 2008). Herbal products are commonly utilized in traditional medicine in India, such as Ayurveda and Unani, to improve the body's defenses without generating significant negative effects. The creation of novel plant-based Unani formulations continues to be scientifically, socially, and commercially important, and it appears to be gaining traction in health-related sectors.

The advantages and pharmacological activity of polyherbal Unani formulation are numerous. It has been employed in Unani Medicine. Toxicity studies in animals using this method may aid in the development of safe doses for humans. *Dawā' al-Kurkum* is a polyherbal formulation that outperforms all of these medications when it comes to treating liver disease (Reshi *et al*., 2021). In a sub-chronic toxicity investigation with *Dawā' al-Kurkum* and its hydroalcoholic extract in Wistar rats, there was no evidence of harm or mortality.

When compared to its corresponding control group of animals, the 90-day repeated dose toxicity study in rats further supports the lack of toxicity of the test sample, as repeated administration of *Dawā' al-Kurkum* and its extract to rats at a dosage level of 500 and 1000 mg/kg bw for 90 days did not induce any observable toxic effects. Biochemical and oxidative indicators were both within normal limits. All of the major organs' histopathology findings were also normal. When converting rat doses to human equivalent doses, 1000 mg/kg bw translates to approximately 11 g daily in humans (Antony *et al*., 2018).

Conclusion

According to the results of this study, *Dawā' al-Kurkum* and its extract show no deleterious or harmful effects in animal models when used at the levels recommended by the OECD. Based on repeated dose toxicity experiments in Wistar rats, it can be stated that *Dawā' al-Kurkum* and its extract are non-toxic at tested dose levels.

Acknowledgement

The research was supported by grants from the Central Council for Research in Unani Medicine (CCRUM), Ministry of Ayush, New Delhi, which is duly acknowledged. The authors are thankful to CRIUM, Hyderabad for providing standardized *Dawā' al-Kurkum* preparations.

Contribution of the authors

Mohd Rafi Reshi was involved in the conduct of experiments, acquisition and analysis of data and drafting of the manuscript. Kavita Gulati was involved in conceptualization, planning and designing of the study. She also helped in the analysis of data and critical review of the manuscript. Asim Ali Khan was involved in the critical reviewing of manuscript. Arunabha Ray was involved in planning of the study, interpretation of data and critical reviewing of manuscript. All authors approved the final version of the manuscript.

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प्रायोगिक चूहों में *दवा अल–कुरकुम* और इसके सत्त का उप–दीर्घकालिक विशाक्तता अध्ययन

मो. रफ़ी रेशी, कविता गुलाटी*, आसिम अली ख़ान, अरुणाभा रे

सारांश

उद्देश्यः वर्तमान अध्ययन का उद्देश्य *दवा अल–कुरकुम* और चूहों में इसके सत्त का उप–दीर्घकालिक (90–दिवसीय) विषाक्तता अध्ययन करना था।

कार्यविधिः चूहों में *दवा अल–कुरकुम* और इसके सत्त का उप–दीर्घकालिक विषाक्तता अध्ययन ओईसीडी दिशानिर्देश 408 के अनुसार चूहों को प्रतिदिन 250, 500 और 1000 मि.ग्रा./कि.ग्रा. शरीर भार पर सत्त देकर किया गया। 90 दिनों तक सत्त देने के बाद उपचारित चूहों के जैव रासायनिक और ऑक्सीडेटिव मापदंडों की तुलना नियंत्रण जीवों के साथ की गई। सभी प्रमुख अंगों का हिस्टोपैथोलॉजी अध्ययन भी किया गया।

परिणामः उप–दीर्घकालिक विषाक्तता अध्ययन में किसी भी जीव में कोई घातकता या विषाक्तता के नैदानिक लक्षण नहीं देखे गए। *दवा अल–कुरकुम* और इसके सत्त को अधिकतम खुराक स्तर शरीर भार पर 90 दिनों तक चूहों में दोहराने से इसके नियंत्रण जीवों की तुलना में कोई प्रत्यक्ष विषाक्त प्रभाव नहीं देखा गया। उपचारित चूहों की जैव रासायनिक और ऑक्सीडेटिव रूपरेखा नियंत्रण जीवों के समान थी और अंतर महत्वहीन थे। सभी नियंत्रण और उपचारित चूहों के प्रमुख अंगों की हिस्टोपैथोलॉजी सामान्य थी।

निष्कर्षः वर्तमान अध्ययन से पता चला कि चूहों में उप–दीर्घकालिक अध्ययनों के साक्ष्य के अनुसार मूल्यांकन की गई खुराक पर जीवों में *दवा अल–कुरकुम* और इसके सत्त का कोई विषाक्त प्रभाव नहीं है।

शब्दकुंजीः ओईसीडी 408, विषाक्तता, *दवा अल–कुरकुम*

Demographic study of dermatophytic infection among the patients attending Skin OPD at AKTC Hospital, AMU, Aligarh

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Abstract

Dermatophytosis is a group of superficial mycosis produced by dermatophytes, which belong to genera of Epidermophyton, Trichophyton and Microsporum. Cutaneous dermatophytic infection is limited to the superficial layer of the epidermis. Hot and humid climate is conducive for the organisms causing superficial dermatophytic infection. Its prevalence has increased during the recent past and resistant cases against antifungal drugs have also been often reported. However, varying data have been recorded from the pockets of geographical zones indicating that along with climatic conditions other factors also determine its spread. The present study was conducted to assess the prevalence of dermatophytic infection among the patients attending the Skin OPD of Ajmal Khan Tibbiya College (AKTC) Hospital, Aligarh Muslim University, Aligarh. An observational study was carried out on the patients who visited the Monday and Saturday OPD during February 15 to June 14, 2018. During this period a total of 4202 patients were screened for being affected with dermatophytic infection. The patients were registered on the basis of observation and clinical signs and symptoms and KOH examination. The prevalence of dermatophytic infection was found to be 21.94%. The prevalence of the infection in adult males was found to be more than adult females. The recurrence rate was found higher than the cure rate. It can be concluded that dermatophytic infection has a significant burden on society. The male and female patients were found to be 59.13% and 40.87%, respectively. The most common clinical pattern in the study was seen in respect of tinea corporis affecting 68.11% patients followed by tinea cruris affecting 48.70%. The grey patch (non-inflammatory type) was the most common type among tinea capitis patients followed by the kerion (inflammatory) variety affecting 3.04% patients. 2.60% of the patients were found infected with tinea unguium and 1.52% with tinea pedis showing the least prevalence. The patients infected with tinea manuum and tinea faciei were found to be 1.95% and 13.88%, respectively. The tinea versicolor was found in 2.06% of patients.

Keyword: Dermatophytic infection, KOH examination, Tinea, Skin disease

1. Introduction

Dermatophytic infection is caused by a group of closely related keratinophilic fungi (dermatophytes) in the genera of Trichophyton. Superficial mycosis is among the most frequent forms of human infections, affecting more than 20–25% of the world population (Havlickova *et al*., 2008). Dermatophytes are the keratinophilic fungi living on the dead keratin. They induce inflammation in the skin due to the permeation of their metabolite products into deeper layers and indurations of the delayed hypersensitivity. They are predominantly Microsporum and Epidermophyton. These groups of fungi invade stratum corneum of the skin or other keratinized tissues derived from the epidermis such as hair and nails. Dermatophytosis is one of the most common superficial fungal infections around the globe (Popoola *et al*., 2006; Ameen, 2010). Dermatophyte infections are seen in countries of the tropical region such as India due to the high level of humidity. They also have the propensity to affect specific population groups living in overcrowded environments, with poor personal hygiene (Peerapur *et al*., 2004). They are called ringworm infections by commoners due to characteristic ring-like appearance at the affected part of the body. However, scientifically it is known as 'Tinea infections', which can be further categorized based on the region of the body affected

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like Tinea capitis for dermatophytosis of the head, Tinea pedis for dermatophytosis of foot, etc. (Huda *et al*., 1995). Dermatophyte infections have been recorded all over the world but with variation in distribution, incidence, epidemiology, and target hosts from one location to another. Geographic location, climate (temperature, humidity, wind, etc.), overcrowding, health care awareness, immigration, environmental hygiene, culture, and socioeconomic conditions have been incriminated as major factors for the variation (Havlickova *et al*., 2008; Hay *et al*., 2003). The prevalence of dermatophytosis has significantly reduced in many developed nations of the world compared to the developing ones due to improved social, economic, health care, and hygiene practices in the former (Havlickova *et al*., 2008; Ilkit, 2010). Clinical feature of the dermatophytic infection results from a combination of keratin distribution and inflammatory host response. The wide variation in the clinical presentation depends upon the species and strain of the fungus, site of the infection and immune status. Variation in the pattern of prevalence and the presentation has been even observed in different small regions. It requires that regional and local data of its prevalence be collected in order to identify the percentage of population affected by this disease along with the type of causative organism and the pattern and presentation of the disease. In view of the above, the present demographic study was undertaken at the Skin OPD of Ajmal Khan Tibbiya College (AKTC) Hospital, Aligarh Muslim University, Aligarh to find the prevalence and related findings so that suitable remedial measures for the management of this disease could be adopted.

2. Materials and Methods

Sample collection

The study was carried out at the Skin OPD of Ajmal Khan Tibbiya College (AKTC) Hospital, Aligarh Muslim University, Aligarh. Data were collected from February 15 to June 14, 2018 from the OPDs held on Mondays and Saturdays. During this period, a total of 4202 patients were screened for being affected with dermatophytic infection.

Subjective parameters

Fungal infection is suspected when a lesion has central clearing, with erytheromatus papules tiny vesicles pustules, scaly, elevated borders of the affected area and pruritus. Nail infection is suspected when there is distal hyperkeratosis when chalky and dull yellow debris is found under the nail if it is separated from its bed, and the nail plate is brittle.

Objective parameters

The collected samples (skin, nail, and hair) were subjected to direct microscopy with KOH (potassium hydroxide) to identify the fungal infection (Lakshman *et al*., 2015). The prevalence of superficial fungal infection was 21.94% (922/4202). The infected patients were enrolled for the study and further analysis was performed on these patients.

Inclusion criteria

Diagnosed cases of tinea corporis, tinea cruris, tinea capitis, tinea unguium, tinea pedis, tinea manuum, tinea faciei, tinea versicolor with positive KOH smear.

Above mentioned cases not on concomitant therapy.

Other variables including age, sex, religion, region, and economic status of the patients, site of the dermatophytic infection, freshly infected cases, cure rate, recurrence rate and resistance rate were taken into account.

Exclusion criteria

(1) Patients having diabetes mellitus

(2) Patients on concomitant therapy

(3) Immuno-compromised patients

Sample size

Data were collected during February 15 to June 14, 2018 from the OPDs held on Mondays and Saturdays. During this period, a total of 4,202 patients who visited the Skin OPD were screened for being affected with the dermatophytic infection. Of them, 922 cases fulfilling the inclusion and exclusion criteria were taken up for further demographic study of dermatophytic infection.

Observation and Result

Of 4,202 patients who visited the Skin OPD, 922 patients were found affected with dermatophytosis indicating a prevalence rate of 21.95% (Fig. 1).

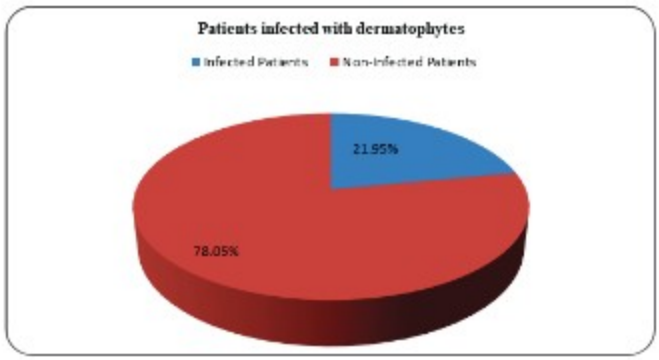

Fig. 1

Among the patients afflicted with dermatophytosis, 545 (59.13%) and 377 (40.87%) were male and female, respectively, indicating a ratio of 1:0.69 (Table 1).

Table 1: Distribution of patients according to sex

S. No.	Sex	No.	%
1	Male	545	59.13
2	Female	377	40.87
Male : Female		1:0.69	

The patients were divided into 5 age groups (1=11–20; 2=20–30; 3=30–40; 4=40–50; and 5=50–60 years). It was found that the maximum number of patients, that is 317 (34.38%), belonged to the age group of 20–30 years, followed by 273 (29.60%) patients of 30–40 of age, 139 (15.07%) belonging to 11–20 years, 123 (13.34%) to 40–50 and the least, that is 70 (7.59%), to 50-60 years of age (Table 2).

Table 2: Distribution of patients according to age

S. No.	Age group	No.	%
1	11–20	139	15.07
2	20–30	317	34.38
3	30–40	273	29.60
4	40–50	123	13.34
5	50–60	70	7.59

The most common clinical pattern in the study was seen in respect of tinea corporis affecting 628 (68.11%) patients followed by tinea cruris affecting 449 (48.70%) patients. The grey patch (non-inflammatory type) was the most common type among tinea capitis patients followed by the kerion (inflammatory) variety affecting 28 (3.04%) patients. A total of 24 (2.60%) patients were found infected with tinea unguium and 14 (1.52%) were found to be tinea pedis showing the least prevalence. The patients infected with tinea manuum and tinea faciei were found to be 18 (1.95%) and 128 (13.88%), respectively. Tinea versicolor was found in 19 (2.06%) patients (Table 3).

Table 3: Site involvement of dermatophyte infection

S. No.	Site	Frequency 922	Percentage
1	Tinea corporis	628	68.11%
2	Tinea cruris	449	48.70%
3	Tinea capitis	28	3.04%
4	Tinea unguium	24	2.60%
5	Tinea pedis	14	1.52%
6	Tinea manuum	18	1.95%
7	Tinea faceie	128	13.88%
8	Tinea versicolor	19	2.06%

A total number of 282 cases were registered as freshly infected, which amounted to 30.58%. The recurrence of the infection was found in 242 (26.25%) cases, while resistance was observed in 214 (23.21%) patients. The cure rate in the patients of dermatophytic infection was 19.95% as only 184 patients reported complete recovery (Table 4, Fig. 2).

Table 4: Distribution of patients according to resistance and recurrence of infection

S. No.	Type of infection	No. of patients	%
1	Freshly infected patients	282	30.58%
2	Recurrence cases	242	26.25%
3	Resistance cases	214	23.21%
4	Cured patients	184	19.95%

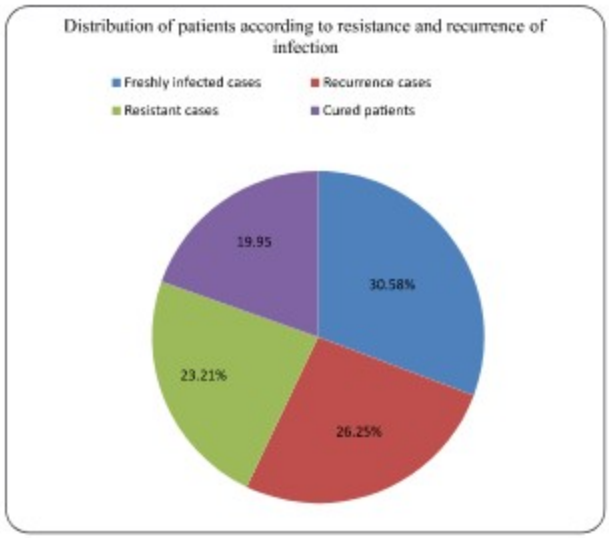

Fig. 2

The disease was found more prevalent in the urban population as compared to the rural population as 508 (55.10%) patients belonged to urban area in comparison to 414 (44.90%) patients from rural area (Table 5).

Table 5: Distribution of patients according to residence

S. No.	Residence	No.	%
1	Urban	508	55.10
2	Rural	414	44.90

In terms of religion, 519 (56.32%) patients were found belonging to the Muslim community whereas 403 (43.68%) patients to the Hindu community (Table 6).

Table 6: Distribution of patients according to religion

S. No.	Religion	No.	%
1	Muslim	519	56.38
2	Hindu	403	43.68

According to Kuppuswamy's socioeconomic scale (Kumar *et al*., 2007), the patients were divided into 5 groups. It was observed that 291 (31.56%) patients belonged to upper lower class, 283 (30.69%) to lower and 197 (21.37%) to lower middle classes. The share of upper middle and upper classes was 113 (12.25%) and 38 (4.12%), respectively (Table 7).

Table 7: Distribution of patients according to socio-economic status

S. No.	Socioeconomic Status	No.	%
1	Upper (I)	38	4.12
2	Upper Middle (II)	113	12.25
3	Lower Middle (III)	197	21.37
4	Upper Lower (IV)	291	31.56
5	Lower (V)	283	30.69

Discussion

Dermatophytic infections are more prevalent in the developing world where it is increasing day by day. The pattern of its prevalence has been reported to be varying and different sections of the population show difference in prevalence rate, pattern, and presentation of disease and causative factors, etc. Therefore, it assumes importance that the demographic studies should be conducted on a relatively smaller population because the management strategies for different locations may be different. Studies on dermatophyte infection in Aligarh district are very limited; therefore we have to rely upon disease patterns of the country.

The present study attempted to determine dermatophyte infection in patients attending the Skin OPD of Ajmal Khan Tibbiya College (AKTC) Hospital, Aligarh Muslim University, Aligarh. Patients suspected to be suffering from dermatophytosis were sent to the laboratory of the Department of Dermatology, AKTC Hospital for a confirmatory test. The dermatophytes were detected in 75 samples by KOH wet mount and most of the samples were found culture positive for dermatophytes. A prevalence rate of KOH proven dermatophytes infection ranging from 53.1% to 100% and a prevalence rate of culture proven dermatophyte infection ranging from 52.2% to 67.1% has been reported by Kannan *et al*. (2006) and Ellabib & Khalifa (2001). The disparity in the prevalence rates of dermatophytosis in different studies could result from differences in the lifestyle, socioeconomic conditions, risk factors associated with study subjects, and environmental factors of the study area (Havlickova *et al*., 2008; Ameen, 2010). The present study showed that more males were affected by dermatophytes than females, with a male-female ratio being 1:0.69. Some studies had indicated a higher prevalence of dermatophytes in females compared to males (Balakumar *et al*., 2012; Rassai *et al*., 2011; Maraki *et al*., 2007; Devliotou-Panagiotidou *et al*., 1995). Meanwhile, few other studies recorded a higher prevalence of dermatophytes in males than females (Adefemi *et al*., 2011; Vena *et al*., 2012). The predominant clinical manifestations of dermatophytosis vary considerably in different studies reported in the literature. In a study conducted in India, tinea corporis (35.4%) was the predominant clinical condition followed by tinea cruris (16.8%) and tinea capitis (16.7%) (Balakumar *et al*., 2012). Almost similar findings have been reported in a study conducted in Iran between March 2005 and March 2007 by Rassai *et al*. indicating that tinea cruris and tinea corporis were the most common clinical manifestation. A 7-year (1997-2003) survey of dermatophytosis in Crete, Greece, conducted by Maraki *et al*. revealed that tinea unguium was the predominant clinical manifestation. A study carried out by Devliotou-Panagiotidou *et al*. between 1981 and 1990 in Greece depicted that tinea pedis was the most frequent clinical feature. Adefemi *et al*. reported tinea capitis as a predominant clinical manifestation. In our study, tinea corporis was the dominant clinical manifestation involving 68.11% of the total cases of dermatophytosis, similar to many other reports. Tinea cruris was the second clinical manifestation accounting for 48.70% of the cases. The finding conforms to other reports (Vena *et al*., 2012). Tinea faciei was found to be the third common clinical presentation in our study accounting for 13.88% share; however, it has been reported as a dominant clinical manifestation in a few earlier studies. The persons of all age groups were found susceptible to dermatophytosis but it appeared to be more common in adults of the age group of 25–44 and 45–64 years. As reported by most of the workers, tinea capitis is an infection of childhood. In the present study, a total of 28 (3.04%) patients were found to be afflicted with tinea capitis, and most of the patients were in the age group of 1–14 years. Almost

similar results were reported by earlier researchers (Atapattu, 1989; Sheikh *et al*., 2009). The changing pattern of hormones after puberty (Oliveira *et al*., 2006) and the production of inadequate amounts of inhibitory fatty acids before puberty (David *et al*., 2003) are responsible for a decrease of tinea capitis with age. On the other hand, tinea unguium was more frequent in the elderly population in the age group of 25 to 64 years (Lange *et al*., 2004; Caputo *et al*., 2001). Reduced growth rate of the ungual plate, an increase in trauma rates, poor peripheral circulation, and inability to maintain good foot care could be attributed to this (Kaur *et al*., 2008). On the other hand, tinea pedis was a dominant clinical manifestation in the age group 45–64 years which is in agreement with the findings of Lange *et al*. and Caputo *et al*. In the present study as opposed to previous studies in East Africa, the heterogeneity in the distribution of dermatophytosis, the etiologic agents, and the predominating clinical manifestation patterns in different parts of the world have been attributed to factors of geographic location, climate, overcrowding, general health care, immigration, environmental hygiene, and socioeconomic conditions (Havlickova *et al*., 2008; & Hay *et al*., 2003).

5. Conclusion

This study has revealed that the prevalence of microscopic and culture infections in the study subjects is high. Tinea corporis is the dominant clinical manifestation involving 68.11% of the total cases of dermatophytosis followed by tinea cruris 48.70%. The fresh cases of dermatophytes infections accounted to 282 (30.58%) and recurrence of infection is found in 242 (26.25%) of the patients, whereas the incidence of resistance against antifungal antibiotics is found in 23.21% patients and 19.95% of the patients is cured.

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एकेटीसी अस्पताल, अलीगढ़ मुस्लिम विश्वविद्यालय, अलीगढ़ के त्वचा बाह्य रोगी विभाग में रोगियों में डर्मेटोफाइटिक संक्रमण का जनसांख्यिकीय अध्ययन

सऊद अहमद*, गुफ़रान अहमद, मो. मोहसिन

सारांश

डर्मेटोफाइटोसिस, डर्मेटोफाइट्स द्वारा उत्पन्न सतही माइकोसिस का एक समूह है जो एपिडर्मोफाइटन, ट्राइकोफाइटन और माइक्रोस्पोरम के जेनेरा से संबंधित है। त्वचीय डॉटोफाइट्स संक्रमण बाह्य त्वचा की सतही परत तक सीमित होता है। गर्म और आर्द्र जलवायु सतही डर्मेटोफाइटिक संक्रमण फैलाने वाले जीवों के लिए सहायक होती है। हाल के दिनों में इसका प्रसार बढ़ा है और फगंसरोधी औषधियों के विरूद्ध प्रतिरोध भी सामने आए हैं। हालांकि विभिन्न भौगोलिक क्षेत्रों से अलग–अलग आकड़ें दर्ज किए गए हैं जो यह दर्शाते हैं कि इसको फैलाने में जलवायु परिस्थितियों के साथ–साथ अन्य कारक भी शामिल हैं। वर्तमान अध्ययन अजमल खान तिब्बिया कॉलेज (एकेटीसी) अस्पताल, अलीगढ़ मुस्लिम विश्वविद्यालय, अलीगढ़ के त्वचा बाह्य रोगी विभाग (ओपीडी) के रोगियों में डर्मेटोफाइटिक संक्रमण की व्यापकता का आकलन करने के लिए किया गया। 15 फरवरी से 14 जून 2018 के दौरान सोमवार और शनिवार की ओपीडी में आए रोगियों पर एक अवलोकन अध्ययन किया गया। इस अवधि में डर्मेटोफाइटिक संक्रमण का पता लगाने के लिए कुल 4202 रोगियों की जांच की गई। रोगियों को अवलोकन और संकेतों एवं लक्षणों तथा केओएच परीक्षण के आधार पर पंजीकृत किया गया। डर्मेटोफाइटिक संक्रमण की व्यापकता 21.94% थी। युवा महिलाओं की तुलना में युवा पुरूषों में संक्रमण की व्यापकता अधिक पाई गई। पुनरावृत्ति दर उपचार दर से अधिक पाई गई। यह निष्कर्ष निकाला जा सकता है कि डर्मेटोफाइटिक संक्रमण समाज पर एक बड़ा भार है। इस संक्रमण से ग्रसित पुरूष और महिला रोगी क्रमशः 59.13% और 40.87% थे। अध्ययन में सबसे सामान्य नैदानिक स्वरूप टिनिया कॉर्पोरिस के संबंध में देखा गया जिससे 68.11% रोगी प्रभावित थे और इसके बाद टिनिया क्रूरिस व्यापक था जिससे 48.70% रोगी प्रभावित थे। टिनिया कैपिटिस रोगियों में ग्रे पैच (नॉन–इन्फ्लामेटरी) और केरियन (इन्फ्लामेटरी) प्रकार सबसे अधिक था जिससे 3.04% रोगी प्रभावित थे। टिनिया यूनगियम से 2.60%, रोगी प्रभावित थे और सबसे कम रोगी (1.52%) टिनिया पेडिस से प्रभावित थे। टिनिया मैन्यूम और टिनिया फेसीई से क्रमशः 1.95% और 13. 88% रोगी ग्रसित थे। टिनिया वर्सिकलर 2.6% रोगियों में था।

शब्दकुंजीः डर्मेटोफाइटिक संक्रमण, केओएच परीक्षण, टिनिया, त्वचा रोग

Assessing safety and efficacy of Unani pharmacopoeial formulation *Jawārish ʿŪd Shīrīn* in *Ḍuʿf al-Ishtihāʾ* (anorexia)

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Abstract

Introduction: *Ḍuʿf al-Ishtihāʾ* is a Unani terminology used for the very common gastric symptom 'anorexia' wherein the appetite of a person is reduced or lost. It leads to weight loss, nutritional deficits, and poor healthcare outcomes. The study was a clinical trial conducted on the patients of *Ḍuʿf al-Ishtihāʾ* (anorexia).

Objective: To assess the safety and efficacy of Unani pharmacopoeial formulation *Jawārish ʿŪd Shīrīn in managing Ḍuʿf al-Ishtihāʾ* (anorexia)

Design: An open label clinical study was carried out on 75 patients for 2 weeks.

Results: Out of 75 cases, 55 patients (73.33%) got partially relieved while 17 patients (22.67%) got completely relieved. The variation in hematological and biochemical parameters was found within normal limits and no adverse effect was observed in the patients.

Conclusion: *Jawārish ʿŪd Shīrīn* is safe and effective in managing *Ḍuʿf al-Ishtihāʾ* (anorexia) and may be used as the first line of drug in the management of anorexia.

Keywords: Unani Medicine, *Ḍuʿf al-Ishtihāʾ*, Anorexia, *Jawārish*, Appetite

Introduction

Anorexia is a condition described in Unani classical literature as *Nuqṣān al-Ishtihāʾ*/ *Buṭlān al-Ishtihāʾ*. *Ishtihāʾ* is an Arabic word meaning appetite. *Nuqṣān* means decrease and *Buṭlān* means complete loss. It is a condition wherein the desire for appetite is decreased or lost (Kabiruddin, 1916). *Ḍuʿf al-Ishtihāʾ* is another word for this condition where *Ḍuʿf* means weakness and *Ishtihāʾ* means appetite (Khawaja, 2010). Anorexia simply manifests as a decrease or loss of appetite. This can present as not feeling hungry or lacking the desire to eat. Sometimes, people do not even notice they lack an appetite until they begin to lose weight from eating less (Ausiello & Edward, 1992; Glynn & Drake, 2012).

Ḍuʿf al-Ishtihāʾ is caused by *Sūʾ-i-Mizāj* (impaired temperament), accumulation of *Ṣafrāʾ*, *Balgham Māliḥ* (saline phlegm), *Balgham Lazij* (viscid phlegm), *Balgham Muntin* (mephitic phlegm), *Khām Akhlāṭ* (raw humours), *Duʿf al-Miʿda* (weakness of stomach), *Duʿf al-Kabid* (hepatic insufficiency) and *Sudad al-Kabid* (obstruction of liver). Accretion of viscous humours in the cardiac end of the stomach decreases contractile power and thus impaired *Quwwat Dāfiʿa* builds up morbid substances within the stomach. Similarly, inflammation of the liver causes heaviness and decreases the appetite (Kabiruddin, 2005).

Anorexia is associated with belching, burning sensation in epigastrium, excessive thirst, excessive salivation and halitosis. Patient with *Ḍuʿf al-Ishtihāʾ* lacks the urge to eat and daily intake of food decreases extremely. A temporary loss in the appetite is an opportunity to have a look at the eating habits and personal health while long continuous stretches of decreased appetite may be a matter of serious health concern (Kabiruddin, 1938; Khawaja, 2010; Das & Roy, 2017).

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Appetite and metabolism are regulated by an intricate network of neural and hormonal factors. The hypothalamic feeding and satiety centers play a central role in these processes. Neuropeptides such as corticotrophin-releasing hormone (CRH), α-melanocytes stimulating hormones (α-MSH), and cocaine and amphetamine-related transcript (CART) induce anorexia by acting centrally on satiety centers. The gastrointestinal peptides like ghrelin, glucagon, somatostatin and cholecystokinin signal satiety and thus decrease food intake. Hypoglycemia suppresses insulin, reducing glucose utilization and inhibiting the satiety center (Larry *et al*., 2005; Penman *et al*., 2006; Tierney, 2007).

The first step to manage anorexia is to assess the duration whether it is of acute onset or chronic. Acute onset anorexia is mainly associated with infections, oral disorders, major surgery, etc. Chronic underlying medical disorders, medications, psychiatric disorders are associated with prolonged anorexia (Das & Roy, 2017). There are many drugs (single and compound) mentioned in Unani classical literature that increase appetite. Most of them are commonly used in our day to day life like *Āmla* (*Emblica officinalis*), *Adrak* (*Zingiber officinale*), *Ilāʾichī* (*Elettaria cardamomum*), *Ajwāyin* (*Tachyspermum ammi*) (Kabiruddin, 2005; Khawaja, 2010). Many *Jawārishāt* have been extensively used by Hakims since ages in gastrointestinal disorders. The present study was carried out to evaluate the safety and efficacy of *Jawārish ʿŪd Shīrīn* in the management of *Ḍuʿf al-Ishtihāʾ* scientifically.

Material and Methods

The present open label clinical study was carried out at the Clinical Research Unit (CRU), Cantonment General Hospital, Begum Bridge (Soti Ganj), Meerut, Uttar Pradesh after obtaining approval from its Institutional Ethical Committee. *Jawārish ʿŪd Shīrīn* was prepared at the Central Research Institute of Unani Medicine, Hyderabad as per the formulation of the drug mentioned in National Formulary of Unani Medicine (NFUM). The test drug was given 5 g twice daily before meals with water. Patients of either sex in the age group of 18-65 years with SNAQ ≤14 were recruited from the general outpatient department of the CRU, Meerut while patients having anorexia nervosa, patients with disorders requiring long term treatment, known cases of hepatic, renal or cardiac ailments, patients with a history of addiction (alcohol, drugs) and pregnant and lactating women were excluded from the study.

The patients were assessed clinically on baseline, day 7 and day 14 of the treatment and efficacy of the test drug was evaluated on the basis of improvement in appetite for which the Simplified Nutritional Appetite Questionnaire (SNAQ) was inquired. All the patients were asked to complete the SNAQ, which is a 4-item single-domain questionnaire. Responses are scored by using a 5-point (A to E), verbally labeled, Likert-type scale.

The safety of the drug was assessed at the baseline and at the end of the study on the basis of the laboratory investigations like CBC (Hb%, TLC, DLC, ESR), LFT (S. Bilirubin, SGOT, SGPT, S. Alkaline Phosphatase), KFT, (Blood Urea, S. Creatinine, Uric Acid), stool for routine and microscopic examination and urine for routine and microscopic examination. Additionally, clinical safety of the drug was also assessed on the basis of adverse events as reported by the patients or observed clinically at follow-ups.

The clinical subjective parameters, hematological and biochemical parameters were statistically analyzed by using Student's t-test. The results were expressed as the mean ± SEM. $P<0.05$ was considered as statistically significant and $P<0.001$ was considered as statistically highly significant.

Results and Discussion

The present open label clinical study was carried out at the Clinical Research Unit (Unani), Meerut. The clinical trial was conducted to evaluate the efficacy of the formulation *Jawārish 'Ūd Shīrīn* in the patients of *Ḍu'f al-Ishtihā'* attending the general outpatient department. Out of 77 registered cases, two cases dropped out of the study, while remaining 75 selected cases of anorexia were treated with *Jawārish 'Ūd Shīrīn* in doses of 5 g (twice daily orally) before meal for 2 weeks.

Demographic interpretation

Age group

The patients were divided into five age groups, i.e. 18–27, 28–37, 38–47, 48–57 and 58–65 years and highest incidence of *Ḍu'f al-Ishtihā'* i.e. 50.65% was observed in the age group of 18–27 years followed by 29.9% in 28–37 years while rest 19.48% were observed in the persons of more than 38 years of age as depicted in Table 1 an Figure 1. As per the literature of Unani Medicine, appetite is greater in *Sinn-i-Numū'* and *Sinn-i-Shabāb* and decreases with age but the present study report is not going hand in hand with the literature, which can be attributed to the fact that stress and anxiety are more common in this age group and thus result in anorexia.

Table 1: *Ḍu'f al-Ishtihā'* cases according to age group

Age Group	Sex		Total	Percentage%
	Male	Female		
18–27 year	24	15	39	50.65%
28–37 year	11	12	23	29.9%
38–47 year	4	5	9	11.69%
48–57 year	4	0	4	5.19%
58–65year	2	0	2	2.60%
Total	**45**	**32**	**77**	**100%**

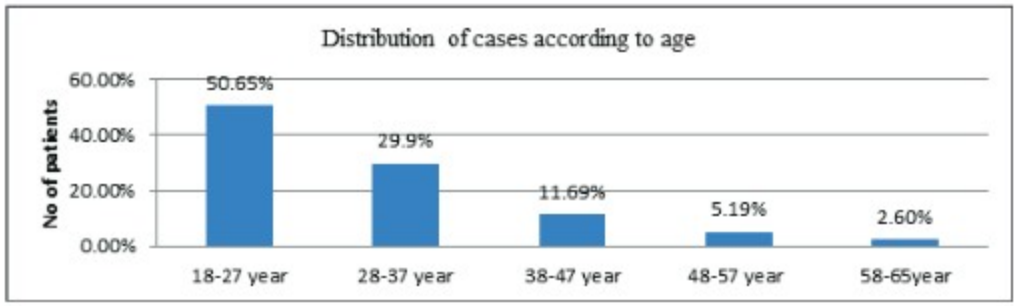


Figure 1: *Ḍu'f al-Ishtihā'* cases according to age group

Socio-economic status

As per the Kuppuswamy scale, maximum number of patients in the study i.e. 54.55% belonged to lower income group while rest 45.45% patients were from middle income group as shown in Table 2 and Figure 2.

Table 2: *Ḍu'f al-Ishtihā' cases* according to social status

Income Group	Sex		Total	Percentage%
	Male	Female		
Lower	22	20	42	54.55%
Middle	23	12	35	45.45%
Higher	0	0	0	0.00%
Total	**45**	**32**	**77**	**100%**

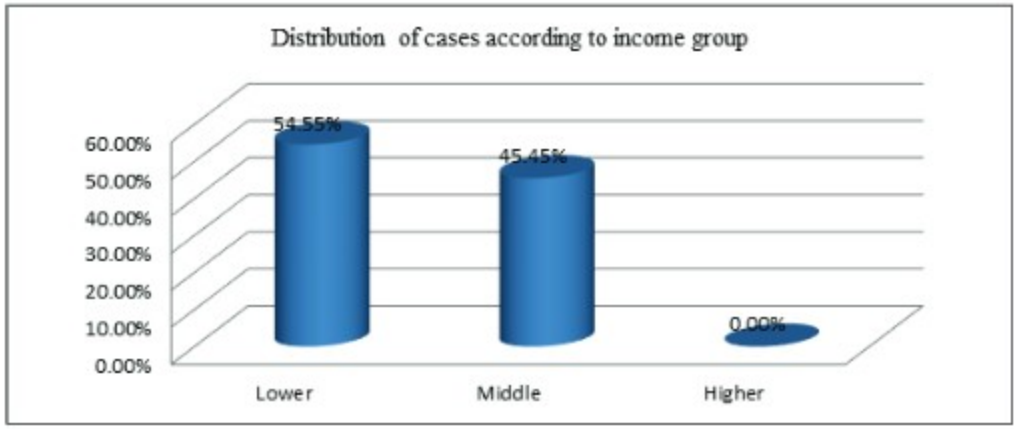


Figure 2: *Ḍu'f al-Ishtihā'* cases according to social status

Mizāj of patients

Out of 77 patients, 48 (62.34%) had *Ṣafrāwī Mizāj*, 22 (28.57%) had *Balghamī Mizāj*, 5 (6.49%) had *Damwī* and 2 (2.6%) has *Sawdāwī Mizāj*. Loss of appetite is a symptom of Ghalba'-i-Balgham but the study reflects that patients with *Ṣafrāwī Mizāj* are more prone to develop it as shown in Table 3 and Figure 3.

Table 3: *Ḍu'f al-Ishtihā'* cases according to *Mizāj*

Temperament	Sex		Total	Percentage%
	Male	Female		
Damwī (Sanguine)	4	1	5	6.49%
Balghamī (Phlegmatic)	8	14	22	28.57%
Ṣafrāwī (Bilious)	31	17	48	62.34%
Sawdāwī (Melancholic)	2	0	2	2.60%
Total	**45**	**32**	**77**	**100%**

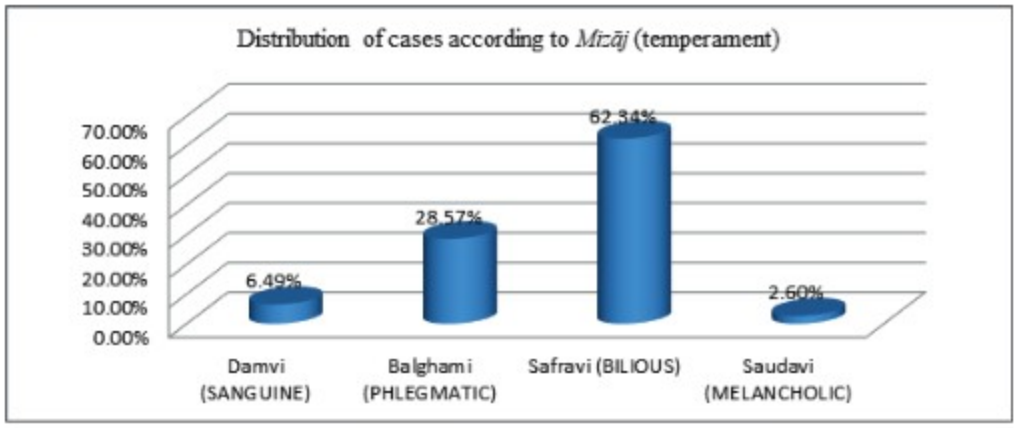


Figure 3: *Ḍu'f al-Ishtihā'* cases according to Mizāj

Duration of disease

Duration of the disease was divided into three categories, i.e. acute, sub-acute and chronic. Out of 77 patients, 47 (61.04%) had chronic history of anorexia, 22 (28.57%) were sub-acute while only 8 (10.39%) were acute cases. As per the fact, acute onset anorexia is mainly associated with infections, oral disorders, major surgery, etc. Chronic underlying medical disorders, medications, psychiatric disorders are associated with prolonged anorexia. Psychiatric conditions like stress, anxiety and depression are more common in 18–37 years of age group that decrease appetite and may be a cause of their prolonged anorexia as shown in Table 4 and Figure 4.

Table 4: *Ḍu'f al-Ishtihā'* cases according to chronicity

Duration of disease	Sex		Total	Percentage%
	Male	Female		
0–3 Months	05	03	08	10.39%
4–6 Months	11	11	22	28.57%
>6 Months	29	18	47	61.04%
Total	**45**	**32**	**77**	**100%**

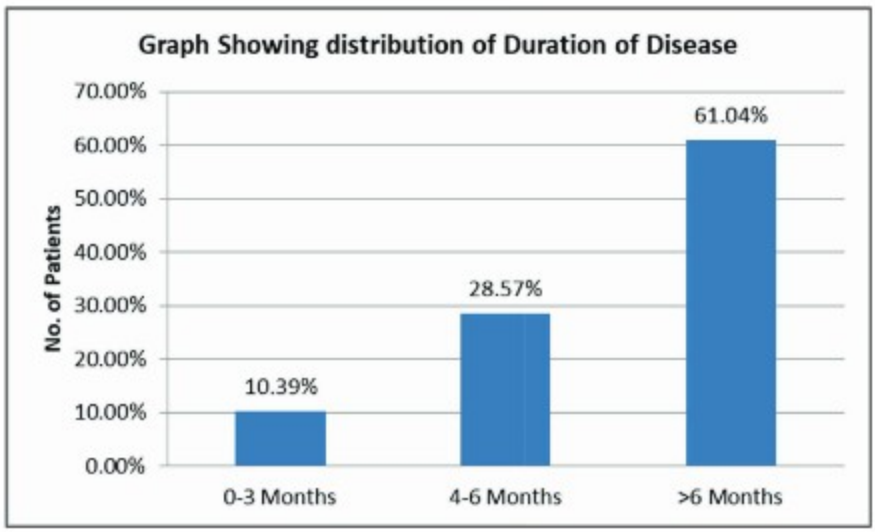


Figure 4: *Ḍu'f al-Ishtihā'* cases according to chronicity

Safety evaluation

For evaluation of safety of the test drug, all the patients were assessed on hematological and biochemical parameters on base line and day 14 of treatment.

Hematological and biochemical parameters

All hematological and biochemical parameters remained normal throughout the treatment duration and the test drug didn't cause any alteration in the safety parameters and it was thus concluded that the drug is safe. While evaluating statistically, p-value was not significant in the parameters evaluated under hemogram (hemoglobin, TLC, DLC and ESR), kidney and liver function as shown in Table 5–6 and Figure 5–6.

Table 5: Variation in hematological parameters of *Ḍu'f al-Ishtihā'* patients

Laboratory tests		Mean ± S.E.M	Percentage(%) increase (↑) or decrease (↓)	t-value	p-value
Hemoglobin (gm/dl)	BT	13.19±0.19	1.27↑	1.06	0.29
	AT	13.36±0.19			
ESR(mm/hr)	BT	13.88±1.95	25.61↓	1.52	0.13
	AT	11.05±0.96			
Total leukocyte count (1000/ cu.mm)	BT	7708.00±205.87	0.53↑	0.20	0.84
	AT	7749.33±177.42			
Polymorphs (%)	BT	65.61±0.82	0.18↑	0.14	0.89
	AT	65.73±0.64			
Lymphocytes (%)	BT	30.89±0.83	1.12↑	0.40	0.69
	AT	31.24±0.61			
Eosinophils (%)	BT	3.27±0.22	7.56↑	0.96	0.34
	AT	3.04±0.17			

BT = Before treatment; AT = After treatment

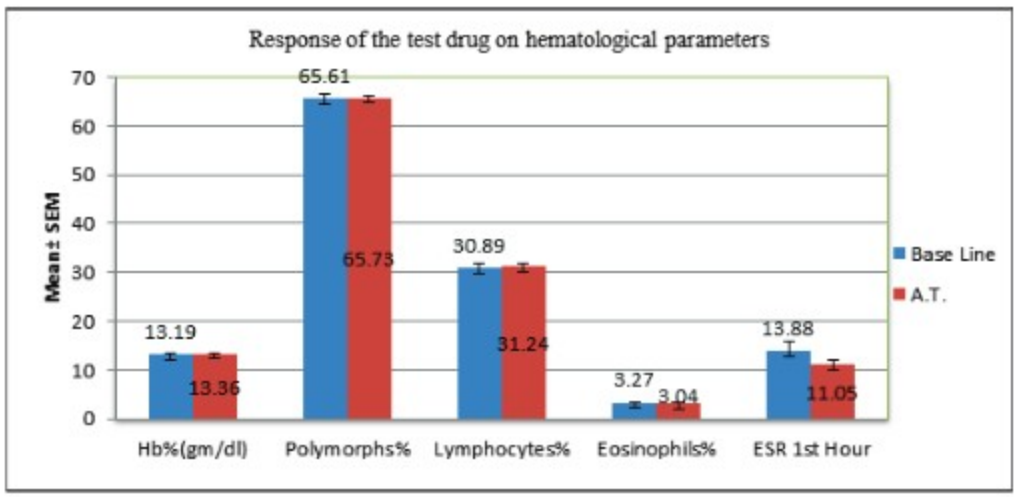


Figure 5: Variation in hematological parameters of *Ḍu'f al-Ishtihā'* patients

Table 6: Variation in biochemical parameters of *Ḍuʿf al-Ishtihāʾ* patients

Laboratory tests		Mean ± S.E.M	Percentage(%) increase(↑) or decrease(↓)	t- value	p-value
Serum bilirubin (mg/dl) total	BT	0.86±0.02	9.74↑	0.82	0.41
	AT	0.95±0.11			
SGOT(U/L)	BT	26.86±1.05	14.41↓	2.71	0.01
	AT	23.48±0.76			
SGPT(U/L)	BT	32.70±1.80	19.43↓	2.73	0.01
	AT	27.38±1.09			
Alkaline phosphatase(U/L)	BT	100.55±4.12	3.39↑	0.97	0.34
	AT	104.09±4.48			
Serum creatinine (mg/dl)	BT	0.81±0.01	1.93↑	0.86	0.40
	AT	0.83±0.13			
Blood urea(mg/dl)	BT	25.80±0.66	3.82↓	1.35	0.18
	AT	24.86±0.57			
Serum uric acid	BT	4.95±0.11	3.32↓	1.14	0.26
	AT	4.79±0.11			

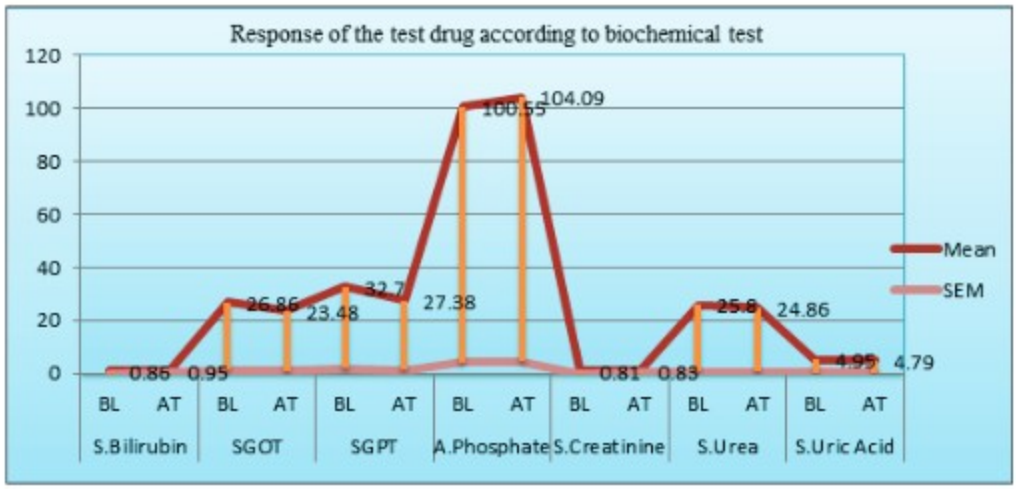


Figure 6: Variation in biochemical parameters of *Ḍuʿf al-Ishtihāʾ* patients

Efficacy evaluation

Clinical parameter - Simplified Nutritional Appetite Questionnaire (SNAQ)

The SNAQ is composed of four items (questions), grouped in a single domain

1. My appetite is…….

Out of 75 patients, 55 (73.34%) patients had complaint of very poor appetite, 19 (25.33%) had poor appetite and 1 had average appetite before starting the treatment. After the treatment, 60 (80%) patients had very good appetite and only 3 (4%) patients had poor appetite as shown in Table 7 and Figure 7.

Table 7: SNAQ question 1 evaluation

SNAQ Score 1	Baseline	%	Day 14	%
Very poor	55	73.34%	1	1.33%
Poor	19	25.33%	2	2.67%
Average	1	1.33%	12	16%
Good	0	0	53	70.67%
Very good	0	0	7	9.33%
Total	**75**	**100%**	**75**	**100%**

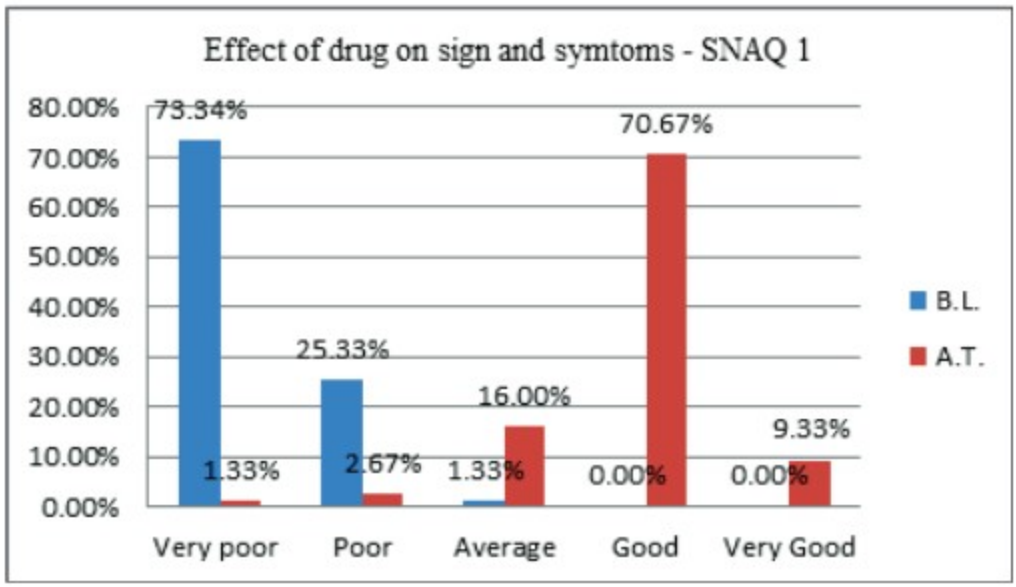


Figure 7: SNAQ question 1 evaluation

2. When I eat …….

Out of 75 patients, 72 (96%) patients felt full after eating a few mouthfuls or about a third of a meal before commencement of treatment, whereas only 2 (2.67%) patients had complaint about the same, while 69 (92%) patients got relieved after the treatment as shown in Table 8 and Figure 8.

Table 8: SNAQ question 2 evaluation

SNAQ Score 2	Baseline	%	Day 14	%
Very poor	9	12%	0	0
Poor	63	84%	2	2.67%
Average	3	4%	4	5.33%
Good	0	0	33	44%
Very good	0	0	36	48%
Total	**75**	**100%**	**75**	**100%**

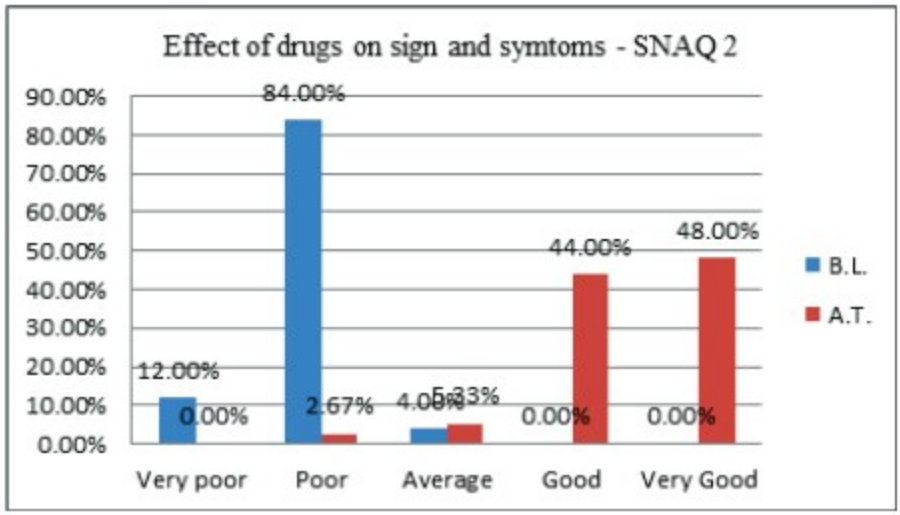


Figure 8: SNAQ question 2 evaluation

3. Food taste ……..

Before treatment, there were 56 (74.67%) patients who complained that the food taste bad but after the treatment there were 71 (94.67%) patients out of 75 who developed good taste for food as shown in Table 9 and Figure 9.

Table 9: SNAQ question 3 evaluation

SNAQ Score 3	Baseline	%	Day 14	%
Very bad	7	9.33%	1	1.33%
Bad	49	65.34%	1	1.33%
Average	15	20%	2	2.67%
Good	4	5.33%	28	37.33%
Very good	0	0	43	57.34%
Total	**75**	**100%**	**75**	**100%**

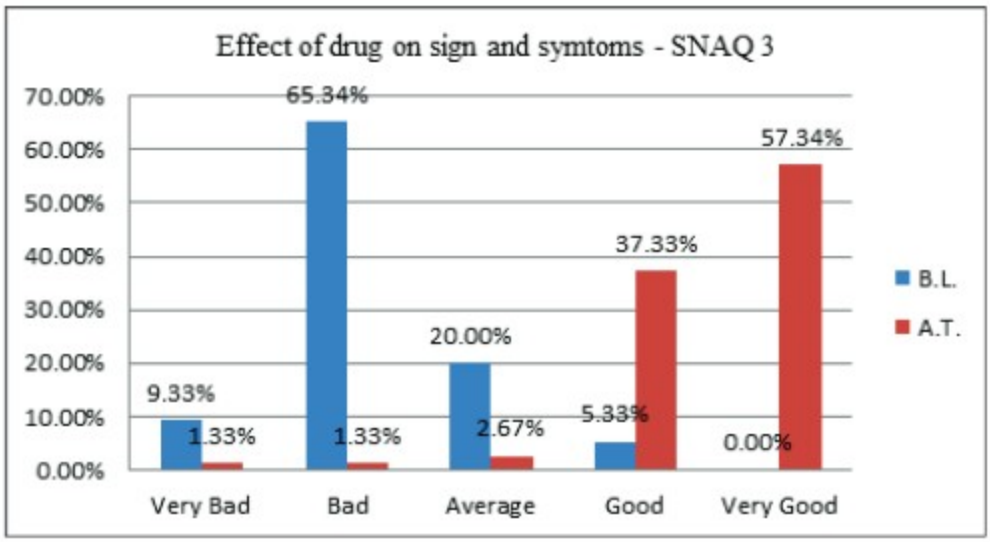


Figure 9: SNAQ question 3 evaluation

4. Normally, I eat……..

Out of 75 patients, there were 28 (37.34%) patients who had very less appetite, they used to have single meal a day, 35 (46.67%) patients had meal twice a day before treatment, whereas 70 (93.34%) had developed good appetite and started to have 3 or more meals a day and after the treatment as shown in Table 10 and Figure 10.

Table 10: SNAQ question 4 evaluation

SNAQ Score 4	Baseline	%	Day 14	%
Less than 1 meal	5	6.67%	1	1.33%
1 meal	23	30.67%	1	1.33%
2 meals	35	46.67%	3	4%
3 meals	11	14.66%	16	21.34%
More than 3 meals	1	1.33%	54	72%
Total	**75**	**100%**	**75**	**100%**

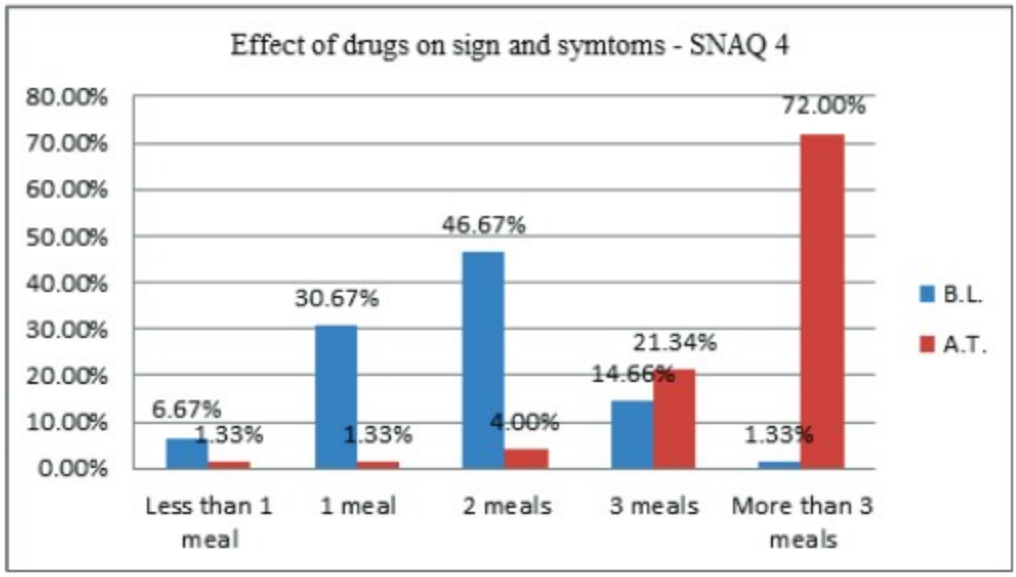


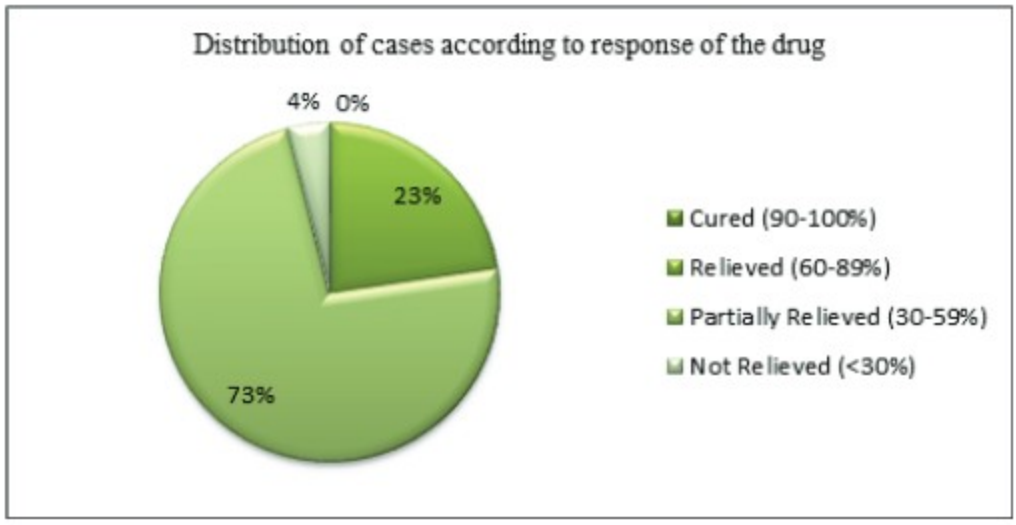
Figure 10: SNAQ question 4 evaluation

Assessment of SNAQ score

Out of 75 patients, 17 (22.67%) patients got completely relieved while 55 (73.33%) got partially relieved and 3 (4%) did not get any relief as shown in Table 11 and Figure 11.

Table 11: Response of drug in *Ḍu'f al-Ishtihā'* according to SNAQ score

Response	Sex		Total	Percentage%
	Male	Female		
Cured (90-100%)	0	0	0	0.00%
Relieved (60-89%)	10	7	17	22.67%
Partially Relieved (30-59%)	30	25	55	73.33%
Not Relieved (<30%)	3	0	3	4.00%
Total	**43**	**32**	**75**	**100.00%**



Discussion and Conclusion

An open-label clinical study was carried out at Clinical Research Unit (Unani), Cantonment General Hospital, Meerut with the aim to validate the safety and efficacy of Unani pharmacopoeial formulation - *Jawārish ʿŪd Shīrīn* in the management of *Ḍuʿf al-Ishtihāʾ* (anorexia). A total of 75 patients were studied and given 5 g of the test drug twice daily. Efficacy of the Jawārish ʿŪd Shīrīn was evaluated clinically on the basis of SNAQ questionnaire. For the safety of the test drug, all the patients were assessed on hematological and biochemical parameters on baseline and day 14. The data was analyzed by IBM® SPSS Statistics 2.0 using statistical tools that include Student's t-test.

The Simplified Nutritional Appetite Questionnaire (SNAQ) used to assess the clinical efficacy of the trial drug showed an overall improvement of 52.92% in patients' responses which were highly significant ($p<0.001$). *Jawārish ʿŪd Shīrīn* is a compound Unani formulation having multiple ingredients with digestive, carminative and tonic properties. Due to these properties, the formulation appears to alleviate the underlying causes of *Ḍuʿf al-Ishtihāʾ*. Thus, the findings of the study are in conformity with the claims of ancient Unani physicians who used these drugs to treat *Ḍuʿf al-Ishtihāʾ* with favorable therapeutic effects.

Throughout the study, no adverse effect was reported and hematological and biochemical parameters done at the baseline and at the end of the study remained normal which signifies that Unani pharmacopoeial formulation *Jawārish ʿŪd Shīrīn* is safe at the given dosage schedule.

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ज़ोफ़ अल–इश्तिहा (एनोरेक्ज़िया) में भेषजकोशीय मिश्रण *जवारिश ऊद शीरीं* की सुरक्षा और प्रभावकारिता का मूल्यांकन

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सारांश

परिचयः ज़ोफ़ अल–इश्तिहा एक यूनानी शब्दावली है जिसे बहुत ही सामान्य गैस्ट्रिक लक्षण *'एनोरेक्ज़िया'* के लिए उपयोग किया जाता है जिसमें ग्रसित व्यक्ति की भूख कम या बन्द हो जाती है। वजन की कमी, पोषण की कमी और खराब स्वास्थ्य इसके परिणाम हैं। यह अध्ययन *ज़ोफ़–अल–इश्तिहा* (*एनोरेक्ज़िया*) के रोगियों पर किया गया एक नैदानिक परीक्षण था।

उद्देश्यः *ज़ोफ़ अल–इश्तिहा* (*एनोरेक्ज़िया*) भेषजकोशीय मिश्रण *जवारिश ऊद शीरीं* की सुरक्षा और प्रभावकारिता का मूल्यांकन करना।

परिणामः 75 रोगियों में से 55(73.33%) रोगियों को आंशिक राहत प्राप्त हुई जबकि 17(22.67%) को पूर्ण रूप से राहत प्राप्त हुई। हेमेटोलॉजिकल और जैव–रासायनिक मापदंडों में भिन्नता सामान्य सीमा के भीतर थी और रोगियों में कोई प्रतिकूल प्रभाव नहीं देखा गया।

निष्कर्षः *ज़ोफ़–अल–इश्तिहा* (*एनोरेक्ज़िया*) का उपचार करने में *जवारिश ऊद शीरीं* सुरक्षित और प्रभावकारी है और एनोरेक्ज़िया के उपचार में प्रथम औषधि के रूप में उपयोग की जा सकती है।

शब्दकुंजीः यूनानी चिकित्सा, *ज़ोफ़ अल–इश्तिहा*, एनोरेक्ज़िया, *जवारिश*, भूख

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