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Review Article

THERAPEUTIC EFFICACY AND PHYTOCHEMICAL INSIGHTS INTO THE CLASSICAL UNANI FORMULATION *NUSKHA-E-KHALAL-E-SHIKAM*

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ABSTRACT

In the Unani System of Medicine, the concept of *Mushtarak-un-nafa' advia* has existed since ancient times. Certain selected *Advia* both single and compound drugs are outlined under this heading. *Mushtarak-un-nafa' advia* refers to medications that are frequently administered for the majority of illnesses; these medications can be administered to patients without waiting for a proven diagnosis, even if they do not successfully treat the illness or even make it worse. *Mushtarak-un-nafa' advia* is exemplified by *Nuskha-e-Khalal-e-Shikam* (NKS) and *Mulayyin* medicines. *NKS* composed of five ingredients, i.e., *Gul-e-Banafsha, Beekh Kasni, Badiyaan, Gaozaban* and *Maveez Munaqqa*. *NKS* is used as *Munjiz* and *Mushil* and is very efficacious in *Ufooni humma* (*Safrawi* or *Balghami*). NKS has traditionally been utilized in situations where a patient's illness is difficult to diagnose. *NKS* can be modify according to the condition of the patient. Gut dysbiosis is implicated in the pathogenesis of numerous inflammatory diseases. *Nuskha-e-Khalal-e-Shikam* (NKS) ingredients are rich in potent phytochemicals with a range of pharmacological actions, which together produce its compound therapeutic benefits across different conditions. However, more research is needed to assess NKS's effectiveness as a compound formulation.

INTRODUCTION

In India and other areas of the world, the Unani System of Medicine (USM) is among the oldest medical practices. The Unani System of Medicine (USM) originated in Greece and was refined into a sophisticated medical discipline by Arabs, building on the teachings of Hippocrates and Galen. USM advocates the Hippocratic (*Buqrat*) theory of four humours (*Akhlat*) i.e., *Dam* (Blood), *Balgham* (Phlegm), *Safrā* (Bile), and *Sawdā* (Black bile) which have specific but different temperament (*Mizāj*) [1,3-5]. The majority of the diseases arise from a qualitative or quantitative impairment of temperament, humor, or both. Unani medicine attempts to address health-related problems with the aid of natural ingredients and has its own philosophical and theoretical framework. Humoural imbalance is often the root cause of diseases in USM. According to Unani physicians, the human body is composed of seven basic principles (*Umoor-e-Tabbiya*)- *Arkān* (element), *Mizāj* (temperament), *Akhlāṭ* (humours), *A'ḍā'* (organs), *Arwaḥ* (vital force), *Quwā* (faculties) and *Af'āl* (functions). Disease is caused by the simple lack of any one of the components, endangering life itself. The primary goal

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of a Unani physician is to help the body's faculties in order to restore equilibrium. *Ṭabī'a-e-Mudabbira-i-Badan* (Medicatrix naturae) [1-3].

Unani physicians also introduced the idea of using *Mushtarak-un-nafa' advia* (*Ḍa'eef ul-a'mal*) for patients with ambiguous conditions, despite the existence of numerous well-known and recognized philosophical and theoretical concepts. where a precise diagnosis of the disease is difficult[2,4]. Even with today's tremendous advancements in medicine, there are still several conditions of the patients where to reach the confirmative diagnosis is very difficult even after the proper screening of the patient. Pyrexia of unknown origin (PUO) is a prime example- it's one of those tough medical puzzles that really challenges doctors. According to Petersdorf and Beeson, PUO is characterized by a temperature that is higher than 38.3 degrees Celsius, develops over a period of at least three weeks, with no diagnosis reached after one week of inpatient investigation. While addressing such issues, it is imperative to utilize all available clinical and investigative techniques while keeping the local epidemiological conditions in mind. Infections continue to be the most significant cause of PUO, accounting for roughly 20–40% of cases, despite some variance in the range of diseases observed in other series addressing PUO [6,7].

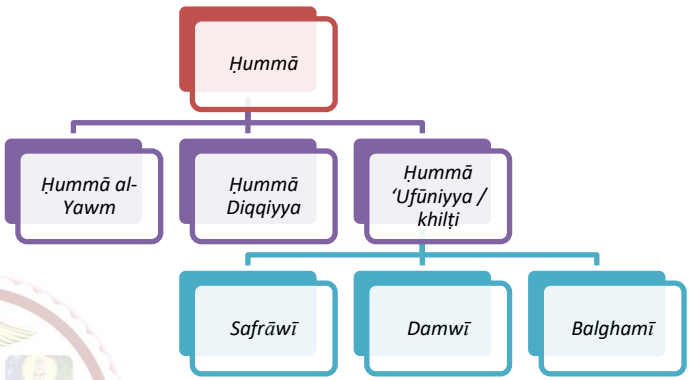
The definition of pyrexia in itself is complex as there is no agreed consensus. The inaccuracy of peripheral thermometers in determining body core temperature further complicates this. Pyrexia has a variety of causes, which lead to various definitions. Fever is typically defined as a temperature higher than 38.3 °C during infection. In the post-resuscitation management of cardiac arrest, a threshold is 37.6°C; in stroke, thresholds of 37.2, 37.5 and 38°C are used. A core temperature of less than 36°C is typically indicative of hypothermia, regardless of the clinical context [8].

The Unani System of Medicine provides a very detailed description of the fever *(Humma).* The various types of fever along with their pathophysiology, clinical features, and management strategies are explained with exceptional clarity.

MATERIALS AND METHODS

Literature for this review was systematically searched from classical Unani texts, including *Kulliyyat-e-Asri, Kulliyyat-e-Nafeesi, Kulliyyat-e-Qanoon, Sharah Asbab, Hummiyat-e-Qanoon, Khazāīn al-Adwīyah*, *Muḥīṭ-i A'ẓam*, and *Makhzan-ul-Mufradāt (al-marūf bi-Khawāṣṣ al-Adwiyah)*. Additionally, the Unani Pharmacopoeia of India and Standard Unani Medical Terminology were referred to ensure accurate description of Unani terminologies. English-language books, research articles, review papers, the Glossary of Indian Medicinal Plants, and publications from journals (PubMed, Google Scholar, and ResearchGate) were also referred to compile evidence-based insights on the formulation's composition, pharmacology, and therapeutic efficacy.

Classification of fever (*Ḥummā*) [9]



The methods of treatment according to USM is divided into four different parts namely Dietotherapy (*Ilāj bi'l Ghidhā*), Regimental therapy (*Ilāj bi'l Tadbīr*), Surgery (*Ilāj bi'l Yad*) and Pharmacotherapy (*Ilāj bi'l Dawā'*) [2,3]. In Unani medicine, therapeutic agents are utilized to restore the body's humoral balance and restore health. Maintaining the humoral balance is also thought to depend on a balanced diet and healthy digestion. Pharmacotherapy involves the use of both single and complex medications. Pharmacotherapy deals with the use of naturally occurring drugs, primarily herbal, though it also includes medications derived from animals and minerals. Since USM places a strong emphasis on each person's unique temperament, medications are administered based on the patient's temperament, thus accelerating the process of recovery and also eliminating the risk of drug reaction. Although single medications are often preferred in USM, compound formulations are also utilized to treat a variety of diseases.

Types of *Ḥummā* [9]	**Treatment**
Ḥummā al-Yawm	Can be cure with various modalities
Ḥummā Diqqiyya	Specific medication is needed
Ḥummā 'Ufūniyya/Khilṭi (on the basis of predominant temperament)	▪ *Mushtarak tadābīr* (*Talliyun*, *Ta'reeq*, *Qai* etc.) ▪ *Mushtarak nafa' adwia* (*Nuskha-khalal-e-shikam*) ▪ Specific treatment after confirmed diagnosis.

In medical conditions where the clear diagnosis of the disease is difficult, Unani Physician used the *Mushtarak-un-nafa' adwia (Ḍa'eef ul-a'mal)* which if not effectively cure the disease, nor even worsen the condition. Keeping in view of this problem Unani physician formulates a unique formulation for all types of fever, irrespective of its diagnosis. *Nuskha e khalal e shikam (NKS)* can be used in all types of *Ḥummā 'Ufūniyya* as a provisional diagnosis, till the confirmation of final diagnosis, without hesitation, it has good results [2-4,9-10]. This nuskha *NKS* can also be given to patients of Gastrointestinal related problems. Similarly, if the patient suffers from coryza, cough or any respiratory disorder of which is difficult to reach the confirmed diagnosis, this Nuskha *NKS* can be used effectively and if necessary, the drug specific for coryza like *Aslussos*, *Tukhm-e-Khatmi* etc can be added to NKS [9,10].

According to confirmative diagnosis, this *NKS* can be modify later according to the related associated medical conditions of the patient.

Ingredients of *Nuskha-e-khalal-e-Shikam* is as follows [2-4,9-10]

S.No	Unani Name	Botanical Name [11]	Parts Used	Mizaj	Quantity [4,9,11]
1.	*Gul-e- Banafsha*	*Viola odorata* L.	Flower	Cold- 1 Moist-1 [12-14]	7 gm
2.	*Beekh kasni*	*Cichorium intybus* L.	Root	Cold- 1 Moist- 1[12-14]	7 gm
3.	*Badyan*	*Foeniculum vulgare* Mill	Seeds	Hot- 2 Dry- 2[13-14]	7gm
4.	*Gaozaban*	*Borago officinalis* L.	Leaves	Hot- 1 Moist- 1[12,14]	5 gm
5.	*Maweez munaqqa*	*Vitis vinifera* L.	Fruit	Hot-1 Moist-1[12-15]	9 no.

Method of preparation and administration

All the dry ingredients (mentioned above in the table) are soaked in warm water overnight and boiled next morning till only one-fourth volume of water remains. The ingredients of the decoction is now rubbed with the hands, then filtered through a sieve. The lukewarm decoction is administered orally in the morning hours to the patient along with *Khameera Banafsha* 40ml [4,9,10].

***NKS* can be modify according to condition of patient**[10]

- If along with fever presents
  - Sore throat (*Dard-e-Ḥalaq*) then add *Barg-e-Toot* in *NKS*.
  - Coryza (*Nazla*) then add *Tukhm-e-Khatmi* and *Tukhm-e-Khubbazi* in *NKS*.
  - Cough (*Khansi*) then add *Aslussos* in *NKS*.
  - Splenomegaly (*Waram-e-Ṭiḥāl*) then add *Anjeer Zard* in *NKS*.
  - Dysentery and *Kharash-e-Ama'a* then add *Luab-e-Resha-e-Khatmi* in prepared decoction in morning.
  - *Fasād-e-Khoon* or Skin diseases then add *Shahtara* and *Chiraita*.
  - Amenorrhoea (*Iḥtibās-e-Ḥaiz*) then add *Tukhm-e-Khayarain* and *Tukhm-e-Kasni* in *NKS*.
  - Pallor (*Yaraqān*) then add *Tukhm-e-Khyarain* in *NKS* and add *Aab-e-Barg-e-Turb* in decoction prepared in the morning.
- After the seven days use of this *NKS*, still the fever persists then add *Khaksi Pasheeda* in *NKS*.
- If *Taḥlīl-e-Ruṭūbat* and *Talṭīf-e-Mādda* is prime concern then add *Beekh-e-Izkhar* and *Beekh-e-Kibr* in the *NKS*.
- To relieve the constipation, add *Gul-e-Surkh* in *NKS* when coryza is not present, otherwise add *Sana makki* or *Rewand chini* in *NKS*.

Brief description of Ingredients

S.No	Drug	Chemical Constituents	Pharmacological Action	Pharmacological Studies
1.	*Gul-e-Banafsha* Arabic: *Banafsaj,*	Flavonoids, tannins, alkaloid, glycoside, saponins, different essential oils (methy ester, salicylic acid,	*Mu'addil,* *Mulaṭṭif* (demulcent), *Mu'arriq* (diaphoretic), *Mulayyin-i-Shikam*	Anti-inflammatory activity [21] Antioxidant activity and radical scavenging activity [22] Antimicrobial activity/antibacterial

	English: Violet, Sweet violet [15]	anthocyanin, gamma sitosterol, phytol, octadecanoid acid), cycloviolacin, eugenol, violin, rutin, tocopherol. [16-20,22]	(Laxative), *Mulayyin-i-Ḥalaq-wa-Seenah, Musakkin -e-Dam, Murattib* (humactant), *Munawwim* (hypnotic), *Mushil* (purgative), *Mushil-i-Safra'* (Cholagogue), *Muzliq, Dāfi'-i-'Uṭāsh, Muḥallil* (resolvent) [12-14,18]	activity [22] Immunological and cytogenic effect[23] Hepato-protective [23] Expectorant [24] Laxative [25] Diuretic activity [25] Antipyretic activity [26] Anti-hypertensive and dyslipidemic activity [27] Anti-tubercular activity [28] Hypnotic activity [29] Pancreatic lipase inhibitors activity[30]
2.	*Beekh kasni* Arabic: *Hindyba* English: Endive [16,18]	Phytosterols, lactones, flavonoids, triterpenoids, terpene, coumarins (including cichorin), tannins, vitamins, pectins. sesquiterpenes lactones like sonchusides A and C, and, cytokinin, crepidiase B, cichoriolide A, B and C, chlorogenic, neochlorogenic, isochlorogenic, lactucin, caffeic & chicoric acids. Series of glucofructosans. [16,18,31,32]	*Mufattiḥ-i-Sudud* (Deobstruent), *Muddir-i-Bawl* (diuretic), *Muṣaffi-i- Dam* (blood purifier), Reduces the *Ḥarārat* of *Dam* and *Ṣafrā'*, *Muqawwī-i-Kabid* (hepatotonic), *Muqawwī-i-Mi'da* (stomachic), *Muskkin-i-'Uṭāsh* (Thirst reliever), *Musakkin* (analgesic), *Muḥallil* (resolvent) [12-14,18,33]	Antioxidant activity [34,37] Hepatoprotective activity [34,35] Antiulcer activity [36,37] Antibacterial activity [38] Antidiabetic activity [39] Antifungal activity [40] Anticancer activity [41] Anti-convulsant activity [42] Immunomodulator activity [43] Analgesic and Sedative activity [44] Cardioprotective Activity [45]
3.	*Badyan* English-Fennel Arabic: *Rajiyanaj* Urdu: Saunf [15,16,18]	Volatile oil (anethole, fenchone, methylchavicol, camphene, terpinene, linalool, estragole, p-cymene, thujene), Fixed oil (petroselinic acid), Cinnamic acid derivatves (Hydroxycinnamic acids, cynarin), Flavonoids glycosides (3-glucuronides of kaempferol, Quercetin), Coumarins	*Mufattiḥ-i-Sudud* (deobstruent), *Muqawwī-i-Mi'da* (stomachic), *Muddir-i-Bawl* (diuretic), *Mudirr-i-Ḥayḍ* (emmenogogue), *Muqawwī-e-Baṣar* (vision improving), *Munḍij-i-Balgham wa Sawdā'* (concoctive of phlegm and black bile), *Muwallid-i-Laban* (galactopoietic), *Mujaffif* (Desicant), *Muwallid-i-Manī* (spermatogenic),	Antifungal activity [48] Antioxidant activity [49] Anti-inflammatory [49] Analgesic [49] Antidiabetic activity [50] Antistress activity [51] Memory-enhancing effects [51] Antibacterial activity [52] Hepatoprotective activity [53] Diuretic [54] Anti-osteoporotic activity [55] Hypolipidemic Activity [56] Emmenogogue and galactogogue, estrogenic activity [57]

		(bergapten) and Sterols (β-sitosterol) [16,18,46,47]	*Kāsir-i-Riyah* (carminative), *Muḥallil* (resolvent), *Mudirr-i-Laban* (galactogogue), *Musakkin-i-Alam* (analgesic) [13-15,33,47]	
4.	*Gaozaban* Arabic: *Lisan-us-Saur* English: Borage [18, 59]	Pyrrolizidine alkaloids, licosamin, intermedin, sopinin, sopindian, fatty acids (ALA & GLA), silicic acid, potassium, calcium, nitrate acetic, lactic and malic acid, δ-bornesitol, cianozhens, mucilage. [18,58,59]	*Dāfi'-i- Ḥummā* (anti-pyretic), *Muqawwī* (tonic), *Muddir-i-Bawl* (diuretic), *Muqawwī-i-Qalb* (cardiotonic), *Mufarriḥ* (exhilarant), *Mulaiyyin* (laxative), *Munaffith* (expectorant), *Mufattit-i-Ḥaṣāh* (lithotriptic) [12,14]	Hepatoprotective activity [60] Cardiovascular activity [61] Respiratory activity [61] Gastrointestinal activity [61] Antioxidant activity [62] Antinociceptive activity [63,65] Anxiolytic activity [64] Anti-inflammatory activity [65] Antibacterial activity [66]
5.	Maweez munaqqa Arabic: Zabeeb-ul-Jabal English: Raisins [16,15,18]	Flavonoids (kaempferol-3-O-glucosides, quercetin3-O-glucosides, quercetin and myricetin) Polyphenols (flavan-3-ol derivatives) Catechins, Epicatechin, Epicatechin-3-O-gallate, Procyanidins or proanthocyanidins [16,18, 67]	*Mughadhdhī* (Nutritive), *Munḍiz-e-Khilṭ ghaleez* (concotive of viscous humour), *Mufattiḥ -i-Sudud* (deobstruent), *Mulayyin-i-Shikam* (laxative), *Muḥallil* (resolvent), *Jālī* (degergent), *Muqawwī-i -Mi'da wa Am'ā* (tonic for stomach and intestine), *Muqawwī-i-Jigar* (hepatotonic), *Muḥarriq-e-Bāh* (stimulant), *Musammin-i-Badan* (adipogenous) [12-14,68]	Hepatoprotective activity [69] Antioxidant activity [70] antidiabetic activity [70] Antiulcer activity [36] Antioxidant effect [71] Anti-hypercholesterolemic potential [71] Cardioprotective activity [72] Antitumour activity [73] Antibacterial activity [74] Anti-stress activity [75] Antifungal activity [76] Anti-inflammatory activity [77]

DISCUSSION

Nuskha-e-khalal-e-shikam is very efficacious medicine, the prescription of *NKS* is mentioned in various classical texts. Various functions of *Nuskha-e-khalal-e-shikam* is attributed to its various ingredients which possess antipyretic, antioxidant, hepato-protective activity, antibacterial, expectorant, anti-inflammatory, antiviral effect, hypolipidemic activity, carminative, tonic for nerves, brain, heart and kidneys, nerve stimulant, immunomodulator activity, emmenagogue, laxative, deobstrient, demulcent, blood purifier, anxiolytic activity, analgesic etc properties. These functions have been proved by scientific studies. Most of the ingredients of the NKS contains flavonoids, terpenes and Coumarins.

Flavonoids

As studies shown that flavonoids have capacity to act as antioxidants. The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species. flavonoids are well known as antibacterial agents against a wide range of pathogenic microorganism [78]. Anti-inflammatory and antipyeratic feature are the key abilities of flavonoids. [78][79]

Essential oil

V. odorata, F. vulgare and C. intybus contain essential oils that include terpenoids, phenylpropanoids. C. intybus is particularly rich in a wide range of natural terpenoids named sesquiterpene lactones. Studies shows that sesquiterpene lactones have antibacterial antiviral anti-inflammatory activities.[80]

Coumarins

C. intybus and F. vulgare in the NSK contain coumarins and its derivatives. Coumarins and their derivatives exert a vast array of bioactive properties such as anticoagulant, antibacterial, anti-inflammatory, antioxidant, antitumor, antiviral. [81]

In Unani medicine, many diseases are indeed believed to originate from *Su-i-Hazm* (faulty or incomplete digestion), because disturbed digestion produces abnormal humors *(Akhlāt)* that then affect the whole body. This concept can be correlated with modern ideas linking chronic dyspepsia, malabsorption, gut dysbiosis, low-grade inflammation, and metabolic disturbance to systemic diseases. [82] Gut dysbiosis is a disruption of normal gut microbial balance, involving loss of beneficial microbes, overgrowth of potentially harmful ones, or reduced overall microbial diversity.

The gut microbiota, a complex ecosystem of microorganisms, regulates immune responses and maintains intestinal homeostasis. Gut dysbiosis, or damaged gut microbioma, contributes to inflammatory diseases like IBD (ulcerative colitis/Crohn's), rheumatoid arthritis, lupus, and skin issues (psoriasis, eczema) by boosting harmful bacteria like Prevotella and reducing helpful ones like Faecalibacterium. This triggers excess inflammation via cytokines like IL-17. It also worsens infections such as COVID-19 and TB through low short-chain fatty acids and bacterial shifts. [83]

Phytochemicals such as polyphenols, flavonoids, terpenoids, saponins, and capsaicin play a pivotal role in modulating the gut microbiota by suppressing pathogenic bacteria and promoting the growth of beneficial genera.[84] The active chemical constituents present in the ingredients of *Nuskha-e-Khalal-e-Shikam*, including flavonoids, polyphenols, coumarins, terpenes, terpenoids, and saponins, exert potent antioxidant and anti-inflammatory effects, which help to repair and to restore the gut microbiome. Consequently, these actions enhance intestinal barrier integrity, strengthen immune function, and contribute to the prevention of inflammatory and metabolic disorders.

However, clinical trials or scientific studies are lacking on *Nuskha-e-khalal-e-shikam* as a compound drug.

CONCLUSION

With the above discussion the inference may be drawn that the *Nuskha-e-khalal-e-shikam* is one of the best Unani formulations with a lot of health benefits. *Nuskha-e-khalal-e-shikam* is effective in the management of several undiagnosed condition of the patient since time immemorial, so it has been found to be a time-tested drug. However more scientific studies and clinical trials are needed on this compound formulation to ensure its scientific validation for clinical use in patients.

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