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# ETHNO-PHARMACOLOGY, THERAPEUTICS, PHARMACOKINETICS, AND TOXICOLOGY OF *SAMM-UL-FAR* (ARSENIC) IN TRADITIONAL MEDICINE: A NARRATIVE REVIEW

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**Abstract:**

*In traditional systems of medicine herbs, minerals, and animal sources are in used as medicine since antiquity. In the Unani system of medicine gold, silver, iron, copper, zinc, lead, salts, earthy matters, gems, arsenic, borax, etc. are used in the various formulation in different forms after the process of detoxification. Samm-ul-Far (Arsenic) is a naturally occurring odorless and tasteless element found in the ores of silver in the island and mountains of Khurasan. Chemically, Samm-ul-Far (SF) is arsenic trioxide. Unani formulations of SF is used in various disease especially nervine disorders, skin disease, sexual disorders, arthritis, blood infection, and blood dyscrasia. Since it is having a 4th degree of hot and dry temperament it is used with caution and diligently even in therapeutic doses. In this review, information related to the history of medicinal use, Ethno-pharmacology, medicinal importance, toxicity study, formulation of arsenic, the pharmacokinetics of arsenic, therapeutic actions, and use of arsenic trioxide in the current scenario has been described. From the review with evidence, it may conclude that the risk-benefit ratio (more risk than benefit) should be kept in mind while using SF as medicine even at a therapeutic dose.*

**Keywords:** *Arsenic trioxide, Samm-ul-Far, Unani Medicine, Toxicity, Ethno-Pharmacology, Pharmacokinetics, Purification*

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## INTRODUCTION:

The Unani Medical Science also known as traditional Persian medicine originated from Greece, was enriched and developed by the Arabs, and introduced by Persians in our country about 1000 years ago [1]. The theory of this system is based on the teachings of *Buqrat* (Hippocrates 460-377 B.C.) and *Jalinoos* (Galen) (130-200 A.D.). Arabs provided it with a scientific basis. Western medicine classifies it as complementary and alternative medicine [1]. The Drugs in Unani system of Medicine consist of herbal, mineral, and animal origin. Metals and minerals such as gold, silver, iron, copper, zinc, lead; salts, earthy matters, and gems are commonly used in traditional systems, especially in Unani medicine [2, 3]. There are an increased number of case reports published on toxicity caused due by the use of ayurvedic compounds containing Lead, Mercury, and Arsenic creating a negative impact on the public for Ayurveda medicine but till yet no report has been found for Unani medicine [4, 5, 6, 7]. Inorganic arsenic is now used as a first-line therapeutic agent against certain hematopoietic cancers and other malignancies in western medicine [8]. These metals and minerals cannot be used systematically because of pharmacokinetic inconvenience and potential toxicity; therefore, they need to be detoxified converted into less toxic form into carbonate or oxide forms which is very effective and safe in small doses. The oxide is known as *Kushta* (calx), which is derived from a Persian word '*Kushtan*' meaning 'To kill" indicating a process by which metals and minerals are killed i.e. burnt at high temperature [9]. This review summarizes the pharmacological properties originating from traditional Unani medicine knowledge, western biology experiments, pre-clinical results obtained from arsenic to decide whether it can develop in medicine or not, clinical use of arsenic in various pharmacopeial formulations, a simple preparation method of arsenic after detoxification, its applications and risk associated with its uses.

## MATERIALS AND METHODS:

Unani classical literature was searched through *khazainul advia, Tazkara Uool-al-Albab, Bayaz-e-Kabeer, Firdos al-Hikmat* for its complete description, viz. temperament, actions, therapeutic and dosage, etc. For various formulations of *Samm-ul-Far* (SF) we searched "National Formulary of Unani Medicine" in all volumes, which is the official book under the central council of research in Unani medicine, India, and abbreviated as NFUM. For toxicological studies, pharmacological activities, and clinical trials computerized databases such as Medline, PubMed, Google Scholar, and Science Direct were searched.

### Historical Aspects of *Samm-ul-far* (Arsenic) As Medicine:

*Samm-ul-Far* is a well-known metalloid poison found in water, soil and air from natural and atmospheric sources [10, 53]. It is a ubiquitous element that ranks 20$^{th}$ in abundance in the earth's crust [11]. Apart from its use in varied fields, it is also in use as a therapeutic agent for 2400 years and is still used in medicine, particularly in Unani Medicine and Ayurveda. Presently, therapeutic use is limited due to its toxicity. In China, it has been in use for over 2400 years as a part of traditional medicine. The therapeutic use of arsenic dates back to 400 B.C with Hippocrates [12,13] recommending arsenic for the treatment of ulcers [12]. The medicinal virtues of arsenic are acclaimed for nearly 2500 years [11]. Galen also used arsenic as a therapeutic agent in his era [4].

## *SAMM-UL-FAR* DESCRIPTION IN UNANI LITERATURE:

**Figure:1 *Samm-ul-Far***

***Samm-ul-Far* (Detoxified)**

*Samm-ul-Far* (Arsenic trioxide) is a mineral origin substance [11, 14, 15, 16, 17, 18] found in white crystalline form [14,16]. According to Unani physicians, it is a scum of silver, which comes from mines of silver [11, 15] Or it is the scum of gold; some believe it to be a by-product of some other substances found in the incomplete form [11, 12] Or it is found with iron and sulphur in mines after processing, it is isolated from them [11, 17, 16].

**Nomenclature:**
Arsenicon is a Latin word made up of two words i.e., Ars means masculine (*muzakkar*) and Nicon means poison (*zahar*) Since it is a powerful poison Unani physician called masculine [11, 20]. *Marg-e-Mosh* is a Persian word, which is again made up of two words i.e., *Marg* means death and *mosh* means rat [11, 19, 21, 22]. Old chemists named it *Zarneekh-e-Safaid* [11, 12, 21, 22]. *Dioscorides* for the first time called Arsenicon and he used a compound of arsenic in his period. *Jālīnūs* (Gallen) also used arsenic [20]. However, it was not used extensively in his period. It was commonly used as a poison [11, 23, 24]. After ingestion of SF, the rats die immediately, hence called *Samm-ul-Far*, *Sam* means *zahar* (poison), and *far* means rat [19]. Earlier, it was not only used for killing rats but also used as a homicidal poison [18, 25]. As per NFUM.

Table 1: Natural Arsenic compound in Unani Medicine

| Tibbi/ Popular Names | English Name / Mineralogical Names | Chemical Composition |
|---|---|---|
| *Hartal Warqi* (Zarnikh-e- Zard) | Orpiment, Yellow Orpiment | Arsenic Tri-sulphide |
| *Samm-ul-Far* (Marg-e- Mosha) | Arsenic | White Oxide of Arsenic |

**Vernacular Names:**
**Arabic**; *Samm-ul-far, Shak, Turab al-Halik, Rahjul-far, Suk.* **Persian***; Marg-e-Mosh, Zahra-e-Adam, Zarneekh-e-Abyaz.* **Hindi***; Sankhiya, Somal Khar, Sanbul khar, Sankhiya, Zehar, Vish.* **Urdu***; Sankhiya, Sankhiya Zahar.* **Sanskrit***; Aakhu Pashan, Gauri Pashan.* **Marathi***; Somal, Shankhiya.* **Gujrati***; Shomal, Shomal Khar, Shankheu.* ***Bengali****; Horital.* **English***; Arsenic, White oxide of Arsenic.* **Latin***; Arsenicon.* **Chemical Name***; White oxide of Arsenic* [11, 15, 16, 17, 10, 19, 22, 24, 25, 26, 18, 28, 31].

**Ethno-pharmacological description of *Samm-ul-far:***
***Hakim Najmul Ghani*** an author of the book *khazainul Advia* stated that; European physicians till the 16th century used it mostly externally but in the 17 century they start using it internally in malaria and episodic fever [11].

**Conventional Doctors;** used it as *Arq*, Tablet, and Pills. When it is used by adding iodine than is known as Arsenian Iodide (Latin) and Arsenious Iodide (English) having a dosage of 1/20-1/5 part of a grain. When it is compound with iron it appears as tasteless green colour powder known as ferric arsenious (Latin) and Arsenate of Iron (English) with; Dose 1/16 part-4 of grain. When mixed with soda then it appears white powder and used in the dose of 1/40-1/10 part of grain [11].

**As *Muhallil* (Resolvent);** Arsenic after mixing with oil is used in dry and wet pruritus. Arsenic with a rose made in paste form and used in Ascites. Application of arsenic formulation results in dilution of all morbid wet humor (*Ratubat)* of all layers of eyes [11].

As per a few **allopathic physicians'** arsenic is tonic (*Muqawwi*) but its long-term use result in weakness, anorexia, Syphilis, gout, leprosy, and arthritis [11].

**Effect of *SF* on Hematopoietic system;** It gets absorbed easily in blood. In the healthy condition, it does not cause any harm but in blood disorders, it increases RBCs of blood. In very small quantity half to 1 drop, it acts as a cardiotonic but in high quantity it lowers blood pressure and pulse rate. It causes capillary hemorrhage [11].

**On Respiration;** The action of arsenic trioxide on respiration is not known but in some addicted people like people of Syria and some parts of India specially snake catchers it has been seen to have a fairer skin tone and strengthen the body. Some people eat a higher amount of arsenic trioxide without any adverse effects. So it has been expected that those people built immunity against arsenic poisoning [11].

**Nervine Tonic;** In lesser amounts arsenic works as a nervine tonic but in the higher amount it weakens the nerves and disturbs the central nervous system activities [11].

**On skin;** There is a role of arsenic in the maintenance of skin texture and functions. The use of arsenic increases its power and fat layer but in higher amounts, as skin expels toxic matter to outside, arsenic is also get excreted through the skin causing ulcers and blackening of the skin [11].

Table 2: Therapeutic uses of *SF* (arsenic) mentioned in *khazainul Advia* [11]

| **Formulation and indication** | **Ingredients** | **Quantity** | **Method of Ingestion** | **Advice** |
|---|---|---|---|---|
| Syphilis | Arsenic | 11.66 gm | Pill in the size of green-gram, followed by ½ seer (466g) curd | Avoid Rice, Green Gram, Milk, Garlic, Sweets & Coitus. |
| | Solanum surattense | 1166 gm | | |
| Syphilitic arthritis | White arsenic | 5.8 gm | Pills in size of Black pepper, daily one pill for 27 days | Avoid cold water and Green Gram |
| | Colchicum Luteum | 11.66 gm | | |
| | Lemon juice | 93.28 gm | | |
| Leprosy | Arsenic | 11.66 gm | Make pills of the size of Rice and take with Milk cream. | Avoid sourness, milk, rice, oily, spicey. Take Ghee & Green Gram in Diet |
| | Lemon juice | 1000 No. | | |
| As per *Hakim Ghulam Imam*: | Senegalia catechu | 46.6 gm | Grinder all 3, make powder, and make a pill having the size of black pepper. | Advice 1 pill before having chill/rigors |
| | Rosa | 4 gm | | |
| | Arsenic | 500 mg | | |
| Piles (as per *Hakim Ali*) | Arsenic powder | Boiled in the milk of a donkey, and keep in it further 3 days | Applied on the piles twice a day, will start improving in 3 weeks | Avoid the healthy area around the rectum. Healed in a month. |

**Distribution and Occurrence:**

SF is found in the Island and mountains of Khurasan [21]. The sources of SF are ores of silver or mines of silver of Khurasan [12, 19]. According to *Ibn Jazla* it is *Dood-e-Zar* (scum of gold), which is obtained from Khurasan, but according to Shareef Khan, it is obtained from the coastal line of Kalikoot (Calicut) [28]. Three types of arsenic are used for commercial purposes; white, yellow, and red. The white colour of arsenic is not its natural color but is given to it and is imported from China to India through the sea route. It is of two types one is clear transparent with a golden-colored layer obtained from the Persian Gulf (*khalij-e-faris*). Another type is opaque and used in industry. Yellow arsenic is used in painting and imported from (Chitral), Town in Pakistan. Red arsenic is imported from Brahma and China. It is used in the colour industry. In fire cracks, red colour is produced by it [2].

**Types of SF:**

According to Ayurvedic physicians, it is of five types: (1) White as an alum - *Fitka*. (2) Yellow as turmeric - *Haldia*. (3) Bluish- *Kodia*. (4) Red as seeds of a pomegranate- *Daria*. (5) Whitest of all-*Sankhiya* [12, 19, 22, 28, 29, 32] (Figure-2).

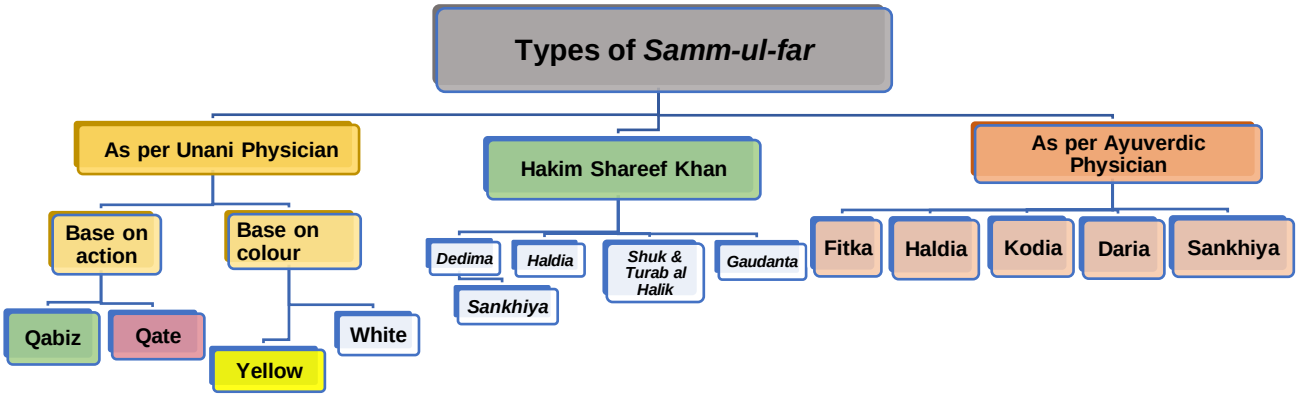



Figure 2; Types of SF [12]

**Physical Properties of SF:**
SF is found in the form of white and shiny crystals [14]. The whiteness is like alum. In the context of the quality of *Samm-ul-Far*, Unani physicians state that when triturated SF is applied on the wing of the bird and burned, it will return to its original state [28]. Pure SF breaks easily, becomes powder, and evaporates without melting. On burning it gives pungent (garlic-like) odour [11, 18, 20, 3, 27, 29]. SF loses its potency after 70 seventy years, which can be identified by its loss of weight and dirtiness. [12, 27, 29]

**Temperament:**
Hot $4^{\circ}$ and Dry $4^{\circ}$ [14, 15, 16, 18, 22, 24, 26]

**Pharmacological Actions:**
Various pharmacological actions of SF have been mentioned in Classical Unani literature. The pharmacological actions areas: *Muqawwī-e-Qalb* (Cardiotonic), *Muqawwī-e-Asab* (Nervine tonic), *Muqawwī-e-Bah* (Aphrodisiac), *Mujaffif* (Siccative), *Muhallil* (Resolvent), *Mushtahi* (Appetizer), *Mumsik* (Retentive), *Dafe Awja-e-Mafasil* (Anti-arthritic), *Muqawwī-e- Badan* (General tonic), *Musaffi-e-Khūn* (Blood Purifier), *Muqawwī-e-Meda* (Stomachic), *Qatil-e-Jaraseem* (Antibacterial), *Daf-e-Tap* (Antipyretic), *Mundamil* (Healer) [14, 15, 16, 18, 22, 24, 26, 30]

**Therapeutic Uses:**
*Zu'f-e-Qalb* (Cardiac weakness), *Zoaf-e-Asab* (Nerve weakness), *Zoaf-e-Bahn* (Sexual weakness), *Falij* (Paralysis), *Zoaf-e-Badan* (General weakness), *Zoaf-e-Meda* (Gastric weakness), *Qillat-e-Dam* (Anemia), *Laqwa* (Facial paralysis), *Waja-ul-Mafasil* (Arthritis), *Erq-un-Nasa* (Sciatica), *Dard-e-Kamar* (Backache), *Dama* (Asthma), *Juzam* (Leprosy), *Aatishak* (Syphilis), *Bars* (Vitiligo), *Bukhar* (Fever), *Khansi* (Cough), *Mausami Bukhar/ Naubati Bukhar* (Seasonal / Malarial fever), *Bawaseer* (Hemorrhoids), *Istisqa* (Ascitis), *Nazul-ul-Maa* (Glaucoma), *Niqris* (Gout), *Nafakh* (Flatulence), *Tahabbuj* (Oedema). The prepared oil of SF can be used as a local application in *Jarb wa Hikka* (scabies and pruritus) [14, 15, 16, 22, 24, 30, 33].

**Formulation and Uses of SF (Arsenic Compounds) based on NFUM:**

Table 3; Different Formulation of SF mentioned in NFUM [34, 35]

| Name | Action | Therapeutic Uses | Doses |
|---|---|---|---|
| *Habb-e-Ahmar* | General Tonic | Loss Of Libido, Neurasthenia | 125-250mg |
| *Habb-e-Falij* | Nervine Tonic. | Paralysis, Bell's Palsy, Tremors | 125-250mg |
| *Habb-e-Shuk* | Detergent | Vitiligo | 150-250mg |
| *Habb-e-Pan* | Blood Purifier | Syphilis, Chronic abnormality of blood | 15-25mg |
| *Habb-e-Sammul Far* | Antipyretic, Nervine Tonic, Blood Purifier | Malaria Fever, Neurasthenia | 100-150mg |
| *Habb-e-Sammul Far Musakkin* | Blood Purifier, Analgesic, Anti-inflammatory | Arthritis, Sciatica, Gout | 50-100mg |
| *Habb-e-Kalaf* | Blood Purifier | Pityriasis versicolor, vitiligo | Mixed pills with lemon water & L.A |
| *Nuqrai* | Tonic Of Principal Organs/Vital Organs. | Weakness Of Principal Organs, Anemia, Sexual Debility | 1-pill with butter |
| *Jauhar-e-Munaqqa* | Blood purifier | Syphilis | 15-30 mg |
| *Jauhar-e-Seen* | Nervine tonic, Blood purifier | Syphilis, loss of libido, Neurasthenia | 15-30 mg |
| *Jauhar-e-Seemab* | Blood purifier, Anti-inflammatory | Lymphadenopathy, Fistula | 15-30 mg capsule |
| *Jauhar-e-Kalan* | Blood purifier | Syphilis | 30 mg cap. |
| *Kushta-e-Sammul Far Aatishaki* | Blood purifier | Syphilis | 10-15mg |
| *Kushta-e sammul Far Aatishaki Qawi* | Nervine stimulants & tonic, Sexual tonic | Anaphrodisia/ Loss of libido, Neurasthenia, Impotency | 10-15mg |
| *Tila-e-Majlooq* | Nervine stimulants. | Ailments due to masturbation | Q.S LA |
| *Tila-e-surkh* | Nervine stimulants. | Weakness of the nerves of Penis, | Q.S LA |

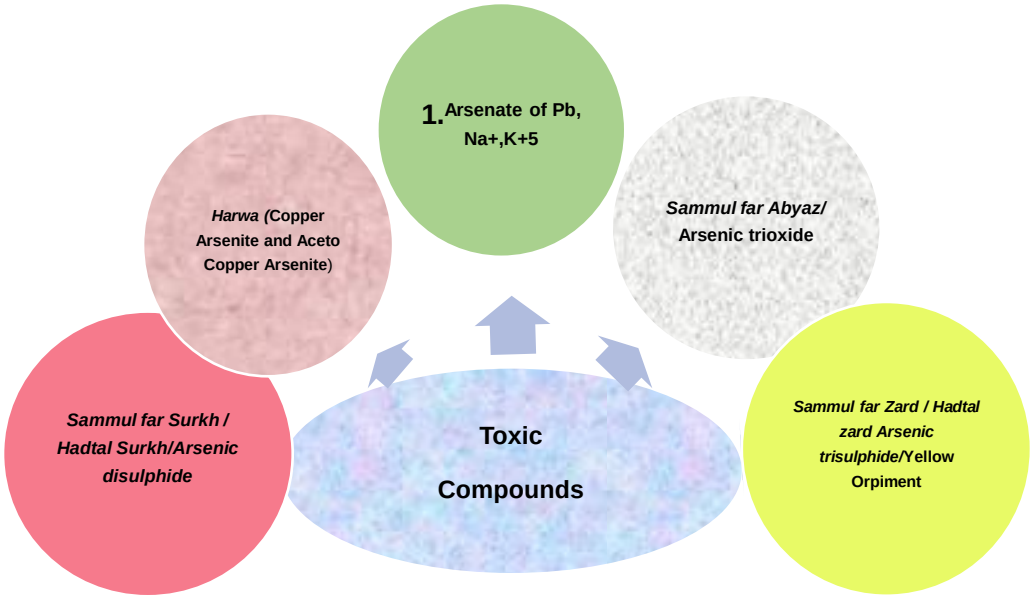
| | | | |
|---|---|---|---|
| | | Ailments due to masturbation | |
| *Tila Ajeeb* | Nervine tonic & stimulants. | Naqais-e-Uzu-e-Tanasul | 500 mg LA |
| *Tila Ahmar* | Tonic for reproductive organ, Excretion of morbid matter | Weakness of reproductive organ | Q.S. LA at bedtime |
| *Tila Nishat Angez* | Tonic for reproductive organ | Deformity in sexual organs, Penile weakness, Pyrone's disease, Erectile dysfunction, Flaccidity of penis. | Q.S. LA at bedtime |
| *Muqawwi Mumsik* | Retentive of semen, Sexual tonic | Premature ejaculation, Sexual debility | 1gm with milk. |

**Dose:**
1/15 – 1/3 chawal (Grain) [14]

**Fatal Dose and Fatal Period:**
*Nisf dirham* (1.5 gm) of SF can cause death [12, 36]. No fixed period of fatality has been described in Classical Unani literature except the description that the fatality is more in the hot season than in the cold season [12, 21].

**Substitute:**
*Zarneekh* is considered the best substitute for SF [12, 20, 27]. However, another type of SF can also be a substitute [15, 16,18].

**Correctives:**
In the poisoning of SF, hot water or saline may use to induced emesis. Afterward, patients should be advised for taking plenty of milk. *Roghan-e-Zard* is the best corrective in the poisoning of SF [15, 16, 18, 37]. *Kath Safed* is also considered a *musleh* (correctives) of SF [15, 16, 18]. Other *muslehat* (correctives) are *Sheer-e-Goolar* [15], *Safedi Baiz-e-Murg* (white part of the egg), *Roghan-e-Bedanjeer*, *Roghan-e-Badam Sheerin*, *Dawa-ul-Misk Har*, *Jadwar*, *Jund Bedastar* and *Tiryāq-e-Farooq* [37]




Figure;3 Toxic Compounds [11, 17, 18, 22, 10, 13]

**Toxic Compounds of SF:**
Arsenic tri-sulphide and Arsenic di-sulphide are not soluble in water and not toxic in pure form, they are toxic when mixed with Arsenic trioxide. Copper Arsenite and Aceto Copper Arsenite, are also not soluble

in water and are used as colouring agents. Arsenic mixed with other substances and formed Arsenate such as Arsenate of Lead Sodium and Potassium [18].

**Toxicity /Adverse Effects:**
It should be taken carefully, especially in hot seasons and those patients who are having hot temperaments [36]. Hypotension, bradycardia, ruptured of capillaries, anesthesia [30], and internal swelling can occur [15]. Finely divided powder of SF can stick to the mucosa of the stomach, if used in an empty stomach, it can produce inflammation [37]. *SF* can also produce mortality, if used in higher doses [15,16]. The clinical manifestations include swelling of the face, burning sensation in GIT, heaviness of tongue, red-eye, vomiting and diarrhea, aesthesia of organs, restlessness, and feeling of heat in the body [3, 38, 39]. Chronic exposure to high concentrations of arsenic in drinking water (> 10 µg/L) is associated with several detrimental effects on human health including skin lesions [1] and cancer of the lung [40], bladder [41], kidney [42], and liver [42]. As a result of chronic exposure to high Arsenic concentrations dermatological, developmental, neurological [43], respiratory [44], cardiovascular [45], immunological [46], and endocrine effects [47] have been reported. The health effects of chronic exposure to low concentrations of Arsenic in drinking water, such as present in many parts of Western Europe and North America, are unclear [48, 49].

**Management of Poisoning:**
Management of poisoning of SF is similar to that of poisoning of mercury, but very few patients get to respond to the treatment because of its highly toxic nature [14, 22]. The line of treatment is aeration, nutrition, and excessive dehydration. Cow's ghee is very much useful. Emesis induced after taking ghee is two times more useful than taking the ghee alone. Taking charcoal made of the shell of animals is also beneficial [3, 29]. If SF causes irritation, skin eruption, and burning sensation in GIT after use, the first and basic principle of treatment is its discontinuation immediately. This dosage form should always be taken just after a meal and started with the lower dose. SF produces a cumulative effect so a gap of two or three days should be maintained after every ten to fifteen days if the treatment period is prolonged. In old people, it has to be used with extreme precautions [20].

**Method of purification of SF:**
SF in Fine powder form is immersed in a sufficient quantity of fresh *Aab-e-Leemu* (lemon juice) and ground in a mortar of China clay or glass till the juice is completely absorbed. This process is repeated seven times to obtain SF *Mudabbar* [35]

**DESCRIPTION OF ARSENIC TRIOXIDE IN MORDEN LITERATURE:**

**Principal Compounds:**
Arsenic has a range of oxidation states from -3 to +5, it can form a variety of different kinds of compounds and complexes. The most important commercial compounds are the oxides, the principal forms of which are arsenious oxide ($As_2O_5$). The major arsenic species found in environmental and clinical samples are arsenite $As^{III}$, arsenate $As^{V}$, arsenious acid ($H_3AsO_3$, $H_2AsO_3$, $HAsO^{2-}3$), arsenic acid ($H_3AsO_4$), $H_2AsO_4$, $HAsO^{2-}4$), di-memethyl-arsenate (DMA), methyl-arsonate (MMA), arseno-betain (AB) and arseno-choline (AC). Among the arsenic compounds in the environment, the most toxic one is arsenite, which is 10 times more toxic than arsenate and 70 times than methylated species like DMA and MMA. AB and AC are virtually non-toxic [33, 53].

**Current Therapeutic uses of Arsenic:**
Arsenic trioxide ($As_2O_3$) is now widely used to induce remission in patients with Acute Promyelocytic Leukaemia (APL), based on its mechanism as an inducer of apoptosis (programmed cell death). Arsenic induces apoptosis by releasing apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space from where it trans-locates to the cell nucleus. AIF then affects apoptosis, resulting in altered nuclear biochemistry, chromatin condensation, DNA fragmentation, and cell death. In relapsed patients with APL, treatment with low dose $As_2O_3$ induced incomplete differentiation of Acute Promyelocytic leukemia cells and resulted in complete remission in over 90 % of patients [51, 52].

**Pharmacokinetics of SF (Arsenic) in Human Body [38]:**

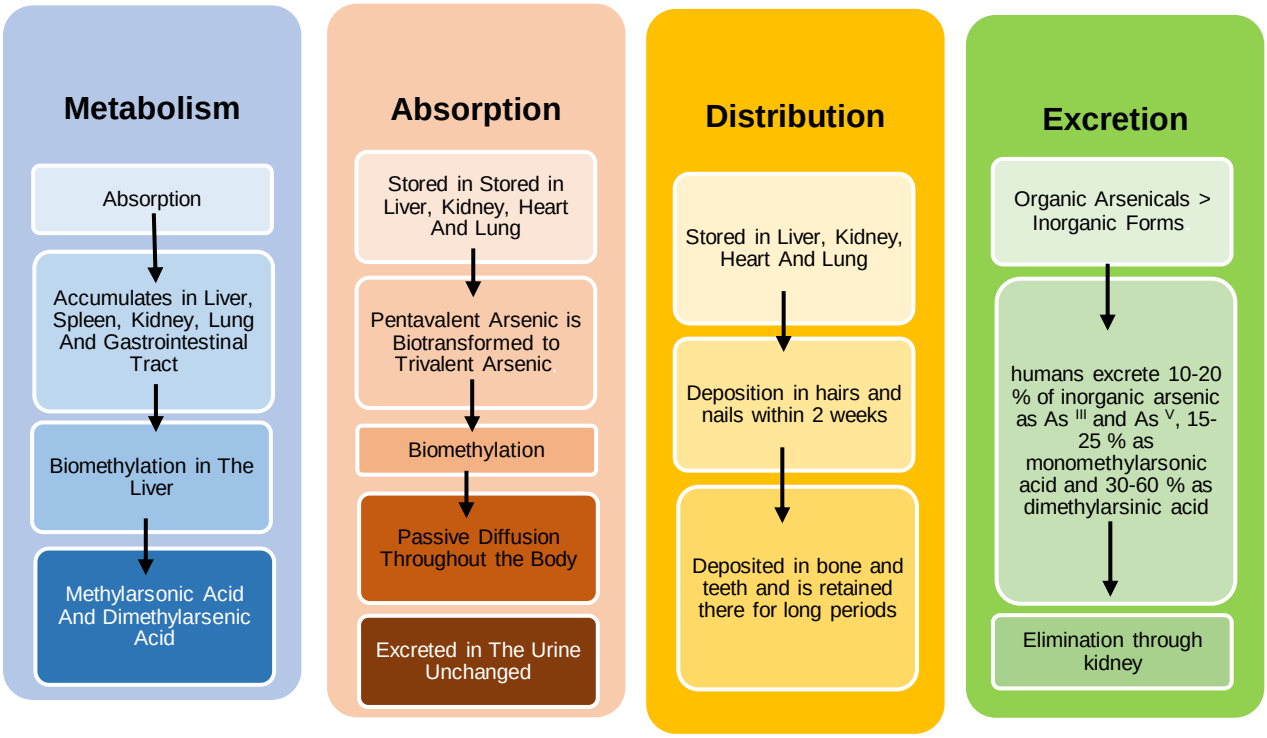



Figure: 4 Pharmacokinetics of SF (Arsenic) in Human Body

**EVIDENCE-BASED SCIENTIFIC STUDY:**

**Study 1: Chronic Toxicity of *Kushta Samm-ul-Far*:**

The study was carried out in healthy Wistar rats in a dose-dependent manner. The animals were divided into four groups. Group, I served as control, whereas groups II, III, and IV were used for three dose levels of the test drug i.e. The effective dose (ED50) of *kushta Samm-ul-Far* (KSF) in humans has been described in Unani literature as 10-15 mg. A low dose (8.75 mg–1 kg) of KSF did not produce remarkable toxic effects. Mild to moderate toxicity was observed in KSF-II (17.50 mg–1 kg) and higher (26.25 mg–1 kg) in KSF- III. Liver and kidney tissues were not markedly damaged, but because of more risk than benefit and low safety margin, the use of KSF in humans must be avoided as self-medication, because it is moderately toxic in rats. The study also validated the claim of Unani physicians regarding the use of KSF in low doses and a gap of certain periods for the next use [9].

**Study 2: Comparative Toxicity Studies on Various Dosage Forms of *Samm-ul-Far:***

An acute toxicity test was carried out in healthy albino mice by the method of Manna et.al. Twenty-four albino mice were divided into 4 equal groups. Group I served as control while groups II, III, and IV were used for determination of LD50 of KSCM (*Kushta Samm-ul-Far* as per NFUM), KSMF (Muffle Furnaces method), and **(***Samm-ul-Far Mudabbar*) (triturating SF with lemon juice) respectively. In the group administered KSCM the first response of decreased motor activity was observed at 341mg/kg and half of the animals died at the dose of 2896.40 mg/kg. The group administered KSMF showed the first response of decreased motor activity at the dose of 331.20 mg/kg. No animal died up to the dose of 8439.20 mg/kg and no further dosing was possible in this group. In the group administered SFM, the first response of decreased motor activity was observed at 200 mg/kg, and at the dose of 341.20 mg/kg, half of the animals died. This is evident that the toxic effect caused by the three samples has been found of different intensity and that caused by Kushta form was significantly lower than the non-kushta form of Arsenic. Further, KSMF induced lower toxicity as compared to KSCM suggesting that the preparation of Kushta by the furnace is safer than prepared by a conventional method [33].

**Study 3: Analgesic, Anxiolytic and Proconvulsant Effect of *Kushta Samm-ul-Far*:**

Siddiqui, et al. carried out analgesic, anxiolytic and proconvulsant activity on *Samm al-Fär*, namely *Kushta Samm-ul-Far Ätshaké* (KS-A) and *Kushta Samm-ul-Far Qawé* (KS-Q) in animals (rat and mice). The investigations were carried out on pentylenetetrazol and maximal electroshock-induced seizures in mice. Both varieties of Kushta in the dose of 5 mg/kg/PO have significant analgesic, anxiolytic and proconvulsant activity. KS-A (5 mg/kg p.o.) caused a significant reduction in onset time for various phases of convulsions and mortality vs vehicle-treated mice. KS-Q showed a similar convulsive tendency but the effects were not significant, the test drugs showed no acute toxicity and had a wide therapeutic index. It was concluded that these drugs have to be used by epileptic-prone individuals with caution [54].

## DISCUSSION:

In Unani medicine, among various formulations, as described in various pharmacopeias only a few drugs and formulations are there in which safety, efficacy, and toxicity studies have been carried out in both animals and human trials. In Unani system of medicine, toxicity studies are not being conducted in a well-organized manner as is carried out in modern medicine, rather is denoted under the heading of *Mazarrat* (toxic effects) observed after giving a certain dose level directly on a human being, which does always not give precise results. Toxicity study and toxicity at different forms and doses have been done till yet in the animal model on *Kushta Samm-ul-Far* but no clinical trial has been carried out scientifically. Thus, it is evident that the various indication and uses have been mentioned of SF in classical Unani books and pharmacopeia. Methods of detoxification used by Unani physicians to make Arsenic safe are rational though the level of safety is different. It is likely the physicians may have adjusted the therapeutic efficacy of the drug at different dose levels.

Siddiqui, et al. study on animals (rat and mice) model showed that *Kushta Samm-ul-Far Ätshaké* (KS-A) and *Kushta Samm-ul-Far Qawé* (KS-Q) has analgesic and anxiolytic activity which was described by an ancient physician as a nervine tonic, a nervine stimulant which proves its health benefit. Similarly, a study carried out by Irshad et al. suggests that (*Samm-ul-Far mudabar*) SFM is toxic as it caused liver damage, renal injury and produced acute hepatitis and acute nephritis confirmed on histological findings. Based on the findings of Irshad et. al study, it can be said that mineral drugs can be used in the form of Kushta and can be prepared with the help of a muffle furnace which was found in his study to be safer even than that prepared by the classical method by using the Thermogram prepared. Studied carried out Wadud et.al on KSF produced dose-dependent toxicity. KSF-1, i.e. low dose of KSF did not produce remarkable toxic effects. Mild to moderate toxicity was observed in KSF-II and KSF- III. Though, liver and kidney tissues were not markedly damaged.

The mode of action (concerning the carcinogenic activity of Arsenic) and dose-response characteristics (especially at low Arsenic concentrations), which are required for the identification of an acceptable exposure level, are not fully evaluated [48, 50]. Apart from that, If Arsenic is regarded as a threshold chemical, a tolerable daily intake (TDI) should be derived. The TDI is an estimate of the dose of a substance, expressed on a bodyweight basis (mg/kg of body weight), that can be ingested daily over a lifetime without appreciable health risk. In general, the TDI can be based on animal or human studies, but for As, the current risk evaluations prefer to rely on human data, because the (carcinogenic) effects of Arsenic on humans are difficult to reproduce in animal studies, probably due to differences in Arsenic metabolism and as consequence differences in toxicological effects [48, 50].

## CONCLUSION:

Unani physicians had described various uses of SF for skin, blood, sexual and nervine disorders. Besides *kushta* form, SF is also used in *Tila, Habb, Majoon*, and *Roghan* forms for both external and internal uses. The old methods of manufacturing the drugs have to be changed by modern technology. Development of hepatitis or nephropathy after administration of the drug is a very serious sign of toxicity and should be ruled out after administrating SF. If possible, it used should be confined for external uses. The use of *SF Mudabbar* as a therapeutic agent should be avoided in clinical practice. Because of the risk-benefit ratio (more risk than benefit) and low safety margin, the use of KSF particularly prolong use in humans should be warned as self-medication must be avoided, as it was found moderately toxic in rats. The study also validated the claim of Unani physicians regarding the use of KSF in low doses and a gap of the certain period for the next use. In the current scenario, scientific studies have been done namely on acute and sub-acute toxicity studies on the animal model in the kushta form. Further research may be done to explore the potentials of SF in various forms and doses both preclinically and clinically with modern scientific parameters.

**Conflict of interest**
There is no conflict of interest

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