

Review Article

Sammulfar pharmacological uses and toxicological effect on systemic organs a revive studies

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ABSTRACT

Sammulfar (Arsenic) is a versatile mineral. It is inorganic and organic compound, it belongs to group VA of the periodic table, arsenic is an anti-leukemic agent. In the form of sodium arsenite solution it was the first effective systemic chemotherapy for a neoplastic disease reported by Lissauer. The "arsenic" utilized by criminals and murderers is typically the trioxide form As_2O_3 , also known as "white arsenic" or the mineral arsenolite, arsenic compounds are classified into three major groups based on their biology and toxicology like Inorganic arsenic compounds, organic arsenic compounds, Arsenic gas. It is used in Unani system of medicine pharmacological actions and therapeutic uses, many important Unani formulations like Kusta Sammulfar, Habb-e-Ahmar Tila-e-Ajeeb etc its temperament (Mizaj) garam khusk 4°. It is toxic element, arsenic have found acute and chronic toxicity effect on systemic organ likes immune system, skin, hepatic portal system, cardiovascular system, gastrointestinal system, neurological system, genitourinary system, respiratory system etc.

Keywords; Sammulfar, Arsenic, Unani classical literature, Pharmacological uses, Toxicological effect

INTRODUCTION

Sammulfar is a versatile mineral, forming various compounds, either inorganic or organic. Inorganic arsenic occurs naturally in many different kinds of forms, including trivalent (As_3^+) and pentavalent (As_5^+). Arsenic has atomic number 33 and atomic mass 74.92, its chemical and physical properties a metalloid, also known as a semimetal, is an intermediate between a metal and a non-metal. It belongs to group VA of the periodic table and can exist in four oxidation states -3, 0 +3 and +5 arsenit as III and arsenate as V, are the predominant oxidation states according to the reducing and oxygenated conditions. Most rocks contain 1-5 ppm of arsenic. Trivalent forms include arsenic trioxide, sodium arsenite, and arsenic trichloride. Numerous living things, including humans and shellfish, create organic arsenic, which is much less toxic than inorganic arsenic, through the biomethylation procedure. The element of arsenic occurs naturally in rocks and soil; industrial manufacturing is

accountable for the vast majority of arsenic discharged into the environment.^{1,2} Up to the 1970s, arsenic was used in medicine in limited applications. Inorganic arsenic was used to treat leukemia, psoriasis, and bronchial asthma, while organic arsenic was used in antibiotics to treat spirochetes and protozoan disease³ Arsenic is an anti-leukemic agent. In the form of sodium arsenite solution it was the first effective systemic chemotherapy for a neoplastic disease reported as far back as in 1865 by Lissauer.⁴ The Greek philosopher Aristotle mentioned a substance in the 4th century BC that was most likely the arsenic sulphide mineral realgar (AsS), and it is almost certain that arsenic compounds were used in the poisoning murders that were so common in imperial Rome. Arsenic occurs naturally in nature, but it is rarely found in its native form. The "arsenic" utilized by criminals and murderers is typically the trioxide form, As_2O_3 , also known as "white arsenic" or the mineral arsenolite, while minerals including arsenic have been known during history, the discovery of the element itself is usually credited to the German a scholar Albertus

Magnus surrounding 1250 AD. But, ironically, given its effect on human health, it was the medieval physician Paracelsus who provided the first detailed methods for the preparation of elemental arsenic.⁵ Sammulfar (arsenic) has been used as a drug in China for more than 2,400 years, with examples such as the arsenic-containing drug realgar mentioned in Shennong's Herbal Classic.⁶ Sammulfar is the Arabic name for arsenic. It is a chemical compound. Arsenic acid is a by-product that exists as a solid, heavy, white powder, stratified masses, or minute transparent and glass-like crystal, tasteless, soluble in water (1 in 100), boiling water (1 in 10), glycerine (1 in 5), very slightly in alcohol, alkalis, carbonates, and hydrochloric acid⁷ it is used in Unani system of medicine. It is used as Muqavvi Bah (Aphrodisiac), Atishak (Syphilis), Suzak (Gonorrhoea), Bawwaseer (Piles), Wajaul Mafasil (Arthralgia), and other Amraz Balghami (phlegmatic diseases), Muqawwi aasab (Nervine Tonic), Mohalil awram (Anti-inflammatory) used in many diseases.^{7,8}

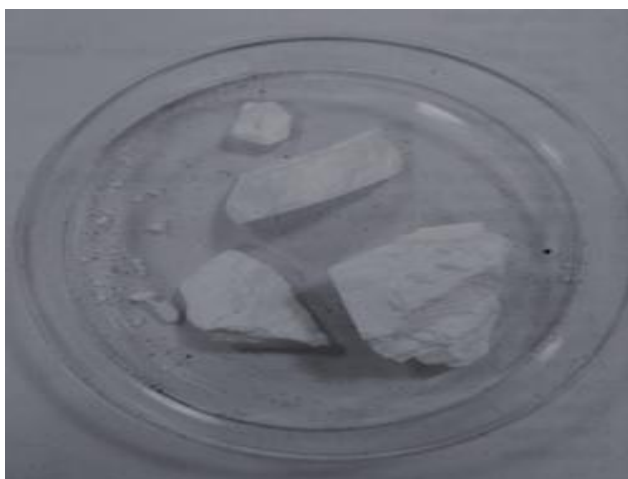


Figure 1: Sammulfar.

VERNACULAR NAMES

Following are the vernacular names-Arabic-Sammulfar, Bengali; Sambulkhar, Burma; Tien, Hypso, Cannad; Sankhya pashana, Duk; Safed sambala, English; Arsenious, White oxide of arsenic, White arsenic, Flowers of arsenic, Gujrati; Somalkhar, Hindi; Sankhya, Konkan; Sankhya ppashana, Malayalam; Warnanganpulih, Marathi; Sankhya sambala, Persian; Margemosha, Sanskrit; Sankhavisha, Darumucha, Sambalakshara, Sindh; Sudu pasanum, Tamil; Vella pashanum, Telugu; Tela pashanum.^{7,8}

SOURCES

Sammulfar (Arsenic) is found in arsenical ores as arsenates of iron, nickel or cobalt; commercial Arsenious acid is obtained by roasting the native ores, in the form of sublimate. Arsenic, a metal, is widely distributed in nature, but in trace amount. With oxygen it forms Arsenious acid.⁷ Sammulfar is an important constituent of

more than 200 mineral species, of which approximately 60% are arsenate, 20% are sulphide and sulphosalts, and the remaining 20% include arsenides, arsenites, oxides, and elemental arsenic.⁹ The primary arsenic mineral is arsenopyrite, FeAsS, and arsenic occurs attached to numerous kinds of mineral deposits, particularly those that consist of sulphide mineralization.¹⁰ Sammulfar (Arsenic) is estimated that approximately one-third of the arsenic in the atmosphere comes from natural sources. Volcanic activity is the primary natural source of arsenic.¹¹ Elevated concentrations (>1 mg As/L) in groundwater of geochemical origins have also been found in Taiwan, West Bengal, India, most districts of Bangladesh, Elevated arsenic concentrations were also found in the drinking water in Chile, North Mexico, and several areas of Argentina, Arsenic contaminated groundwater was also found in parts of PR China (Xinjiang and Inner Mongolia) and the USA (California, Utah, Nevada, Washington and Alaska).¹¹ Arsenic is mainly transported in the environment by water. In oxygenated water, arsenic usually Occurs as arsenate, but under reducing conditions, for instance, in deep well-waters, arsenites Predominate. In water, the methylation of inorganic arsenic to methyl- and dimethyl arsenic acids is associated with biological activity. Some marine organisms have been shown to transform inorganic arsenic into more complex organic compounds, such as arsenobetaine, arsenocholine and arsonium phospholipids. In oxygenated soil, inorganic arsenic is present in the pentavalent form. Under reducing conditions, it is in the trivalent form. Leaching of arsenate is slow because of binding to hydrous oxides of iron and aluminium. There is ample evidence of bio methylation in the soil and of the release of methyl arsines into the air. However, airborne arsenic is mainly inorganic.¹²

Types of sammulfar

Arsenic compounds are classified into three major groups based on their biology and toxicology. -Inorganic arsenic compounds, organic arsenic compounds and arsenic gas.¹³

COMMON ARSENIC COMPOUNDS

Common arsenic compounds are as follows-Arsenic (As), Arsenic acid (CH_6AsNO_3), Arsenic pentoxide (AsO_5), Arsenic sulfide ($\text{As}_2 \text{S}_3$), Arsenic trichloride (AsCl_3), Arsenic trioxide (AsO_3), Arsenobetaine ($\text{C}_5\text{H}_{11}\text{AsO}_2$), Asinine (AsH_3), Calcium arsenate (AsO_4)₂ 3Ca, Dimethyl arsenic acid ($\text{C}_3\text{H}_7\text{AsO}_2$), Lead arsenate (HAsO_4Pb), Methane arsenic acid disodium salt ($\text{CH}_4\text{AsO}_3\text{2Na}$), Methane arsenic acid (CH_4AsO_3), Potassium arsenate ($\text{H}_2\text{AsO}_4\text{K}$), Potassium arsenide (AsO_2K), Sodium arsenate (AsO_4Na), Sodium arsenide (AsO_2Na), Sodium cocodylate ($\text{C}_2\text{H}_6\text{AsO}_2\text{Na}$).¹⁴⁻¹⁶

IMPORTANT UNANI FARMULATIONS

Some of important unani formulations are as follows-Kusta Sammulfar, Habb-e-Ahmar, Johar-e-Seen, Habb-e-

Ahmar, Habb-e-Falij, Habb-e-Shuk, Habb-e-Pan, Habb-e-Sammul Far, Habb-e-Sammul Far Musakkin, Habb-e-Kalaf, Nuqrai, Jauhar-e-Munaqqa, Jauhar-e-Seen, Jauhar-e-Seemab, Jauhar-e-Kalan, Kushta-e-Sammul Far Aatishaki, Kushta-e sammul Far Aatishaki Qawi, Tila-e-Majlooh, Tila-e-surkh, Tila Ajeeb, Tila Ahmar, Tila Nishat Angez, Muqawwi Mumsik.¹⁷⁻²⁰

Table 1: Temperament (Mizaj) and doses.

Variables	Values
Temperament (mizaj) ^{8,54}	Garam khusk 4°
	Garam khusk 4°
Doses ^{7,8,17,19,20,54}	1/60 to 1/12 Chawal
	10-15 mg
	3-5 grain
	1-5 mg

PHARMACOLOGICAL ACTIONS IN UNANI CLASSICAL LITERATURE

Following are the pharmacological actions in unani classical literature-Amraz-e- Balghami (Phlegmatic disease), Daf-e-Atishak (Anti-syphilis), Daf-e-humma (Antipyretic), Daf-e-Nafakh shikam (Antiflacculant), Daf-e-zeequn-nafs (Anti-asthmatic), Mohalil (Anti-inflammatory), Moharrik (Stimulant), Moharriq Qalb (Cardiac Stimulant), Muharrik tanaffus (Respiratory Stimulant), Mukharriz (Irritant), Muqawwi aasab (Nervine Tonic), Muqawwi bah (Sexual stimulant), Muqawwi -e-Aam (General Tonic), Musaffi khoon (Blood Purifier), Musakkin aasab (Nerve sedative), Musakkin-e-Alam (Analgesic), Mushil (Purgative), Raqs (Chorea), Wajaul Mufasil (Arthralgia).^{7,8,17,19}

THERAPEUTIC USES IN UNANI CLASSICAL LITERATURE

Aatishak (Syphilis), Abyazud Dam (Leukemia), Daus sadaf (Psoriasis), Faqr-ur Dam (Anaemia), Hudar (Rheumatism), Humma-e- Ajamiya (Intermittent fever), Iltehab sabat ur riya (Bronchitis), Is-hal (Diarrhea), Istisqa (Ascitis), Laqwa (Paralysis), Qillatu dam (Pernicious anaemia), Sailan-e-Rahem (Leucorrhoea), Sartan (Cancer), Sil (Phthisis), Sual (Cough), Su-e-Hazam (Dyspepsia), Uqr (Impotence), Usr-e-Tanaffus (Dyspnea), Wajaul Mufasil (Joint Pain), Wjaul -Asab (Neuralgia), Zeequn-nafs (Asthma), and Ziyabetus (Diabetes) are some therapeutic uses in unani classical literature.^{7,8,17}

NORMAL TISSUE AND BLOOD LEVELS

In Bombay, human serum arsenic levels have been determined to be below 0.02 µg/mL using atomic absorption spectrometry, the average daily urinary excretion of arsenic ranges from 2 to 25 µg, 788 US adults had a median urine level of 7.1 µg / L for total arsenic, 3.0 µg/L for dimethyl arsenate, and 0.9 µg/L for arsenobetaine. The arsenic level found in hair was

0.15±0.35 mg/kg, nails 0.34±0.25 mg/kg, and liver 0.16±0.04 mg/kg.²¹

TOXIC EFFECT OF SAMMULFAR

Arsenic has five valence states (As³⁻, As⁰, As²⁺, As³⁺, and As⁵⁺). The toxicity of arsenic varies with its valence state. Organic arsenic is less toxic than inorganic arsenic, while trivalent arsenic is more toxic than pentavalent arsenic, there are two types of arsenic poisoning, acute and chronic poisoning.²²

Acute toxicity

Immediate arsenic poisoning may occur from the accidental ingestion of pesticides or insecticides, as well as the attempt suicide. Taking less than 5 mg cause vomiting and diarrhoea, which resolve within 12 hours without treatment? Acute poisoning lethal doses range from 100 mg to 300 mg, and depending on the total amount, death occurs within 24 hours to 4 days, some clinical features observed are nausea, vomiting, abdominal pain, acute psychosis, skin rash and seizures.²³ Haematological abnormalities, respiratory failure, pulmonary oedema, frequent neurological manifestations like peripheral neuropathy and metabolic changes are also reported. Best indicator of recent ingestion (1-2 days) is urinary arsenic concentration.²⁴

Chronic toxicity

Long term exposure to arsenic leads to arsenic poisoning or arsenicosis. The absorbed arsenic accumulates in liver, lungs, kidney, muscles, nervous system, spleen and heart with smaller amounts depositing in keratin rich tissues like hair, skin and nails even at low exposure. This leads to multiple organ failure and hence malignancy. General clinical features include skin lesions with hyperpigmentation, depigmentation, and hyperkeratosis, arsenic-related malignancies of the skin, lung, kidney and liver, vascular diseases such as peripheral and cardiovascular diseases, arteriosclerosis, Blackfoot disease (BFD), and Hypertension. Non-specific symptoms include abdominal pain, diarrhoea, dyspepsia and mental slowing or loss of memory.²⁵ Exfoliative dermatitis, keratosis, vitiligo, skin cancer, peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepatomegaly, splenomegaly, non-cirrhotic portal fibrosis (NCPF), peripheral vascular disease and, diabetes, and cancers of urinary bladder, lung and internal organs.²⁶

SYSTEMIC ORGAN TOXICITY OF SAMMULFAR

Immune system

Workers exposed to arsenic in air from burning coal (not further specified) did not have altered levels of antibodies in their blood, depression of white blood cells has not been reported in workers exposed by the inhalation route,

leukopenia is observed in cases of oral exposure to inorganic arsenicals.¹¹

Skin

Some information is available on effects due to direct dermal contact with inorganic arsenicals, but several studies indicate the main effect is local irritation and dermatitis, with little risk of other adverse effects. Usually the effects are mild (erythema and swelling) but may progress to papules, vesicles, or necrotic lesions in extreme cases.²⁷ Skin variations are common, and the initial clinical diagnosis is usually based on hyperpigmentation palmar and solar keratosis. The keratosis may present as smooth thickening or as discrete nodules.²⁸ It is emphasized that both palmar and solar keratosis are a significant diagnostic criterion. Hyperpigmentation occurs as diffuse dark brown spots, or less discrete diffuse darkening of the skin, or has a characteristic "rain drop" appearance.²⁹ Bowen's disease, an arsenic-related skin cancer, is uncommon in Asians and may be caused by high skin melanin content and increased exposure to ultraviolet radiation. Arsenic may cause basal cell carcinoma in non-melanin pigmented skin. The latent period after exposure can last up to 60 years and has been reported in patients treated with Fowler's solution, sheep dip workers, vineyard workers using arsenical pesticides, and from drinking contaminated wine.³⁰ Arsenic deposition in keratin-rich areas also causes prominent transverse white lines in the fingernails and toenails known as Mee's lines.³¹ Large population based studies from West Bengal in India show a relationship between arsenic concentration in tube well water, dose per body weight, and hyperpigmentation and keratosis, and those persons with a poor nutritional status were more susceptible. However, study reports that arsenic induced skin lesions occur among. At a Camino people in northern Chile, despite a good nutritional status, eyes are affected locally.²⁹ Workers exposed to arsenic dusts in the air have been observed to develop chemical conjunctivitis, characterized by redness, swelling, and pain, usually in conjunction with facial dermatitis.^{32,33}

Hepatic portal system

Santra et al have studied hepatic abnormalities in 248 clinic patients (195 men) with clinical evidence of chronic arsenic toxicity, which had been exposed to arsenic contaminated drinking water for up to 15 years. Twenty-three control subjects from the same area who were exposed to arsenic-free water for 12 years were also included. Of these 248 patients, 77% had hepatomegaly, 20% splenomegaly, ascites 2%, 'rain drop' pigmentation of skin in 94%, keratosis in 65%, anemia in 44%, cough in 67%, and dyspnoea in 62% is found.³⁴ These workers and others, as stated above, also found in non-cirrhotic portal fibrosis (NCPF) patients (exposed to increased arsenic contaminated water), an increased levels of arsenic in serum, hair, nails and liver tissue.³⁵

Gastrointestinal system

Gastrointestinal diarrhoea is a significant and early symptom of acute arsenic poisoning; it occurs in recurrent bouts and may be accompanied by vomiting in chronic toxicity. If other symptoms like skin changes and neuropathy are present, arsenic ingestion should be suspected.³⁶ Arsenic inhalation, whether acute or sub-acute, can cause a variety of gastrointestinal symptoms, ranging from mild abdominal cramping and diarrhoea to severe, life-threatening haemorrhagic gastroenteritis with shock. Mild-to-moderate hepatocellular necrosis, demonstrated by increases in serum transaminase, may occur with chronic exposure to arsenic, overt gastrointestinal symptoms are often absent; however, and chronic concentrations might nonetheless be associated with important organ-system pathology.³⁷ No cirrhotic portal hypertension is a rare but relatively specific gastrointestinal symptom caused by chronic inorganic arsenic ingestion from medications or drinking water. Because hepatic function remains intact, the condition might not come to clinical attention until advanced stages when the patient might present with gastrointestinal haemorrhage secondary to oesophageal varices.⁴⁹⁻⁵³

Cardiovascular system

County, USA, based on a matrix for cumulative arsenic exposure, a significant increase in mortality in both males and females from hypertensive heart disease occurred. In 1999, Rahman et al in Bangladesh identified an increased incidence of hypertension in a large study of 1481 subjects who consumed arsenic in well water.³⁸ Small doses of inorganic arsenicals induce mild vasodilatation: large doses (acute intoxication) evoke prominent effects on the circulatory system.²¹

Neurological system

Signs of peripheral and/or central neuropathy are common in humans exposed to inorganic arsenicals by the inhalation and oral route. Acute, high-dose exposure Effects can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability.³⁹⁻⁴¹ The nervous system is the primary target for the harmful effects of many metals, particularly heavy metals such as mercury, lead, and arsenic. The neurological effects are many and varied. The most frequent finding is a peripheral neuropathy mimicking Guillain-Barré syndrome with similar electromyography findings.⁴² An increased prevalence of cerebrovascular disease, especially cerebral infarction, was observed in a large study of 8102 men and women who experienced long term arsenic exposure from well water.⁴³

Genitourinary system

The Millard County study also found an increase in deaths from nephritis and prostate cancer. Guo et al investigated information from cancer registry records

(1980-87) of tumours of the bladder and kidney in Taiwan and reported that high arsenic levels in drinking water from wells were associated with transitional cell carcinomas of the bladder, kidney, ureter, and all urethral cancers in both males and females, and adenocarcinomas of the bladder in males.⁴⁴

Respiratory system

Inhalation of inorganic arsenic dusts (usually containing mainly arsenic trioxide) is irritating to the nose, throat, and lungs, and can lead to laryngitis, bronchitis, and rhinitis (without an indication of an allergic response).^{32,33} Studies from West Bengal, India draw attention to both restrictive and obstructive lung disease.²⁸ Patients with chronic arsenic toxicity's characteristic skin lesions were more likely to develop respiratory disease.⁴⁵ Similar findings of an association between skin manifestations and lung disease was reported in Chilean children.⁴² The possibility of increased deposition of arsenic in the lung, although the reason is not known, is supported by necropsy studies in a limited number of patients.^{46,47} An increased incidence of bronchitis occurs in a study on patients with black foot disease in Taiwan.⁴⁸

CONCLUSION

Sammulfar (Arsenic) is used in traditional system of medicine Ayurveda Siddha and Unani, it is the first effective systemic chemotherapy for a neoplastic disease reported by Lissauer. But arsenic is toxic elements The "arsenic" utilized by criminals and murderers is typically the trioxide form As_2O_3 , also known as "white arsenic" Two types of toxicity found by arsenic, acute and chronic. Acute adverse effects nausea, vomiting, abdominal pain, acute psychosis, skin rash and seizures, haematological abnormalities, respiratory failure, pulmonary oedema, frequent neurological manifestations like peripheral neuropathy and metabolic changes are also reported. Chronic adverse effects hyperpigmentation, depigmentation, and hyperkeratosis, arsenic-related malignancies of the skin, lung, kidney and liver, vascular diseases such as peripheral and cardiovascular diseases, arteriosclerosis, BFD, and hypertension, abdominal pain, diarrhoea, dyspepsia and mental slowing or loss of memory, exfoliate dermatitis, keratosis, vitiligo, skin cancer, peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepatomegaly, splenomegaly, NCPF, peripheral vascular disease and, diabetes, and cancers of urinary bladder, lung and internal organs etc. Organs that function as a system Adverse and toxic effects include, Immune system, leukopenia, Skin hyperpigmentation, palmar and solar keratosis, and hepatic portal system. NCPF of the Gastrointestinal system diarrhoea, vomiting, cardiovascular system; hypertensive heart disease, Neurological system; encephalopathy, confusion, hallucinations, Guillain-Barre syndrome, Genitourinary system; nephritis, prostate, cancer, transitional cell carcinomas of the bladder, kidney, ureter, and all urethral cancers in both males and

females, adenocarcinomas, respiratory system; laryngitis, bronchitis, and rhinitis, obstructive lung disease etc.

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