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Review Article

HISTORICAL AND PHARMACOLOGICAL REVIEW ON A UNANI DRUG OF MINERAL ORIGIN: NUQRA (SILVER)

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Abstract:

Nuqra (Silver) is one of the precious metals used medicinally for a long time. It is soft, ductile and white coloured metal having resistance to corrosion. Mexico is the world leader in silver production. In India it is obtained in Rajasthan and Karnataka. Owing to sterilization property, the Persian kings used silver vessels to store and transport the drinking water. Nuqra possesses a cold and dry temperament. Nuqra is medicinally used in three forms: Warq (Leaves), Kushta (calx) and in liquid form (Nuqra sayyal/Ma ul Fizza). Its preparations are used for the treatment of cardiac ailments like Khafqan (palpitation), weakness of vital organs, premature ejaculation, increased nocturnal emission, attenuated semen and decreased libido, insanity, Melancholia and obsession. Purification of silver is recommended before its medicinal use. Long term exposure to silver may cause toxic effects; turning the colour of skin and other body tissues to gray or blue-gray (argyria). In a recent clinical trial Warq Nuqra (silver leaves) exhibited to have hypolipidemic, hypoglycemic, hepatoprotective and cardioprotective effects. Other studies have confirmed antiviral, antifungal, antibacterial, analgesic, antiinflammatory and hypnotic activity of silver. Nano silver particles (AgNPs) are a recent trend as bioenhancer (to enhance the activity) for other drugs. Present review will be helpful for researchers for further research on Nuqra and its preparations.

Key words: Nuqra, Silver, Unani Medicine, Kushta Nuqra, Warq Nuqra, Fizza

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INTRODUCTION:

Nuqra (silver) is brilliant white, malleable, ductile and soft metal having resistance to corrosion or atmospheric oxidation even at high temperatures. *Nuqra* (silver) loses lustre or turns black when it comes in contact with sulfur vapours. The silver reacts with sulfur to form a thin coating of black coloured silver sulfide. It is a very good conductor of heat and electricity.^[1,2] The word silver is derived from *silabar or silubr or silfr, silubra*, the words of Teutonic (Germanic) languages. In Latin language the silver is called *Argentum* which means 'white or shining' and chemical symbol of silver Ag is also derived from its latin name^[3]

The Unani physicians use *Nuqra* (Silver) and its preparations for strengthening vital organs and treatment of other ailments like weakness of nerves, palpitation, melancholia, and premature ejaculation.^[4] Various forms of silver are described for medicinal purpose by the famous Unani scholar Ibn Sina (Avicenna) in his book *Al Qanoon fil Tibb (Canon of Medicine)*; (i) *Sohaala* (سھالہ): It is splinter of silver. (ii) *Qalimiah fizza* (Litharge of silver/Dross of Silver/ قليميا): it is smoke or dross emanating at the time of metal casting. It is also something which settles down like the scales of metal. (iii) Burnt silver (*Ihraagh*, احراق): It is obtained by burning silver *sohaala* with water, salt and sulfur. The Ibn Sina also used different medical equipment made up of silver namely; (i) Silver tube as a breathing tube: in cases of *khonaagh* (*Diphtheria*), hollow tube made from silver or gold to help patients breathe was referred. (ii) Catheter, (قناطير) with silver needle: Ibn Sina used a hard, hollow and thin needle made of silver, with a round point with several holes on it for treating problems in the urinary system. (iii) Silver *Anboob* to excise warts: It is a sharp edged, hollow thin silver cylinder. This cylinder is placed around the wart, and wart is excised with a sudden pressure and twist. Ghee is applied on the wound. (iv) Silver nail protection: Ibn Sina recommended use of silver thimble having holes for ventilation to protect the nail, and to provide a safe environment for it to grow.^[5]

Colloidal silver is the liquid form of silver which contains its particle suspended in a liquid. It was extensively used as a germicide in hospitals at the beginning of the 20th century. Intravenously colloidal silver did not cause irritation in kidney and pigmentation of the skin in early nineteenth century. The use of colloidal silver discontinued after development of antibiotics.^[6]

In today's world silver is being used in nanotechnology. Silver particles in size of 25 nm are used as nano silver in a wide range of healthcare products for example dressings for acne and cavity wounds, burns, scald, skin donor and recipient sites. It is also used in female hygiene products-panty liners, sanitary towels and pants. Nano silver is fast acting, non-allergic, nontoxic and hydrophilic in nature. Nano silver coating improves bactericidal and fungicidal effects in healthcare products by enhancing the surface area and increases its contact with microbes (bacteria or fungi).^[7]

Material Methods:

The present review includes the information available in Unani classical literature for its complete description viz. temperament, actions, therapeutic, and dosage uses etc. For History, quality standards, pharmacological actions, toxicity and other aspects to prove the importance of *Nuqra* the information available in computerized databases such as Medline,

PubMed, Ovid SP, Google Scholar and Science-direct has been included.

History of Medicinal Use of *Nuqra* (silver):

Though no native silver or silver ores occur in Egypt, the earliest use of *Nuqra* (Silver) was reported in Egypt before 5000 BCE. Silver objects of the Predynastic Period such as beads and amulets have been found.^[8] Mining of Silver was first reported in Anatolia, located in modern-day Turkey around 3,000 BCE. The precious metal helped to flourish early civilizations in the Near East and Ancient Greece.^[9] Herodotus, the Father of History, says that Persian kings, including Cirrus, were aware of the sterilization property of silver that's why they drink water stored only in silver vessels. During military conflicts fresh water from natural sources was transported in silver containers, which kept water fresh for years.^[10] *Buqrat* (Hippocrates) the father of medicine used silver preparations for the treatment of ulcers, prevention of infections and to promote wound healing. The ancient Greeks, Romans, Phoenicians, Egyptians, and others also used silver in various forms to preserve food and water, and this practice was continued till World War II. The Macedonians are thought to use silver plates to achieve better wound healing and this was supposed to be the first attempt to prevent or treat surgical infections. The medical use of silver nitrate was mentioned in a pharmacopeia published in Rome in 69 B.C.E. The medicinal properties of *Nuqra* (Silver) became popular between 702AD to 980 AD in the Middle East. *Jabir Bin Hayyan* (Gabor) and *Ibne Sina* (Avicenna) used silver filings as a blood purifier, to prevent palpitations, other cardiac ailments and to treat bad breath (halitosis). The Alchemists connected the seven planets to the seven days of the week as well as to parts of the body. He also connected silver to the moon and the brain, giving rise to terms such as 'the silver moon' and 'lunatic.' The lunatic is synonymous with insanity. Silver coin was later used to prevent tongue bite during epileptic seizures.^[11] In the North American continent, to drop the silver coin in a water vessel for preservation during transportation was common practice. Without knowing the fact that silver prevents bacterial growth, the North Americans also used silver coins to preserve milk and prevent spoilage. The prevalence of argyria (silver poisoning) was not documented prior to 1800. During plaque epidemics argyria was reported to be associated with a reduced mortality rate other infectious diseases. Peoples using silver utensils for food usually developed a bluish-gray discoloration of the skin (argyria). They often avoid sunlight owing to fear that bluish discoloration might become even more prominent. Owing to the healing property of silver, James Marion Sims (1813-1883), the father of modern gynaecology was the first American Surgeon who sutured vesico-vaginal fistula by using silver wire. He also used silver catheters for urinary diversion until the repairs had healed.^[12] Carl Siegmund Franz Credé (1819-1892) a German gynaecologist and obstetrician introduced the use 2% silver nitrate solution as eye drop to prevent *ophthalmia neonatorum*^[13]. Colloidal form of silver was used by AL Roe for the treatment of infected corneal ulcers, interstitial keratitis, blepharitis, and dacryocystitis.^[14]

The great Unani Physician of India, Hakim Ajmal Khan (1868-1927), introduced the use of silver in liquid form in his *Matab* (clinic) to strengthen the vital organs. He named it *Nuqra Sayyal*. This liquid was prepared by adding 01 tola (10 gm) powdered

silver with Nitric acid; 05 tola (50 ml) and water; 03 tola (30 ml). This mixture was subjected to heat on low flame till silver particles dissolved. Then the liquid was strained and one tenth of water was added in it. Preserved in a sterile container. It was given to the patients in the dose of 02-03 drops with water.^[15]

Occurrence:

Silver is rarely found in its pure metallic form (native form). In India, only a small deposit of native silver is found in Rajasthan. *Nuqra* Silver is generally found associated with lead, zinc, copper and gold ores. It is obtained as a co-product as well as by-product from electrolysis or chemical methods. Silver is obtained as from gold, lead, zinc and copper refining and smelting as co product. Globally Mexico leads in terms of silver production, followed by Peru, Australia, China, Chile, Bolivia, USA and Russia.^[16]



Silver Ore (Courtesy: Dept of Geology, AMU Aligarh)

Vernacular names^[1,4,17-28]

Arabic: Fizz, Bangla: Rupa, English: Silver, Hindi: Chandi, Rupa, Persian: Nuqra, Seem, Latin: Argentum, Sanskrit: Rajata, Rupa, Rupya, Urdu: Chandi

Temperament: Cold and Dry^[4,17-28]

Actions: As per Unani literature its action are; *Mufarreh* (Exhilarant), *Muqawwi-e-Qalb* (Cardiac tonic), *Muqawwi-e-Dimagh* (Brain tonic), *Muqawwi-e-Kabid* (Liver tonic), *Muqawwi-e Meda* (Stomachic), *Mughalliz-e-Mani* (Inspissant to semen), *Muqawwi-e-Badan* (General tonic).^[4,17-28]

Therapeutic Uses: *Nuqra* is medicinally used in three forms: *Warq* (Leaves), *Kushta* (calx) and in liquid form (*Nuqra sayyal/Ma ul Fizza*). Its preparations are used to treat cardiac ailments like *Khafqan* (palpitation), to strengthen vital organs, to treat male sexual disorders such as premature ejaculation, increased nocturnal emission, attenuated semen and decreased libido, to treat neuropsychiatric disorders like *Junoon* (insanity), *Melancholia* and *Waswas* (obsession), to treat respiratory disorders like cough, asthma and phthisis, to treat spleen inflammation, to treat gastrointestinal disorder like diarrhoea and to treat obesity. Taking meals in silver utensils is exhilarating. It is believed that consuming alcohol in silver utensils may lead to early drunkenness/intoxication. Application of *Surma* (Collyrium) in eyes with a silver stick improves vision. Putting pure silver in your mouth can quench the thirst. A confection made of *Gaozaban*, amber, silver leaves and sugar equal parts is useful to treat hysteria and other anxiety disorders. A preparation made of *Warq Nuqra* (silver leaf) 4 no, *Filfil Daraz* (*Piper longum* Linn.) 6 no, *Filfil siyah* (*Piper nigrum* Linn.) 2 no, *Saad Kufi* (*Cyperus rotundus*) 2 g, rock salt 2 g, and borax 4 parts; the whole triturated in cow's urine is useful to treat the obesity.^[1,4,17-28]

Potent Action: *Muqawwi-e-Aza-e-Raeesa* (tonic for principal organs).^[4,17-28]

Dosage: For *Kushta* (calx); 30-125 mg (calx), *Warq* (silver leaf); 1-2 no^[18-21,23-27] *Sayyal*; 02-03 drops with water.^[15]

Adverse Action: According to Unani literature *Nuqra* can produce adverse effects on Intestines and Urinary Bladder^[4,18-21,23-28].

Correctives: To counter the adverse effects of *Nuqra, Kateera* (*Astragalus gummifer*) and Honey has been recommended by Scholars^[4,18-21, 23-28].

Substitute: In case of non-availability of *Nuqra, Firoza* (Turquoise) may be used as a substitute.^[4,18-21,23-28]

Purification: Before using *Nuqra* for medicinal purposes, a purification process is recommended to remove its impurities. It can be purified in following manner:

- Heat the thin Silver foils till it becomes red and damp down them by immersing in the leaves juice of Agati plant (*Sesbania grandiflora* L) for seven times.
- Make a very thin foil of silver in which a needle can penetrate, heat them and damp down by immersing in lemon juice for seven times.^[29]
- Heat the silver foils till it becomes red and damp down them by immersing in the juices of tamarind and grapes separately for seven times.^[18]

Quality Standards of Nuqra: The Scientists have laid down the quality standard of *Nuqra* for its medicinal use.

Physical properties: Nature: It should be granular, nuggets and feather like dendrites, Colour: It should be Silver white, turning greyish black due to tarnishing, Streak: White, Cleavage: None Fracture: Hackly, Lustre: It is metallic, Tenacity: malleable, Sectile and ductile Transparency: it is opaque and hardness 2.5 to 3.0, with Sp.Gr: of 10.1 to 11.1.

Chemical Properties:

Reaction with Acids: Prepare solution of *Nuqra* in nitric acid and add Hydrochloric acid to it. A dense white curdy precipitate, soluble in ammonia of silver chloride is obtained. **Solubility:** Soluble in nitric acid. **Assay:** *Nuqra* should contain not less than 98.5% Silver (Ag) when analysed by Atomic Absorption Spectrophotometer.

Heavy metals and Arsenic: In *Nuqra* Mercury, Lead, Arsenic and Cadmium should be absent.

Other Elements: May contain the following within \pm 20% of the stated limits: Copper; 1.40 %, Sulphur; traces and Gold; 0.001%. [30]

Important Formulations: Some important classical Unani formulations having *Nuqra* as ingredients mentioned in National Formulary of Unani Medicine are as follows:

Habb-e-Jawahir, Habb-e-Muanaish, Habb-e-Nishat, Kushta Nuqra, Kushta Marjan Jawahar Wala, Anoshdaru Lulavi, Khamira Gaozaban Ambari Jawahar wala, Khamira Zahar Mohra, Majoon Hamal Ambari Alvi Khani, Mufarreh Barid Jawahar Wali, Mufarreh Barid Qawi, Mufarreh Yaqooti Motadil, Jawahar Mohra^[31] *Jawahar Nuqra, Majoon Petha Pak, Jawarish Amla Ambari*^[32] *Habb-e-Kafoor Marwaridi, Habb-e-Taon Qawi, Kushta Sang-e-Yashab Qawi, Mufarreh Azam*^[33] *Habb-e Quadrat*^[34]

*Habb-e-Jalinoos, Habb-e-Jawahar, Habb-e-Khas, Habb-e-Mumsik Ambari, Habb Mumsik-ul-Surkh, Habb-e-Nazla, Habb-e-Seen, Habb-e-Zeequn Nafas, Qurs Fizza, Kohlul Jawahar, Dawa-ul-Misk Barid Jawahar Wali, Itrifal Muqawwi Dimagh, Khamira Abresham Hakim Arshad Wala, Khamira Gauzaban Ambari, Khamira Gauzaban Ambari Jadwar Ood Saleeb Wala, Khamira Gauzaban Ambari Jawahar wala, Khamira Marwareed, Khamira Marwareed Banuskha-e-Kalan, Khamira Murakkab, Khamira Nazli Jawahirwala, Majun Jiryana Khas, Majun Murawweh ul Arwah, Majun Mughalliz Jawaharwali, Majun Muqawwi Reham, Majun Muqawwi-wa-Mumsik, Majun Musaffi Khas, Majun Nuqra, Majun Salab, Majun Tila, Mufarrah Shaikh-ur-Rais^[35], Habb-e-Mumsik Jadeed, Habb-e-Nishat Jadeed, Nuqrai, Qalbeen, Halwa Baiza-e-Murgh, Halwa Muqawwi, Khamira Sadaf, Zehbi, Majoon Moin-ul Hamal Ambari, Majun Nishat Angaiz, Muqawwi Mumsik, Shababi^[36]. Apart from above formulations, Hakim Kabiruddin in his book *Kitab Al Taklis* has mentioned seventy varieties of *Kushta Nuqra*^[37].*

Nuqra(Silver) toxicity in Human Body: *Nuqra* (Silver) is a non-essential, accumulative and ultratrace element to the human body. No physiological functions or deficiency syndrome of silver has been reported. Absorption of silver in the human body occurs through the dermal, respiratory and oral route. Silver may enter the human body by drinking water that contains silver or eating food grown in soil containing silver. Ten percent of absorbed silver is retained in the reticulo-endothelial system and 90% is excreted through faeces and urine within a week. Exposure to dust containing high amounts of silver may cause irritation in the throat and lungs, breathing problems, and stomach pain. In some individuals dermal contact with silver compounds may cause mild allergic reactions, such as rash, swelling, and inflammation. Long term exposure to silver may lead to gray or blue-gray colour of skin and other body tissues (argyria). This discoloration of skin is irreversible. Permissible limit of silver in drinking water upto 0.10 milligrams per liter of water (0.10 mg/L). The National Institute of Occupational Safety and Health (NIOSH) has recommended maximum limit of silver in air at workplace air upto 0.01 mg/m³.^[38,39]

Pharmacological activities of *Nuqra* (Silver):

Analgesic activity:

Kushta Nuqra, Rupyha Bhasm and *Chandi Warq* in the dose of 25-50 mg/kg orally exhibited moderate to marked analgesic effects in the animal model.^[40] Ash of silver in a dose of 50 mg/kg p.o showed analgesic activity against thermal, mechanical, and chemical stimuli compared aspirin in chemical stimulus.^[41]

Antiallergic effect:

Application of 1% nanocrystalline silver cream significantly inhibited allergic contact dermatitis in mice.^[42]

Antibacterial activity:

In vitro antibacterial activity of silver nanoparticles have been reported against methicillin resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Pseudomonas aeruginosa*, *Vibrio cholera* and *Bacillus subtilis*. Silver nanoparticles in low concentration consistently inhibit the growth of *E. coli* while the growth inhibitory effect on *S. Aureus* was minimal. Silver nanoparticles have shown synergistic antimicrobial effect with *ampicillin*, *penicillin G*, *amoxicillin*, *kanamycin*, *erythromycin*,

clindamycin, *chloramphenicol* and *vancomycin* against *S. aureus*, *E. coli*, *Salmonella typhi* and *Micrococcus luteus*.^[43]

Anticancer activity:

It is the fact that *Nuqra* (silver) possesses anticancer activity, the silver nanoparticles can be used for cancer treatment. It will be an advantage for anticancer treatment in two ways; intrinsic anticancer properties of silver, and silver nanoparticles can be used as carriers of anticancer drugs.^[44]

Antifungal activity:

Nano particles of silver have exhibited significant antifungal activity against *Penicillium citrinum*, *Aspergillus niger*, *Trichophyton Mentagrophytes* and *Candida albicans*^[43,45-46].

Antiinflammatory activity:

Vidhu Aeri *et al* conducted in vitro study on *Rupyha Bhasma* (Silver calx) to evaluate its antiinflammatory effect. It was concluded that *Rupyha Bhasma* possessed a significant in vitro anti-inflammatory effect against the denaturation of protein.^[47] Silver nanoparticles (AgNPs), have shown anti-inflammatory activities in both animal models and in clinical trials.^[48]

Antimalarial effect:

Silver nanoparticles (AgNPs) have shown significant activity against malarial parasite (*P. falciparum*) and its vector (female *Anopheles* mosquito).^[49]

Antiviral activity:

Silver nanoparticles have shown antiviral activity against wide range of viruses viz; Human immunodeficiency virus type 1 (HIV-1), Hepatitis B virus, Respiratory syncytial virus, *Herpes simplex virus type 1*, *Monkey pox virus*, *Influenza virus* and *Tacaribe virus*.^[43]

Cardioprotective activity:

Warq Nuqra significantly reduces the heart specific CPK fraction (CPK MB) in human subjects. When given in a dose of 50 mg wrapped around 10 gm of milk cake for 20 days and not causing any side effect on the heart and other organs of the body.^[50]

Effect on Cystitis:

Intravesical administration of nanocrystalline silver (1%) decreased the urinary bladder inflammation without any toxic effect.^[51]

Effect on Ulcerative Colitis:

Nanocrystalline silver in the dose of 4 mg/kg intracolonicly or 40 mg/kg orally, significantly reduced colonic inflammation in animal model (rat) in comparison to the placebo and no-treatment groups.^[52]

Hepatoprotective activity:

Treatment with *Warq Nuqra* in the dose of 50 mg wrapped around 10 gm of milk cake for 20 days has significantly reduces the liver enzymes (glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT)) in human volunteers cared to its baseline markers with end of the treatment^[50].

Hypoglycemic, activity

Warq Nuqra in the dose of 50 mg wrapped around 10 gm of milk cake for 20 days significantly control blood glucose level compared to baseline and end of the treatment. No adverse effect was observed in the volunteers after the treatment^[50].

Hypolipidemic activity:

In human volunteers *Warq Nuqra* in the dose of 50 mg wrapped around 10 gm of milk cake for 20 days significantly control the lipid profile (cholesterol and HDL-cholesterol) in comparison to baseline and after intervention. The drug was well tolerated and no adverse effect was reported in human trial^[50].

Neuropsychobehavioural Effects:

Kushta Nuqra, *Rupya Bhasm* and *Chandi Warq* in the dose of 25-50 mg/kg orally in the animal model exhibited anti cataleptic, anti-anxiety and anti-aggressive effects.^[53]

Sedative-Hypnotic effect:

Ash of silver in the dose of 50 mg/kg per oral exhibited statistically significant sedation in comparison to the control group of mice.^[54]

CONCLUSION:

Unani system of medicine is one of the oldest health care system of medicine established in India. Its materia medica is so rich covers herbal, mineral and animal sources of medicine for all the ailments^[55-67]. Minerals and metals have a great importance for their medicinal use in Unani Medicine. *Nuqra* (Silver) is one of precious metals used as medicine in different forms since antiquity. The antibacterial activity of *Nuqra* has been recognised since the time of *Buqrat*. The recent pharmacological activities of silver and its preparations viz; antibacterial activity^[40], cardioprotective activity^[50], anti-cataleptic, anti-anxiety activity^[53], anti-inflammatory activity on urinary bladder inflammation, ulcerative colitis^[47-48,52] justify the claim of Unani scholar for its use in cardiac, neuropsychiatric, gastrointestinal and urinary bladder disorders ailments. The ash of silver/*Kushta Nuqra*/silver calx may be called traditional nano-silver. The particle size of *Kushta Nuqra* is found to be 10-15 nm. As per Unani literature, to get nano sized *kushtas* through various processes have to be followed e.g. purification of metal/mineral followed by levigation (powdering) and repeated calcinations till the loss of impurities in final formulation. Use of nano-silver particles for targeted drug delivery is trending to enhance safety and efficacy of drugs. To synthesize nano-silver in the laboratory, the fruit extract of Amla (*Emblica officinalis*) and leaf extract of Neem (*Azadirachtaindica*), Kishneez (*Coriandrum sativum*) etc are used as reducing agents.^[47] Quality standards of *Nuqra* for medicinal use have been established. Various pharmacological activities have been conducted. Further, studies may be planned to evaluate the safety and efficacy of *Nuqra* formulations.

Conflict of Interest: none

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