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## Azaraqī (*Strychnos nux-vomica* L.) herb for nervous and musculoskeletal system

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### ABSTRACT

Nature has always been a giver, bearing rich heritage of natural products which are being utilized by mankind since their existence. Azaraqī (*Strychnos nux-vomica* L.) is a potential herb used for the treatment of various neuronal illness, musculoskeletal and joint disorders. This comes under category IV of drugs as per Unani literature which needs to be detoxified prior to clinical use. The healing properties of Azaraqī (*Strychnos nux-vomica* L.) are substantially those of the alkaloids strychnine and brucine, which are considered toxic. The perception of lesser side effects of herbal formulation among the people especially in developing countries raised the market of treatment by natural products. However, there is need to put forward the scientific evidence of these formulation regarding toxicity as well as efficacy as then only evidence based medicine would only be able to make position in globalized world as an alternative of conventional treatment available. This review article will discuss the potential pharmacological actions; toxicity developed due to Azaraqī resulted out in different preclinical and clinical studies. The authors will try to make a suggestion for future based on finding of these studies.

**Keywords:** Herbal drug, Azaraqī, strychnine, brucine.

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## Introduction

The inquisitive attitude of mankind and the contribution of nature have led to discovery of enormous beneficial as well as toxic herbs. Azaraq, is one such herb that is therapeutically potent yet toxic in nature, which consist of dried, ripe seeds of *Strychnos nux-vomica* L., belonging to family Loganiaceae rich in alkaloids of the indole and oxindole groups [1]. It is a deciduous medium sized tree, leaves are ovate and 2-3.5 inches in size [2], seeds are hard, round to disclike, one side being convex while other is concave, with a dark gray horny endosperm, bitter in taste. Flowering and fruiting occurs in March and April [3]. The active principles are the alkaloids strychnine and brucine, the latter being more abundant in the bark of the tree. They act at the spinal anterior horn cells where they inhibit the post synaptic inhibitor glycine by competitive antagonism; the result is uncontrolled contraction of all muscle groups [4]. Strychnine exerts a more powerful influence on the spinal cord and particularly on the motor tracts; it also stimulates the special senses like sight, hearing and touch [5]. The alkaloid strychnine has human LD50 as 0.7-2.1mg/kg [6]. The usual lethal dose of strychnine is reported to be between 50 and 100 mg and the common cause of death is respiratory failure [7]. Azaraq is a deadly poison [8] and is detoxified (*mudabbar* in Unani) before its use for the preparation of drug. Azaraq *mudabbar* (*Strychnos nux-vomica* L.) which is endowed with properties like Musakkin (Analgesic), Muqawwi-e-Asaab (Nervine tonic), Moharrik (stimulant) and Muhallil (Resolvent) [9] is used in clinical practice.

A toxic effect of a drug is a result of excessive pharmacological action of the drug due to over dosage or prolonged use [10]. According to Unani theory, there are four degrees in which plant derived drugs are categorized, first and second degree of drugs is generally considered to be safe, while third and fourth degree of drugs is naturally toxic in their properties. Therefore, these third and fourth category drugs are detoxified or purified in order to reduce their

toxicity and to enhance their therapeutic action. The process is known as Tadbeere Advia and the drugs which undergo this process are suffixed with the term; Musaffa/Mudabbar/Maghsool [11]. Many studies have given indication and proven that the herbal formulations are also associated with several side effects including allergic reactions, hepatotoxicity [12], nephrotoxicity [13, 14], cardiac toxicity [15], neurotoxicity [16] and even death [17].

Azaraq is to be used with caution and prolonged use may cause toxicity and this has been mentioned by Najam-ul- Ghani in his book *khazaen-e-Advia*, Hakeem Mohd Azam in his book *Muheet-e-Azam* [18] and Hakeem Mohd kabeeruddin in his book *Bayaz-e-kabeer* [19]. The differential diagnosis of *Strychnos nux-vomica* poisoning is done with tetanus and this can be traced in ancient classical Unani literature [20]. Compound formulations containing Azaraq are Habb-e-Azaraq, Majoon Azaraq, Qurs hudar, Majoonlina [21]. As per Unani literature, compound formulations containing Azaraq are contraindicated in hypertension [22].

## History

It is derived from Greek word *Strychnos*, meaning poisonous and *nux vomica* indicates a nut with vomiting effects. The drug was used in sixteenth century to kill animals because of its poisonous nature. The alkaloids that were first isolated were strychnine in 1817, and brucine in 1819 [23].

## Scientific classification:

Kingdom	Plantae
Clade	Angiosperm
Clade	Eudicots
Clade	Asterids
Order	Gentianales
Family	Loganiaceae
Genus	<i>Strychnos</i>
Species	<i>S. nux-vomica</i>

**Vernaculars:** [24] The plant is known by different names in different languages, areas and traditions, which are stated below-

Arabic	Khanekulkella, Izaragi, Leuzalke.
Bengali	kachila, kuchila, thalkesur
Cambodia	Slengthom
a	
Catalan	Mataca
Chinese	Ma qianzi
Danish	Braeknoed
Dutch	Braaknoot, kraanoog
English	Nuxvomica, Snakwood, poisonnut, quakerbuttons, crow-fig, Semenstrychni.
French	Noixvomique
German	Brechnuss, Gemeinerbrech, Nussbaum
Gujarati	Kuchla
Hindi	Bailewa, Chibbenge, Kajra, Kuchla
Italian	Nocevomica, Stricnina
Japanese	Machin.
e	
Urdu/Urdu	Azaraq, Kuchla, Khaniqulqalb, Habbul-
ni-	gurab

**Geographical Distribution** –It is distributed in Ceylon, India, Burma, Thailand, Cambodia, and South Vietnam<sup>[25]</sup>. Basically it is indigenous to East India and found abundantly in South India, largely collected from forests of Tamil Nadu, Kerala and Malabar Coast.

**Mizaj (Temperament)** - The mizaj of Azaraq has been described unanimously by Unani physicians as Hot and Dry in third degree<sup>[26]</sup>.

**Therapeutic Dose- 60-250 mg**<sup>[27]</sup>

**Detoxification of Azaraq-** Azaraq needs detoxification before its use and it is achieved by several methods mentioned in classical Unani texts that are described as follows-<sup>[28]</sup>

- Using water and cow milk-Azaraq seeds are immersed in excess of water for 5 days with change of water every day, followed by immersion in milk for 2 days, changing the milk every day. The seeds are washed with water and boiled in milk till the seed coat become soft, they are then removed and cotyledons are powdered.
- Using cow milk- Azaraq seeds are immersed in milk for 7 days with change in milk every day, then seeds are washed and boiled to make seed coat soft for removal and cotyledons are powdered.
- Using clarified butter-Azaraq seeds are roasted in *Roghan-e-zard* (clarified butter

from cow milk) till the color of seed coat turns light reddish and seeds swell for its removal and cotyledons are powdered.

- Using yellow clay and milk-Azaraq seeds (70gms) are buried in yellow clay for 10 days keeping the clay moist throughout, then seeds are washed and seed coats are removed and cotyledons are separated after removing the embryo, the healthy cotyledons are then washed with hot water, put in cloth bag and are boiled in 2 litres of milk till it evaporates and now this water washed cotyledons are then used subsequently.

### Pharmacological Actions and Uses-

Various systems of medicine have been using nuxvomica since antiquity as it possesses stimulant properties. Seeds are Mushtahi (Appetizer), Muharrik (Stimulant) and Muqawwi-e-asab (Nervine tonic), Muharrik marakaz-e-tanaffus and qalb and dauran –e-khoon (Stimulant to respiratory, cardiac and circulatory system), Muqawwi-e- bah (Aphrodisiac), tiryaq-e-sumoom (Antidote), hayya (larvicidal), daf-e-amraz-e-balghamiya (cures phlegmatic diseases) and usbaniya, Muqawwi-e-meda (stomachic) and masana (urinary bladder tonic), musaffi-e-dam (Blood purifier), munaffis and mukhrij-e-balgham (Expectorant), Muhallil (Resolvent). Unani system of medicine have used this herb in Falij (paralysis), Laqwa (facial palsy), Niqris (gout) and Waja –al-Mafāsīl (rheumatoid arthritis)<sup>[29]</sup>. It increases peristaltic movement of gastro intestinal tract, increasing the flow of gastric juice therefore acts as gastrointestinal stimulant. Powdered seeds are used for atonic dyspepsia. Moreover, mainly used in paralytic and neuralgic disorders, in cases of debility or inactivity of the spinal system of nerves. Seed is considered as nervine, stomachic, tonic, aphrodisiac and cardiac, respiratory and spinal stimulant. Bark is used as tonic and febrifuge. Also used in rheumatism, habitual constipation. Locally, it is beneficial in treating chronic chloasma, dermatophytosis.

**Scientificallly Validated Studies of *Strychnos nux-vomica* L.**

Pharmacological activity	Part used	Effect
Anticonvulsant activity	Ethanollic seed extract	Reduction of spontaneous motor activity and inhibition of catalepsy <sup>[30,31]</sup>
Analgesic and anti-inflammatory activity	aqueous methanolic leaf extract	Inhibitory action on the synthesis and /or release of inflammatory mediators such as PGE <sub>2</sub> ,TNF- $\alpha$ and thereby reduced pain and writhing behavior. <sup>[32,33,34]</sup>
Antioxidant activity	Alcoholic seed extract	Inhibition of lipid peroxidation in a dose dependent manner (FeSO <sub>4</sub> induced lipid peroxidation was inhibited through chelation of Fe <sup>++</sup> / Fe <sub>+++</sub> ion in the system) <sup>[35]</sup>
Anti-cancerous activity	Aqueous seed extract,root extract, aqueous methanolic leaf extract	G2/M phase arrest and apoptosis in AGS gastric carcinoma,Anti-proliferative and cytotoxic activity in a dose and time dependent manner on human Multiple Myeloma-cell,RPMI 8226 through apoptosisand disruption of mitochondrial membrane,cytotoxic to human epidermoid larynx carcinoma (Hep-2),breast carcinoma (MCF-7) and colon carcinoma cell lines. <sup>[36,37,34]</sup>
Anti-tumor activity	major alkaloids from seed extract	Inhibits human hepatoma cell line-SMMC-7721(Hep G2) proliferation.apoptosis by brucine via participation of caspase-3 and cyclooxygenase-2.Mitochondrial membrane depolarization through Ca <sup>2+</sup> and Bcl-2 mediated pathway <sup>[38,39,40,41]</sup>
Anti-amnesic activity	Loganin	Inhibits acetyl cholinesteraseactivity in the hippocampus and frontal cortex. <sup>[42]</sup>
Anti-diabetic activity	Alcoholic and aqueous seed extract	Increases uptake of glucose at tissue level,increases pancreatic beta cell function and inhibition of intestinal absorption of glucose. <sup>[43,44]</sup>
Anti- diarrhoeal activity	Methanolic root bark extract	Reduced induction time of diarrhea and total weight of faeces. <sup>[45]</sup>
Antipyretic activity	Aqueous methanolic leaf extract	Dose dependent inhibitory effect on hyperthermia.antipyretic effect started as early as 1 h and maintained upto 5h after extract administration I given at 400mg/kg bw. <sup>[34]</sup>
Hepatoprotective and anticholestatic activity	Loganin	Dose dependent activity on the viability of hepatocytes and the reversal of reduced parameters of bile. <sup>[46]</sup>
Anti-snake venom activity	Seed extract	Effectively neutralized <i>Daboiarusselii</i> snake venom induced lethal hemorrhage,defibrinogenating,PLA2 enzyme activity and <i>NajaKaouthia</i> venom induced cardiotoxic,neurotoxic,PLA2 enzyme activity.bears potential polyvalent snake venom antiserum properties. <sup>[47]</sup>
Anti-allergic and immunomodulatory activity	Aqueous stem extract	Suppressive activity on allergen-specific IgE antibody response <sup>[48]</sup>
Helicobacter pylori	Ethanollic extract	Potent inhibitors of HB-EGF-like growth factor gene expression <sup>[49]</sup>
Larvicidal activity	Leaf extract	Potent larvicidal effect against third instar larvae of <i>Culexquinquefasciatus</i> <sup>[50]</sup>
Inhibitory corrosive activity	Seed extract	Effective inhibitor of corrosion of mild steel in hydrochloric acid media. <sup>[51]</sup>

**Preclinical Studies on *Strychnos nux-vomica* L.**

YEAR	STUDY TITLE	RESULT	REFERENCE
1998	Prevention of galactosamine-induced hepatic damage by natural product loganine from the plant <i>Strychnos nux-vomica</i> L.: studies on isolated hepatocytes and bile flow in Rats	Loganine showed Hepatoprotective and anticholestatic activity	52
2003	Pharmacokinetics of the alkaloids from processed seeds of <i>Strychnos nux-vomica</i> L. in Rats.	Good reference for pharmacokinetics in human bodies.	53
2003	Analgesic and anti-inflammatory properties of brucine and brucine N-oxide extracted from seeds of <i>Strychnos nux-vomica</i> L.	Reduction in the content of 5-HT in FCA-induced arthritis rat's blood plasma.	54
2004	<i>Strychnos nux-vomica</i> L. extract and its ultra-high dilution reduce voluntary Ethanol intake in Rats	Significant reduction of ethanol and increased water intake in rats	55
2008	Suppressive effect of <i>Strychnos nux-vomica</i> L. on induction of ovalbumin-specific IgE antibody response in mice	Suppressive activity on allergen-specific IgE antibody response	56
2009	Anti –inflammatory and anti-oxidant activity of <i>Strychnos nux-vomica</i> linn.		57
2012	Analgesic and anti-inflammatory activity and pharmacokinetics of alkaloids from seeds of <i>Strychnos nux-vomica</i> L. after transdermal administration: effect of changes in alkaloid composition	Strychnine removed from TAF to improve analgesic and anti-inflammatory activity and there is enhanced transdermal absorption of brucine.	58
2016	Study on anti-inflammatory and analgesic effects of different processing products of <i>Strychnos nux-vomica</i> L. seeds.	The anti –inflammatory and analgesic effects of vinegar processing <i>Strychnos nux-vomica</i> seeds was better than that of oil and sand processing products.	59
2016	Zebrafish model for assessing induced organ toxicity by <i>Strychnos nux-vomica</i> L.	Effect on the different organs of zebrafish, including heart, central nervous system, liver, and kidney, and cardiotoxicity induced by <i>Strychnos nux-vomica</i> L. was reversible to some extent.	60
2017	A novel Brucine gel transdermal delivery system designed for anti-inflammatory and analgesic activities	Inhibited arthritis symptoms and proliferation of synoviocytes in rat adjuvant arthritis model. Significantly relieved the xylene-induced ear edema in mouse ear swelling test	61
2018	Toxicological effects of <i>Nux-vomica</i> in rats urine and serum by means of clinical chemistry, histopathology and 1H NMR-based metabolomics approach	Disruption in glycolysis, lipid and amino acid metabolism, toxic effects aggravated in liver and kidney as dosing time prolonged.	62
2018	Prophylactic neuroprotection of total glucoside of <i>Paeoniae Radix Alba</i> against <i>Semen Strychni</i> -induced neurotoxicity in rats; suppressing oxidative stress and reducing the absorption of toxic components	SAs induces neurotoxicity after continued SA exposure and TGP showed significant pre-protective effects against neurotoxicity induced by SAs by suppressing oxidative stress and reducing the absorption of toxic components.	63
2018	Plasma metabolic profiling analysis of <i>Strychnos nux-vomica</i> Linn. And <i>Tripterygium Wilfordii</i> Hook F- induced renal toxicity using metabolomics coupled with UPLC/Q-TOF-MS.	Established nephrotoxicity induced by SNV and TwHF, revealing mechanism of renal injury.	64

## Phytochemistry

Total alkaloidal content ranges from 2.6%-3.0%, out of which, major chemical constituents are strychnine and brucine, others constituting to chlorogeniccolubrines, pseudostrychnine, novacine, icajine, isostrychnine, vomicine, trucine, brucine N-oxide, strychnine N-oxide, 3-hydroxy- $\alpha$ -colubrine, 3-hydroxy- $\beta$ -colubrine, 16-hydroxy- $\alpha$ -colubrine, 16-hydroxy- $\beta$ -colubrine, isobrucine, isobrucine N-oxide, isostrychnine N-oxide, 15-hydroxystrychnine, 2-hydroxy-3-methoxystrychnine, loganic, 6'-O-acetylloganic, 3'-O-acetylloganic and 7-O-acetylloganic acids<sup>[52]</sup>. Seeds contain 1.5% strychnine and brucine, and a glucoside, loganine while leaves contain 1.6% brucine and .025% strychnine. A study isolated a colored monoquaternary bisindole alkaloid from the roots<sup>[53]</sup>. Strychnine is a well-known potent antagonist of glycine receptors in the vertebrate central nervous system and a strong blocker of various types of muscle and neuronal nicotinic acetylcholine receptors<sup>[54, 55]</sup>. On the other hand, Brucine and brucine N-oxide have been proved to be mainly responsible for the analgesic effects produced by nux-vomica.

## Discussion

This article comprehensively reviewed the literature regarding *Strychnos nux-vomica* L. for its pharmacological and toxicological profile. The paper emphasizes, elaborates and widens the knowledge of this herb as it is considered as very potent and effective but toxic. Traditional medicines including Unani system of medicine has been using this herb as single and compound formulation since time immemorial depending upon well established literature indicating its efficacy; however safety data is yet to be accomplished. As per Unani system of medicine, compound formulation of *Strychnos nux-vomica* L. such as *Habb-e- Azaraq* is not recommended for prolonged use as it affects memory and brain functions, as indicated in

literature to use for 14 days then taper off the dose if possible<sup>[56]</sup>.

Similarly, toxicity studies on *Qurs-e-hudar* in albino rats revealed that if the same dose of drug containing the seed of strychnine without detoxification is given to the rats for the same period, animals showed convulsions and increased sensitivity towards light, smell and sound<sup>[57]</sup>. Medicinal capability of this herb is proven in both *in vitro* and *in vivo* studies. As evident from thorough literature review, complex science is involved as far as its alkaloids is concerned. The basic mechanism on which strychnine acts is glycine receptor antagonist that produces convulsion<sup>[58]</sup>.

Drug's toxicity is the degree to which a substance can do harm when acting on the human body with a certain dosage and time (Shaw et al., 1997). A drug cannot be just banned just because it contains toxic ingredients but its wide use in clinical application and its toxicity should be correctly understood and developed.<sup>[59]</sup> *Strychnos nux-vomica* L. having various alkaloids have been known and documented for toxic effects, fore.g. the apoptotic effect of brucine from seeds on human hepatoma cells is mediated via Bcl-2 and Ca<sup>2+</sup> involved mitochondrial pathway<sup>[60]</sup>.

Herbs and supplements can be toxic when used for inappropriate indications, or prepared inappropriately, or used in large excessive dosages, or for a prolonged duration of time<sup>[61]</sup>. Keeping in mind, the potential therapeutic uses of this herb in several ailments it is the need of the hour to have safety data of Unani drug that's lacking and which is creating hindrance in propagation and development of research in Unani system of medicine. Ensuring the safe use of *Strychnos nux-vomica* L. and in respect of its splendid efficacy, this herb should be taken into account for proper extensive research and analysis.

## Conclusion

The scientific field is inching towards advancements day by day and for this purpose

research data needs evidence. In this review paper, an approach is made to understand a broader framework of the use and toxicological profile of Azaraqi (*Strychnos nux-vomica* L.) which is being used for several decades in Unani system of medicine. The fact that it is detoxified as per Unani literature and have remarkable results in terms of its efficacy, this herb needs research attention. Keeping in consideration of the effectiveness of this herb and herbal remedies usage as self-medication by many people, it is necessary to be studied to its maximum extent and toxicity to be correctly understood thereby generating evidence based data in order to contribute to the ailing masses of the society and strengthening the research field.

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