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STRYCHNOS NUX VOMICA: A DRUG WITH MODERN THERAPEUTIC VALUES

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ABSTRACT

Strychnos nux vomica is a medicinal drug from the family Loganiaceae. In Indian and Chinese medicine, seeds of plants have been used traditionally. Despite it being a poisonous plant, its widely used for treating diseases like insomnia, rheumatism, epilepsy, emotional disorders, dysentery, joint pain, urinary disorders, itching, dyspepsia, neuralgia, and/or paralytic diseases. It has been shown to contain mainly alkaloids along with phenolic glycosides, iridoids, and flavonoids. Various preparations of *nux vomica* have shown properties such as neuropharmacological, anti-snake venom, anti-alcoholic, antidiabetic, gastroprotective, antipyretic, anticancer, antimicrobial, anti-inflammatory, anti-allergic, antinociceptive, antioxidant, and hepatoprotective. Also, clinical studies have shown that it has efficacy for rhinitis, insomnia, and sinusitis. The studies on *nux vomica* are preliminary demanding more in vivo and in vitro studies to definitively assess the role of its varying constituents and formulations. As it has brucine, strychnine, and alkaloids, it is highly toxic. Hence, more focus should be given to detoxifying it and reducing its toxicity without affecting its therapeutic efficacy. The present review is to assess its ethnomedicinal knowledge and scientific evidence about *nux vomica* to assess its future perspective, toxicity, and therapeutic potential.

Keywords: pharmacology, *S. nux vomica*, therapeutic value, toxicity

INTRODUCTION

Strychnos nux vomica is a medicinal plant with a high therapeutic value and is commonly known as a poisonous nut or *nux vomica* having high clinical application and therapeutic role. This plant is an inhabitant of mainly tropical Asia, Taiwan, North

Australia, Hainan, Guangxi, Guangdong, Fujian, the European Union, and the United States. In different countries, various parts of these plants have different indications and use, mainly the bark and the seeds. The plant is considered highly toxic to the human race and

domestic animals owing to its composition of main alkaloids especially due to Strychnine. When used in small doses, it has a valued

medicinal use in Chinese medicine and Indian Unani, Ayurveda, and Homeopathy.^{1,2}

In the current scenario, nux vomica is used in more than 60 forms in the Indian medicine system. Different plant components belonging to different phytochemical categories comprising alkaloids are utilized in the medical field. A wide range of therapeutic applications and the toxicity of the nux vomica are attributed to brucine, strychnine, and indole alkaloids' presence in the plant composition. Nux vomica has wide biological and pharmacological actions along with its high toxicity.³

In the past few decades, marked progress is seen in the toxicologic, pharmacologic, and phytochemical aspects of nux vomica. As detailed reviews are scarce in the literature for the pharmacologic and therapeutic aspects of nux vomica, the present review aimed to present collective data on the therapeutic value of nux vomica in various disorders and diseases.⁴

Ethnomedicinal use

The presence of Brucine, strychnine, and alkaloids are mainly attributed to the medicinal properties of the nux vomica. In the Indian scenario, along with the homeopathic use, the fruits are used in the Unani and Ayurvedic systems as antipyretic, aphrodisiac, tonic, and appetizer. Also, nux vomica is reported as an acceptable treatment modality for limb weakness, lumbago, joint pain, urinary disorders, jaundice, anemia, ulcers, piles, ringworm, itching, blood disorders, and leukoderma. The seeds of nux vomica, in India, are used for treating neuralgic affections, paralysis, spermatorrhea, urine incontinence, insomnia, hydrophobia, rheumatism, gout, fever, epilepsy, hysteria, emotional disorders, diabetes, cholera, atonic diarrhea, dysentery, nervous system disorders, dyspepsia, and as an alcohol antidote.^{5,6}

The juice obtained from the root bark and stem of the nux vomica is proven to be effective in acute dysentery, cholera, and intermittent fever cases. Bark infusion is also used in epilepsy and topical application is used for treating leprosy and ulcers. Leaves are applied topically to promote the health of the ulcers and sloughing wounds, mainly in maggots' formation.⁷

Pharmacological effects

Nux vomica is a plant with proven toxicity. However, it is widely used as a therapeutic formulation of various

kinds in different countries. Pure compounds, fractions, and the formulations of the plant have been widely assessed to identify its pharmacologic actions in both in vitro and in vivo models. Various pharmacologic actions considered are gastroprotective, anticancer, antibacterial, anti-inflammatory, anti-allergic, antinociceptive, hepatoprotective, antioxidant, and other actions described in subsequent sections.^{8,9}

Hepatoprotective

Nux vomica is considered a toxic drug. However, the extracts after processing are used in various formulations to treat various diseases including jaundice and liver ailments. In vivo setup has proved the hepatoprotective action of the processed seed extracts of nux vomica done on the liver injury induced in the rats. Reduced lipid peroxidation, restoration of glutathione (GSH), reduced cholesterol, bilirubin, alkaline phosphatase (ALP), glutamate oxaloacetate transaminase (GOT), and glutamate pyruvate transaminase (GPT) serum levels were seen for the oral dose of nux vomica given for the 5 days.¹⁰

Another study utilizing the nux vomica fruit has shown it to have hepatoprotective potential in galactosamine-induced liver injury in both in vivo and ex vivo models.¹¹ The hepatoprotective potential of nux vomica extract, login is established in treating the galactosamine-induced liver injury that reduces the bile contents, bile volume, and the viability of the hepatocytes.¹²

Antioxidant

Tripathi YB et al in 1996 were the first to establish the antioxidant property of the nux vomica. The ethanol extract of the nux vomica has been shown to inhibit lipid peroxidation in a dose-dependent manner by chelating the ferrous/ferric ion by tapping the hydroxyl radicals.¹³ Consecutively Chitra et al in 201¹⁴ showed that methanol extract of the nux vomica seeds showed a potent antioxidant action by increasing the antioxidant enzymes as catalase and SOD (superoxide dismutase) levels and reducing the lipid peroxidation as seen in the alloxan-induced diabetic rats. The antioxidant efficacy of nux vomica seed extract can be due to the presence of antioxidants including caffeic acid, hydroxybenzoic acid, lupeol, maltol, loganin, uvaol, and secoxyloganin.¹⁵

Apart from the methanol extracts, ethyl acetate, and chloroform extracts of nux vomica shows antioxidant capacity in vitro model concerning the scavenging of the free radicals. High scavenging activity is seen in the

methanol extract compared to the chloroform and ethyl acetate. Nux vomica is also shown to have high levels of enzymatic (ascorbic acid, α -tocopherol, and reduced glutathione) and non-enzymatic (superoxide dismutase, can be attributed to the presence of enzymatic and non-enzymatic antioxidant contents in its composition. However, to assess the antioxidant potential of nux vomica, further clinical studies are warranted. Also, a high free-radical scavenging action is seen in the methanol flower extract of the nux vomica.^{16,17}

Antinociceptive

In conventional Chinese medicine, seeds vomica seeds have been used in analgesic medicines. With the help of the hot plate, tail pressure, and acetic acid-induced writhing tests, PAF (processed alkaloidal fractions) and CAF (crude alkaloidal fractions) nux seed extracts were administered intraperitoneally and shown to exhibit antinociception in the mice model. Higher nociception was seen in the processed alkaloidal fractions administration compared to the crude alkaloidal fractions administration.¹⁸

In the same mice model, when MTAF (modified total alkaloid fractions) are given transdermally having the high brucine and low strychnine, a significant improvement in the analgesic effect was seen in comparison to the administration of the TAF (total alkaloid fraction). Strong antinociceptive action is seen with the brucine N-oxide and brucine, whereas, Strychnine shows a small antinociceptive action. It is also seen that brucine of MTAF has significantly higher transdermal absorption compared to brucine alone which can be a reason for the higher nociceptive action seen with MTAF. Hence it is reported that the antinociceptive efficacy of nux vomica seeds can be due to the synergistic action of the low strychnine levels with brucine N-oxide and brucine secondary to inhibition of the monoamine oxidase and COX (cyclooxygenase) activities.¹⁹

Recent literature data have reported that oral administration of nux vomica leaf extracts shows dose-dependent results where the analgesic efficacy in the animal models is seen at a dose of 400 mg/kg compared to 100mg/kg dose of the diclofenac. The analgesic efficacy is attributed to strychnine, brucine, and analgesic flavonoids. The mechanism behind the analgesic effect of nux vomica is the inhibition of central pain receptors along with lipoxygenase and COX.²⁰

Anti-allergic

ascorbate peroxidase, catalase, peroxidase, and polyphenol oxidase) antioxidant levels. Hence, it can be considered that the antioxidant efficacy of nux vomica

In traditional medicine, nux vomica has been used to cure allergic symptoms along with joint pain, arthritis, and inflammation. In vivo studies have shown that when the aqueous stem extract of nux vomica is administered intraperitoneally, it significantly reduced the expression of the IgE antibodies response that was specific to the ovalbumin in the mice hepatocytes without causing any significant alteration in total IgE antibody response against the ovalbumin.^{21,22}

Anti-inflammatory

In the test models, anti-inflammatory action is shown by different extracts from various parts of the nux vomica plant. Mitra S et al in 2011²³ reported that raw and purified seed extracts of nux vomica show a high anti-inflammatory action in the induced paw edema in the rats. Another study of 2014 by Kalaivanan C reported that MTAF of seed extracts from nux vomica having a low content of strychnine has higher anti-inflammatory action compared to TAF as a similar dose when assessed in the rat edema.²⁴ Brucine N-oxide, brucine, and strychnine, alkaloids of nux vomica seeds are the primary components of nux vomica responsible for its anti-inflammatory actions. In comparison to strychnine, a high anti-inflammatory potential is seen with Brucine N-oxide and brucine. Both brucine N-oxide and brucine have shown inhibition on the release of the PGE2 (prostaglandin E2) in inflammation cases along with reducing the vascular permeability induced by acetic acid and 6-keto- PGF1a content in the blood plasma of rats with induced arthritis.²⁵

Antimicrobial

A strong antimicrobial effect is seen for nux vomica bark of ethyl acetate extract in the MIC (minimal inhibitory concentration) and disc diffusion models. This antimicrobial effect of nux vomica is seen for pathogenic bacterial strains of both gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, and *Proteus Vulgaris*) and gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus faecalis* and *Staphylococcus Albus*) bacteria. Growth inhibitory potential is also seen in the leave extracts as ethanol, ethyl acetate, chloroform, and hexane with methanol extract showing the highest inhibitory action against *Shigella flexneri*, *P. mirabilis*, *P. Vulgaris*, *Vibrio cholera*, *E. coli*, *P. aeruginosa*, *S.*

aureus, *Salmonella typhimurium*, *K. pneumoniae*, and *Enterobacter faecalis*.^{26,27}

In a study by Gnanavel G et al in 201²⁸ n-butanol extract has shown a strong inhibitory action against pathogenic fungal strains including *A. niger*, *A. flavus*, and *A. terreus*, and the pathogenic bacterial strains and *B. subtilis*, *K. pneumoniae*, and *S. aureus*. In the disc diffusion method, a high anti-microbial effect is seen for fungal and bacterial strains including *Albicans*, *K. pneumoniae*, *B. subtilis*, *S. aureus*, *P. aeruginosa* by nux vomica flower methanolic extract. Nux vomica in dilution of 200 C has shown a strong antiviral action in Chicken embryo virus of fowls.²⁹

Anti-cancer

Methanol leaf extract from the nux vomica has been reported to have anti-proliferative action against the colon, breast, and larynx carcinoma cells at varying doses. In cancer development and progression, angiogenesis is a vital step. It has also been reported that Methanol leaves extract from the nux vomica has potential anti-angiogenic potential when assessed in an allantoic-chorion membrane assay model.³⁰

The extract from the roots of nux vomica has depicted the anti-proliferative activity in a time-dependent and dose-dependent manner in human myeloma cell lines. This showed that apoptosis of myeloma cells from the nux vomica root extracts with the potential of mitochondrial membrane destruction and leakage of mitochondrial cytochrome c is caused by brucine and strychnine.³¹

Various alkaloids that are biologically active including the icajine, pseudostrychnine, isobrucine N-oxide, isobrucine, isostrychnine N-oxide, 2-hydroxy-3-methoxystrychnine, isostrychnine, brucine N-oxide, strychnine N-oxide, β -colubrine, brucine, and strychnine are extracted from the nux vomica and has the inhibitory action of varying degree against various cancer cells. In these alkaloids, brucine is extensively studied for its anti-cancer properties. Various studies reported that brucine suppresses the angiogenesis in tumors mediated by VEGF (vascular endothelial growth factors) by inhibiting the signaling pathway for VEGFR2.^{32,33}

Also, brucine has shown strong anti-cancer activity against human carcinoma cells via caspase-dependent cell death by programmed apoptosis which shows the suppression of Bcl-2 protein overexpression, the elevation of intracellular Ca²⁺, caspase-3 activation, phosphatidylserine externalization, cell cycle arrest,

DNA fragmentation, and formation of apoptotic bodies. Brucine is also shown to inhibit lung metastasis in hepatocellular carcinoma by the HIF-1 (hypoxia-inducible factor 1) pathway.³⁴

Antipyretic

In the nux vomica, the antipyretic effect is exerted by the leaf extracts against the pyrexia against the yeast in the rat models as reported in 2015 by Eldahshan and Abdel-Daim. The methanolic leaf extracts show an antipyretic activity which is dose-dependent. However, high extract dose has shown comparable efficacy in comparison to standard paracetamol drugs.³⁵

Gastroprotective

In homeopathy, different formulations of seed extracts from nux vomica usually show a clinically vital treatment for the relaxation of bowels and stomach and atony, gastric ulcers, and gastritis. Recent data on highly diluted nux vomica seed extract formulated in ethanol has shown to decrease *Helicobacter pylori*-induced gene expression.³⁶

Antidiabetic

Nux vomica seeds are conventionally used to manage different disorders including diabetes. In recent times, oral administration of 50% ethanol and aqueous extract of nux vomica seeds has had hypoglycemic effects in diabetes-induced rats. Effectively significant results are seen to reduce glucose levels and results are comparable to gliclazide. The methanol seed extract of nux vomica was also shown to decrease the blood glucose levels along with reduced serum levels of BUN (blood urea nitrogen), creatinine, cholesterol, and total protein in diabetes-induced rats. These nux vomica leaves extract has shown an anti-diabetic potential which is dose-dependent by inhibiting the non-enzymatic hemoglobin glycosylation and α -amylase activity.³⁷

Neuropharmacological actions of nux vomica

Crude extract of the nux vomica is rarely used in the clinical scenario owing to it having a high strychnine content. However, it is used widely in alternative medicine following processing. Processed seed extracts in the sub-convulsive dose have been shown to significantly inhibit the convulsions induced by pentylenetetrazole and barbiturate-induced hypnosis in animals depicting its CNS depressant activity of the seed extract of nux vomica.³⁸

Processed seed extracts of nux vomica have an antagonist effect of morphine-induced catalepsy in rats that can support the use of nux vomica in various clinical situations in cases with muscle rigidity. Also,

brucine is shown to increase the acetylcholine binding to muscarinic receptors. Hence, nux vomica seed extract has proven beneficial in drug development for treating various neurologic diseases including Alzheimer's disease and Parkinson's disease.³⁹

Anti-snake venom

Nux vomica seed extract has a high anti-snake venom action in low doses. It has also been shown to neutralize the *Daboia russelii* venom inducing the phospholipase A2 (PLA2) enzyme activity inducing the defibrinogenation, hemorrhage, and lethal actions. It also decreases the PLA2 enzyme activity which is neurotoxic, cardiotoxic, and lethal and is induced by the venom of *Naja Kaouthia*.⁴⁰

Anti-alcoholic

Nux vomica in various dilutions of 30C, 200C, and 1000C has been shown to exert an anti-alcoholic effect in rats. Nux vomica in all three potencies restores the ethanol-induced righting reflex loss in mice fast compared to the controls. The in-vivo studies conducted on the mice and toads showed that nux vomica in 30C and 200 C dilution showed a significant reduction in ethanol-induced sleep time.⁴¹

Toxicity

A poisonous plant nux vomica is attributed to the presence of Brucine, alkaloids, and strychnine. All these compounds are the competitive antagonist of glycine receptors and are neurotoxic on the spinal cord's postsynaptic membrane, in higher centers, and in the brain stem. In higher doses, lethal strychnine dose results in CNS convulsions and death via cardiac arrest, spinal paralysis, and respiratory paralysis. However, common symptoms of strychnine poisoning in moderate and low doses result in painful muscle spasms, dark urine, myalgia, stiff joints, photophobia, abnormal eye movements, restlessness, and agitation.⁴¹

Brucine and strychnine can cause direct damage to the hepatic microsomal enzymes and epithelium of the renal tubules that can cause liver injury, uremia, and acute renal failure. As brucine is a weak alkaloid, poisoning of brucine can cause life-threatening conditions such as acute renal failure and rhabdomyolysis. Brucine and strychnine in lethal doses in adults are seen in doses of 1000mg and 30-120mg. The toxicity assessment in the in-vivo fashion results in typical signs of strychnine poisoning including tremors, convulsions, balance loss, muscle spasms, and ataxia. In the lethal strychnine poisoning was found to be 4.974 and 0.680 mg/g per body weight as assessed in mice.⁴²

CONCLUSION AND FUTURE PERSPECTIVES

Nux vomica is widely used in homeopathic formulations in clinical settings against various disorders and diseases. Leaves and seeds of nux vomica are the main interest areas in pharmacologic research. However, other parts showing efficacy were stems, flowers, and barks. Previous literature data showed that different extracts, potencies, and preparations from various parts of nux vomica have shown various pharmacologic actions including anti-snake venom, neuropharmacological, antidiabetic, gastroprotective, antipyretic, anticancer, antimicrobial, anti-inflammatory, anti-allergic, antinociceptive, antioxidant, and hepatoprotective actions. However, to prove its efficacy, various controlled and longitudinal clinical trials are needed in both in-vitro and in-vivo settings to validate the preliminary data reported in the literature.

For nux vomica, anti-snake venom, neuropharmacological, antidiabetic, gastroprotective, antipyretic, anticancer, antimicrobial, anti-inflammatory, anti-allergic, antinociceptive, antioxidant, and hepatoprotective actions need to be extensively evaluated for the effective factors and their mechanism of action.

Previous literature data establish the efficacy of nux vomica as an anti-dyspeptic, anti-anxiety, antileprotic, anticonvulsant, antiulcer, antidiarrheal, and antirheumatic role. However, long-term data is missing and the preliminary findings need to be validated.

Nux vomica is considered a medicinal plant which is also a poisonous plant. However, large attention should be placed to decrease the toxic and adverse effects of nux vomica using the validated and appropriate techniques for detoxification of the poisonous properties of nux vomica. Pharmacological assessment and studies on the extraction and processing of nux vomica have great efficacy and low toxicity compared to the unprocessed extracts of nux vomica. However, long-term and further clinical studies should be conducted to assess the efficacy and safety of the nux vomica dose to impart its therapeutic values.

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