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Review

Strychnos nux vomica, a traditional phytomedicine for nervine & joint disorders: A short review

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Abstract

Strychnos nux-vomica L. (Strychnine tree) is from the genus Strychnos of the family Loganiaceae. It is a medium sized tree with white flowers and 3 nerved leaves. Traditionally, Unani/Eastern Medicine (EM) physicians have used it for hundreds of years. According to the philosophy of EM, it is used in phlegmatic diseases like paralysis, facial palsy, ptosis, gout, joint pain, sciatica etc. It is used as a single medicine as well as in compound formulations. This article is focused to elaborate its uses in nervine and joint disorders. Scientific databases including, PubMed, Elsevier and Google scholar were explored for the research. Articles were included from 2008 to 2023 in the above-mentioned search engine. Different key words used were "Azaraqi", "*Strychnos nux vomica*", "Sciatica", "arthritis", "nervine disorders", and "joints disorders". *Strychnos nux vomica* as an individual drug and its combination with other drugs as a compound medicine can be used in treatment of facial palsy, epilepsy, gout, arthritis, rheumatoid arthritis, cervical spondylosis, and sciatica. It was also found that the species has promising anti-inflammatory, anti-convulsant, anti-arthritic, anti-epileptogenic, and anti-oxidant activities. Additionally, it can also help in the regeneration of damaged nerve. From this study, it can be concluded that Strychnine tree can be a leading candidate in treating different nervine and specially, joint disorders which is supported by case studies. However, more mechanistic evidence and research through in-vitro, in-vivo, and clinical studies are required particularly for joint disorders.

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Introduction: *Strychnos nux-vomica L.* (Strychnine tree) is from the genus Strychnos of the family Loganiaceae and naturally grows in South-East Asia and Australia [1]. The plant can grow well in warm, dry or humid tropical areas [2]. It is a medium sized tree with height up to 49.2 ft (15 m). The nux vomica has small white flowers while leaves are simple, 3-nerved, opposite, orbicular to ovate, 7.5–11.5 cm long and 6–10 cm broad [3]. The medicinal parts of the plant, traditionally used, are seeds, bark wood and roots. It has numerous applications in traditional medicines of Asia, Europe and the United States [4,5]. The plant is widely distributed in South-East Asia while it was introduced and locally naturalized in tropical Africa [5]. This species has also revealed various therapeutic effects against different disorders like rheumatoid arthritis, stomach pain, muscle pain, breast cancer, liver cancer and colon cancer [1]. These effects are coined due to its chemical constituents such as strychnine, brucine (alkaloids) and glycosides [6-9].

To the best of our knowledge, previous review and research articles reported the analgesic, anti-inflammatory, anti-alcoholism, and anti-tumor effects of the compound medicine of this plant. However, a compilation of evidence for its use in nervine disorders, as an anti-inflammatory and analgesic against joint pain and arthritis is still required. The current research aimed to take a precise review on the traditional and modern utilization of this poisonous (but medicinal) plant on various nervine & joint disorders.

Methodology: Scientific databases including PubMed, Elsevier and Google scholar were explored to select articles. The focus of this search was on the therapeutic effects of "Strychnine tree" on nervine and joints disorders. The utilized terms were *Strychnos nux vomica* (SNV), Strychnine tree, Azaraqi, and Kuchla. Besides, information about the plant was collected by reading different textbooks on pharmacognosy including Pharmacognosy (pharmacognosy and phytochemistry) [6], Medicinal plants [7], A Textbook of Pharmacognosy [8], and Monograph of Unani Medicine [9].

Inclusion / exclusion criteria: The inclusion and exclusion criteria were adopted for the selection of review and research articles. Articles were included from 2008 to 2023 in the aforesaid search engine. Earlier it was decided that articles would be added from 2013 to 2023. However, due to scarcity of articles on the gathered topic, more five years were added. Some non-medicinal articles were included to only explain the organoleptic characters of nux vomica. On the other hand, books after 2000 were selected due to the unavailability of the latest books for required information. Different keywords like "Azaraqi", "*Strychnos nux vomica*", "Sciatica", "arthritis", "nervine disorders", and "joints disorders" were searched for inclusion purposes. Different books were included on the basis of traditional and medicinal uses of the plant. The articles reporting the therapeutic effects of the plant on other disorders were excluded. Articles or books which did not meet the inclusion criteria were excluded.

Ethno-medicine aspects: This plant has also been used in Unani/Eastern medicine (EM), which is Pakistan's traditional medicine, and the species is well known for hundreds of years for its medicinal effects. According to the philosophy of EM, its temperament is hot and dry (3rd order) and used in phlegmatic diseases like paralysis, facial palsy, ptosis, gout, joint pain and sciatica etc. [8,10]. The plant is individually used as single or compound medicine for treatment purposes. Its famous compound formulations are Habb e Azaraqi (Tablets), Majoon-e-l'ana and Majoon e Azaraqi (jam or paste) [11]. It is a highly poisonous medicine, and it needs to be detoxified (mudabbir) before using [10]. 0.4g/kg of SNV contains 4.68 mg/kg of Strychnine and 3.16 mg/kg of Brucine. The fatal dose might be effected by the age, sex and the health condition of the patient. However, the human lethal oral doses of strychnine is reported which is 15 mg for children and 30–100 mg for adults. According to a study, strychnine poisoning was observed in mice with 0.5-61mg/L concentration of strychnine in blood [1]. In case, a person eats the crushed seeds of the species, the person can take the Corrigent / antidote of this species, which are sugar, oils, and mucilaginous substances [9]. As shown in Figure 1, the seeds of this plant are mostly used for medicinal purposes by EM physicians [9,10].

Compound preparations: Indigenously, different compound preparations of SNV are indicated in different diseases which are as follow:

Habb e Azaraqi, Habb e Kuchla, Majoon e Azaraqi, Ikseer e Azaraqi, Majoon e Lana, Roghan e Azaraqi, Roghan e Kuchla, Dawa e Azaraqi, and Roghan e Surkh etc. These compound medicines are indicated in different diseases like, Nerve weakness, Neuralgia, Arthritis, Gout, Hemiplegia, Bell's palsy, Tremor, Epilepsy, Sciatica, Rheumatic affections, Flaccidity of Urinary Bladder, and Earache etc. [11].

Nervine disorders: These disorders are summarized as given in Table 1.

1. **Sciatica:** This disease is caused by injury or pressure on sciatic nerve. The injury or pressure on this nerve can lead to pain, numbness or tingling of leg [12]. An in-vivo experiment was done by Razzaq et al. on mouse model of induced sciatic nerve lesion [13]. In 14 days, the study was completed. Two mouse groups were produced. There was caused sciatic nerve damage in both mouse groups. One of the mice in the group received a dose of 250 mg/kg of detoxified Nux vomica seeds following injury. The dose was given orally in the form of powder. Sensory and motor functions of mice were also observed by hot plate test, formalin test & muscle grip strength test respectively. The sciatic nerve is one of the mixed type of nerve which contains both sensory and motor nerve fibers. Therefore, it was important to perform different tests for the sensory and motor function examination. Since the nerve regeneration would be visible in this evaluation. A muscular grip test was used to assess the motor function of the muscles that the injured sciatic nerve supplied. On the 4th day,

there were observable improvements in muscle grip strength. For the first time, N. vomica effect on Sciatic functional index became noticeable on day 3 and a difference appeared significant on day [9]. Additionally, it should be remembered that monitoring the return of sensory function after an injury is just as important as testing motor function. It was noted that N. verbica had an effect on the recovery of sensory functions, such as a discernible reduction in the ipsilateral hind paw's withdrawal latency. Similar to this, an early first lick reaction in an animal fed N. vomica also signifies that pain fibers were activated following the injection of formalin. It was also noted in those results that N. vomica has the potential to be just as beneficial for the peripheral nervous system. According to the findings of this animal experiment, Nux vomica may be an effective medication for the regeneration of peripheral nerves in cases of traumatic nerve damage. However, it might need more in-vitro & in-vivo experimental evidence for the utilization of this potent poisonous plant as an effective medicine for sciatica.

2. **Epilepsy:** Epilepsy is a brain disorder of unknown cause and can be identified with the help of repeated seizures. It is a serious brain disorder, almost 70 million people are affected by it [14]. Mishra et al. done a series of experiments to evaluate SNV effects on epilepsy [15]. In the experiment, 12 groups of mice were created. Control group animals were given normal saline (NaCl 0.9% solution) only. In the diseased group of animals, acute seizures and kindling effect were induced in the mice by the intraperitoneal injection of Pentylenetetrazol (PTZ) (70 mg/kg and 30 mg/kg in 0.9% saline solution respectively). The extract of processed seeds of the plant was prepared by simple percolation process using 100 grams of powdered *Strychnous nux vomica* seeds in 200 ml distilled water and 824 ml ethanol (95%). In acute seizures model, aqueous ethanolic extract (50 microliter) was orally given to the 3 groups of mice 30 minutes before PTZ (70 mg/kg) inoculation. And 1 group was intraperitoneally administered with Clonazepam (0.1 mg/kg) 30 minutes prior to PTZ injection. In kindling effect model, 3 groups of mice were given 50 microliters extract sublingually 30 minutes before entering (30 mg/kg) PTZ intraperitoneally into the body. Sodium valproate was administered intraperitoneally at a dose of 300 mg/kg in 1 group of mice prior to the inoculation of PTZ (30 mg/kg). Moreover, different behavioral tests like elevated pulse maze test, open field test, object recognition test, Rotarod test and Morris water maze test were performed on the animals of chronic model to analyze and determine transfer latency (seconds), locomotion and exploratory behavior, recognition memory, motor coordination and spatial memory retention of animals respectively. This study was completed in 40 days. In the acute seizures model, it was observed that the extract delayed the latency and reduced the duration of Generalized tonic-clonic seizures (GTCS). Thus, signifying possible regulation of GABAergic neurotransmission (anti-convulsant activity). On the other hand, in the kindling effect model, kindling was significantly hindered by the extract that justified the improved cognition, memory and motor activity impairment (anti-epileptogenic activity). The results of this in-vivo study on mice revealed that the plant may have anticonvulsant and anti-epileptogenic potency in acute and chronic models of epilepsy. Based on the results of this animal experiment, more in-vivo studies should be done on different animals other than mice. Moreover, further in-vitro experiments should also be done to identify chemical constituents responsible for such activity. Therefore, it may be clinically used to control epileptic seizures.

3. **Facial palsy:** Facial palsy is caused by damage to the facial nerves (cranial nerve VII) supplying to facial muscles. These muscles are responsible for the movement of the face. In this disease, facial muscles don't get any signals from brain and get weakened [16]. Qaiyyum et al. done a clinical case study to examine the effect of SNV on facial palsy [17]. Two male patients of age 19 and 34 years diagnosed with facial palsy appeared. They were given 6 different simple and compound herbal medicines for 4 weeks. Strychnine tree detoxified seeds (5mg powder in 250 mg sugar) (Ikseer e Azaraqi-20mg) twice a day were also used as compound medicine. The parameters of House Brackmann scale were observed after an interval of 7 days for 2 times. The parameters of the scale were “deviation of mouth toward right side”, “unable to blow the cheeks”, “improper closure of eyes”, “eyebrows lift up”, and “smiling sign”. The patients were advised to take the food of hot temperament. It was observed that patient had the complaints of difficulty in speaking and swallowing at base line

which improved after 8 days of treatment at the first follow up. The other mentioned symptoms faded till the end of the treatment within 15 days. The symptoms completely vanished in the post-treatment follow up period of 1 month. The vitals of the patient remained stable during course of observation and treatment. Complete blood profile, kidney profile (serum creatinine and blood urea nitrogen) and liver function profile (SGOT, SGPT, Serum Alkaline Phosphatase, Serum bilirubin) at baseline and post-treatment were within normal ranges. It was also observed that no adverse drug reaction was found during the treatment period. Almost full recovery was observed in both cases at the end of the study. More clinical trials are required to affirm the use of SNV for facial palsy. Physicians can use detoxified seeds of strychnine tree with other compound medicine for the treatment of facial palsy. To the best of our knowledge, there are no in-vivo or in-vitro studies that report the anti-paralytic activity of this plant.

Joint disorders: The uses of Nux vomica in joint disorders are summarized as given in Table 2.

1. **Gout:** It is a type of inflammation of the joint which is caused by the accumulation of uric acid (crystal) within and around the joints. Initially, inflammation of toe joint can mostly be observed [18]. Arfeen et al. done an open label, multicenter clinical study [19]. 96 patients of gout were selected irrespective of sex. Those patients were satisfying the criteria of American Rheumatism Association. Only 75 people completed the study. 21 people did not participate in the study. All of them were given 2 compound medicines (Habb e Azaraqi 1 tablet for 2 times & Majoon e Suranjan 5g for 2 times after meal) for 60 days. Clinical parameters (pain, tenderness, swelling, and redness) and laboratorial tests (CBC, LFT, KFT, and urine R/M) were observed in the patients. Out of 75 only 34 got completely cured, 36 were partially fit and 5 patients didn't show any relief. It might be possible that those cases which were partially cured could be fully cured if they were given the medicine for some more time. Those patients who did not show any response might be suffering from other undiagnosed diseases. Based on results of this clinical study of gout, more clinical trials should be done in future by using different compound medicines of strychnine tree. No articles were observed reporting the in-vivo or in-vitro study of this drug for gout. Hence, in-vivo or in-vitro experiments can be done to examine the activity of the chemical constituent in the Strychnine tree against gout.
2. **Cervical spondylosis:** It is a diseased condition in which there is shrinkage or degeneration of intervertebral disc of cervical vertebrae which can lead to osteoarthritis resulting in immobility of neck or pain of neck [20]. Tausif et al. done study of a clinical case[21]. A 28-year-old male patient diagnosed with cervical spondylosis was admitted in the hospital. Patient let the physicians perform 4 wet cupping therapy sessions (0,5th,10th,15th day). The reason for doing this was that it unlocks the pathway of vital force which is blocked by the pathologies of disease. It was also reported that cupping wet therapy improves blood circulation. They also gave a compound medicine of strychnine tree known as Majoon e Azaraqi (6g) two times a day for 30 days (about 4 and a half weeks). The patient was examined under Neck Disability Index (Vernon and Mior cervical spine questionnaire). Before therapy the top index score was 4 and on the 30th day the index score reduced to 0. The result of this case reported the regeneration of inter-vertebral disk. More clinical trials should also be taken for the management of this condition. Different formulations of Azaraqi could also be used in management of this disease. Those formulations might be much more effective than Majoon e Azaraqi. This plant has been traditionally used to treat this disease. However, in-vivo and in-vitro studies are required to determine this activity of plant.
3. **Osteoarthritis & Rheumatoid arthritis:** Arthritis is the inflammation of joints. Mostly knee joints are affected, and it can be due to several causes. Rheumatoid arthritis is a type of arthritis specifically caused by degeneration of chondrocytes by white blood cells. A series of experimental studies was done by Farooq et al. [22]. This study aimed to investigate the in vitro anti-inflammatory and anti-arthritic properties of aloe vera, Colchicum and Nux-vomica. These plants were prepared into aqueous-ethanolic extracts, which were then subjected to Fourier Transform Infrared (FTIR) examination. Protein denaturation was used to observe the anti-arthritic activity, and membrane stabilization of human red blood cells (HRBCs) was used to verify the anti-inflammatory action. A common medication called Diclofenac was used to compare the efficacy of a few chosen plants. Crude extracts extracted from the aforementioned medicinal herbs were produced at concentrations of 125,

250, and 500 µg/ml. Colchicum showed 88.4, 96.0, and 98.5% reduction of the decomposition of protein, Nux-vomica showed 83.83, 90.55, and 92.30% inhibition, and Aloe-vera showed 10.2, 75.72, and 66.16% inhibition, in that order.

The results of all the extracts were similar to those of the usual medication, Diclofenac sodium, with 30.7, 50.74, and 74.98% suppression of protein denaturation. Additionally, it was intended to use the HRBC membrane stability method to examine the membrane-stabilizing effects of crude extracts of "Colchicum, Nux-vomica, and Aloe vera" at concentrations of 125, 250, and 500 µg/ml. According to the results, the percentage of protection provided by Colchicum is 30.31, 31.37, and 40.20%. In a similar vein, Nux-vomica demonstrated impressive percent protection at 30.58, 34.36, and 35.67%, whereas Aloe-vera shown protection of 29.33, 35.58, and 40.17% when compared to the reference medication, Diclofenac sodium, which demonstrated percentage protection of 15.89, 17.05, and 29.36%. The findings indicated that alternative medicines for anti-inflammatory and anti-arthritic illnesses can also be made from the other two plants and the strychnine tree. It is suggested that different in-vitro studies should also be done before going for animal trials.

An in-vivo study was done by Wu et al. [23]. In the experiment adjuvant induced arthritis model was followed to observe the anti-arthritic, anti-inflammatory and analgesic effects of brucine gel (extracted from *Strychnos nux vomica*) were observed by mouse ear swelling test and formalin test respectively. During examining the anti-arthritic activity, the brucine gel activity was compared with Yunnan Baiyao powder [24]. Anti-arthritic experiment was performed on albino mice. Four groups of albino mice were created. Those four groups were named control group, model group, high dose group, and low dose group. Animals were inoculated with Freund's adjuvant complete (FAC) to induce arthritis. Primary arthritis symptoms were observed after injection and secondary arthritis signs were observed on the 13th day after injection of FAC. A high dose of Brucine gel was smeared over the affected part. A high dose of brucine gel showed reduction in the swelling. The thickness size of the affected (swelled) part was observed. Brucicine, a chemical component isolated from Nux vomica, may prevent PGE2 from being produced while maintaining cell viability. It was also concluded that brucine gel could be used in rheumatism. If strychnine was also used with brucine, it might have shown good results due to synergism because of the similarity in the structural formula of both chemicals.

Conclusion: In previous studies, different compound preparations of *Strychnos nux vomica* and as a single drug, it can be used in treatment of facial palsy, epilepsy, gout, arthritis, rheumatoid arthritis, cervical spondylosis, and sciatica. However, it was also observed that compound formulations of this species are used with compound medicines of other species. It may be because other drugs help to enhance the efficacy of the compound medicines of strychnine tree. We can also conclude that the plant species may have promising anti-inflammatory, anti-convulsant, anti-arthritic, anti-epileptogenic, and antioxidant activities. However, more evidence and research by vitro methods, in vivo models, and clinical trials are required to justify its potential use in diseases discussed here.

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Figure 1. Seeds of *Strychnos Nux vomica*

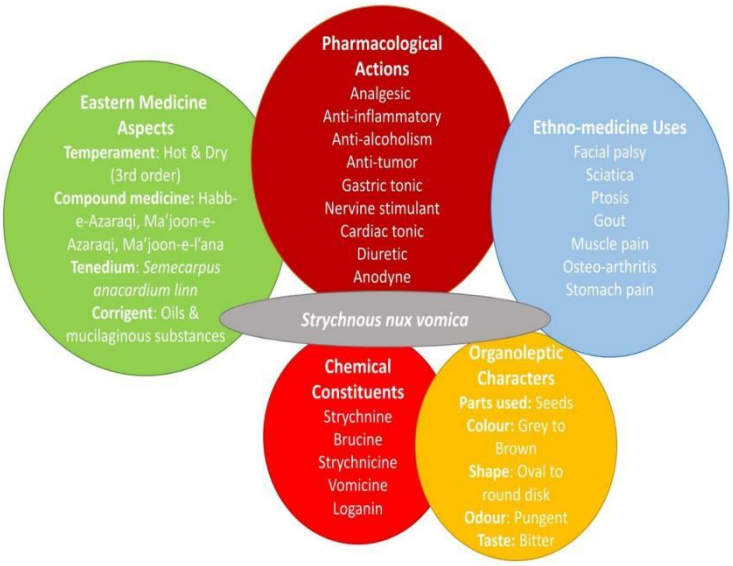

Figure 2. The depiction of different aspects of Nux vomica

Table 1. Summary of nervine disorders

Sr. No.	Disease	Method	Herb/ Formulation	Dosage form	Dose	Frequency	Duration	Result	References
1.	Sciatica	In vivo	*Strychnos Nux vomica*	Powder of seeds	250mg/kg (mass of mice)	---	14 Days	Nerve Regenerated	Razzaq *et al.* [13].
2.	Epilepsy	In vivo	*Strychnos Nux vomica*	Aqueous ethanolic extract	4.85 mg	---	40 Days	Anti-convulsant Anti-epileptic	Mishra *et al.* [15].
3.	Facial Palsy	Clinical study	Ikseer e azaraqi	Powder	20mg	Twice daily	28 Days	Anti-paralytic	Qaiyyum *et al.* [17].
			Joshanda e Mundji	Decoction	45g (100ml)	Twice daily			
			Ikseer momiyat	Powder	5mg	Twice daily			
			Habb e balchad	Tablet	250mg	Twice daily			
			Roghan e farfiyun	Oil	---	---			
			Anacyclus pyrethrum DC	Plant shoots	---	Twice daily			

Table 2. Summary of joint disorders

Sr. No.
1.
2.
3.1.

Disease	Method	Herb/ Formulation	Dosage form	Dose	Frequency	Duration	Result	References
Gout	Clinical study	*Habb e azaraqi*	Tablet	250mg	Twice daily	60 Days	93.3% (+) 6.67% (-)	Arfeen *et al.* [19].
		Majoon Suranjan	Paste	5g	Twice daily			
Cervical Spondylosis	Clinical study	*Majoon e azaraqi*	Paste	6g	Twice daily	30 Days	Anti-inflammatory, Analgesic, Anti-spondylitic	Tausif *et al.* [21].
Osteo-arthiritis Rheumatoid arthritis	In Vitro	*Colchicum autumnale, Strychnos Nux vomica, Aloe barbadensis*	Aqueous ethanolic extract	125mg, 250mg, 500mg	---	---	Anti-inflammatory Anti-arthritic	Farooq *et al.* [22].

Sr. No.	
3.2.	

Disease	Method	Herb/Formulation	Dosage form	Dose	Frequency	Duration	Result	References
Osteo-arthritis Rheumatoid arthritis	In Vivo	*Strychnos Nux vomica* (extracted brucine)	Brucine gel	0.5-2g	---	30 Days	Anti-inflammatory, Anti-arthritic, Analgesic, Anti-rheumatism	Wu *et al.* [23].