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Importance of Drug Safety and Efficacy W.S.R to *Strychnos Nux Vomica* Detoxification

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Abstract

The medicine in present era is much advanced and evidence based. Ayurveda offers a unique opportunity to evolve a science of healthy, harmonious and long life. Its holistic approach to health and disease, involving body, mind and spirit, can provide a broader framework to understand research data emerging from reductionist biomedical Sciences. A fresh perspective on the scope of scientific research on the basic concepts of Ayurveda came from a decadal vision document highlighting the importance of Ayurvedic biology. In ancient system of healing all Ayurvedic drug formulation have an inbuilt safety profile but it is necessary to produce the evidence based documents for the safety and efficacy of Ayurvedic drugs. Therapeutic efficacy of any drug or formulation mainly depends on quality control of pharmaceutical processes.

The branch – *Rasashastra* (Alchemy) is based on the uses of metals and minerals for the therapeutics. It refers various techniques for the purification and detoxification of metallic or mineral ingredients, ie., - Purification, *Marana, Amratikaran, Jarana*, etc. A great debate is emerging time to time that the Rasa drugs are not safe. They are toxic. The facts speak that the toxicity and adverse effect of Rasa drugs occurs due to avoiding or the negligence of classical references of safety and efficacy, as mentioned in Ayurveda. Modern pharmaceutical science gives stress to the application of SOP (Standard Operating Practice) in the drug manufacturing.

Furthermore, Ayurveda refers "A wise physician may use the poisonous material like nectar but with following the directions, which are time tested and safe." The ancient sages advocates and emphasize to following the proper classical drug manufacturing methodology, which starts from the authentication to the finished product. It may be given name SOP (Standard Operating Practice). Moreover, the ancestors refers that like the minerals and metals the medicinal plants which posses the poisonous property should also be detoxified first. Strychnos Nux-vomica contains the poisonous substances which may harm to body. , But, Ayurveda refers its therapeutic uses at various places. For the use of Strychnos Nux-vomica it is clearly mentioned in Ayurveda that this drug should be purified and detoxified first. Present paper is an attempt to explore the Ayurveda principles of Standard Operational Practice wsr to the Strychnos Nux-vomica, supported by the current studies and scientific evidences. The outcome of paper may open the path for the drug standardization, safety, efficacy and quality control.

Keywords: Rasashastra; Marana; Amratikaran; Jarana

Introduction

The medicine in present era is much advanced and evidence based. Ayurveda offers a unique opportunity to evolve a science of healthy, harmonious and long life. Its holistic approach to health and disease, involving body, mind and spirit, can provide a broader framework to understand research data emerging from reductionist biomedical Sciences. A fresh perspective on the scope of scientific research on the basic concepts of Ayurveda came from a decadal vision document highlighting the importance of Ayurvedic biology [1].

Ayurveda includes knowledge about physiological, pathological and psychological aspects of botanical, zoological and mineral sources, along with detailed information about them. Ayurvedic physicians and hospitals have long histories of drugs used-compositions, formulations and dosage regimens, therapeutic and untoward effects. These records are particularly valuable since effectively these medicines have been tested on people for thousands of years [2].

The branch – *Rasashastra* (Alchemy) is based on the uses of metals and minerals for the therapeutics. It refers various techniques for the purification and detoxification of metallic or mineral ingredients, i.e., - Purification, *Marana, Amratikaran, Jarana*, etc. A great debate is emerging time to time that the Rasa drugs are not safe. They are toxic. The facts speak that the toxicity and adverse effect of Rasa drugs occurs due to avoiding or the negligence of classical references of safety and efficacy, as mentioned in Ayurveda. Modern pharmaceutical science gives stress to the application of SOP (Standard Operating Practice) in the drug manufacturing.

Ayurveda refers "A wise physician may use the poisonous material like nectar but with following the directions, which are time tested and safe." The ancient sages advocates and emphasize to following the proper classical drug manufacturing methodology, which starts from the authentication to the finished product. It may be said that SOP (Standard Operating Practice) is close to the Ayurveda Drug Operational Practice (ADOP).

Moreover, the ancestors refers that like minerals and metals the medicinal plants which posses poisonous property should also be detoxified first.

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Strychnos Nux-vomica contains the poisonous substances which may harm to body. But, Ayurveda refers its therapeutic uses at various places. For the use of Strychnos Nux-vomica it is clearly mentioned that this drug should be purified and detoxified first [3].

Strychnos nux vomica

Strychnos Nux-vomica is a convulsion producing herb (*Aksapjanana*) which is included in *upavisha varga* (poisonous plant) by Ras Shastra as Vishtinduka [4]. *Strychnos Nux Vomica* Linn is a poisonous tree of Loganiaceae family found abundantly in India [5]. This is a medium-sized tree with a short thick trunk. The wood is dense, hard white, and close-grained. The leaves are about 4 inches (10 cm) long and 3 inches (7.6 cm) wide with an opposite arrangement, short stalked, are oval shaped, also have a shiny coat and are smooth on both sides. The flowers are small with a pale green colour with a funnel shape. The ripe fruit contains seeds which are poisonous, flat, circular discs, 2.5 × 0.6 cm, dark grey in colour completely covered with hairs radiating from the center of the sides. Unbroken seed produce no poisonous effect until its pericarp dissolves [6]. In ancient classics its properties mentioned as *Katu Tikta* **Rasa** (In Taste) , *Katu* **Vipaka** (Final Metabolic Produce) and Ushna **Virya** (Potency) with *Ruksha* (Dry), *Laghu* (Light) and *Tikshna* (Sharp) **Guna**. The chief active principles of Nux Vomica's seeds are such as *strychnine, brucine* and *loganin*. It also contains *vamicine*, *colubrine, logamine* glycoside and fatty substance up to 3% alkaloids. Total alkaloids range from 2.6-3.0% out of which 1.25 – 1.5% *strychnine* and 1.7% *brucine*. Both of these alkaloids are very potent toxins [7].

Therapeutically uses of *Strychnos nux vomica*:

Seeds of *Strychnos Nux vomica* used as nervine tonic, alexiteric, aphrodisiac, anthelmintic, digestive, purgative and stimulant. Detoxified *Strychnos Nux vomica* seeds used in various Ayurvedic drugs like Agnitundi vati, Navjeevan Rasa and vishatinduka vati as an important ingredient [8].

Toxicity of plant

The Charaka Samhita has described the properties such as *Laghu* (Light), *Ruksha* (Dry), *Aashu* (Fast acting), *Vishada* (Clarity), *Vyavayi* (Synergetic), *Teekshna* (Sharp), *Vikasi* (Channel Blocker), *Sukshma* (Subtle), *Ushna* (Hot in tendency) and *Anirdeshyarasa* (Unexplainable taste) [9]. Ingestion of this herb can cause death of person but after regulating its properties by purification it prove excellent medicaments in various disorder. Purification process is not done only for detoxification but also to increase its medicinal properties (*Gunotkarsha*).

Detoxification process of *Strychnos nux vomica*

As mentioned earlier, the ayurved science advocates for proper purification and detoxification to such plants. That is why, the *Strychnos nux vomica* seed used therapeutically after proper detoxification process.

Its general as well as specific purification process is clearly mentioned in ancient system of medicine which discussed here:

A. **General purification** - *Strychnos Nux vomica* seed are cut into small pieces up to the size of gram. These small pieces are soaked into *gomutra* (cow urine) for three days with daily *gomutra* change. After three days when these seeds soaked *gomutra* completely kept under sunlight until moisture in it. When these dry completely, preserve in air tight bottle for future use [3].

B. **There are four specific method for purification described in different textbooks of Ayurveda which are given below**:

a. **Seeds** of *Strychnos Nux vomica* are soaked in *kanji* (Acidic fermented medicated water0 for three days. After three days its outer covering is removed by scraping with knife and left under sunlight for dry. Make a powder of completely dry seeds and store in air tight container.

b. Seeds of *Strychnos Nux vomica* fries in *goghrtia* (Cow's ghee) on slow heat (Table 2 and 3). After completely frying process their skin separates. Skinless seeds are powdered & store.

c. In third process swedana done in dolayantra for three hours of complete soaked cow milk seeds of Nux Vomica. After completion of swedana process outer covering is removed by scraping & left into direct sun light till dry. Dried seeds of *Strychnos nux vomica* pulverized into fine powdered & can be stored for long duration [4].

d. In fourth method seeds of *Strychnos nux vomica* soaked into Gomutra for seven days with changing gomutra daily [7]. Complete soaked seeds after seven days scraped to remove outer cover and kept under swedana in cow milk for three days. At the end of each day of boiling these washed with boil water & dry before use next day. After complete process of swedana these seeds fry in to goghrtia as therapeutic agent [5]. Fried seeds pulverized into powder for long duration storage.

Scientific study evidences on ayurveda classical SOP

Various research studies show percentage change of *strychnine* and *brucine* (Table 1) alkaloids of in detoxified seeds of *Strychnos Nux vomica* which are studies after the purification of Ayurveda SOP.

It shows that cotyledon portions contain higher percentage of strychnine than that present in seed coat for the entire sample except the milk purified seeds. Purification with milk markedly reduces the toxicity of crude nux-vomica than the sample treated with *Ghrita* [10].

On the above basis it is clear that two things are important in purification process of *Strychnos Nux vomica* seeds to make its therapeutic viz media and involved process.

Evidence

- *Nimajjan* process (soaking of *Strychnos Nux vomica* seeds in cow's urine, *kanji* and cow's milk) can be correlated with the maceration method of extraction. Maceration method consists of placing the coarse powdered drugs in a vessel with the whole of the menstrum or extraction solvent and allowing them to stand for seven days with or without shake. In general purification of *Visha* (Poison) it is indicated that the

StrychnosNux Vomica seeds	% of Strychnine	% of Brucine
Crude form	1.92%	0.93%
Seeds after purified with *gomutra*	0.96%	0.19%
Goghrtia fried seeds after purification by *gomutra*	0.068%	0.012%

Table 1: Percentage of Strychnine and Brucine in crude and purified seeds of *Strychnos nux vomica* sample.

StrychnosNux Vomica seeds	Cotyledon Portion	Seed Coat
Crude drug	1.2 %	5.67%
Purified seed (by *Goghrtia*)	0.7 %	2.55 %
Purified seeds (by *Godugdha*)	0.116%	4.54%

Table 2: Percentage of total alkaloids in crude and purified seeds of Strychnos nux vomica sampleBy modified B.P. 1958 method.

StrychnosNux Vomica seeds	Cotyledon Portion	Seed Coat
Crude drug	2.18 %	0.4366%
Purified seed (by *Goghrtia*)	1.212 %	0.052 %
Purified seeds (by *Godugdha*)	0.4375%	1.112%

Table 3: Percentage of total Strychnine in crude & purifiedseeds of StrychnosNux Vomica sample by modified B.P. 1980 method[1] Agarwal and Joshi [10].

Gomutra (Cow urine) should change everyday it is the repeated maceration method for better extraction of toxic alkaloids as the mass transfer phenomenon is directly proportional to the concentration gradient and occasional shaking of solvent is also done to bring the fresh solvent in the contact of coarse powdered drug to increase the concentration gradient [11].

- In swedana process, flow of media occurs through the coarse powdered drug kept in a swing during boiling due to temperature gradient. So, this method can be correlated with percolation method of extraction, where media soluble toxic principles get separated from the coarsely powdered poisonous drug through the process of boiling [12].
- On heat treatment, the contents of the major alkaloid Strychnine ($C_{21}H_{22}N_2O_3$) and Brucine ($C_{23}H_{26}N_2O_4$) declined significantly [13] (appx. 63%) with increase in the amount of isostrychnine, isobrucine, strychnine –N-oxide and brucine N-oxide. The cleavage of an ether linkage and the occurrence of N-oxidation were demonstrated by heat treatment of authentic strychnine and brucine isolated 16 alkaloids from heat treated and untreated seeds of Nux Vomica. Isobrucine N-oxide, iso strychnine -N-oxide and 2 hydroxy 3 methoxy strychnine were new alkaloids found in heat treated samples [14].
- **Effect on LD_{50}** - It has been reported that LD_{50} values of the seeds treated with different processing methods ranged from 2.18-2.57 mg/kg. In the mouse, while that of the unprocessed seeds was 1.21 mg/kg. Thus, the processing of *Strychnos Nux Vomica* decreased the toxicity down to one half that of the unprocessed substance.
- **Effect on antinociceptive property** - Not only safety but pharmacological activities are also altered by these processing methods. In a study the antinociceptive effects of crude alkaloid fractions of processed and unprocessed *Strychnos Nux Vomica* were demonstrated. Crude alkaloid fraction of sand processed *Strychnos Nux Vomica* showed distinct antinociceptive effects in all analgesic tests performed i.e Tail pressure test (Mechanical noxious test), Hot-plate test (Thermal noxious test) and writhing behaviors test induced by acetic acid (Chemical noxious test) [14].

Discussion

Whole review reveals that the *Strychnos nux vomica* seeds are the useful part which is poisonous needs to detoxified and purified. The Ayurveda classical purification and detoxification classical method makes it suitable to use on human body for the treatment of various ailments.

In Table 2, the total alkaloid percentage in the seed coat has estimated by titremetric method was found to be fairly high. This could have been due to the basic constituents, other than the alkaloids which interfered with the estimation of alkaloid by this method.

- In traditional Chinese medicine there are seven detoxification methods of Nux Vomica i.e. Sand processing, Licorice processing, Oil processing, Vinegar processing, Vinegar and sand processing, Urine processing, Urine and sand processing. Out of these sand processing was found good for the analgesic potency of *Strychnos nux vomica* as its antinociceptive potency was similar to that of unprocessed seeds (to the suppression of mechanical nociception) but the LD_{50} value (2.35 mg/kg) is about twice that of unprocessed (1.21 mg/kg).
- Therefore, it is suggested that the sand processing doubled the therapeutic index (to the supression of mechanical nociception) of the crude alkaloid fraction of Nux Vomica [15].
- It was also noted that although the crude alkaloid fraction from the unprocessed seeds was without significant effects at doses examined in the hot plate and acetic acid induced writhing tests that of sand processed seeds showed significant antinociception in either analgestic test.
- The Purification methods of *Strychnos nux vomica* alter the composition of strychnos alkaloids and produce novel alkaloids. Thus it is conceivable that alterations in composing alkaloids are responsible for change in antinociceptive potency [15].

So all the steps mentioned in the Purification process of *Strychnos nux vomica* should be performed carefully with respect to time, temperature and purity of media. It means:

- Soaking and boiling of seeds in the suitable media should be for proper time for successful extraction of toxic alkaloids.
- During the frying of seeds, the heat should be slow.
- The skin of the seeds should be separated.

Conclusion

Drugs containing poisonous substance like *Strychnos nux vomica* in impure form can be injurious to human. There is need of proper detoxification of *Strychnos nux vomica* to reduce its toxicities and increase its therapeutic index. This study proved that by adopting proper detoxification (*Sodhan karma*) process therapeutic efficacy of *Strychnos nux vomica* gets increased as well as toxicity get decreased approximately to half.

Therefore it is important to standardize each operative procedure of *Strychnos nux vomica* detoxification (*Sodhan karma*) at every step to maintain efficacy as well as safety. However more efforts are needed for subsequent validation and replication of these results in clinical trials.

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