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A TOXICOLOGICAL AND THERAPEUTICAL REVIEW OF *KUPEELU* (STRYCHNOS NUXVOMICA)

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ABSTRACT

Kupeelu is described under *upavisha* group and is one of the most potent spinal poisons. In Ayurveda, the use of *Kupeelu* has been started from *sangrahakaala* only. In classical texts a wide range of utility, especially, the qualities viz. *Vedanasthaapana, Naadibala, Shoolahara, Hridya etc.* have been mentioned for it. From various researches also it has been proved that the *Kupeelu* has the properties viz. Analgesic and anti-inflammatory, Anticonvulsant, Anti tumor etc. In spite of all these proven qualities, it is very true that *Kupeelu* is a very strong poison having the fatal dose of 1-2 seeds (30-120 mg of strychnine) and on consumption can produce very fatal convulsions along with other symptoms. Considering this aspect different *shodhana* procedures have been mentioned for *Kupeelu* in Ayurvedic classics after which only the drug can be used safely in the preparation of different medications. The following article deals with its different aspects of toxicological and therapeutical perspect.

Keywords: *Kupeelu*, spinal poison, convulsions, *shodhana*

INTRODUCTION

Kupeelu is considered as one among the drugs of *Upavisha varga* and botanically it is identified as Strychnos nuxvomica Linn. We get many references regarding the *Kupeelu* in classical texts that are mentioned according to the time period. There is no reference of *Kupeelu* in *Vedakaala* or *Samhitakaala*. In Sushruta Samhita the word *Vishamushtika* is mentioned under the *Surasaadigana*, but commentator Dalhana considered *Vishamushtika* as *Raajanimba*. In Ashtaanga Sangraha, while explaining *Sarpavishapratishedhaadhyaaya*, in *vishaghna dhaarana gana*, *Vishamushti* is mentioned. But the commentator Indu considered *Vishamushtika* as *Paathaa*. In Ashtaanga Hridaya, the term *Vishamushti* is mentioned under *Surasaadi gana*, but commentator Hemaadri considered *Vishamushti* as *Karkoti* and *Mahaanimba*. In Charaka Samhita, neither the word *Kupeelu* nor any of its synonyms has been mentioned anywhere. Hence it is clear that the use of *Kupeelu* drug might not have started during the *Samhita* period. In *Sangrahakaala*, particularly in *Sharangadhara* Samhita[1] *Vishamushti* is mentioned as one of the ingredient of the formulation *Agnitundi Vati*. Thus, it can be inferred that the use of *Kupeelu* has started from *Sangraha kaala* onwards. After this period the details of *Kupeelu* have been found in various *nighantus* and it has been considered as

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upavisha by various *rasashaastra* authors. Especially the poisonous side of *Kupeelu* has been highlighted in the *rasashaastra-granthas*. Anyhow it has been considered under *Upavisha varga* and it is being given importance as a medicinal drug as well, hence for the therapeutic use, the *shodhana* procedures are mentioned before its use. In Amarakosha[2], *Kupeelu* is mentioned under the *Vanoushadhi varga* with many synonyms like *Kaakendu, Kulaka, Kaakapiluka, Kaakatinduka*.

Kupeelu with the Botanical Name Strychnous nuxvomica Linn belongs to the Family Loganiaceae. In English it is known as Strychnine tree, snake wood, nux-vomica, poison nut, Quaker button etc.

Morphological characters:[3]

Kupeelu is a deciduous tree sometimes reaching 30m in height, often with sharp strong axillary spines; Bark – Thin, grey, smooth or rough with lenticles; Leaves - 7.5-15 by 4.5-7.5cm, 5 nerved broadly elliptic, glabrous and shining; Flowers – Numerous, pedunculate, greenish white in terminal, compound cymes. Fruits - 2.5-7.5cm diameter slightly rough but shining, when ripe orange red in colour; Seeds – Discoid about 2cm in diameter and many in number, much compressed, one side concave and on another side convex, on both sides clothed with very fine oppressed grey silky hairs radiating from the centre. *Kupeelu* is distributed throughout tropical India, West Bengal, Odisha, Uttar Pradesh, Bihar and ascending up to an altitude of 1350m.[4]

Parts used:[5] Seed, bark, root, leaf

Flowering and Fruiting Time: [6]Flowers inMay – July and Fruits in November – January

PHARMACOLOGICAL PROPERTIES OF *KUPEELU*:

Regarding *rasapanchakas* of *Kupeelu*, there is difference of opinions among various *samhitas*. Primarily by maximum authors it has been considered to have *ushna veerya* and *katu vipaaka* where as *nighantus* viz. Bhavaprakaasha[7] and Madanapaala[8] have considered it as *sheetaveerya*. As per Dhanwantari nighantu[9] *Kupeelu* has *madhura rasa* and *madhura vipaaka*. It has the qualities of *laghu, ruksha, teekshna* and *sara*. Basically it has *tikta* and *kashayarasa*.[10-15]

CHEMICAL COMPOSITION: [16]

- **Fruits**: Glucoside-loganin
- **Leaves and root bark:** Brucine, strychnine, vomicine and methoxystrychnine
- **Root**: C-mavacurine, strychnoclysine
- **Plant**: Brucine, strychnine, pseudobrucine, psuedostrychnine,α-β colubrines, vomicine, novacine, P-hydroxybenzoic, kaempferol, quercetin, protostrychnine, normacusine β and 4hydroxy -3- methoxystrychnine, 3-methoxyicajine.
- **Seeds**: Strychnine, Brucine, Loganin, 4-hydroxystrychnine, N-mehtyl –see-pseudo- βcolubrine 15-hydroxystrychnine, isobrucine, isobrucine-n-oxide, isostrychnine-noxide, 2-hydroxy-3-methoxystrychnine.

As Strychnine and Brucine are the main chemical composites of *Kupeelu* we concentrate on the descriptions of Strychnine and Brucine in brief.

Strychnine[17] ($C_{21}H_{22}N_2O_2$)

Strychnine is natural alkaloid obtained from the dried seed of the plant Strychnos nuxvomica. This is a colourless, odourless, crystalline substance having an intensely bitter taste. It dissolves very sparingly in water or ether but dissolves in alcohol and benzene. It is a BPC preparation, the dose being 2-8 mg. Strychnine is

very stable and does not change in process of putrefaction and can be detected even some years after death.

Strychnine is used as a rodenticide and is highly toxic to humans as well as most domestic animals. It is used as a respiratory stimulant and forms the chief ingredient of several vermin killers. These consist of starch and mixed with some colouring material such as soot, indigo, Prussian blue or ultra-marine.

Brucine [17]($C_{23}H_{26}O_4N_2$)

Brucine occurs in the form of colourless, prismatic crystals with an intensely bitter taste. It is slightly soluble in cold water, but more in boiling water and freely in alcohol, chloroform and amyl alcohol, but not in ether. It resembles strychnine both chemically and physiologically, but its toxic effects are only one eighth of that of strychnine.

THERAPEUTIC USES OF *KUPEELU*:

On scrutinizing the different Ayurvedic as well as modern text books, it has been revealed that different parts of the plant have a broad spectrum of activities in a number of diseases.

Inside the body, *Kupeelu* has the action on *tridoshas*. It has been considered as *Vaatahara, Vaatalam, Kaphapitta Asranaashanam, Kapha-vaatahara and Pitta krit.*[18-26] *Kupeelu* also has the following actions on the body: *Vaajeekara, Kandughna, Graahi, Balya, Madakaari, Paachana, Deepana, Vedanasthaapana, Naadibala, Shoolahara, Hridya. Swedahara, Kaamottejaka, Vranahara, Kanduhara, Krimihara, Jantuhara, Medahara* [27-33]

As per the classical text books *Kupeelu* has the action on the following conditions:*Vrana, Jwara, Kushta, Arsha, Bhagna, Kaarshya, Prameha, Visuchika, Shwaasa, Gulma, Mushika Visha, Ardiita, Kampa, Naadi shoola, Baadhirya, Shayaamutra, Napumsakata, Ajeerna, Agnimaandya* [34-40]

Various text books of medicinal plants also mentioned the therapeutic uses of different parts of *Kupeelu* as below:

Fruit: The unripe fruit vitiates *Vaata*, causes constipation while the ripe fruit alleviates all three *doshas* and is used in urinary disorders and in diseases due to impure blood. [41]

Seeds: Atonic; anti-diarrhoeal; anti-dysenteric, antispasmodic, emetic, febrifuge, stimulant and tonic; used in cholera; diabetes; emotional disorders, hysteria; epilepsy; intermittent fevers; gout, rheumatism, hydrophobia; impotence; insomnia; paralytic and neuralgic afflictions; prolapsed rectum; antidote to alcoholism; beneficial in general exhaustion; opium poisoning: retention or nocturnal incontinence of urine; spermatorhoea; given in combination with carminatives and antacids in dyspepsia and vomiting.[42] Nux-vomica seeds produce a sort of intoxication, for which they are habitually taken by some natives as an aphrodisiac by cutting down into small pieces and chewed with a packet of betel leaf. [43] The seeds also yield oil, and a dye; the dye gives a brown colour to cotton fabrics. Oil, obtained by heating the fresh seeds, is used externally in rheumatism.[44]

Leaves: The leaves when applied as poultice, promote healthy action in sloughing wounds or ulcers, more especially in those cases when maggots have formed. It arrests further formation of them, and those in the deeper parts perish immediately when the poultice is applied. [45]

Bark: The juice of the stem bark is given in cholera and acute dysentery. [46]

Wood: The juice of the fresh wood is reported to be a popular remedy for dysentery, fever, cholera and dyspepsia. [47]

Root: The root bark is bitter and is useful in cholera and intermittent fevers. In Sri Lanka, the roots are applied externally for the management of snakebite. In Cambodia, the seed is used as an emetic. Internally, an infusion of the bark is given in epilepsy; externally, the bark is used in the treatment of ulcers, atonic and leprotics. [48]

Various researches have been conducted to prove the efficacy of *Kupeelu* in various fields affecting the multisystem of the body. A review of certain published research data reveals the following actions of *Kupeelu.*

1. **Analgesic and anti-inflammatory property**[49]

An animal experimental model shows the analgesic and anti-inflammatory effect of brucine and brucine N-oxide which are the content of the seeds of *Kupeelu*. Results suggested that central and peripheral mechanisms are involved in the pain modulation and anti-inflammation effects of brucine and brucine N-oxide.

2. **Anti convulsant activity**[50]

From the research it is proved that extract of Strychnos nuxvomica seeds reduced spontaneous motor activity and inhibited catalepsy.

3. **Anti tumor effect**[51]

A research study reported that the major alkaloids present in the seeds of Strychnos nuxvomica especially brucine, strychnine and isostrychnine are effective against HepG2 cells proliferation.

4. **Anti amnesic activity**[52]

In an experimental study, it has been found that loganin (an iridoid glycoside found in Strychnos nuxvomica) has effect on the learning and memory impairments induced by scopolamine. In this study, it has also been found that loganin significantly inhibited acetylcholinesterase activity in the hippocampus and frontal cortex. The study clearly suggests that loganin possess anti amnesic activity that may hold significant therapeutic value in alleviating certain memory impairments observed in Alzheimer's disease.

5. **Anti-diarrhoeal activity**[53]

A study was undertaken to evaluate the effect of the aqueous and methanolic plant extracts of Strychnos nuxvomica root bark for their anti-diarrhoeal potential against castor oil induced diorrhoea in mice. It was observed that the methanolic extracts were more effective than aqueous plant extracts.

6. **Immunomodulatory effect** [54]

In an experimental study, the possible immunomodulatory effect of Strychnos nuxvomica on induction of ovalbumin specific IgE antibody response in a murine model was evaluated. In this study various findings suggest the suppressive activity of Strychnos nuxvomica on allergen specific IgE antibody response and suggest its possible application in allergic conditions.

7. **Antisnake venom activity**[55]

In a research study it has been reported that the whole seed extract of S. nuxvomica (low doses) effectively neutralised Daboia Russelii venom induced lethal haemorrhage, defibrinogenating, PLA2 enzyme activity and Naja kauthia venom induced lethal cardiotoxic, neurotoxic, PLA2 enzyme activity. The seed extract potentiated polyvalent snake venom antiserum action in experimental animals.

8. **Hepato-protective and anticholestatic activity**[56]

In an experimental study, loganin, an iridoid glycoside extracted from the fruit of the plant Strychnos nuxvomica showed significant hepatoprotective and anticholestatic activities in rat model. Loganin showed a dose dependant activity as observed by an increase in the viability of the hepatocytes and the reversal of reduced parameters of bile.

FATAL DOSE: [57]

- Children : Lethal dose may be as low as 15 mg (Goodman & Gilman, 1985).
- Adults : For adults the lethal dose will vary. The minimal oral lethal dose of human ranges from 30 to 120 mg. When given subcutaneously or intravenously, the lethal dose is significantly lower.
- Animal data :
  - Intravenous-rat LD50 : 960 µg/kg
  - Oral-rat LD50 : 16 mg/kg
  - Subcutaneous-rat LD50 : 1200 µg/kg
  - Intraperitoneal-rat LD50 : 2500 µg/kg (NIOSH, 1983-84 Supplement)

FATAL PERIOD: [57]

Usually 1-2 hours. In few cases within 5-30 minutes after swallowing poison death has occurred and in rare cases death has been delayed 6-18 hours.

TOXICOLOGICAL EFFECTS ON THE BODY: [57]

Respiratory: The abdominal muscles, diaphragm and chest are in a sustained stage of spasm and breathing becomes difficult. Cyanosis and hypoxia occur followed by death.

Cardiovascular: Difficult to detect the pulse, and there may be hypertension and tachycardia.

Neurological effects: On Central nervous system, Strychnine poisoning major symptoms are seizures and are caused by excitation of all parts of the CNS. The onset of symptoms may occur with a prodromal syndrome that includes: tonic twitching of the face and neck muscles, preceded by restlessness, muscular cramps in the legs, apprehension, and heightened acuity of perception (hearing, vision, and feeling) and hyper reflexia. However, the initial symptoms may be only generalized violent convulsions. After any minor sensory stimulus these convulsions can begin suddenly and last from 50 seconds to 2 minutes. Initially, the convulsions are clonic but are soon followed by tonic contractions similar to convulsions due to tetanus. The patient remains conscious and has intense pain. After the convulsions, all the muscles relax and sometimes the patient falls asleep from exhaustion. Suddenly hyper excitability recurs after 10 to 15 minutes. Repeated convulsions (1 to 10) are common before recovery or death. In severe untreated poisoning, each convulsion lasts longer than the previous one, and the intervals between them are shorter.

Skeletal and smooth muscle: All voluntary muscles contract simultaneously after strychnine poisoning, although there is no direct effect on skeletal muscles. By the central action of the drug there increase in muscle tone (Goodman & Gilman, 1985). The major effects are caused by the action of the most powerful muscle on the joint. During the convulsions, the patient shows hypertonicity of the muscles beginning by trismus, risus sardonicus, and cramps of the arms and legs, that are soon followed by opisthotonus.

POST-MORTEM APPEARANCE [57]

- **Internal findings:** The lungs are congested, occasionally the patches of ecchymosis or congestion seen in the mucous membrane of the stomach and duodenum. The heart is usually empty and contracted, but its right side is sometimes gorged with dark fluid blood. The liver and kidneys are generally congested. The brain and its membranes and the upper part of the spinal cord are found congested.
- **External findings:** Usually at the time of death the muscles are relaxed and soon become extremely rigid, but in some cases the tetanic spasm may pass into cadaveric rigidity without the initial stage of relaxation. Rigor mortis more rapidly sets in and may persist

for a long time. Livid patches may be observed on the body, and may be mistaken for bruises caused by violence.

TREATMENT

The patient should be kept in a dark and quiet room as a slight stimulation can provoke the convulsions in the patient. An emetic should be given or stomach should be washed with charcoal and tannic acid. 1–2mg of atropine and chloral hydrate can be given as physiological antidotes. Stimulants should be given and oxygen inhalation and artificial respiration may be resorted to, if necessary. Morphine / aminophylline should not be given.[57] Artificial respiration, oxygen and supportive therapy may be necessary.

DISCUSSION

- As the drug *Kupeelu* is mentioned in Sharangdhara Samhita and not in the *Brihattrayees* it can be inferred that the usage of *Kupeelu* started during the *Sangrahakaala*.
- Though *Kupeelu* is considered as a toxic plant it has been used for thousands of years in Ayurvedic medications after the purification. The ancient texts of Ayurveda quoted that the *visha* (poison) acts as an *amrita* (nectar) if utilized legitimately. *Kupeelu* is considered as one among the *upavishas.* After its proper *shodhana* through a few particular media like *goghrita*, *kanji* and *godugdha*[58] it is used for clinical trials. Nowadays it is practiced extensively in various conditions of the body affecting the different systems. It has the properties of aphrodisiac, analgesic, anti inflammatory, anticonvulsant, anti-diarrhoeal, anti-dysentery, immune-modulator, anti-tumor, hapatoprotective, anti-amnesic, antioxidant, wound healing properties etc.
- Toxicological point of view, in higher doses, *Kupeelu* produces tetanic convulsions ultimately resulting in death. It affects the central nervous system predominantly. It also affects respiratory, cardiovascular, skeletal and smooth muscles when it is consumed in excess dose.

CONCLUSION

In Ayurveda, *Kupeelu* (Strychnos nuxvomica Linn.) has been described as one among the *upavishadravyas*. The descriptions available in the classical texts reveal the potency of this drug in various disorders related to different systems in the body. The various researches carried out in certain fields also provide the evidence of its efficacy in such diseases. When we look into the toxicological aspect, this is a most potent spinal poison with a high fatality rate. Anyhow different *shodhana* procedures mentioned in Ayurveda can reduce the toxicity of this drug and can make it safer for the therapeutical usage. However more researches should be carried out for validation of the potency of this drug clinically.

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