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Full Length Research Article

A Comprehensive Review on the Therapeutic Properties of Poison Nut (*Strychnos nux-vomica* L.) of Loganiaceae Family

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Abstract

Poison nut (*Strychnos nux-vomica* L.), also known as *nux-vomica*, has a long history of use in the treatment of a variety of health conditions, including digestive issues, headaches, and mental disorders. In recent years, scientific research has supported many of the traditional therapeutic uses of *nux-vomica*, making it a promising herb The goal of this review is to investigate the medicinal properties of Poison Nut (*Strychnos nux-vomica* L.). A full computerized literature search was conducted to find clinical research publications. To gather the necessary information, several works of literature were also read. For this review, a total of 45 research articles were examined, with 40 of them being included. This review also includes 12 textbooks written by different authors. The articles were chosen using inclusion criteria. This comprehensive review explains the use of poison nut in various medical systems such as homoeopathy, ayurveda, Unani, and siddha. More research is also needed to fully understand the potential benefits of poison nut and its safety profile.

***Key words*:** *Nux-vomica*, Strychnine, Brucine, Analytical techniques, Alternative systems of medicine

According to the World Health Organization (WHO), 80% of developing-country populations rely on traditional medicines, primarily plant pharmaceuticals, for basic health care. Furthermore, at least 25% of current medications are derived from plants, with many others being synthetic counterparts based on prototype chemicals derived from plants. About 2000 medicinal plants are used in our country by the Indian systems of medicine, Ayurveda, Siddha, Unani, and Homoeopathy [1-2].

Poison nut (*Strychnos nux-vomica* L.) [3] of the Loganiaceae family [4] is a medium-sized, [5] poisonous medicinal deciduous tree of the tropical and sub-tropical biome having various names in different languages representing its usage in different regions. It is also described in the *Surasadi gana* of *Sushruta* and *Amradi phala varga* of *Bhavprakasa* [6]. It is a potential pharmacological plant used in various traditional medical systems such as Unani, Ayurveda, Tibetan, Chinese, and Homoeopathy [7-9].

Vernacular Names (Table 1) [3], [5], [10-15]

Table 1 Poison nut vernacular names

Language	Common name
English	*Nux-vomica*, poison nut, strychnine tree, quaker button, venom orange, dog button
Hindi	Kuchla, kanjiram, muhti
Sanskrit	Vishmushti, kapilu, kupilu
Thai	Kodka- kling
Chinese	Ma qian zi
French	Noix vomiques
German	Krahenaugen

This table represents common names of poison nut in different languages.

Botanical classification [5], [9-10]

Kingdom	:	Plantae (Plants)
Sub-kingdom	:	Tracheobionta (Vascular plants)
Super division	:	Spermatophyta (Seed plants)
Division	:	Magnoliophyta (Flowering plants)
Class	:	Magnoliopsida (Dicotyledons)
Subclass	:	Asteridae
Order	:	Gentianales
Family	:	Loganiaceae
Genus	:	*Strychnos*
Species	:	*Nux-vomica* L.

History and distribution

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The drug was known as early as 15 A.D. when Valerius Cordus wrote an astonishingly accurate description of it. "Due to the popularity of the nut, the term *Nux-vomica* ' is derived from the Latin words 'Nux' meaning nut and 'Vemere' meaning vomiting" (Allens Encyclopedia Materia Medica Vol. VII, 83) [11]. During the 18th century, Hahnemann's provings published in 1805 extended the medicinal use of *Nux-vomica* [11]. Flaeming, Friedrich, and Wahle assisted Dr. Hahnemann in this proving [12]. Kupeelu (*Nux-vomica*) has been recorded as a fatal poison and a cure for demonic possession in the 9th-century Arabian poison book Kitab Al-Summam. [13] *Nux-vomica* was also listed in the Japanese Pharmacopoeia (JP17) Database [14]. Since the discovery of strychnine and brucine from *Nux-vomica* around two centuries ago, understanding their physiological effects has been more accurate, and the medication has steadily become an essential therapeutic agent in both human and animal medicine [15].

Strychnos, named after Linnaeus in 1753, is a genus of gentian trees and climbing plants. The genus is pantropical, with around 75 species found in Africa, 73 species in America, and 44 species in Asia. The Strychnos genus has five endemic species in South India and the Andaman Islands [16]. It is often seen in wet deciduous and semi-evergreen forests in West Bengal, Bihar, Maharashtra, Odisha, Central, and South India [10]. Poison nut is widely distributed in India and found throughout tropical areas of India, Sri Lanka, Vietnam, Thailand, Cambodia, and Malaysia [6]. This species is currently uncommon in forests and has been listed as a rare endangered tree (RET) in various states, including Chhattisgarh [10].

Morphology

Strychnos nux-vomica is a deciduous tree of modest stature [16] and is native to Southeast Asia and India. Natural populations of poison nut, in the Eastern Ghats region produce heavy blooms from February to April and the flowers open in the evening [5]. It is an evergreen, tiny tree or shrub that grows to a height of 5-25m [5], [16]. The trunk is tall, robust, straight, and cylindrical, with yellowish-grey to dark-grey bark that is smooth and thin. The wood is solid, hard white, and finely grained. The character of wood changes with the seasons. Spring promotes the production of additional tracheary components and the broadening of rays. Summer marks the beginning of the production of longer rays and wider parenchymatous bands [16]. Its leaves are opposite decussate and papery, with a leaf blade that is suborbicular, widely elliptic or ovate, 5-18 cm long, and 4-13 cm wide. It has 5-merous flowers that are dull green and white. Its fruit consists of brownish-yellow berries the size of tiny oranges with a gelatinous flesh containing one to five seeds. The dried mature seed is quite hard, measuring 1.5-3 cm in diameter and 3-6mm thick. The seed has a flattened disk form, is slightly concave, and is entirely covered in hairs spreading from the center to the sides, giving it a distinctive shine [15].

Assessment

Since the discovery of poison nut and its inclusion in medication for humans and animals various analytic techniques have been used to provide evidence for its pharmacological effects. Several analytical techniques for quantitative assessment of strychnos alkaloids, such as HPLC with UV detection [17], TLC [18-19] fluorescence spectrophotometric method, column chromatography [20], 1H NMR, GC-MS [21] LC-MS, and LC-MS/MS, have been published [2], [14]. To establish the quality of plant-based medicines, fingerprint profiling gives data on accuracy, precision, specificity, detection limits, quantitation, and linearity [22]. The WHO guidelines were used to establish the pharmacogenetic specification. The seeds were thoroughly extracted in ethanol using the Soxhlet device. The concentrations of strychnine and brucine in the extracts were determined using the TLC densitometric technique [23].

Micellar liquid chromatography (MLC) is a distinct liquid chromatographic technique that satisfies the requirements of a "green chemistry" idea by employing environmentally friendly chemicals that are non-toxic, non-flammable, biodegradable, and reasonably affordable in contrast to other techniques. The approach employs a direct injection micellar liquid chromatography technology that has been optimized by ICH criteria (Table 2). The following properties were assessed: selectivity, linearity, detection limit, quantification, repeatability, reproducibility, and robustness [24].

Table 2 Poison nut alkaloid content after various treatments

Alkaloids	Dried seeds (10 mg)	Homoeopathic treatment (10 mg)	Ayurvedic treatment (10 mg)	
			Vishtindukvati	Agnitundikvati
Strychnine	800 mg mL^{-1}	25.70 mg Ml^{-1}	72 mg mL^{-1}	69 mg mL^{-1}
Brucine	760 mg mL^{-1}	26.33 mg Ml^{-1}	65 mg mL^{-1}	620 mg mL^{-1}

This table represents the amount of alkaloids observed in 10 mg of dried seeds of poison nut after the application of the MLC technique, Homoeopathic treatment, and Ayurvedic treatment.

Babu Ganesan *et al*. [38] gave a simple, precise, and accurate UV first-order derivative spectrophotometric method for the quantitative determination of strychnine and brucine in herbal formulations. It was developed and validated by ICH guidelines (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) [25]. As per Swarnendu Mitra *et al*. [7] raw seeds were processed through HPTLC [18], [26-27] and after purifying in Kanji and Ardraka Swarasa, the strychnine concentration was reduced by 39.25% and 67.82%, respectively, while the brucine content was lowered by 17.60% and 40.06%, respectively, in comparison to the raw seeds [18], [27-30]. Rajesh Bhati *et al*. [31] explained the study of raw and processed *S. Nux-vomica* seeds using matrix-assisted laser desorption ionization (MALDI) and time of flight mass spectrometry (TOFMS) which allows for quick screening of alkaloid components [31]. Mohsen Behpour *et al*. gave the conclusion that Strychnine and brucine can both be determined simultaneously by employing a new method of multi-walled carbon nanotube-modified carbon paste electrodes (CNT/CPE). Strychnine and brucine have been effectively analyzed in raw and treated seeds of *S. nux-vomica* utilizing hot sand or oil baths as well as a mixture of boiling milk and seawater as the processing method. In their article, 32 Rajeev Jain *et al*. explained that the US-DLLME-TLC-image analysis approach i.e., straightforward necessitates small amounts of solvents and samples, is environmentally friendly, and does not require any expensive equipment. As a result, the technique can be used to analyze dangerous plant poisons like strychnine and brucine for forensic purposes [30].

Phytochemistry

Phytochemically the plant *Nux-vomica* contains 2.6%-3% total alkaloids, with strychnine ($C_{21}H_{22}O_2N_2$) [5] accounting for 1.25%-2.5%, brucine ($C_{23}H_{26}N_2O_4$) [5] accounting for 1.5%-1.7%, [4], [7] although only brucine is found in the bark [7] and vomicine ($C_{22}H_{21}N_2O_4$) majorly in leaves [9] and igasurine accounting for the remainder [5], [32].

Colubrine ($C_{22}H_{24}O_3N_2$), Colubrine, 3-methoxyicajine, Protostrychnine, Novacine, N-oxystrychnine, Pseudostrychnine ($C_{21}H_{22}O_3N_2$), pseudobrucine ($C_{24}H_{28}O_5N_2$) [9]. Isostrychnine, Chlorogenic acid, Glycoside [4], Cafeotannic acid, Copper, Loganin, Strychnicine [8] Vomicine, N-oxystrychnine [31] are some more minor alkaloids.

Strychnine

The deadly indole-type alkaloid strychnine is a member of the Strychnos genus. A genus of trees and climbing shrubs belonging to the gentian order, strychnos was named by Linnaeus in 1753. French chemists Joseph-Bienaime Caenoiu and Pierre-Joseph Pelletier first found strychnine in the Saint Ignatius bean in 1818 [33]. Strychnine is commercially produced from the seeds of *Strychnos ignatii* (Saint-Ignatius bean) and *Strychnos nux vomica* (*Nux-vomica*) [10].

Strychnine is an alkaloid, rhombic crystal made of its fundamental component that is colorless or white. This taste bitter and melt at about 290 degrees Celsius. First discovered in plants of the genus Strychnos, Family Loganiaceae. Sir Robert Robinson initially established the structure of strychnine in 1946, and Robert W. Woodward first synthesized this alkaloid in a lab in 1954. One of the most well-known syntheses in the annals of organic chemistry is this one. Both chemists—Robinson in 1947 and Woodward in 1965—were awarded the Nobel Prize [33].

Strychnine is rapidly absorbed from the gastrointestinal system, and symptoms might appear as soon as 20 minutes after intake. Strychnine's active dosage causes competing blocks on the neuroinhibitory transmitter glycine at postsynaptic locations [14]. The chemical is mostly processed in the liver, with different degrees of renal excretion based on blood levels. Due to its intense bitterness, it induces stomach and salivary discharge. Strychnine was thought to have healing powers since it stimulates the appetite and is used to combat the loss of appetite brought on by the illness [33]. Strychnine is a stimulant, a laxative, and a treatment for other gastrointestinal disorders in medicine [2].

Brucine

In 1819, Pelletier and Caventou isolated brucine from the bark of the *Strychnos nux-vomica* tree. Brucine is a low-concentration alkaline indole alkaloid [36]. *Nux-vomica* is mostly made up of brucine and their nitrogen. Brucine is commonly used to treat arthritis and traumatic pain as an anti-inflammatory and analgesic medication. In recent years, brucine has shown promising anti-tumor activity against a wide range of cancers. In the case of hepatocellular carcinoma, brucine may inhibit cell growth by modulating calcium concentration and mitochondrial depolarization. By modulating the Wnt/b-catenin signaling pathway, brucine may also inhibit the development and migration of colorectal cancer cells LoVo [34]. Brucine is primarily used to treat high blood pressure and other mild cardiac conditions [2].

Brucine is absorbed much more slowly than strychnine, and while it has a greater effect on sensory neurons, it is far less dangerous. However, in high doses, brucine is a lethal toxin that causes tetanic convulsions [32], [35-36].

Mechanism of action

Strychnine functions as a blocker or antagonist at ligand-gated chloride channels in the spinal cord and brain. The glycine receptor (GlyR) is the receptor for the amino acid neurotransmitter glycine. It is one of the most broadly distributed inhibitory receptors in the central nervous system. Glycine receptors are located in most brain locations, including the hippocampus, amygdala, ventral tegmental area, and periaqueductal gray [33]. Strychnine inhibits the glycine receptor, which is a primary inhibitory route in the spinal cord [37]. The strychnine-sensitive glycine receptor is a member of the ligand-gated ion channel family. This ionotropic receptor may be triggered by a variety of simple amino acids, except glycine, -alanine, and taurine, and can be selectively inhibited by the high-affinity competitive antagonist strychnine [33]. *Nux-vomica* appears to have a particular effect on the spinal cord, motor nerves, and the ganglionic system [35].

MATERIALS AND MEDTHODS

Poison nut also known as *nux-vomica* plays a vital role in traditional medication methods since earlier times. Its wide range of usage has been identified in almost all alternative medicine systems. The purpose of this review article is to elucidate the therapeutic indications of poison nut.

Search strategy

The following study attempts to integrate the physiological actions of alkaloids of Poison nut and the current state of scientific proof on the therapeutic applications of Poison nut accessible on PubMed, Google Scholar, Science Direct, and Thieme-E-Journal from April 2000 to August 2021. This study is taken with the following search strategy terms '*Strychnos Nux-vomica*', 'Loganiaceae family', 'Strychnine', 'Brucine', 'Therapeutic properties of *Nux-vomica*', 'Poison nut', '*Nux-vomica* and Homoeopathy', '*Nux-vomica* and Ayurveda', "'*Nux-vomica* and Unani' The above mentioned are searched in different databases and various Textbooks.

Selection criteria

Study materials were included if they met the following inclusion criteria: 1) *Nux-vomica* is being used as an intervention. 2) The study was published in English. 3) The study was published between April 2000 to August 2021. 4) The study was conducted on human participants or plants or animals. 5) Quantitative Assessment studies using different analytical techniques.

Data extraction

The reviewer has independently screened the titles and abstracts of all identified articles to determine eligibility for inclusion. Full-text articles were obtained for all potentially eligible studies and reviewed in detail. Data were extracted from each study, including study design, participant characteristics if present, intervention details, and outcome measures. Various books have also been referred to obtain the necessary information.

Data synthesis

To summarize the findings of the included studies and present literature, a narrative synthesis was performed. The search yielded 45 articles, 40 of which met the inclusion criteria, as well as 12 textbook materials.

RESULTS AND DISCUSSION

Therapeutic properties of poison nut

Poison nut is hazardous since their processed extract has been employed in many traditional formulas from various nations. Several extracts, fractions, and pure chemicals derived from various portions of this plant have been examined to determine their potential pharmacological effects in both in vivo and in vitro settings. Behera *et al*. [8] explained poison nut uses in agriculture. Unscientific and overexploitation of seed and habitat degradation have placed this medicine plant on the endangered list [16]. Every plant component has a wide spectrum of therapeutic indications which is summarized here (Table 3) [7], [16], [36].

Table 3 Poison nut plant parts therapeutic indications

Poison nut plant parts	Medicinal utility
Leaves	Anticancerous, antioxidant, antipyretic, analgesic, and anti-inflammatory properties, as a poultice, stimulate healthy activity in sloughing wounds or ulcers, particularly where maggots have hatched.
Flowers	Antibacterial and antioxidant properties.
Fruits	Antiamnesic activity, hepatoprotective, anti-cholestatic activity, urinary disorders, and diseases due to impure blood.
Seeds	Anticancerous, anti-tumor, antioxidant, anticonvulsant/ neuropharmacological activity, anti-diabetic and antisnake venom activity, atonic, antidiarrhoeal, antidysenteric, antispasmodic. anti-alcoholic, used to relieve pain, promote blood circulation, alleviate blood stasis, and treat indigestion.
Bark	Effective against cholera and severe dysentery.
Wood	Fresh wood juice is supposed to cure diarrhea, fever, cholera, and dyspepsia.
Root	Antidiarrhoeal potential, anticancerous, antisnake venom activity, emetic

This table represents various therapeutic potentials of different parts of the poison nut.

Poison nut is used in traditional medicine to treat a variety of ailments (Table 4) [7], [10], [16], [31], [38-43].

Table 4 Research articles with their outcomes

S. No.	Authors of the article	Therapeutic uses of poison nut
1.	Sukul *et al.*	Investigated the anti-alcoholic effects of *Nux-vomica* dilutions (30 degrees Celsius, 200 degrees Celsius, and 1000 degrees Celsius) in mice. All three *Nux-vomica* potencies reversed the ethanol-induced loss of righting reflex in mice faster than in controls.
2.	Nirmal C. Sukul *et al.*	NuxMT and Nux30c can reduce ethanol intake in rats. Using electronic (ES) and nuclear magnetic resonance (NMR) spectra, it is thought that the altered solution structure of Nux30c mimics NuxMT and causes ethanol aversion in rats.
3.	Ipshita Chatterjee *et al.*	*Nux-vomica* seeds extract significantly neutralized Daboia russelii venom as well as Naja kaouthia venom-induced lethality, phospholipase A2 (PLA_2) enzyme activity, and other toxicities.
4.	Roland Hofbauer	Even at dilutions greater than Avogadro's number, a highly diluted version of *Nux-vomica* seeds extracts (10c) synthesized in ethanol reduced Helicobacter pylori-induced up-regulation of HB-EGF gene expression in KATO-III cells.
5.	Swarnendu Mitra *et al.*	Antifungal, antibacterial, antioxidant, anti-inflammation, anticancerous, antidiabetic, analgesic, anti-diarrheal, anti-tumor, wound-healing, and anti-snake venom properties were discussed. It is used as a delectable appetizer, nervine tonic, and aphrodisiac.
6.	Rajesh Bhati *et al.*	In alloxan-induced diabetic rats, it was found that oral administration of ethanolic (50%) and aqueous extracts (3.6 mg/kg) of *Nux-vomica* seeds has a strong hypoglycemic potential, showed effective and substantial benefits in lowering blood glucose levels, and the results were equivalent to the standard (gliclazide, 10 mg/kg).
7.	Jun Chen *et al.*	*Nux-vomica* is a common constituent in several proprietary Chinese medications, including "Maqianzi Powder," "Jiufen Powder," "Fengshimaqian Tablet," "Shufengdingtong Pill," and others possessing antitumor, analgesic, and anti-inflammatory activity.
8.	Maji Amal K *et al.*	Various authors' observations were reviewed for pharmacological activities such as antioxidant, hepatoprotective, antinociceptive, anti-allergic, anti-inflammatory, antibacterial, anticancer, and gastroprotective properties.
9.	Madhab Chandra Behera *et al.*	Plant extracts from *Nux-vomica* exhibit the following properties: antibacterial (against E. coli, Bacillus subtilis, Staphylococcus aureus, Salmonella typhi, Candida albicans, Klebsiella pneumonia, and other bacteria), antifungal (against Paecilomy variety Penicilliumlium rubrum, Aspergillusgilus flavus), analgesic effects, anti-inflammatory effects, usage below ground as a bait application to control pocket gophers in the United States and protection against thermal and chemical stressors.
10.	Madhab Chandra Behera	The effects of poison nut on the gastrointestinal tract, bone cells, and cardiovascular systems. In addition to therapeutic uses, poison nut has been used as a rodenticide, avicide, insecticide, nematicide, and piscicide.

This table represents the titles of the selected research articles along with various therapeutic properties of poison nut explained in the respective article.

Usage of poison nut in alternative systems of medicine

Homoeopathy

Dr. M. L. Tyler said, “Every household should have a small Homoeopathic medicine chest for common ailments, and every Homoeopathic medicine chest should have Nux [44].

The term "homoeopathy" comes from the Greek terms "homoios," which means "alike," and "pathos," which means "suffering." [2] *Nux-vomica* is regarded as the king of our Polychrest remedies. "Spasm" is the first keynote of Nux and the second is "exaggerated sensitiveness" [45].

Thin physique, fast movements, anxiousness, activeness, and irritability are characteristics of *Nux-vomica* patients [46]. All of their anxieties, worries, and fears revolve around their work and business [47]. Mental pressures, a sedentary lifestyle, extensive studying, and long hours at the office are some of the contributing reasons. *Nux-vomica* patients crave rich and spicy foods and engage in alcohol and women to escape their tough schedule [48]. Homoeopaths use this medication to treat hangovers, back pain, digestive disorders like stool recurring ineffective urging, incomplete and unsatisfactory sensation as if not finished [49] headaches, allergies, colds, flu, mental stress, constipation, menstruation problems, and hemorrhoids. It also includes a modality for marked morning aggravation of symptoms [50].

Prescription: 1. First to 30th potency and higher. 2. Nux is said to be most effective when taken in the evening [51].

Ayurveda

The term "Ayurveda," which means "the science of longevity," is derived from the Sanskrit terms "Ayu," which means "life" or "span of life," and "Veda," which means "knowledge." (2) The plant is referred to as "Upavisa Vargas" in Ayurveda (semi poisonous group). According to Ayurvedic texts, if used properly, the Visha (poison) can act as an Amrita (nectar). After proper Samaskar called Shodhana (purificatory procedures) through a few specific media like Godugdha, Kanji, and Goghrita, ayurvedic physicians have successfully used plants in the management of several diseases. The ultimate goal of Shodhana is to improve the drug's biological efficacy. It is primarily used as an aphrodisiac, appetizer, anti-period, digestive, purgative, and stimulant. They are also used to treat anemia, asthma, bronchitis, intermittent and malarial fever, and extremity weakness [34].

Unani

The Unani system of medicine also uses poison nut in its formulations to provide relief to the suffering (Table 5). [7], [52].

Table 5 Indications of Unani formulations of poison nut

S. No.	Unani formulations	Uses
1.	Habkhas	(i) Brevine tonic, (ii) Aphrodisiac, (iii) Cerebral and heart tonic, (iv) Stomachic, (v) Blood circulation enhancer, (vi) Palatable, and (vii) Tonic for the elderly. It is recommended that young people only use this drug during the winter.
2.	Roghankuchla	Applied topically as an antirheumatic and antiarthritic treatment
3.	Majunizaraqi	(i) Nervine tonic, (ii) Beneficial in facial paralysis and paralysis, (iii) Antirheumatic, (iv) Stomachic, and (v) Primarily as a preventive for elderly people in cold weather.
4.	Capsule Hudar	(i) Efficient in raising blood pressure

This table represents the various therapeutic uses of formulations of poison nut in the Unani system of medicine.

Siddha

Meganadha thailam is a well-known Siddha medicinal oil formulation used to treat skin ailments and rheumatic conditions [10], [20].

CONCLUSION

However, this review comprehensively summarizes Poison nut's history, phytochemistry, pharmacology, and therapeutic uses. *Strychnos Nux-vomica* research has demonstrated a wide range of therapeutic actions, including anti-inflammatory, analgesic, antidiabetic, anti-tumor, and immunomodulatory activity. It has long been used for the treatment of various diseases in Traditional Chinese Medicine (TCM) and traditional Indian systems of medicine such as Ayurveda, Homoeopathy, Unani, and Siddha. According to review of literature, various types of preparations, extracts, and individual compounds derived from different parts of poison nut have been found to have a variety of pharmacological activities. To validate pre-clinical data and traditional knowledge in the context of rational phytotherapy, well-controlled, double-blind clinical trials on *Nux-vomica* with a statistically significant number of patients are required. Just a few studies have been conducted on this plant, and there is still much to be discovered. As a result, it is necessary to investigate its potential in the fields of medicinal research and pharmaceutical sciences to obtain fruitful applications of this plant.

Conflict of interest

The authors have no conflict of interest among them regarding the research.

Author contributions

1. Dr. Shruti - Conceived and designed the analysis; Collected the data; Performed the analysis; Contributed data or analysis tools; Wrote the paper.

2. Dr. Vaishali V. Dolas - reviewed the results and approved the final version of the manuscript.

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