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Piper betle and *Piper nigrum*: Siddha, Traditional and Modern Perspectives on their Role as Antidotes Against Toxic Effects

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Abstract: *Piper betle* and *Piper nigrum* are highly valued in traditional medicine systems and have been used since ancient times to treat various disease conditions. This review aims to systematically evaluate the scientific evidence supporting their potential role as antidotes against toxic effects, integrating insights from modern pharmacology, Siddha, Ayurveda, and other traditional medical systems. In Siddha Medicine, *Piper betle* (*Vettilai*) is esteemed for its role in balancing the three humours and treating a range of ailments. *Piper nigrum* (*Milaku*) is recognized for its broad therapeutic properties. Traditionally, *Piper betle* and *Piper nigrum* have been utilized in the treatment of various toxic conditions, including food poisoning, venomous bites, snakebites, and gastrointestinal disorders. The leaves of *Piper betle* have also been applied as a hemostatic agent in cases of snakebite. Contemporary research has highlighted the antimicrobial, anti-inflammatory, and antioxidant properties of these plants. Notably, significant antibacterial activity, which may help prevent secondary infections at envenomation sites. Furthermore, the anti-inflammatory and analgesic properties of *Piper nigrum* and its active constituents, such as piperine, suggest a potential role in reducing pain and inflammation associated with toxic bites and explores as potential antidotes for various toxic effects and highlighting the potential of these plants in mitigating toxicity and promoting health. However, studies specifically validating anti-venom effects are limited, and clinical trials are needed to confirm efficacy and safety in humans. While these plants show promise as adjunct therapies, they should not replace conventional medical treatments for serious envenomation, emphasising the importance of integrating traditional knowledge with evidence-based medicine.

Keywords -*Antidote, Betle, Detoxification, Pepper, Poison, Toxicity, Venom,*

I. INTRODUCTION

Ethnobotanically, the genus Piper is widely distributed in tropical regions belongs to piperaceae family and have been used for culinary and medicinal purposes from ancient siddha era(Bahara Salehi et al, 2022). Among the piper genus *Piper betle* (betel vine) and *Piper nigrum* (black pepper) are important species with significant cultural and pharmacological value(Arambevela et al, 2011 : Bahara Salehi et al, 2022) in addition Piper species have been used to treat various ailments, including urological problems, skin disorders, liver and

stomach ailments, and to promote wound healing.(Bahara Salehi et al, 2022). Both plants are found in hotter and damper parts of countries in South-East Asia, including India, Vietnam, Sri Lanka, and China.

Piper nigrum is a most commonly used spice, thus also called "the King of Spices". Different types of black peppers are available having different colors. The most commonly known peppers are black and white peppers (Ahmad N et al, 2012 : Achrya S.G et al, 2012). It is Used for pain relief, rheumatism, chills, flu, colds, muscular aches, and fever and applied externally as a rubefacient for sore throats and skin disorders.

Piper betle is commonly known as betel vine. It is a dioecious, perennial creeping plant that is widely cultivated in Southeast Asian countries, including India, Bangladesh, Sri Lanka, Thailand, Taiwan, and Malaysia (Satyal, P., & Setzer, W. N. 2012). Different varieties of *Piper betle* are found in India, including Sirugamani, Karpoori, and Vellaikodi. Traditionally used for preventing oral malodour due to its antibacterial activity, serves as a mouth freshener and masticatory, promoting wound healing, Used to enhance digestive and pancreatic lipase stimulant activities (Fazal. F, 2014) and to prevent catarrhal and pulmonary afflictions (cold, bronchial asthma, and cough). And it is valued as an aphrodisiac and for treating diseases such as halitosis, boils, conjunctivitis, and constipation. In siddha and traditional system betel leaf juice is used as an adjuvant with other medicines for better effects. And also Tamboolam leaves are described as aromatic, sharp, hot, and valuable for voice, acting as a laxative and appetizer (Nayaka.N.M.D.M.W et al, 2011).

In traditional toxicology management, a common remedy involves the consumption of one Piper betle leaf and nine Piper nigrum (black pepper) seeds to neutralize and eliminate toxins from the body. This practice is deeply rooted in cultural knowledge and is supported by traditional beliefs. A well-known Tamil proverb—"*Pathu milagirunthaal pakaivan virundhilum unnalam*"—translates to "If you have ten black peppers, you can safely eat even at an enemy's feast." This proverb underscores the traditional belief in black pepper's potent detoxifying properties, particularly in counteracting ingested poisons.

Piper betle and *Piper nigrum* hold significant positions in Siddha, Ayurveda and traditional medicine, with medicinal uses stretching across diverse cultures and healing systems. This review explores the multifaceted roles of these plants, particularly focusing on their applications as antidotes against toxic effects in humans.

II. METHODOLOGY

This narrative review focuses on the potential antidotal effects of *Piper betle* and *Piper nigrum* against poisons and venoms. The review incorporates information from classical Siddha literature as well as modern scientific research. A comprehensive search was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Search terms included "*Piper betle*", "*Piper nigrum*", "antidote", "toxicity", "detoxification", "protective effects", and other related keywords. Additionally, traditional texts and books were reviewed to gather insights into the historical and ethnomedical use of these plants as antidotes.

III. RESULTS

Based on the present analysis, the findings highlight the traditional uses, phytochemical composition, pharmacological activities, mechanisms of action, and safety profiles of *Piper nigrum* and *Piper betle*. These results collectively provide a comprehensive understanding of their potential therapeutic roles, particularly in the context as an antidot.

4.1Traditional perspective of *Piper nigrum* and *Piper bitle*

Traditional medicine has long relied on plant-based remedies to counteract the effects of poison. *Piper betle* is traditionally used in Sri Lanka, India, China, and Thailand for oral hygiene, digestive health, and as an aromatic stimulant (Bahara Salehi et al, 2022). Leaf juice is used as an adjuvant with other medicines for better effects. *Piper nigrum* used for pain relief, rheumatism, chills, flu, colds, muscular aches, and fever. Applied externally as a rubefacient for sore throats and skin disorders. In addition, the plant is used as an antidote for snakebites in some communities in north-eastern Brazil, especially in Paraíba State. *Piper betle* leaves are used in Brazil to treat snake bites (Wealth Asia: 1997).In eastern Colombia, the leaves are used as a hemostatic in venomous snake bites (Bahare Salehi et al, 2029).

A comprehensive review of Siddha and Ayurvedic formulations reports *Piper nigrum* as a key antidote for snakebite, along with other toxic exposures such as metals, plant poisons, and animal venoms. altogether fourty nine (49) Siddha remedies were included, among them including Fifteen (15) specific for snakebite, four (4) for plant poisons, and others for bites from dogs, rats, spiders, and more (Lavanya P et al, 2019) in addition, *Piper betle* is widely employed in traditional systems to treat a range of conditions including wounds, bleeding, and toxic exposures like fish poisoning and venomous bites. Its leaf is often used as a hemostatic agent to stop bleeding (Protha Biswas et al, 2022)

4.2 Phytochemical constituents of *Piper nigrum* and *Piper betle*

Peculiar activity of pepper and betel phytochemical and pharmacological actions of these plants take the leading roles against to the poisons.

Piper nigrum contains the phytochemicals of Piperine, a nitrogenous pungent alkaloid, flavanones, Flavonoids, lignans, chalcones, and dihydrochalcones. Various aromatic compounds,like Amides, Steroids, Terpenes, Phenolic compounds, Starch, proteins, minerals, vitamins, carotenoids, and essential oils (β-caryophyllene, limonene, sabinene, α-pinene, β-bisabolene, α-copaene, pinene, phellandrene)(Ashokkumar et al. 2021)

Piper betle possess the phytochemicals of phytosterols, alkaloids, starch, Carbohydrate, tannins, amino acids, steroidal compound(Satyal, P., & Setzer, W. N. 2012)diastases, an essential oil composing of terpinen-4-ol(Sugumaran M, et al, 2011),p-cymene carbohydrates, water, flavonoids, allylkatekol, allylpyrocatechol monoacetate, allyl catechol, cineol, estragol,(Sugumaran M, et al, 2011) caryophyllene, cardinene, p-cymenedan eugenol methyl ether, eugenol methyl either(Bhalerao S & Verma D, 2013), eugenyl acetate cineole, caryophyllene and cadinene, safrole Betle phenol(Chovicol,carvacrol Chavibetol)(Rawat AKS et al, 1989), Hydroxychavicol, Eugenol, Estragole, Methy eugenol, Hydroxycatechol,α-pinene, caryophyllene, β-pinene, and 1,8-cineol(Daniel M, 2013)Piperol-A, Piperol-B, methyl piper betlol(Chopra RN et al, 2015)

4.3 Pharmacological activities of *Piper nigrum* and *Piper betle*

Contemporary research has increasingly focused on elucidating the scientific basis for these traditional uses, particularly highlighting the antimicrobial, anti-inflammatory, and antioxidant properties of *Piper betle* and *Piper nigrum*(Biswas et al, 2022) Extractions from *Piper betle* display antibacterial activity, Hepatoprotective, Gastroprotective effects, antihemolytic activities which may help to prevent secondary infections at bite sites(Bandaranayake et al, 2018). Piper nigrum and its constituents exhibit anti-inflammatory and analgesic effects, antifungal, antioxidant, Antiparasitic, Anticancer, neuroprotective, potentially alleviating pain and inflammation resulting from bites(Bahara Salehi et al, 2022 :Junaid, 2019) Hydroxychavicol is a key component, exhibits antioxidant, anticancer, and antimicrobial properties.

4.4 Safety Profile of *Piper nigrum* and *Piper betle*

The European Food Safety Authority (EFSA) has established a NOAEL for piperine at 5 mg/kg b.w. per day, based on a 90-day dietary toxicity study in rats (Jens Rohloff, 2018). In silico models predict a non-carcinogenic effect for piperine. Piperine is categorised as a Cramer Class III compound, with a threshold of toxicological concern (TTC) of 1.5 µg/kg b.w./day`(Elenora T, 2020). Acute toxicity studies of piperine in mice, rats, and hamsters indicate that high doses can be lethal. However, *Piper nigrum* extracts have shown no signs of toxicity in rats at doses up to 5000 mg/kg b.w.. High doses of piperine can lead to a decrease in the weight of the spleen, thymus, and mesenteric lymph nodes, as well as a reduction in total leucocytes. Most of the books mentioned the toxic properties of *Piper nigrum* and *Piper betle* and its effect on the body when consumed excessively.

4.5 Experimental evidence of piperine on toxicity

A study analysed the ethanolic fruit extract of *Piper longum* (a Piperaceae species) demonstrated significant neutralization of Russell's viper venom in vivo, with piperine identified as a key active compound responsible for this anti-venom activity(Shenoy.P.A, et al, 2013). Another systematic review of Piper species

highlights that several, including *Piper longum* are traditionally utilized against snakebite envenomation and have shown protective effects in experimental models(Bahara Salehi et al, 2022) Traditionally, *Piper betle* leaves have been employed as a hemostatic agent in cases of venomous snake bites(Biswas et al, 2022), and in some communities, it is used as an antidote for snakebites(Bahara Salehi et al, 2022) Related species of Piper have also been used traditionally as medicine for snakebites

In addition another study show that, Piperine enhances the activity of detoxification enzymes and protects against drug-induced toxicity (Majumdar B, 2003). And *Piper betle* has shown promise in mitigating the toxic effects of ethanol on the liver and brain in animal models. Antioxidant properties of *Piper betle* help reduce oxidative stress induced by ethanol(Chopra RN, 2015) as well as *Piper nigrum* and its components, particularly piperine, can modulate drug metabolism and enhance bioavailability and Piperine inhibits certain enzymes (e.g., P-glycoprotein and CYP3A4), which can affect drug metabolism.(Bhalerao S,2013). And also nephroprotective study on methanol extracts of *Piper nigrum* showed significant protection against toxin-induced kidney damage (e.g., MSG-induced toxicity) in animal models, highlighting its protective effects beyond just venom-related injury(Obiageli, 2023)

More over a preclinical study demonstrated that *Piper betle* leaf extract significantly attenuated cadmium-induced oxidative damage in the liver. The extract improved antioxidant markers (e.g. increased superoxide dismutase, catalase) and reduced biochemical indicators of hepatic injury (e.g. ALT, AST) compared to controls (Milton Prabu S et al, 2012). As a additional evidence an In vivo studies using animal models revealed that *Piper betle* extract enhances wound closure and reduces bleeding time, likely due to its coagulant and collagen-stabilizing activities (Anggi Aprilyani et al, 2022).Although direct experimental evidence of *Piper betle* neutralizing snake venom is limited, reviews highlight its traditional use in anti-ophidian formulations. Other Piper species have clearly demonstrated in vivo anti-venom activity, suggesting a possible similar role for *Piper betle*(Lien et al, 2015)

At last the leaves are rich in bioactive compounds such as hydroxychavicol, chavibetol, eugenol, and estragole, all of which contribute to strong antimicrobial, antioxidant, anti-inflammatory, and coagulant properties and mechanisms collectively supportive of antidotal action (Protha Biswas et al, 2022)

4.6 Modern Antidote usage against to toxic effects

Nowadays various antidotes commonly used to counteract the effects of toxic substances in the body. Some examples such as N-acetylcysteine (NAC) is used in both early and late presentations of acetaminophen poisoning to reduce the impact of the toxic metabolite NAPQI by restoring glutathione stores, enhancing NAPQI elimination, and reducing oxidative stress. An atropine is used to counteract the muscarinic effects of organophosphorus poisoning. And a Naloxone is used for opioid overdose to reverse life-threatening respiratory depression, as well as an antivenom: Used to treat envenomation from snake bites and other venomous animals

Other treatments and considerations in managing toxic consumption include an activated charcoal is decrease toxin levels by adsorbing chemicals within minutes of contact(Junaid R. et al: 2019) Multiple doses may be considered for carbamazepine, dapsone, quinine, phenobarbital, and theophylline poisoningas well gastric decontamination were Interference with the absorption of ingested poison from the gastrointestinal tract. Additionally enhanced elimination Techniques such as haemoperfusion and urinary alkalinisation can be used to enhance the elimination of toxins (Warnasekara, J. et al: 2019) Urinary alkalinisation is useful for acidic toxins like salicylates and phenobarbital .Extracorporeal treatments: Haemodialysis can remove poisons from the blood (Chopra RN et al: 2025)

IV. DISCUSSION

According to narrative review of *Piper nigrum* and *Piper bettle* activity over the toxicity more effective. Both plants are rich in antioxidants that can neutralize free radicals and reduce oxidative stress caused by toxins. Antioxidants counteract the damaging effects of free radicals and toxins in the body. Ethanolic extracts of *Piper nigrum* have significant antioxidant activity. Phenolic compound of eugenol in *Piper betle* can

scavenge free radicals and inhibit lipid peroxidation, thereby protecting cells from oxidative damage caused by toxins (Bahara Salehi et al, 2022)

Phenols, such as chavibetol and eugenol in *Piper betle*, possess antimicrobial properties. Phenols can disrupt microbial cell membranes, leading to cellular damage.

Anti-inflammatory properties of *Piper betle* and *Piper nigrum* can help reduce the inflammatory damage caused by various toxins. By modulating inflammatory pathways and terpene found in some Piper species, can suppress pro-inflammatory markers they can preventi nflammation-related..*Piper nigrum* has shown nephroprotective effects against monosodium glutamate (MSG)-induced renal toxicity in rats.Both can support liver function and enhance detoxification processes.with aid in the elimination of toxins from the body by promoting the activity of detoxification enzymes.

Siddha and other traditional systems emphasizes the balance of Vata, Pitta, and Kapha. *Piper betle* and *Piper nigrum* can help restore this balance and counteract the effects of toxins that disrupt it. Siddha medicine uses Piper species for their detoxification and rejuvenating properties. They are incorporated into formulations that target specific toxic conditions and promote overall health. Many traditional communities use *Piper betle* and *Piper nigrum* as part of their daily diet to prevent and treat various ailments. These practices provide valuable insights into the long-term safety and efficacy of these plants. Further human studies are needed to validate the efficacy and safety of *Piper betle* and *Piper nigrum*, particularly piperine-rich extracts, in managing toxicity. *Piper nigrum* demonstrates potential as a supportive therapy for snake envenomation by neutralizing toxins, reducing inflammation, and mitigating oxidative damage. However, integrating traditional knowledge with evidence-based medicine remains essential

V. CONCLUSION

Piper betle and *Piper nigrum* show strong potential as antidotes due to their rich phytochemical profiles and antioxidant, anti-inflammatory, and hepatoprotective properties. Integrating traditional use with modern science may lead to effective herbal therapies for toxicity. However, comprehensive clinical trials are essential to confirm their safety and efficacy in human toxicological applications.

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