An Insight into *Piper Betle* Linn: Traditional Usage, Ayurvedic Benefits, Chemical Constituents, and Pharmacological Potential

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ABSTRACT: -

Piper betle L., better known as Betel leaf, is a plant with medicinal properties that belongs to the Piperaceae family. It's commonly found to grow in Southeast Asia. Traditionally, people use betel leaf for its health benefits, due to its rich mix of bioactive compounds like flavonoids and tannins, which offer various healing properties. Scientific studies support this traditional use, demonstrating that betel leaf has antibacterial, antifungal, and antioxidant properties that can help manage conditions such as diabetes, high blood pressure, and oral health issues. The medicinal benefits of *Piper betle* mainly come from its hydroxychavicol content and essential oils. Besides its health properties, betel leaf is also economically important because it supports many livelihoods in areas where it's cultivated. Even with its long history of use and scientific backing, researchers still need to explore its medicinal potential more deeply, especially for clinical applications. This review looks at all the existing research on *Piper betle* L., aiming to understand its health benefits and economic impact better, while emphasizing the need for more studies to release its full medical potential.

KEY WORDS: - *Piper betel* L, Traditional uses, Phytochemicals, Ayurvedic and Unani medicine.

INTRODUCTION: -

Piper betle L., commonly called betel leaf, is a well-loved medicinal plant with a rich history across Asian cultures. In India, for instance, people have been cultivating it since approximately 400 BC. This evergreen vine loves to climb and belongs to the Piperaceae family. It has been a staple in traditional systems like Ayurveda, with mentions dating back to ancient texts such as the Charaka and Sushruta Samhitas. The plant is quite tough; it can grow up to 10 to 15 feet high. Its leaves are heart-shaped, shiny, and usually measure between 4 to 7 inches long and 2 to 4 inches wide. Betel leaves thrive best in warm, humid tropical or subtropical settings. The plant is dioecious, meaning it has separate male and female flowers, with major cultivation happening in places like India, Malaysia, Thailand, and Sri Lanka. The semi-woody, climbing *Piper betle* has stems that noticeably swell at the nodes, starting with a papillose texture when young and becoming smooth as it gets older. Its leaves grow alternately along the stem and range from about 15 to 20 cm. There are two types of leaves: the female ones, which are broad, ovate, and heart-shaped at the base, and the male leaves, which are narrower and a bit slanted. They also value their medicinal properties. Traditionally, they're used to aid digestion, respiratory health, and even as natural antimicrobial agents [1]

Fig. 1 *Piper Betle* Linn.

TAXONOMY CLASSIFICATION: - [2]

Kingdom: Plantae

Division: Magnoliophyta

Class: Magnoliopsida

Order: Piperales

Family: Piperaceae

Genus: Piper

Species: Piper betle L.

VERNACULAR NAME: - [2]

Sanskrit: Tambool, Mukhbhushan, Nagavalli, Varnalata, Nagavallari Hindi, Bengali

Urdu: Paan

Telugu: Nagballi, Tamalapaku

Marathi: Vidyache pan

Malayalam: Vettilakkoti, Vettila

Kannada: Veeleya, Veeleyada yele, Vilya, Villayadel

English: Betle, Betle pepper, Betle- vine

AYURVEDIC SIGNIFICANCE: - [2]

The betel plant is highly treasured in both Ayurvedic and Unani medicine, due to its wide range of healing uses. It's commonly used as a remedy to expel worms, boost appetite, act as an astringent, and even as an aphrodisiac. Besides these, betel leaves are known to be a natural mouthwash with antiseptic properties, help with digestion, support heart health, freshen breath, promote urination, regulate menstrual cycles, ease bowel movements, and calm the nervous system. People also use betel leaves to strengthen gums and ease urinary issues. These leaves are believed to have stimulant, energizing, antiseptic, and antioxidant qualities. Traditional remedies often involve making a decoction from betel leaves, which has been used to help with body odor and to treat issues like diarrhea, sore throats, skin allergies, and leucorrhea. Sometimes, cooked betel leaves are added to vegetable soups to enjoy their medicinal benefits.

PHYTOCHEMICALS: - [3]

The main component found in the leaves is the volatile oil known as Betel oil, which contains two phenols: chavibetol and chavicol. These leaves also hold an alkaloid called arene, which exhibits effects similar to cocaine. The oil's composition ranges from 0.8% to 1.8% and includes compounds like chavicol, betel phenol, eugenol, allyl pyrocatechin, terpene, cineol, caryophyllene, cadinene, and menthone. The specific makeup of this oil can vary: safrole appears in the leaf, stalk, stem, and roots, whereas ß-phellandrene is primarily found in the fruit. Interestingly, younger leaves tend to produce more essential oil. Several compounds isolated from different parts of the plant include hydroxychavicol, hydroxychavicol acetate, allylpyrocatenol, chavibetol, piper metal, methyl piperbetol, piper A, and piper B. An analysis of the leaf's essential oil and ether-soluble fraction identified 14 components, eight of which are allylpyrocatechol analogs. The most abundant were chavibetol, making up about 53.1%, and chavibetol acetate at 15.5%. Other constituents included allylpyrocatreflectl diacetate (0.71%), camphene (0.48%), chavibetol methyl ester or methyl eugenol (0.48%), eugenol (0.32%), α-pinene (0.21%), β-pinene (0.21%), limonene (0.14%), safrole (0.11%), 1,8-cineole (0.04%), and allylpyrocatreflectl monoacetate. The hexane extract from the leaf stalks yielded four pure aliphatic compounds: pentadecyl 6-hydroxytridecanoate, pentatriacontane, methyl hexacos-7-enoate, and 6,9-heptacosa diene. A study from Sri Lanka identified safrole as the dominant compound in the leaves, stems, stalks, and roots, with ß-phellandrene primarily in the fruit. besides, the chemical content of certain leaves can change as they mature.

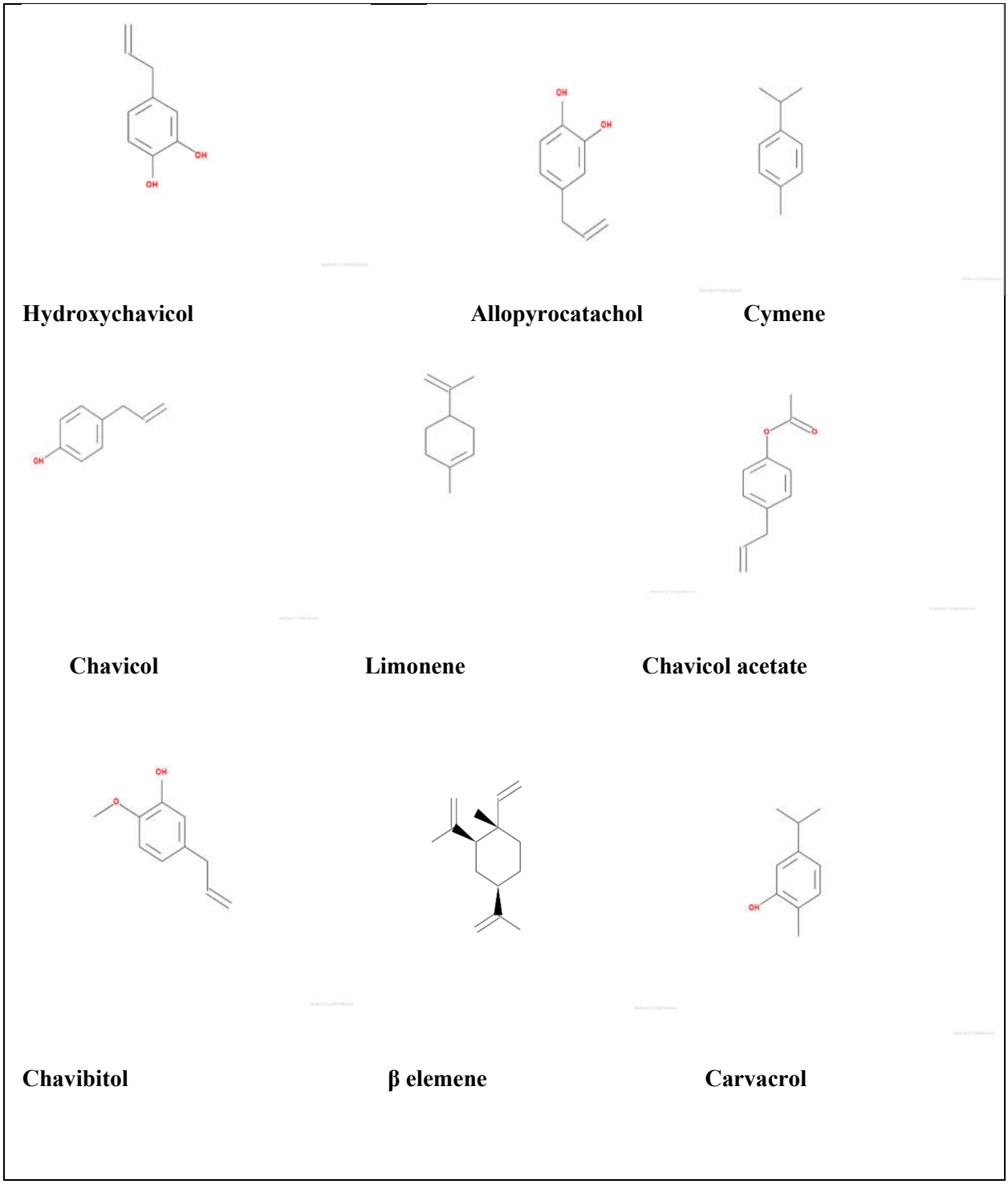

Fig. 2 Chemical Constituents of *Piper Betle* Linn

TRADITIONAL USES OF *PIPER BETEL* L: - [4]

- Treatment for Filariasis: A paste consisting of *Piper betel* leaves, salt, and warm water has long been used to treat filariasis.
- Obesity: It is thought that combining one *Piper betel* leaf with *Piper nigrum* and using it for two months can help treat obesity.
- Coughs and Dyspnea: Betel leaf juice combined with honey is used to treat indigestion, coughs, and dyspnea, particularly in children.
- Lactation: To encourage milk production in nursing mothers, betel leaves smeared with oil are applied to the breasts.
- Betel leaves can be applied locally to treat mastitis, arthritis, and orchitis.
- For children and the elderly, leaves diluted with mustard oil are applied to the chest to relieve coughing and dyspnea.
- Bad Breath and Body Odor: Betel leaves are used to prevent tooth decay and reduce body odor and bad breath.
- Vaginal Itching and Infections: Betel leaves help prevent and alleviate vaginal infections and itching.
- Nose Bleeding: To prevent nose bleeding, apply betel leaves.
- Nutritional Value: Vitamins such as riboflavin (B2), thiamine (B1), niacin (B3), and carotene is present in the leaves.
- Rheumatism and Eczema: Rheumatism and eczema can be cured with betel leaves.
- Wound Healing: To promote better healing, a paste made from betel leaves is applied to cuts and wounds.
- Sterile: Black pepper and *Piper betel* roots are traditionally used to make women sterile.
- Laryngeal and throat irritation can be relieved by applying betel leaf oil.

ETHNOBOTANICAL USES: - [4]

Leaves: The extract from leaves has health benefits like fighting free radicals, fungi, and malaria. It's also helpful for soothing indigestion and reducing coughs, especially in children. Plus, it can be toxic to some cells and has properties that battle malaria, bacteria, insects, and problems like diabetes and stomach issues.

Stems: They are known to help with bronchitis, asthma, indigestion, and coughs.

Whole plant: People use piper betel as both a spice and a food. Its strong flavour makes it popular in perfumes, oils, and medicines that fight infections or even cause hallucinations. Recent research also shows it can help get rid of worms. It helps keep the digestive system balanced and healthy. Its light colour and gentle effects are part of why it works so well.

PHARMACOLOGICAL ACTIVITIES: -

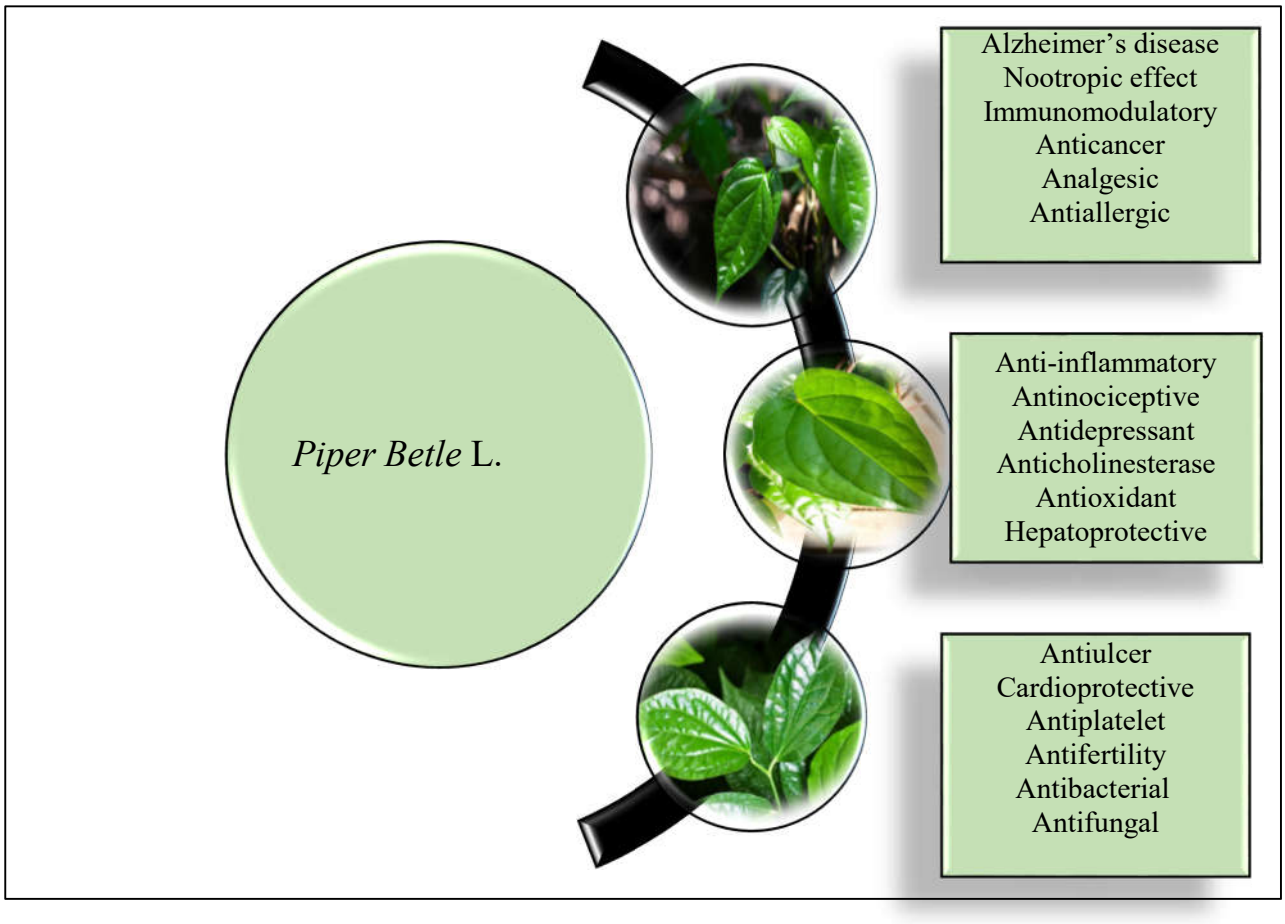

Fig. 3 Pharmacological Activities

Alzheimer's disease: -

Piper betle has shown promise in improving cognitive abilities like memory and learning, which could help with Alzheimer's disease treatment. An extract from the leaves of the *Piper betle* plant has been found to improve learning and memory in rats that exhibit symptoms similar to those of Alzheimer's disease, which is brought on by exposure to aluminium chloride. Better results in the passive avoidance and Morris's water maze tests support this improvement. Furthermore, *Piper betle* is known for its antioxidant properties, which may aid in preventing oxidative stress, a condition associated with the

pathophysiology of Alzheimer's disease. According to research, *Piper betle* may have an inhibitory effect on acetylcholinesterase, an enzyme implicated in the development of Alzheimer's disease.[5]

Nootropic effect: -

The nootropic effects are believed to be caused by flavonoids and phenolic compounds, such as eugenol, chavibetol, and chavicol, which are also thought to enhance its neuroprotective and antioxidant qualities [7] Its leaves hydroalcoholic extract improved object recognition in Swiss albino mice, while the aqueous extract reversed scopolamine induced amnesia in albino rats by boosting spontaneous changes in the Y-maze test [6] and dramatically lowering retention latency. Research has shown that both water-based and alcohol-based extracts of *Piper betle* leaves can help improve memory, with many studies indicating that the alcohol-based extract tends to be more effective.[7]

Anticancer activity: -

Betel leaf, scientifically known as *Piper betle*, is showing some impressive potential in fighting cancer, and a lot of that's down to what's inside it. Specifically, compounds such as hydroxychavicol and other phenolic compounds are receiving a lot of attention. Research indicates that extracts from *Piper betle* can kill various cancer cells – think KB, HeLa, and MCF-7 cells – by kicking off apoptosis and slowing down how quickly they grow.[8] The plant's cancer-fighting abilities also come from its antioxidant properties, which help lower oxidative stress and support the body's defenses. Studies have also found that extracts from *Piper betle* can significantly slow down tumor growth and improve blood profiles in animal studies, suggesting it could be a useful cancer treatment.[9,10] Hydroxychavicol, a key component of *Piper betle*, is a strong agent against the growth of several cancer cell lines.[10] All things considered, the anticancer activity of *Piper betle* points to its potential in developing new chemotherapy drugs.

Analgesic activity: -

Betel leaf, scientifically known as *Piper betel* Linn., is widely recognized for its pain-relieving properties, a claim that's backed by scientific investigations into its ethanolic and hydroalcoholic extracts. [11,12] Animal studies, using methods like the hot plate and tail-flick tests, have shown these extracts' effectiveness. The studies revealed that the extracts significantly increased reaction times when administered at doses of 100 and 200 mg/kg, implying central analgesic actions. [13] The pain-reducing capabilities of *Piper betle* are thought to originate from its phytochemical components, including flavonoids, tannins, and

phenols, all of which contribute to its ability to relieve pain. Moreover, methanolic extracts derived from *Piper betle* leaves have been shown to increase pain thresholds and lessen writhing responses, with the effects varying depending on the dosage, further reinforcing its analgesic effectiveness.

Anti-inflammatory activity: -

Piper betle L., a plant that's quite well-known, exhibits some rather remarkable anti-inflammatory qualities. Research into both ethanolic and aqueous extracts of betel leaves has brought to light their ability to combat protein denaturation in a manner that's directly related to the dosage. The concentration required to stop 50% of the process (IC50) was found to be comparable to that of well-established anti-inflammatory drugs, like diclofenac sodium.[14] Hydroalcoholic extracts have demonstrated their effectiveness too, leading to a significant decrease in inflammation in situations such as carrageenan-induced paw edema. The presence of substances like flavonoids, tannins, and phenols is thought to be behind this impact. Furthermore, methanol extracts derived from betel leaves and stems have demonstrated the ability to reduce the production of pro-inflammatory cytokines. This is achieved through the adjustment of the NF-κB and MAPK signaling pathways, thereby boosting the plant's anti-inflammatory prowess. Taking all these observations into account, the longstanding traditional use of *Piper betle* L. for treating inflammatory conditions appears quite justified.[15]

Antinociceptive activity: -

Multiple studies suggest that *Piper betle* L., often referred to as betel leaf, possesses notable pain-relieving properties. In trials involving rats, both the crude ethanol extract (CEE) and the hot water extract (HWE) derived from betel leaves demonstrated a reduction in pain responses, as measured by the hot plate and tail flick tests. This suggests that the betel leaf extracts may exert their analgesic effects by interacting with the central nervous system. Moreover, since naloxone, an antagonist of opioid receptors, counteracts these pain-reducing effects, it is proposed that the extracts operate via opioid pathways. The extracts further exhibited Painlessening capabilities in both the early and late phases of the formalin test, hinting at an influence on sensory transmission and the release of inflammatory substances.[16]

Antidepressant activity: -

Piper betle L. has been found to have notable antidepressant effects, according to studies using both water-based and hydroethanolic extracts. When given at 100 mg/kg, the water extract showed strong antidepressant activity in Swiss albino mice, mainly by reducing the time they spent immobile in tests like the forced swim and tail suspension tests [17]. Likewise, hydroethanolic extracts at doses of 200 and 400 mg/kg also showed major antidepressant effects. These effects are thought to happen because the extracts may block the reuptake of key neurotransmitters like dopamine, noradrenaline, and serotonin.[18]

Anticholinesterase activity: -

Piper betle L. shows strong anticholinesterase activity. Its aqueous and ethanol extracts effectively inhibit both acetyl- and butyrylcholinesterase. This activity comes from its varied phenolic compounds, including apigenin and luteolin derivatives, which were identified through HPLC/DAD-ESI/MSn analysis.[19] Researchers have assessed a standardized extract of *Piper betle* L. leaf as a possible anti-cholinesterase agent, suggesting it may help treat neurodegenerative diseases such as Alzheimer's.[20] Additionally, studies indicate that *Piper betle* could be a promising natural option for addressing several medical conditions due to its safety and bioactive compounds.

Antioxidant activity: -

Piper betle L. has strong antioxidant effects, mainly due to its phenolic compounds like hydroxychavicol, chavibetol, and eugenol. Leaf extracts have shown antioxidant activity in several tests, including DPPH, hydroxyl, nitric oxide, and superoxide anion radical scavenging, as well as ferric reducing antioxidant power (FRAP) assays.[21] Interestingly, ethanolic extracts of *Piper betle* L. have more antioxidant power than aqueous extracts and are effective in reducing oxidative stress. Eugenol, an important part of *Piper betle*, is especially good at scavenging nitric oxide and hydroxyl radicals. [22,23]

Hepatoprotective activity: -

Piper betle L. shows strong liver protection activity, mainly due to its antioxidant effects and its ability to prevent lipid peroxidation in liver damage models. Studies have found that the aqueous and ethanolic extracts of *Piper betle* L. can safeguard the liver from damage caused by carbon tetrachloride (CCl4) and ethanol. These extracts lower elevated liver enzymes like AST and ALT and boost antioxidant defenses such as superoxide dismutase (SOD) and catalase. Furthermore, the extracts have shown promise in preventing liver fibrosis by reducing alpha-smooth muscle actin (α-SMA) expression, which is a marker for

fibrosis. The liver protective effects likely come from the plant's varied phytochemical makeup, including compounds like chavicol and chavibetol that help with its antioxidant and anti-inflammatory properties.[24]

Antiulcer activity: -

Piper betle Linn, known as betel leaf, has been used traditionally for its medicinal properties, including its ability to help with ulcers. Leaf extracts have shown strong protective effects against gastric ulcers in various experimental models. Ethanol extracts of *Piper betle* have shown effective antiulcer activity by increasing (SOD) and (CAT) activity, boosting mucus production, and reducing oxidative damage in gastric tissues.[25] Also, hydroalcoholic extracts have demonstrated significant antiulcer activity in rat models, protecting different experimental setups like HCl-ethanol, acute stress, and pylorus ligation.[26] The antiulcer effects come from compounds like alkaloids, flavonoids, steroids, saponins, and tannins, which have antioxidant and protein-precipitating properties. The gastroprotective effect likely happens by improving mucosal defenses mechanisms and antioxidant properties, instead of just blocking gastric acid secretion [27]

Cardioprotective activity: -

Piper betle has shown promise in protecting against heart injuries and oxidative stress. Key findings highlight its strong protective effects against isoproterenol-induced heart damage. Studies suggest that *Piper betle* extracts can reduce heart damage by lowering oxidative stress and regulating cardiac marker enzymes like creatine phosphokinase-MB (CK-MB) and lactate dehydrogenase (LDH). These extracts also help restore antioxidant levels in the heart, including (SOD), (CAT), and glutathione peroxidase.[28] Furthermore, the juice extract of *Piper betle* has anti-hypertrophic properties. It restores electrolyte balance and decreases cardiac hypertrophy caused by isoproterenol.[29] The protective effects are linked to phytochemicals such as flavonoids and phenolic compounds, which have antioxidant qualities. This cardioprotective activity likely works through antioxidant mechanisms that improve cellular defenses and lessen oxidative damage, rather than directly affecting heart function.[30]

Antifertility activity: -

Piper betle has shown strong antifertility effects, especially through its extracts. Alcoholic extracts of *Piper betle* petiole have demonstrated 51% antifertility activity, while aqueous extracts showed 37.2% activity in female Wistar rats. These effects influence reproductive outcomes by causing anti-implantation and abortifacient effects.[31] In male Swiss albino

mice, the alcoholic extract of the leaf stalk reduced fertility to 0% within 60 days. This happened by lowering sperm count and motility, without changing hormonal levels. The effects were reversible after stopping the treatment.[32] Ethanol extracts of *Piper betle* leaves have also been found to decrease sperm count, motility, and normal morphology in rats, indicating a possible contraceptive mechanism. Additionally, *Piper betle* extracts have been shown to reduce human sperm mitochondrial activity, further supporting their antifertility potential.[33]

Antiallergic activity: -

Piper betle shows potential for reducing allergy symptoms, especially with its antihistamine effects. Research indicates that the ethanolic extract and essential oil of *Piper betle* can significantly lessen symptoms of allergic reactions in guinea pigs exposed to histamine aerosol. This suggests it can help with respiratory issues and other allergic responses. The antihistamine properties come from various plant compounds, including flavonoids and essential oils, which may prevent histamine release or block its effects at receptor sites. More studies are needed to fully understand how these antiallergic effects work.[34]

Immunomodulatory activity: -

Piper betle has shown notable immunomodulatory activity, mainly due to its methanolic extracts. The methanolic extract of *Piper betle* (MPb) contains a blend of phenols, flavonoids, tannins, and polysaccharides. It can suppress lymphocyte proliferation in a dose-dependent way. This extract also influences immune responses by affecting interferon-γ receptors and nitric oxide production, hinting at possible immunosuppressive effects that may help treat autoimmune disorders.[35] Ethanolic extracts of *Piper betle* have anti-inflammatory and immunomodulatory effects. They reduce reactive nitrogen species and modify T-helper 1 pro-inflammatory responses, which can help with conditions like arthritis.[36] Water extracts of *Piper betle* boost interferon-γ production from human peripheral blood mononuclear cells, indicating that they play a role as a Th1-type immunomodulator.[37] Additionally, bioactive compounds from *Piper betle* have demonstrated strong immunomodulatory activity by inhibiting pro-inflammatory cytokines like TNF-α. This suggests potential for treating inflammatory diseases.

Antiplatelet activity: -

Piper betle, known as betel leaf, shows antiplatelet activity mainly through its aqueous extract of the inflorescence. This extract acts as a scavenger for (ROS), including hydrogen

peroxide, superoxide radical, and hydroxyl radical.[38] It inhibits platelet clumping caused by arachidonic acid and collagen, with IC50 values of 207 and 335 μg/mL, respectively. It also significantly lowers thromboxane B2 production, which is important for platelet aggregation. Other parts of *Piper betle*, like triterpenes and β-sitosterol, are also reported to have antiplatelet and anti-inflammatory effects.[39]

Antifungal activity: -

Betel leaf, known scientifically as *Piper betle* L., is actually pretty good at fighting fungi. Research has shown that extracts from betel leaves, especially those made with ethyl acetate and methanol, can target and kill different types of fungi like Candida albicans and Aspergillus species, which are known to cause health problems.[40] The reason these leaves are so effective comes down to compounds like eugenol, which can break apart fungal cell walls and mess with their enzymes, making it harder for the fungi to survive.[41] People have even turned these extracts into products like gels and soaps to make it easier to use for antifungal purposes. The strength of this antifungal effect depends on the concentration of more extract, which generally means better results, and scientists have confirmed this through various tests, like measuring the areas where fungi don't grow and determining the lowest amount needed to kill them.[42]

Antibacterial activity: -

Piper betle L. has been shown to have strong research that shows extracts from *Piper betle*, especially those prepared with ethanol, can effectively combat different bacteria, including both Gram-positive and Gram-negative types. In particular, they seem to work well against bacteria like Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa.[43] This antibacterial action is likely due to compounds such as phenolic substances, tannins, and glycosides found in the leaves. Beads made from *Piper betle* leaf extracts have demonstrated high antibacterial properties, which could make them useful in cleaning wastewater. The ethanol-based extracts are usually more potent in inhibiting bacteria compared to water-based ones [44]

DISCUSSION

The review of *Piper betle* L. shines a light on its impressive therapeutic potential. It's packed with a variety of phytochemicals and has been widely used in traditional medicine for ages. all these bioactive compounds — think phenols, flavonoids, and alkaloids that form the backbone of its numerous medicinal benefits. For generations, people have turned to betel leaf for relief from various health issues, particularly those related to oral health, respiratory

problems, and wound healing. Studies have shown that betel leaf possesses solid antimicrobial, antioxidant, anti-inflammatory, and even anticancer properties. This not only backs up what folks have been saying for years but also opens the door to some exciting new treatment possibilities. And then there's the intriguing research into how betel leaf might protect the brain, the heart, and help manage metabolic disorders. It's a promising area for future research and real-world applications. But let's not ignore the flip side. The review does point out some challenges and gaps in our understanding of betel leaf. Sure, lab studies have shown some great results, but when it comes to clinical trials, we're still a bit behind. We need more thorough research to really nail down how effective and safe it is for humans. Plus, there's the issue of how the concentration of its beneficial compounds can vary based on where it's grown, how it's cultivated, and even how it's harvested. That makes it tricky to standardize any treatments based on betel leaf. And here's something to think about: there's a potential risk of toxicity with long-term or heavy use of betel leaf, especially with the traditional practice of chewing betel quid, which has been linked to oral cancer. It's a stark reminder that while we want to harness all the good stuff betel leaf has to offer, we also need to tread carefully. Balancing the therapeutic benefits with the risks is crucial.

CONCLUSION

Betel leaf (*Piper betel* L.) is a special plant that has been used traditionally for a long time, and it shows lots of potential in modern medicine today. This study looks at the many natural compounds in the plant, which help explain its various health benefits, like fighting bacteria, acting as antioxidants, reducing inflammation, and even fighting cancer. Modern research confirms many traditional uses of betel leaf, especially for healing wounds, helping with respiratory problems, and maintaining dental health. Still, more research is needed to fully understand what betel leaf can do. To make the most of it in today's healthcare, scientists need to focus on standardizing the active compounds, thoroughly testing their safety, and conducting longer clinical studies. It's also important to be cautious about possible risks, especially since chewing betel quid can be addictive or harmful if misused. Overall, betel leaf is a promising natural resource that combines traditional knowledge with scientific research to develop new health treatments. Future work should aim to solve current challenges so we can safely and effectively include betel leaf in modern medicine.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCE: -

1. Tarmale VA, Wankhede S, Sen AK, Uppalwar SV. Pharmacological Properties and Traditional Applications of Betel Leaf (*Piper betle* L.). Journal of Pharma Insights and Research. 2024 Dec 5;2(6):131-41. Arawwawala LD, Arambewela LS, Ratnasooriya WD. Gastroprotective effect of *Piper betle* Linn. leaves grown in Sri Lanka. Journal of Ayurveda and Integrative Medicine. 2014 Jan;5(1):38.
2. Biswas P, Anand U, Saha SC, Kant N, Mishra T, Masih H, Bar A, Pandey DK, Jha NK, Majumder M, Das N. Betelvine (*Piper betle* L.): A comprehensive insight into its ethnopharmacology, phytochemistry, and pharmacological, biomedical, and therapeutic attributes. Journal of Cellular and Molecular Medicine. 2022 Jun;26(11):3083-119.
3. Shah SK, Garg G, Jhade D, Patel N. *Piper betle*: phytochemical, pharmacological and nutritional value in health management. Int J Pharm Sci Rev Res. 2016 May;38(2):181 9.
4. Afridi M, Muhammad IM, Ahmad T, Hussain A, Akram M, Ghotekar S, Oza R, Marasini BP. Ethno-medicinal uses of *Piper betel*—A review. Adv. J. Chem.-Sect. B. 2021; 3:199-208.
5. Upadhyaya S, Gangachannaiah S, Chandrashekar PL. Effect of *Piper betel* leaf extract on learning and memory in Aluminium chloride-induced Alzheimer's disease in Wistar rats. Biomedical and Pharmacology Journal. 2019 Sep 25;12(3):1425-31.
6. Saka VP, Babu SP, Himaja V. Effect of aqueous *piper betle* leaf extract against scopolamine-induced amnesia on albino rats. J Chem Pharm Sci. 2017;10(1):116-20.
7. Roopa PN, Uttara K, Chaitra SR. Effect of *Piper betle* leaf extracts on enhancement of memory and learning in rodents.

8. Veettil SR, Sunil EA, Mukunda A, Mohan A, John S, Pynadath MK. Anticancer effect of *Piper betle* leaf extract on KB cell lines in vitro study. Oral & Maxillofacial Pathology Journal. 2022 Jan 1;13(1).
9. Alam B, Majumder R, Akter S, Lee SH. *Piper betle* extracts exhibit antitumor activity by augmenting antioxidant potential. Oncology letters. 2015 Feb 1;9(2):863-8.
10. Satapathy BS, Biswal SK, Maharana L, Pattnaik S. Bioactive Components of *Piper betel* Could be Potential Anticancer Agents: A Short Review on Pre-clinical Investigations and Practical Challenges. Current trends in biotechnology and pharmacy. 2023;17(2):918-29.
11. Datta A, Bhalerao SV, Shidore PP, Tilak AV, Patil S, Deshpande T. To evaluate the analgesic efficacy of an ethanolic extract of *Piper betle* Linn. (Paan) and its probable mechanism of action using animal models.
12. Reddy PS, Gupta RK, Reddy SM. Analgesic and anti-inflammatory activity of hydroalcoholic extract of *Piper betle* leaves in experimental animals. Int. J. Basic Clin. Pharmacol. 2016 May;5(3):979-85.
13. Alam B, Akter F, Parvin N, Pia RS, Akter S, Chowdhury J, Sifath-E-Jahan K, Haque E. Antioxidant, analgesic and anti-inflammatory activities of the methanolic extract of *Piper betle* leaves. Avicenna journal of phytomedicine. 2013;3(2):112.
14. Williams LA, Vasquez EA, Milan PP, Zebitz C, Kraus W. In vitro anti-inflammatory and antimicrobial activities of phenylpropanoids from *Piper betle* L. (Piperaceae). Natural Products in the New Millennium: Prospects and Industrial Application. 2002:221-7.
15. Ganguly S, Mula S, Chattopadhyay S, Chatterjee M. An ethanol extract of *Piper betle* Linn. mediates its anti-inflammatory activity via down-regulation of nitric oxide. Journal of Pharmacy and Pharmacology. 2007 May;59(5):711-8.
16. Arambewela LS, Arawwawala LD, Ratnasooriya WD. Antinociceptive activities of aqueous and ethanol extracts of *Piper betle*. leaves in rats. Pharmaceutical biology. 2005 Jan 1;43(9):766-72.
17. Nayak RP. Preclinical evaluation of antidepressant activity of aqueous extract of *Piper betle* leaves in Swiss albino mice. International Journal of Basic & Clinical Pharmacology. 2019 Jan;8(1):143.
18. Gulhane HI, Misra AK, Reddy PO, Pandey DE, Gulhane RU, Varma SK. Effects of *Piper betle* leaves (paan) extract as an anti-depressant and anti-anxiety in experimental animals. Mintage J Pharm Med Sci. 2015 Apr:12-5.

19. Ferreres F, Oliveira AP, Gil-Izquierdo A, Valentão P, Andrade PB. *Piper betle* leaves: profiling phenolic compounds by HPLC/DAD–ESI/MSn and anti-cholinesterase activity. Phytochemical analysis. 2014 Sep;25(5):453-60.
20. Dalai MK, Bhadra S, Bandyopadhyay A, Mukherjee PK. Evaluation of anti-cholinesterase activity of the standardized extract of *Piper betel* L. leaf. Oriental Pharmacy and Experimental Medicine. 2014 Mar; 14:31-5.
21. Sujatha Venugopalan SV, Alka Sharma AS, Vijayalatha Venugopalan VV, Gautam HK. Comparative study on the antioxidant activities of extracts from *Piper betle* leaves.
22. Aara A, Chappidi V, Ramadas MN. Antioxidant activity of eugenol in *Piper betel* leaf extract. Journal of Family Medicine and Primary Care. 2020 Jan 1;9(1):327-31.
23. Dasgupta N, De B. Antioxidant activity of *Piper betle* L. leaf extract in vitro. Food chemistry. 2004 Nov 1;88(2):219-24.
24. Saravanan R, Ramesh B, Pugalendi KV. Effect of *Piper betle* on hepatotoxicity and antioxidant defense in ethanol-treated rats. Journal of herbs, spices & medicinal plants. 2007 Jan 4;12(1-2):61-72.
25. Majumdar B, Chaudhuri SR, Ray A, Bandyopadhyay SK. Potent antiulcerogenic activity of ethanol extract of leaf of *Piper betle* Linn by antioxidative mechanism. Indian Journal of Clinical Biochemistry. 2002 Jan; 17:49-57.
26. Vyawahare NS, Kagathara VG, Katedeshmukh RG, Sharma PK, Mohod SM. Evaluation of antiulcer activity of *Piper betel* leaves extract in rats. Research Journal of Pharmacology and Pharmacodynamics. 2010;2(4):278-82.
27. Arawwawala LD, Arambewela LS, Ratnasooriya WD. Gastroprotective effect of *Piper betle* Linn. leaves grown in Sri Lanka. Journal of Ayurveda and integrative medicine. 2014 Jan;5(1):38.
28. Arya DS, Arora S, Malik S, Nepal S, Kumari S, Ojha S. Effect of *Piper betle* on cardiac function, marker enzymes, and oxidative stress in isoproterenol-induced cardiotoxicity in rats. Toxicology mechanisms and methods. 2010 Nov 1;20(9):564-71.
29. D Doss VA. Cardioprotective activity of *Piper betle* juice in isoproterenol-induced hypertrophic rat models. International journal of research in pharmaceutical sciences. 2020;11(4):5214-20.
30. Sudhan, Janakiraman, Ahmad SF, Wani A, Ahmed SS. Phytochemicals from *Piper betle* (L.) as Putative Modulators of a Novel Network-Derived Drug Target for Coronary Artery Disease: An in-silico Study. Processes. 2023 Oct 25;11(11):3064.

31. Shah SK, Jhade DN. Evaluation of antifertility potential of *Piper betle* (Petiole) on female Wistar rats "rising approaches of herbal contraception''. Biochemistry and Biophysics Reports. 2018 Sep 1; 15:97-102.
32. Sarkar M, Gangopadhyay P, Basak B, Chakrabarty K, Banerji J, Adhikary P, Chatterjee A. The reversible antifertility effect of *Piper betle* Linn. on Swiss albino male mice. Contraception. 2000 Nov 1;62(5):271-4.
33. Lubis M, Syahfitri W. Antifertility Effect of Sirih Leaf (*Piper betle* L.) Ethanol Extract on Male Wistar Rats' Spermatogenesis. Journal Farmasi Galenika (Galenika Journal of Pharmacy) (e-Journal). 2023 Mar 7;9(1):110-8.
34. Hajare R, Darvhekar VM, Shewale A, Patil V. Evaluation of antihistaminic activity of *Piper betel* leaf in guinea pig. Afr J Pharm Pharmacol. 2011 Feb 1;5(2):113-7.
35. Kanjwani DG, Marathe TP, Chiplunkar SV, Sathaye SS. Evaluation of immunomodulatory activity of methanolic extract of *Piper betel*. Scandinavian journal of immunology. 2008 Jun;67(6):589-93.
36. Ganguly S, Mula S, Chattopadhyay S, Chatterjee M. An ethanol extract of *Piper betle* Linn. mediates its anti-inflammatory activity via down-regulation of nitric oxide. Journal of Pharmacy and Pharmacology. 2007 May;59(5):711-8.
37. Bandyopadhyay S, Pal B, Bhattacharya S, Ray M, Roy KC. Extracts of *Piper betle* leaves as an immunomodulator. Google Patents. 2002.
38. Lei D, Chan CP, Wang YJ, Wang TM, Lin BR, Huang CH, Lee JJ, Chen HM, Jeng JH, Chang MC. Antioxidative and antiplatelet effects of aqueous inflorescence *Piper betle* extract. J Agric Food Chem. 2003 Mar 26;51(7):2083-8. Doi: 10.1021/jf0210223. PMID: 12643677.
39. Saeed SA, Farnaz S, Simjee RU, Malik A. Triterpenes and B-sitosterol from *Piper betle*: isolation, antiplatelet and anti-inflammatory effects. Biochem Soc Trans. 1993 Nov;21(4):462S. Doi: 10.1042/bst021462s. PMID: 8132030.
40. Nayaka NMDMW, Sasadara MMV, Sanjaya DA, Yuda PESK, Dewi NLKAA, Cahyaningsih E, Hartati R. *Piper betle* (L): Recent Review of Antibacterial and Antifungal Properties, Safety Profiles, and Commercial Applications. Molecules. 2021 Apr 16;26(8):2321. Doi: 10.3390/molecules26082321. PMID: 33923576; PMCID: PMC8073370.
41. Putranti W, Asterina C, Witasari HA. Formulation and antifungal activity of *Piper betle* L. leaf extract in emulsion gels against Candida albicans. Majalah obat tradisional. 2021;26(1):28-34.

42. Selvaraj, Ganesh Kumar1; Wilson, Jayaraj John2; Kanagaraj, Nalini2; Subashini, Eswarapandian2; Thangavel, Sivakumar2, Enhanced Antifungal Activity of *Piper betle* Against Candidiasis Infection Causing Candida Albicans and In Silico Analysis of Its Virulent Protein. Biomedical and Biotechnology Research Journal (BBRJ) 6(1) p 73-80, Jan–Mar 2022. | DOI: 10.4103/bbrj.bbrj_154_21
43. Nayaka NMDMW, Sasadara MMV, Sanjaya DA, Yuda PESK, Dewi NLKAA, Cahyaningsih E, Hartati R. *Piper betle* (L): Recent Review of Antibacterial and Antifungal Properties, Safety Profiles, and Commercial Applications. Molecules. 2021 Apr 16;26(8):2321. Doi: 10.3390/molecules26082321. PMID: 33923576; PMCID: PMC8073370.
44. Khan JA, Kumar N. Evaluation of antibacterial properties of extracts of *Piper betel* leaf. Journal of pharmaceutical and biomedical sciences. 2011;11(11).