Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
https://www.phytojournal.com
JPP 2024; 13(2): 249-258
Received: 01-01-2024
Accepted: 03-03-2024

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Betel leaf (*Piper betle*): Ethnomedicine to emerging therapeutic frontiers

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DOI: https://doi.org/10.22271/phyto.2024.v13.i2c.14887

Abstract
Native to Southeast Asia, the betel, also known as *Piper betle*, is a species of flowering plant in the Piperaceae family of pepper plants. This article provides a thorough exploration of the traditional and ethnomedical uses of the betel leaf (*Piper betle*) across various cultures, with a focus on its extensive therapeutic properties. The review encompasses the historical significance of betel leaf in Ayurvedic and Unani systems, detailing its diverse applications, ranging from anthelmintic to neuropharmacological effects. Furthermore, the article delves into the rich phytochemical composition of betel leaves, highlighting the presence of various compounds, such as phenols, alkaloids, flavonoids, and essential oils. The article dedicates a significant portion to elucidating the emerging research on betel leaf's potential in the realm of cancer treatment, showcasing its antitumour and anticancer properties. Additionally, the review explores betel leaf's efficacy in addressing various health issues, including its analgesic, anti-inflammatory, Antinociceptive, and neuropharmacological activities. The article also discusses the antioxidant, hepatoprotective, anti-ulcerogenic, Antihyperglycemic, antihyperlipidemic, anti-atherogenic, cardio protective, antifertility, and antimicrobial activities of betel leaves. Through a comprehensive examination of preclinical studies and scientific findings, this article aims to present a holistic understanding of the therapeutic potential of betel leaves, emphasizing its multifaceted contributions to traditional medicine and its promising role in contemporary healthcare.

Keywords: Betel leaf. Ethnomedicine, therapeutic properties, phytochemical composition, multifaceted benefits

Introduction
The well-known perennial creeping plant *Piper betle* L. (also known as *Piper betel* Blanco) is a member of the Piperaceae genus and is native to central and eastern Peninsular Malaysia. It is also present in East Africa and tropical Asian nations [1]. primarily grown in Malaysia, Taiwan, Bangladesh, Sri Lanka, Thailand, and India, along with a few other Southeast Asia countries, it is a commercial cash crop. The betel vine is referred to as the "green gold of India" since the production, handling, processing, and preparation of betel leaves provides a living for about 20 million people in the country [2, 3]. The betel vine is a plant that is often grown asexually. It comes in different varieties and produces both male and female plants. There are about a hundred different types of betel plants in the world; of these, forty are unique to India, and thirty of those are known to have originated in Bangladesh and West Bengal [4]. *P. betle* is referred to by numerous names in different parts of the world; however, "Paan" is the most common term in Bangladesh, India, Pakistan, and Nepal [5]. In Hinduism, areca nuts and betel leaves are essential components of many social, cultural, and religious rituals [1]. Betel quid is widely used as a natural mouth freshener and tonic to avoid oral malodour in many regions. According to a survey conducted by the International Agency for Research on Cancer, there are 200–600 million users worldwide [6]. *P. betle* is used in many traditional medical systems, including the folk medical systems of the West Indies and Latin America, traditional Chinese medicine, and the Indian Ayurvedic medical system. *P. betle* plants, also known as Brhat Sarwajwarahara, Brhat Visamaj Warantaka Rasa, Laghu-sutaseknara Rasa, Lanha, and Puspadhava Rasa, are used as preparation variants in the Ayurvedic medical system to treat a variety of ailments. In Ayurvedic medicine, practitioners typically use betle leaf juice as an adjuvant in numerous herbal combinations with various other medicinal plants to enhance outcomes.
The plant has long been used to treat a wide range of illnesses, including the common cold, bronchial asthma, cough, stomach-aches, and rheumatism. It is also used to treat a variety of non-communicable injuries and cuts, as well as boils, bad breath, constipation, conjunctivitis, gum swelling, and abscesses [7, 8].

There are more uses for this plant, including fish poisoning, fish bait, pesticides, decorations, oils, fragrances, and hallucinogens.

Fig 1: Images of fresh and dried *Piper Betel* leaf

There is several bioactive phytochemicals of pharmaceutical and biological importance that are mainly responsible for the pharmacological characteristics of therapeutic plants [9]. Numerous kinds of phytoconstituents, including alkaloids, glycosides, tannins, phenolic compounds, flavonoids, terpenes, and oligosaccharides, have been found to be present in plants. These phytochemicals have also been reported to be effective against a variety of human illnesses [9, 10]. Because betel leaves contain a significant amount of phenols and terpenes in their essential oil, the leaves give off a strong, pungent scent [11]. At room temperature, the betel leaf essential oil has a somewhat oily, slick, and sticky liquid consistency. The environment, soil types, growth location, and landrace types all influence the large diversity of bioactive chemicals found in betel leaves [5]. The betel plants contain a diverse spectrum of phytochemicals, including hydroxychavicol, chavicol, eugenol, estragole, methyl eugenol hydroxycatechol, α-pinene caryophyllene, β-pinene, 1,8-cineol, and others [12]. In a recent study, researchers boosted the preventative and therapeutic benefits of herbs to treat patients with Corona. Betle leaves) and herbo-minerals (Swarna bhasma) in a dosage-dependent way [13].

Researchers have identified the techniques for extracting volatile oils from betel leaves, such as hydro distillation, steam distillation, solvent extraction, and supercritical fluid extraction, using GC-MS and NMR [1]. Numerous studies have demonstrated the effectiveness of the bioactive compounds found in essential oils as antioxidants to prevent neurodegenerative diseases, cancer, and inflammation. These compounds are also effective as antimutagenic, antifertility, antilipidemic, anti-glycaemic, cardioprotective, and other properties [14]. Insect attacks as well as bacterial, protozoan, and fungal illnesses can be fought off by betel leaf essential oil.

Fig 2: Essential oil of betel leaf [*Brand: RV essential*]

Botanical assessment

As a dioecious root climber, the plant can reach shoot heights of 3 to 10 m, depending on the facilities for climbing that are available. The plant has lateral branches that extend a few feet above the ground all the way along its length. The stems have dichotomous branching and roots at the nodes, and they are large and articulate. When young, the light green stems have pinkish stripes along the node and short, rising, whitish streaks. The stems are sturdy, nearly terete, and slightly flattened. The internodes typically reach 1.2 cm in diameter and 12 cm in length. Petioles are 2–5 mm long, pubescent, and channelled; leaves are described as simple blades that alternate, spiral, and ex-stipulate. The leaf blades are smooth.

Chemical constituents

The plant contains a wide range of biologically active phytochemical, with the main constituents being phenols and terpenes. The phenol content in betel leaves varies by gender, with male plants having three times higher total phenols and thiocyanate content compared to female plants. The amount of phenol in a leaf determines its quality; higher phenol content corresponds to higher grade. The strong smell of betel leaves is caused by phenols, which include alkaloids, flavonoids, tannins, sterols, phenols, glycosides, saponins, and terpenoids. The leaves also contain berries that contain cadinene, 1,8-cineole, chavicol, chavibetol, safrole, camphene, limonene, caryophyllene, pinene, carvacrol, allyl pyrocatechol, and eugenol. The main ingredients of betel leaf oil include safrole (48.7%), chavibetol acetate (12.5%), allylpyrocate choldiacetate (34.0%), ρ–cymene, 4-terpinol, eugenol, and β-caryophyllene. Sesquiterpenes, cadinene, caryophyllene, safrole (52.7 percent), eugenyl acetate (5.8 percent), allylpyrocatecholdiacetate (15.4%), and eugenol are also present in the essential oil (6.4 percent). Researchers subjected two types of betel leaves to phytochemical analysis, which verified the presence of acids, steroids, tannins, saponins, flavonoids, and cardiac glycosides. The betel vine contains various compounds, including monoterpenes, sesquiterpenes, and phenylpropanes. The essential oil of *P. betle* var Bangla contains thirty-five compounds [15].

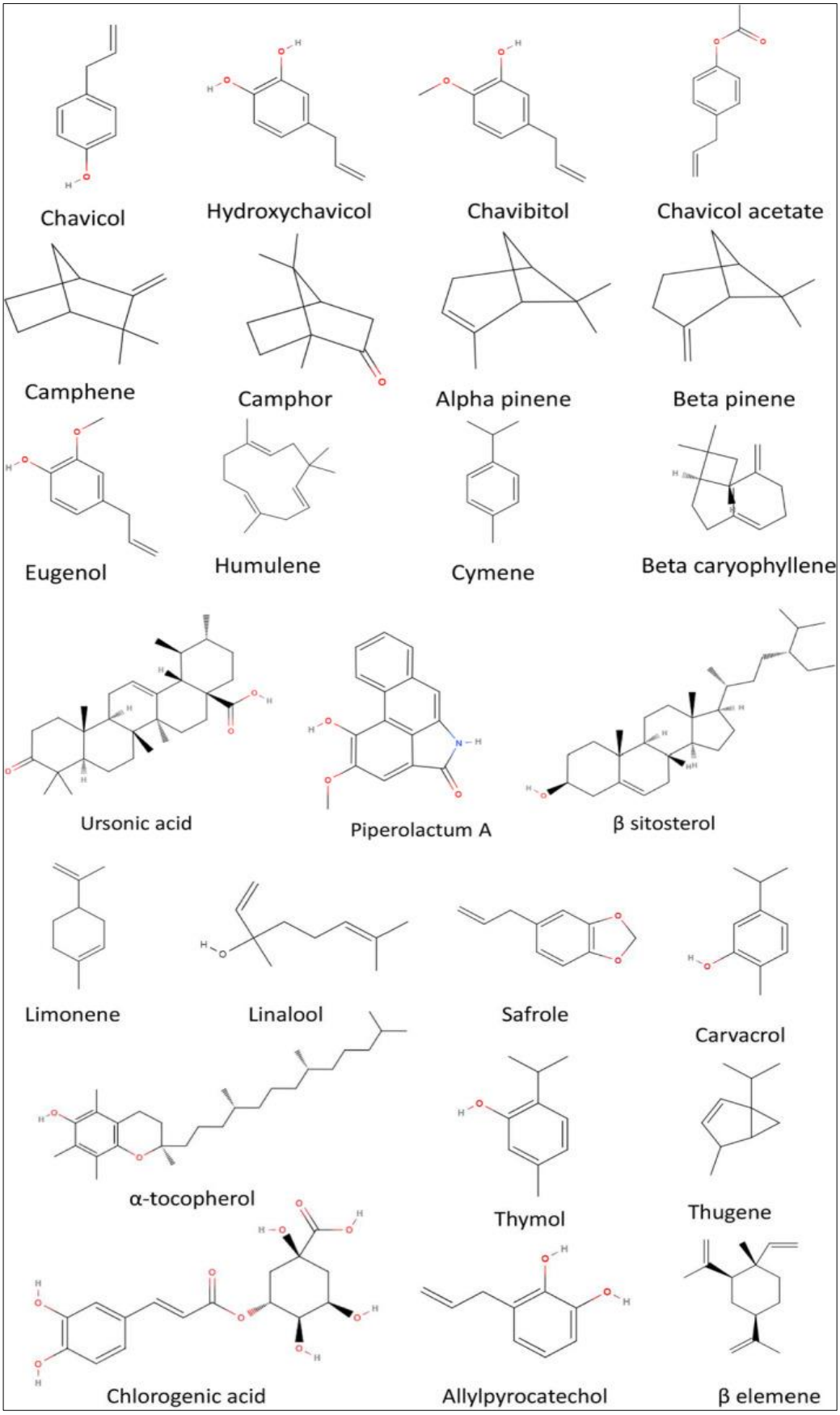

Fig 1: Some Chemical Constituents present in the Betel Leaf (*Piper betle*) [15].

Traditional and Ethnomedical Significance

Since ancient times, people have identified betel leaf as an astringent, stimulo-carminative [16] (katu), fragrant, and aphrodisiac (kamagnisandipanam) [17, 18]. It is said that the leaves have the ability to cure wounds [19]. The Indian traditional medical system [20] has linked the leaves to pancreatic lipase stimulation and digestion. Betel leaf has long been used to cure a wide range of illnesses, including rheumatism, cuts, bruises, mastitis mastoiditis, gum swelling, betel leaf boils and abscesses, conjunctivitis, constipation, headaches, and itches [21]. Numerous ayurvedic medicines use the fresh juice of betel leaves [22]. People believe that leaves

have beneficial effects in treating dyspnoea and bronchitis. Singers chewed the leaves to get a better voice. The fruit of the *Piper betel* plant is used to treat coughs along with honey [23].

Fresh betel leaves have antibacterial, antifungal, antiseptic, anti-ringworm, and anthelminthic properties. As a baby lotion for newborns, leaves are helpful for coughs, asthma, constipation, and to stop milk secretion. Additionally, they also use leaves as eye drops for eye injuries and infections [24]. This plant's essential oil has a history of being used as an antiseptic and for treating respiratory catarrhs. Leaf extract is said to inhibit male reproductive capability. The leaves have anti-motility effects on washed human spermatozoa and antifertility effects on male rats. Traditional medicine practitioners employ the root as a long-acting oral contraceptive for women. The consumers think that chewing "paan" increases their endurance and productivity. *Piper betel* exhibited smooth, skeletal muscle relaxant, cardiotonic, and hypotensive properties [25].

Antitumour and anticancer properties

The antitumour and anticancer properties of plant-derived compounds have shown great promise in cancer treatment. Studies have shown that betel leaf extracts can inhibit preneoplastic and neoplastic changes, inhibit tumour emergence, and reduce the tumour-forming efficacy of nitrosamines. Additionally, betel leaf extracts have been found to inhibit the incidence of virus-induced and 7-12-dimethylbenz(a) anthracene-induced skin tumours in mice.

Additionally, the betel leaf ethanol extract has demonstrated promise in cancer chemoprevention in Raji cells stimulated by 12-O-hexadecanoylphorbol-13-acetate. Both the ethanol and aqueous leaf extracts demonstrated cytotoxic and antiproliferative effects on human epithelial carcinoma cells and breast cancer T47D cell lines. The MCF-7 breast cancer cell line demonstrated dose-dependent inhibitory effects in response to ethyl acetate and hexane leaf extracts.

P. Furthermore, researchers have discovered that betle leaf extracts inhibit the growth and proliferation of human prostate cancer cells and affect the activity of P. *betle* in BALB/c nude mice. *betle* in BALB/c nude mice. *In vitro* studies have shown that hydroxychavicol-containing leaf extracts show sensitivity to androgen-independent human prostate cancer cells and the activity.

Besides its anticancer benefits, betel leaf extracts have also shown cytotoxicity, suppressed cell migration, and inhibited cell proliferation and epithelial-to-mesenchymal transition in pancreatic cancer cell lines. These findings suggest that betel leaf extracts may have potential as a potential chemopreventive agent for human oral cancer.

Analgesic/anti-inflammatory/antinociceptive activity

Inflammation is a complex pharmacological process characterized by swelling, warmth, redness, and pain in tissues. By modifying TRPM8/TRPA1 channels and endogenous opioid signalling pathways, food supplements have been shown to be safe, natural analgesics that function as adjuvants for a variety of clinical pain and inflammation conditions. Studies have shown that the antinociceptive activity of *P. betle* extracts is higher than the hot extract via the opioid-mediated pathway. Researchers have discovered that the ethanol extract from betel leaves possesses anti-inflammatory and anti-arthritic properties by dose-dependently decreasing the production of nitric oxide. Researchers evaluated the analgesic effect of betel leaf extracts using various solvents and cell lines and found that five varieties exhibited significant anti-inflammatory activity. Leaf essential oil has also been found to have effective anti-inflammatory activity with 85% inhibition.

Neuropharmacological property

Numerous neurological and psychiatric disorders such as Alzheimer's disease and Parkinson's disease as well as epilepsy, migraine and essential tremors have caused severe human morbidity and mortality [26, 27]. Within neurological diseases, the most common comorbid diagnoses are depression, anxiety disorders, and cognitive impairment. Medication, cognitive behavioural therapy, somatic therapies, and electroconvulsive therapy are among the available treatment options. Oral antidepressants have certain benefits, but they also have certain drawbacks, including as inefficiency, side effects, and drug interactions. To find a better and safer alternative treatment of neurological conditions, natural compounds of plant origin such as terpenes, alkaloids, flavonoids, lipids and phenolic acids are being studies extensively [28].

Anti stress and Anti-anxiety activity

Experts define anxiety as an uncomfortable emotional state with no apparent cause or a feeling of being out of control. It causes a host of symptoms that are not medically explained, reduces functioning, causes insomnia, and decreases efficiency [29]. The antianxiety activity of *P. betle* leaves was evaluated in Swiss albino mice using a hydroalcoholic extract. In the light/dark exploration test, there was a progressive improvement that was dose dependent, and in the antianxiety model, there was a rise in the plus when compared to the control group that was given diazepam as usual [30].

P. The researchers evaluated the impact of P. *betle* to determine its potential role in stress-induced sleep disturbance mediated by early life exposure. In this investigation, zebrafish larvae underwent post-fertilization stress produced by dexamethasone (DEX) to receive betel leaf ethanol extract. The outcomes demonstrated enhanced levels of stress-related gene expression (NF-kB) and melatonin-related behavioural gene expression (MT1, MT2, aanat1 and aanat2). These levels were comparable to positive control melatonin [31].

Alzheimer's disease

Because butyrylcholinesterase (BchE) and acetylcholinesterase (AChE) break the neurotransmitter acetylcholine, it is crucial to suppress both enzymes to increase brain activity. Cholinesterase inhibitor medications can be used to treat Alzheimer's disease, a neurodegenerative condition that affects the elderly and causes dementia, memory loss, and cognitive impairment. Human neuroblastoma cells (SH-SY5Y) were used to assess the viability of P. *betle's In vitro* anticholinesterase activity by lowering the leakage of lactate dehydrogenase and 3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide. Strong inhibitory efficacy against AchE and BchE was demonstrated by both the ethanol extract and the aqueous extract [32].

The standardised betel leaf methanol extract containing hydroxychavicol and chlorogenic acid was also tested by Dalai *et al.* for its ability to inhibit AchE and BchE. The results indicated that hydroxychavicol had a stronger cholinergic impact than chlorogenic acid; however, a mixture of the two (1:1) had the strongest inhibitory efficacy, with IC50 values against AchE and BchE of 21.23 ± 0.33 µg/ml and 45.55 ± 1.89 µg/ml, respectively [33]. The study involved testing betle leaf extract in Wistar rats with Alzheimer's

disease induced by aluminium chloride (AlCl3) to examine its effects on memory and learning capacity. The treatment of the aqueous extract of leaves increased spatial memory retention and decreased the mean escape latency period in two tests, the Morris water maze test and the passive avoidance test, in a manner similar to that observed in mice treated with rivastigmine [34]. According to these studies, *P. betle* may prove to be a highly effective anticholinergic medication with promise for the treatment of Alzheimer's disease.

Antidepressant activity

The forced swim test and the tail suspension test were used to assess the antidepressant potential of the betel leaf ethanol extract in Swiss albino mice. When compared to imipramine-treated control mice, oral treatment of leaf extract demonstrated significant antidepressant effect by shortening the period of immobility [35]. In their investigation, Gulhane *et al*. also discovered that when imipramine was used as the conventional medication, the hydroalcoholic extract from betel leaves could regulate depression by reducing immobility time in the tail suspension test and forced swim test [30]. By employing the forced swim method, albino mice treated with the volatile oil extracted from *P. betle* fruit demonstrated a noteworthy antidepressant effect in comparison to the conventional antidepressant medication fluoxetine [36].

Nootropic effect

The hydroalcoholic extract of *P. betle* leaves was shown to have nootropic effect by the experiment in which the extract was administered to Swiss albino mice and the result showed an increase in discrimination index in the object recognition test [37]. In another experiment, the nootropic effect of *P. betle* in scopolamine-induced amnesia in albino rats was evaluated using the Y-maze test and it was found that the aqueous extract of leaves can reverse the effect against amnesia with a significant decrease in retention latency, a major decrease in the inflection ratio [38].

Antioxidant activity

Reactive oxygen species (ROS) production is a key indicator of disease pathology, and antioxidants function as a barrier to prevent ROS from causing degenerative and chronic illnesses. Antioxidants are beneficial because they reduce the oxidative injury of cell proteins, carbohydrates, and lipids, helping prevent these disorders.

The extract of P. *betle's* inflorescence was found to scavenge free radicals with a 50% inhibitory concentration using an *In vitro* assay. The leaf aqueous extract showed 83% antioxidant activity in the human ductal breast epithelial tumor (T47D) cell line [39], and the ethanolic extract of leaves scavenged more than 50% free radical in the HeLa cell line using the superoxide dismutase activity assay.

Jaiswal *et al*. performed an antioxidant assay using methanol, ethanol, acetone, ethyl acetate, and distilled water extract from betel leaves (Banarasi, safeda, Calcutta, Cuttack, Desibagla, Maharashtra, and Sofia varieties) [40]. The tests that revealed the highest levels of antioxidant activity were the photochemiluminescence assay for the Calcutta variety, the FRAP (ferric reducing antioxidant power) assay, and the ABTS (2,2′-Azinobis-(3-Ethylbenzthiazolin-6-Sulfonic Acid) assay of *Banarasi safeda*.

In every experiment, it was discovered that certain leaf solvent extracts (ethanol, ethyl acetate, hexane + petroleum ether, and aqueous extract of leaves) may have antioxidant qualities. The DPPH radical scavenging assay in human breast cancer MCF-7 cells showed antioxidant activity with an IC50 of 30.0 ± 0.1 µg/ml. [41].

Antiulcerogenic property

Prolonged use of NSAIDs, alcohol abuse, and stress can lead to peptic ulcers. Studies have shown that *P. betle* can protect against gastric injury induced by indomethacin in rats. The ethanol leaf extract of betel leaves has antioxidant properties, reducing the ulcer index by 93.4%, accelerating healing, and improving mucin content. Additionally, it exhibits antiulcer action in models of pylorus ligation in Swiss albino mice and Wistar rats, as well as in HCl-ethanol and acute stress. It has been demonstrated that the hydroalcoholic extract of betel leaves raises stomach pH, reduces gastric fluid volume, and reduces ulcer index. These findings support the traditional claim that *P. betle* could be an excellent gastroprotective and antiulcerogenic agent in therapeutics [42, 43].

Hepatoprotective property

The hepatoprotective activity of *P. betle* was studied using a Wistar rat model of ethanol-intoxicated hepatotoxic injury. The betel leaf ethanolic extract showed the highest activity, reducing AST, TBARS, ALT, and lipid hydroperoxides, improving antioxidants, and free radical detoxifying enzymes. Additionally, by reducing the production of a-smooth muscle actin, attenuating total glutathione S-transferase activity, and suppressing AST and ALT activities, the extract lessened liver fibrosis. The extract also enhanced the expression of active-matrix metalloproteinase-2 and inhibited the level of TIMP2 [44]. The ethanol extract also mitigated methotrexate-induced hepatotoxicity in rats by reducing ALT, AST, and ALP levels.

Antihyperglycemic activity

The study investigated the antihyperglycemic efficacy of *P. betle* in streptozotocin-diabetic albino Wistar rats. The blood glucose levels, glycosylated haemoglobin, liver fructose-1,6-bisphosphatase, glucose-6-phosphatase activity, and liver hexokinase were all shown to be lower in the results. The methanolic extract from betel leaves prevented the thiol group and carbonyl production in dose-dependent ways as well as the various stages of glucose-induced protein glycation. The ethanolic extract also inhibited human recombinant aldose reductase, preventing long-term diabetic complications [45, 46].

Antihyperlipidemic activity

The Wistar rat brain showed increased lipid peroxidation and antioxidant protection when treated with ethanol. *P. betle* leaf extract showed improvement in toxicity symptoms, with the highest activity at 300 mg/kg dose. It also reduced lipid peroxidation markers and increased antioxidants. The leaf methanolic extract showed depletion in total cholesterol, triglycerides, LDL, and VLDL activities [47, 48].

Anti-atherogenic activity

Venkadeswaran *et al*. found that the *P. betle* plant's anti-atherogenic potential can alleviate hypercholesterolemia-induced high levels of TC, TG, LDL, and VLDL in Wistar rats. The betel leaf ethanol extract and its constituent eugenol reduced AST, alkaline phosphatase, ALT, enzymes for lipid metabolization, lactate dehydrogenase, antioxidant enzymes, and induce Furthermore, the leaf extract and eugenol, a bioactive component, enhanced cellular defence, reduced ROS, and provided protection against oxidative stress. Furthermore, the leaf extract and eugenol, a bioactive

component, enhanced cellular defence, reduced ROS, and provided protection against oxidative stress. Furthermore, the leaf extract and eugenol, a bioactive component, enhanced cellular defence, reduced ROS, and provided protection against oxidative stress. malondialdehyde in liver tissue and hemolysate [49].

Cardio protective activity

The study evaluated the cardio protection of *P. betle* in rats with isoproterenol-induced myocardial infarction. Oral administration of betel leaf hydroalcoholic extract significantly improved ventricular function, restored catalase levels, decreased CK-MB isoenzyme leakage, and reduced lipid peroxidation [50]. Additionally, the leaf extract and its bioactive component eugenol protected against oxidative stress, decreased ROS, and improved cellular defense.

Antifertility activity

Studies have demonstrated the anti-implantation and abortifacient qualities of the betel plant, which has been discovered to have antifertility effects. The alcoholic extract of the betel stalk has been found to reduce the number of pups and have anti-oestrogenic properties in adult male, female rats, and rabbits. It also has gentle progestational action in oestrogen-primed immature rabbits. The antifertility efficacy of betel petiole extract was studied in female albino Wistar rats, showing a reduction in fertility, reproductive organ weights, oestrogen levels, litter number, serum glucose concentration, acid phosphatase, SGOT and SGPT activity, increased cholesterol, and ascorbic acid activity [51]. The plant also has potential contraceptive activity with high binding affinity to the oestrogen and progesterone receptors.

Antimicrobial activities

Antibacterial activity

The high death rate of the global epidemic of microbially-caused infectious diseases contributes significantly to the burden of global health. Infectious diseases are one of the biggest risks to human health worldwide because of antimicrobial resistance and a dearth of innovative vaccinations. Studies have shown that the antimicrobial efficiency of *P. betle* leaf stalk against human pathogenic bacteria such as Staphylococcus aureus, *Vibrio cholerae* Ogawa, *Klebsiella aerogenes*, and *Diplococcus pneumoniae* is remarkable [52]. The ethyl acetate and ethanol extracts exhibited remarkable activity against most bacteria, while the hexane and benzene extracts showed moderate activity. Essential oil of betel leaves showed potential antibacterial activity against various bacteria.

The ethanol extract of betel leaves also showed antibacterial efficacy against foodborne bacteria such as E. *coli*, Shigella dysenteriae, Staphylococcus aureus, and Vibrio cholera [53]. P. Bettle's antibacterial experiment revealed that betel leaf extract in n-hexane and ethyl acetate suppresses fish infections in a promising way, indicating that it can be used to preserve fish.

Antifungal activity

Preclinical research employing different solvent extracts has demonstrated P. *betle's* antifungal potential against a range of fungi. Betel leaf essential oils and ethanolic extracts demonstrated potential against Aspergillus flavus, Candida tropicalis, and *Candida albicans*. Essential oil, methanolic, and aqueous leaf extracts of betel against *Candida albicans*, *Malassezia pachydermatis*, and Saccharomyces cerevisiae also showed significant antifungal activity [54]. The ethanol extract of *P. betle* also showed complete fungal inhibition against foodborne fungi. The addition of betel essential oil to apple juice and tomato pastes improved antioxidant capacity and inhibited microbial growth, enhancing shelf life under refrigerator conditions [55].

Antiparasitic activities

Anthelmintic property

Helminths, found in livestock foods, pose significant health risks. Studies have shown that P. *betle's* anthelmintic activity against adult Indian earthworms, such as *Pheretima posthuma*, is less pronounced than standard *albendazole*. Leaf methanol extracts also showed similar activity. The essential oil of *P. betle* also inhibited *Ascaridia galli* burden in poultry birds [56].

Anti-protozoan activity

The chloroform extract of *P. betle* leaves has shown anti-giardial activity against trophozoites of Giardia intestinalis and Leishmaniasis, a protozoan parasitic infection [57]. Ethanolic betel leaf extract has shown antileishmanial potency against promastigotes and amastigotes [58] of Leishmania donovani, mediated by apoptosis, morphological changes, loss of mitochondrial membrane potential, DNA fragmentation, and cell cycle arrest [59]. The methanol extract of betel leaves of Bangla Mahoba variety also inhibited promastigotes and amastigotes, accelerated apoptosis, and ROS generation. The betel leaf extract also inhibited the invasion of *Toxoplasma gondii* and *Neospora caninum* parasites in human foreskin fibroblast cells.

Antifilarial activity

P. *betle's in vivo* antifilarial efficacy was assessed by giving Balb/c mice varying doses of crude methanolic extract, chloroform, and n-hexane extracts. All extracts showed antigen-specific immune response, increased antifilarial IgG antibody and also suppressed microfilaraemia, showed potential macrofilaricidal efficacy, and induced sterilization of female worms [60].

Insecticidal activities: The insecticidal activity of *P. betle* was evaluated using an old grain test against the cowpea weevil, smaller grain borer, and bean weevil (*Sitophilus zeamais*) (*Callosobruchus maculatus*). The 30% volatile oil dust formulation was harmful to adult insects, stopped adult C. *maculatus* from surviving, and shielded maize from S. *zeamais* and R. Dominica up to 52% of the time. It also hindered both live and emerging progeny [61]. Nair and Kavrekar discovered that betel leaf methanol extract can effectively repel insects like *Sitophilus oryzae*, *Tribolium castaneum*, and *Bruchus pisorum* [62].

Larvicidal property

The study used methanol extract and the essential oil from the leaves to assess P. *betle's* mosquito larvicidal effectiveness against *Aedes aegypti*. The methanol extract displayed LD50 values of 153 and 125 ppm, but the essential oil displayed LD50 values of 86 and 48 ppm after 2 and 24 hours. The betel leaves essential oil also inhibited larval growth of *Aedes aegypti*, *Chrysomya bezziana* larvae, and Drosophila melanogaster larvae. The study found that essential oils can kill 100% *Chrysomya megacephala* larvae in 3.5 hours [63].

Miscellaneous

To assess the antiplatelet activity of P. *betle*, three substances (B-sitosterol, ursonic acid, and 3B-acetyl ursolic acid) were extracted from the betel root extract. Platelet activation factor (PAF), adenosine diphosphate (ADP), and arachidonic acid (AA) promoted human platelet aggregation (PA). All three substances can effectively suppress PA, according to *In vitro* research. *P. betle* extract includes substances that can prevent ROS accumulation or reduce the synthesis of TXB2 to prevent platelet aggregation [64].

The effects of aqueous extract of P. *betle's* inflorescence on rabbit PA caused by AA and collagen were studied. When the extract was treated *In vitro*, it reduced platelet aggregation caused by AA and collagen, with IC50 values of 335 and 207 µg/ml, respectively. It also inhibited the production of AA, collagen, and thrombin-induced thromboxane B2 (TXB2), induced by >90% [64].

Using an *In vitro* saliva chip model, *P. betle* demonstrated antibacterial activity against oral bacteria and decreased the generation of volatile sulphur compound (VSC) by oral anaerobic bacteria. APC also potentially reduced methyl mercaptan and hydrogen sulphide and prevented periodontal infection [65].

P. betle leaf has antiallergic effects on human lung epithelial cells and on BMMC (murine bone marrow mast cells) production of histamine and GM-CSF. Treatment with the extract markedly reduced histamine and IgE-mediated hypersensitive reaction-mediated GM-CSF production and inhibited eotaxin and IL-8 secretion produced by an allergic reaction induced by TNF-α and IL-4 [65].

Certain zoonotic dermatophytic fungus, including *Trichophyton mentagrophyte*, Microsporum gypseum, Microsporum canis, and *Candida albicans*, were evaluated for P. *betle's* dermatological activity. The results suggest that *P. betle* has notable therapeutic importance for the treatment of dermatophytosis comparable to the ketoconazole drug [66].

The betel plant has been found to have several antihemolytic, immunomodulatory, radioprotective, and anti-acne properties. In an *In vitro* study, the plant's methanol extract reduced haemolysis without toxicity compared to ascorbic acid. It also showed a dual role on thyroid function in rats, with higher doses increasing LPO concentration and decreasing SOD and CAT activities. The plant's methanol extract also showed dose-dependent suppression of T-cell, B-cell, and immune responses mediated by antibody. *In vivo* experiments showed enhancement in both humoral immune responses and cell-mediated immune responses [67].

The plant's radioactive property was evaluated using mitochondria from rat liver and plasmid DNA. The ethanol extract of leaves prevented ray-induced lipid peroxidation and DNA strand breaks, improved HO and SOD radical scavenging activity, and enhanced lymphoproliferative properties. The betel leaf ethanol extract also showed antibacterial efficacy against acne, with MIC values of 4.5% and 4.0%. In another experiment, a gel containing essential oil from betel leaves inhibited P. acnes in Franz diffusion cell [68].

Toxicity study

Mice and rats were used in a preclinical toxicity investigation that included acute and long-term evaluations using an alcoholic extract of *P. betle* leaf stalk at different doses. Assessments involving haematological, biochemical, and chemical analyses demonstrated no toxicity at doses of 100, 200, and 300 mg/kg bodyweight for a 60-day duration. Interestingly, even at a higher dose of 3200 mg/kg bw, no toxicity was observed [69]. In a separate acute toxicity study on guinea pigs, betel leaf extract administered at doses of 100 and 200 mg/kg showed no fatalities within 24 hours. However, at doses exceeding 300 mg/kg, a 50% mortality rate was observed, indicating the safety of doses between 100 and 200 mg/kg. Venkateswarlu and Devanna reported the safety of the leaf aqueous extract of *P. betle* up to a dose of 1000 mg/kg (po) body weight when administered to albino rats [70]. Mice given hydroalcoholic betel leaf extract did not exhibit any toxicity at doses up to 2000 mg/kg. After betel leaf methanol extract (up to 5000 mg/kg) was given to ICR mice, no adverse general symptoms, necropsy, or histological lesions were seen for 14 days (20). De *et al*. similarly found that the ethanol extract of betel leaves is safe up to 2000 mg/kg bw without any toxicity or morbidity during the 14-day observation period in Sprague-Dawley rats [71]. Taken together, these trials indicate that *P. betle* has the potential to be used as a medicinal agent to treat a variety of illnesses and remains safe at greater doses.

Conclusion

Piper betle, also known as "green gold," is a world-renowned herbal cash crop with significant social, economic, and therapeutic importance. For a variety of illnesses, including cancer, inflammation, neurological disorders, asthma, dental and oral infections, allergies, thyroid, diabetes, and skin conditions, it has been utilised in traditional and folkloric medical systems. The plant has bioactive phytochemicals that can treat a variety of illnesses, including tannin, phenol, terpenoid, alkaloids, and flavonoids. The phenolic and terpenoid chemicals in the plant give it a beautiful and strong aroma, which makes it a highly valued flavouring agent. For a variety of illnesses, including cancer, inflammation, neurological disorders, asthma, dental and oral infections, allergies, thyroid, diabetes, and skin conditions, it has been utilised in traditional and folkloric medical systems. The plant has bioactive phytochemicals that can treat a variety of illnesses, including tannin, phenol, terpenoid, alkaloids, and flavonoids. The phenolic and terpenoid chemicals in the plant give it a beautiful and strong aroma, which makes it a highly valued flavouring agent.

Piper betle reels found in many varieties and cultivars, and proper taxonomic identification of landraces is crucial in research. Genetic and molecular markers must be used to differentiate different landraces, and modern extraction and detection techniques must be used to identify phytochemicals. It is also necessary to take care of the standardisation and validation of chemical constituents for both quantitative and qualitative assessments.

Structural-activity relationships, bioavailability, synergism, and molecular mechanisms of action against various disease pathologies must all be investigated in order to accelerate pharmaceutical and medical innovation. Further research is needed to explore the efficacy of the plant preparations and the derived compounds.

Future perspective

The medicinal importance of the betel leaf is evident, with its potency acting as a natural antioxidant, antimicrobial activity against various bacterial strains, gastroprotective activity, oral protective action against acid-producing oral pathogens, cardio-tonic action, platelet inhibition activity, and immunosuppressive effect on cellular and humoral response. The *Piper betle* is considered the "Golden heart of nature" and has a tremendous strength to come out as a future green

medicine. 5. Multiple drug resistance has emerged due to the excessive use of antibiotics in treating infectious diseases. This has led to the need for alternative antibacterial molecules. A review found that betel leaf phenolic antibacterials suppress bacterial activity in the oral cavity and prevent halitosis. Researchers identified alkylpyrocatechol (APC) as having antimicrobial activity against Staphylococcus aureus. Researchers have found that piper betel leaf extract effectively combats other oral microbes, such as Streptococci, *Lactobacilli*, Staphylococci, Corynebacteria, *Porphyromonas gingivalis*, and *Treponema denticola.* The leaf extract's essential oil can serve as a medicinal ingredient and an active component in mouthwash products. The leaf also has the potential for drug delivery through the gastric route, enhancing drug bioavailability.

Declaration

Conflict of interest: None
Funding Source: Nil

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