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Phytochemistry, Pharmacological Profile and Therapeutic Uses of *Piper Betle* Linn. – An Overview.

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Review Article

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ABSTRACT

The Betle (*Piper betle* Linn.) is the leaf of a vine belonging to the Piperaceae family. The most likely place of origin of betle vine is Malaysia but it is also cultivated in India, Srilanka, Bangladesh, Burma and Nepal. The betle plant is an evergreen and perennial creeper, with glossy heart-shaped leaves and white catkin. Phytochemical studies show that *Piper betle* contains a wide variety of biologically active compounds whose concentration depends on the variety of the plant, season and climate. It is valued as a stimulant and also for its medicinal properties. *Piper betle* contains diosgenin, eugenol, allylpyrocatechol, methyl eugenol, chavibetol, hydroxychavicol, triterpenes and β-sitosterol. Pharmacological Profile has shown antiplatelet, anti-inflammatory effects as well as immunomodulatory, gastroprotective and antidiabetic activity. In India, Burma, Nepal, Srilanka and other parts of South Asia, the leaves of *Piper betle* are chewed together in a wrapped package along with the areca nut (which, by association is often called the betle nut) and mineral slaked lime (Calcium hydroxide). The areca nut contains the alkaloid arecoline, which promotes salivation and itself acts as a stimulant. In this review emphasis is lead upon research related to Therapeutic properties, Phytochemistry, and Pharmacological profile of *Piper betle* Linn.

INTRODUCTION

Piper betle Linn., (Figure 1) commonly known as the betle vine is a important medicinal and recreational plant in Southeast Asia [1]. Based on the color, size, taste and aroma there are many varieties of betle leaf. Some of the most popular Indian varieties are the Magadhi, Venmony, Mysore, Salem, Calcutta, Banarasi, Kauri, Ghanagete and Bagerhati [2].

Betle (*Piper betle)* is a tropical shade-loving perennial evergreen vine. It may climb as high as 10-15 ft. Sometimes the plant can also grow as a ground cover and it has a growth pattern similar to that of the pepper plant. The *Piper betle* leaf prefers a warm and humid climate [3]. Leaves are simple, alternate, ovate, cordate, acuminate or acute, entire and bright green. This plant has Male spikes which are dense and cylindrical while female spikes are pendulus. Roots arise from each node which aid in fixing the plant to the host tree. The leaves are used in a number of traditional remedies such as for treatment of stomach ailments, infections and as a general tonic. Some research suggests that betle leaves can have abilities to boost the immune system [4]. In the Indian subcontinent, a small bundle of betle, known as a 'pan-supari' is offered to guests as courtesy. There are millions of Asians who consume daily the betle leaf, mostly in combination with betle nut, kava kava and kolanut [5]. There are about 125 to 150 cultivars of betle vine in India. Betle is typically propagated asexually from stem cuttings rather than from seeds [6,7].

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Betle is grown in all over the country but the commercial production of export quality betle, with bigger leaves with dark green colour combined with thickness, known as "Kalu bulath" is significantly confined to few districts such as Kurunagala, Gampaha, Kegalle and Kalutara. Today betle is grown for local consumption and exports and Major betle growing countries are Sri Lanka, India, Thailand and Bangladesh. Pakistan is the major importer of Sri Lankan betle [8].

Indian Languages	Names	Other Asian Languages	Names
Marathi	Vidyache pan	Thai	Plue
Hindi, Bengal, Gujarati, Urdu	Paan	Malay	Daun sirih
Sanskrit	Nagavalli, Nagavallari, Nagini	Mon	Plu
Konkani	Phodi paan	Sinhalese	Bulath
Malayalam	Vettila, Vettilakkoti	Khmer	Maluu
Telugu	Tamalapaku	Kapampangan	Bulung samat
Kannada	Vilya, Veeleya, Villayadel	Arabic	Tanbol
Tamil	Vetrilai	Chamorro	Papulu

Table 1: Vernacular Names of betle plant in Indian and in other Asian languages.

Phytochemistry

Betle vines are one of the highly investigated plants and their phytochemical studies show that *Piper betle* contains a wide variety of biologically active compounds whose concentration depends on the variety of the plant, season and climate. Chemical compositions of essential oil constitute safrole present in the leaf, stalk, stem, root and ß-phellandrene present in the fruit. The aroma of betle leaf is due to the presence of essential oils, consisting of phenols and terpenes [9]. Younger leaves reported to yield more essential oil.

The chief constituent of the leaves is a volatile oil whose chemical composition is dependent on the region it is found. It is also known as betle oil. Leaf and other plant parts have yielded active compounds like hydroxychavicol, hydroxychavicol acetate, allypyrocatechol, chavibetol, piperbetol, methylpiperbetol, piperol A and piperol B. Leaves of *Piper betle* reported to yield an alkaloid: arakene, with properties similar to cocaine.

The active ingredient of piper betle oil which is obtained from the leaves are primary a class of allyl benzene compounds, chavibetol (betlephenol; 3-hydroxy-4-methoxyallylbenzene), Chavicol (p- allyl-phenol; 4-allyl-phenol), Estragole (p-allylanisole; 4-methoxy-allylbenzene), Eugenol (allylguaiacol; 4-hydroxy-3-methoxyallylbenzene; 2-methoxy-4-allyl-phenol), methyl Eugenol (Eugenol methyl ether; 3,-dimethoxy-allylbenzene) and hydroxycatechol (2,4-dihydroxy-allylbenzene) [10].

Study of essential oil and ether soluble fraction of leaves yielded fourteen components including eight allypyrocatechol analogs. Major constituents were chavibetol (53.1%) and chavibetol acetate(15.5%). Other constituents were allypyrocatechol diacetate (0.71%), campene (0.48%), chavibetol methyl ester (methyl eugenol 0.48%), eugenol (0.32%), a-pinene (0.21%), ß-pinene (0.21%), a-limonene (0.14%), safrole (0.11%), 1,8-cineole (0.04%) and allypyrocatechol monoacetate [11].

Hexane fraction of leaf stalks yielded four alipathic compounds in pure form i.e. pentadecyl 6-hydroxytridecanoate, pentatriacontanol, methyl hexacos-7-enoate and 6,9-heptacosa diene. [12]The extract of betle leaves possesses antimutagenic, anticarcinogenic, antidiabetic, anti-inflammatory and antibacterial activities [13]. Hydroxychavicol (HC) and eugenol (EU) are important phytochemicals found in betle leaves. They are reported to contribute too many bioactivities in betle leaves [14]. HC and EU are phenolic compounds which consist of a monocyclic aromatic ring with an alcoholic, aldehydic or carboxylic group [15].

Allylpyrocatechol

The phenolic constituent allylpyrocatechol from the leaves showed activity against obligate oral anaerobes responsible for halitosis. The leaf extract also has a stimulatory effect on pancreatic lipase and antioxidant activity [16].

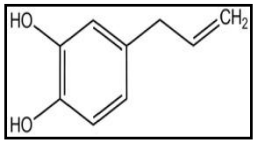

Figure 1: Structure of Allylpyrocatechol

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Chavibetol

Chavibetol is an organic chemical compound of the phenylpropanoid class. It is one of the primary constituents of the essential oil from the leaves of the betle plant (*Piper betle*). It is an aromatic compound with a spicy odor [17].

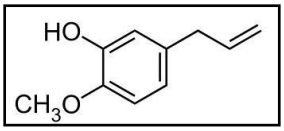

Figure 2: Structure of Chavibetol

Eugenol

Eugenol, one of the principal constituent of betle leaf has also been shown to possess anti-inflammatory effects in various animal models of studies with various inflamogens [Dohi et al., 1989; Lee et al., 2007]. Mechanistic studies with in vitro systems showed that eugenol blocked the release of the bone resorbing mediators, including IL-1β, TNF-α, and PGE2 from of LPS-stimulated human macrophages by suppressing the messenger RNA expression of LPS-induced IL-1β, TNF-α and COX-2 in macrophages [Lee et al., 2007b]. Eugenol suppressed the COX-2 gene expression in LPS-stimulated mouse macrophage cells [18].

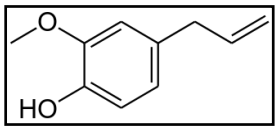

Figure 3: Structure of Eugenol

Hydroxychavicol (HC)

The phenolic compound, Hydroxychavicol, found in the aqueous extract of betle leaf is reported to exhibit useful bioactivities - anticarcinogenic and antimutagenic activities [13].

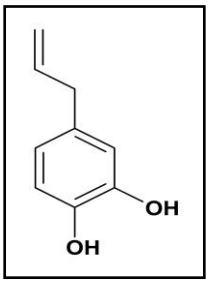

Figure 4: Structure of Hydroxychavicol

Pharmacological Profile

Antimicrobial activity

The leaf has a significant antimicrobial activity against broad spectrum of micro-organisms [19].The betle shows the antimicrobial activity against *Streptococcus pyrogenes, Staphylococcus aureus, Proteus vulgaris, Escherichia coli, Pseudomonas aeruginosa* etc. Beside this the leaf extract also possess the bactericidal activity against the urinary tract pathogenic bacteria such as *Enterococococcus faecalis, C.koseri, C.fruendi, Klebsiella pneumonia* etc. [20,21] The bioactive molecule thought to be responsible for anti-bacterial activity is sterol, which has been obtained in large quantities in betle leaf extracts. The mode of action may be due to surface interaction of sterol molecule present in the extracts with the bacterial cell wall and membrane leading to alteration in the primary structure of cell wall, ultimately lead to pore formation and degradation of the bacterial components. It is reported that sterol act through the disruption of the permeability barrier of microbial membrane structures [21]. Gram-positive bacteria were more susceptible to the inhibitory effects of the plant extract because of single layer and lack the natural sieve effect against large molecules, whereas gram negative bacteria are multi layered and complex cell wall structure [22]. The leaf has also poses the antifungal activity against many fungal infections [23]. One of them is dermatophytosis. Dermatophytosis is a disease of the keratinized parts of the body (skin, hair, and nail) caused by athree genera (*Trichophyton, Microsporum,* and *Epidermophyton*) of highly specialized fungi called

the Dermatophytes [24]. The chloroform extract of *Piper betle* shows the much more efficiency than the methanol fraction against dermatophytes because of presence of non-polar components in the fraction [25].

Protective and healing activity

Most recently, a study was undertaken to evaluate the protective and healing effects of allylpyrocatechol against the indomethacin induced stomach ulceration in rat model. Results showed that allylpyrocatechol can protect indomethacin induced gastric ulceration due to its antioxidative and mucin protecting properties [26].

Antidiabetic activity

Both the aqueous and ethanolic extracts of *P. betle* leaves possess marked hypoglycaemic activity when tested in fasted normoglycaemic rats. In glucose tolerance test, the extract showed antihyperglycaemic activity in the external glucose level. The ability of lowering blood glucose levels of streptozotocin (STZ) induced diabetic rats gives a suggestion that the extracts have insulinomimetic activity [27].

Gastroprotective activity

The hot water extract significantly increased the mucus content adhering to the wall of the gastric mucosa. Mucus layer is considered to be important in mucosal defenses against endogenous aggressors, e.g., acids, and also as an agent in facilitate the repair process. It is generally believed that enhanced acid secretion is the most important factor for the induction of gastric lesions. The higher dose of hot water extract does not cause significant inhibition in acidity or pH of gastric fluid. Therefore, gastroprotective effect of *Piper betle* was not mediated via inhibition of acid secretion in the gastric mucosa but by increasing its mucus content. The gastroprotective activities of the higher dose of hot water extract significantly greater than Misoprostol [28]. The extensive research has been proven that anti-oxidants might be effective mechanism not only in protecting against gastric mucosal injury, but also inhibiting progression of gastric ulceration. Ulceration progression is caused by free radical-induced chain process. Consequently, its arrest by radical scavengers helps in the faster healing [29, 30]. Allylpyrocatacol has shown a powerful anti-oxidant potential in various in-vitro models. Treatment with Allylpyrocatacol significantly accelerated the ulcer-healing process, which increases the mucus production usually assist the healing process by protecting the ulcer crater against irritant stomach secretion (HCl and Pepsin) thereby enhancing the rate of local healing process [31].

Immunomodulatory activity

Many of the disorders today are based on the imbalances of immunological processes. This necessitates the search for newer and safer immunomodulators. The methanolic extract has lymphocyte proliferation, interferon-C receptors and the production of nitric oxide were measured in vitro. Further, the extract at different dose levels was studied in vivo for the humoral and cellular immune responses on mice immunized with sheep red blood cells. The result showed that it significantly suppressed haemaglutinin stimulated peripheral blood lymphocyte proliferation in a dose-dependent manner. The decrease in antibody titre and increased suppression of inflammation suggests possible immunosuppressive effect of extract on cellular and humoral response in mice [32]. From literature it conclude that betle leaf a novel candidate for immunosuppressive activity. The same could be further evaluated for its anticancer activity or as a potential candidate in the treatment of autoimmune disorders such as rheumatoid arthritis, systemic lupus erythomatous oremphysema [33].

Platelet inhibition activity

Hydroxychavicol (HC) was tested for its inhibition effect on platelate aggregation. The result showed hydroxychavicol to be a potent inhibitor for cyclooxygenase activity, reactive oxygen scavenger and inhibits platelet calcium signaling, thrombaxan B2 production and aggregation. HC could be a potential therapeutic agent for prevention and treatment of artherosclerosis and other cardiovascular diseases through its anti-inflammatory and antipatelets effects, without effects on homeostatic function [34].

As an Oral care agent

Dental caries is a chronic endogenous infection caused by the normal oral commensally flora. The carious lesion is the result of demineralization of enamel and later of dentine by acids produced by plaque microorganisms as they metabolize dietary carbohydrates [35 - 37]. The bacteria primarily responsible for dental decay in man are *Streptococcus mutans*. *Streptococci* belong to four main species groups: *mutan, salivarius, anginosus and mitis.* In addition to *Streptococcis mutans, Lactobacillus acidophilus* bacteria probably also pay a minor role in acid production in the plaque [38]. The stickiness of the plaque is caused by dextran, which is produced by the fermentation of dietary sucrose by *Streptococcus mutans*. The plaque bacteria, particularly *Streptococcus mutans*, act on dietary fructose to produce lactic acid, which causes enamel decalcification (at below or above 5.5 pH) [39].

The plaque and dietary carbohydrates are in the initiation of enamel caries. Certain cariogenic and highly acidogenic strains of streptococci, especially *S. mutans* have the ability to metabolize dietary sucrose and synthesize glucan by cell-surface and extracellular glucosyl transferase. This enzyme is considered to be of special importance in the establishment of *S. mutans* in the dental plaque [40 - 42]. The aqueous extract inhibit the different acid-producing oral pathogens which changes in the ultra-structure of the enamel and its properties like *Streptococci, Lactobacilli, Staphylococci, Corynebacteria, Porphyromonas gingivalis* and *Treponemadenticola*. So it is best natural substance and itsrating as second most popular daily consummation item in Asia, which contribute the best oral hygiene to oral cavity [43].

Antioxidant activity

Oxidative damage is an important effect of ionizing radiation on biological membranes. It is a chain reaction [44]. Free radicals generated from the radiolytic decomposition of water can attack fatty acid chains of membrane lipid. A free radical that has sufficient energy to abstract an allylic hydrogen from the methylene carbon of polyunsaturated fatty acids can initiate the peroxidative process. Here the presence polyphenols compounds like chatecol, allylpyrocatecol etc. in betle leaf extract inhibited the radiation induced lipid peroxidation process effectively. This could be attributed to its ability to scavenge free radicals involved in initiation and propagation steps [45]. The extracts reduced most of the Fe3+ ions and possess strong reductive ability [46]. The extract also showed strong hydroxyl radical and superoxide anion radical scavenging property when compared with different standards such as ascorbic acid and BHT [47,48,49,50].

Antifertility activity

A study to develop an orally effective male contraceptive agent was extensively carried out in male mice with various doses of the leaf stalks extract of *Piper betle.* The result show no toxicity in all metabolically active tissue of mice and interestingly, the contraceptive efficacy emphasized reversible fertility after withdrawl of treatment [51].

Neuropharmacological profile

Hydroalcoholic extract of betle leaves exhibited improvement in the discrimination index, potentiating the haloperidol induced catalepsy, reduction in basal as well as amphetamine induced increased locomotors activity and delay in sodium nitrite induced respiratory arrest. These results from review suggest possible facilitation of cholinergic transmission and inhibition of dopaminergic as well as nor adrenergic transmission by the extract [52, 53].

Pro-apoptotic Effect / Anti-Leishmaniasis

In a comparative in vitro anti-leishmanial activity of methanolic extracts from two landraces of Piper betle. The PB-BM (P betle landrace Bangla Mahoba) selectively inhibited both stages of Leishmania parasites without macrophage cytotoxicity. The efficacy mediated through apoptosis is probably due to higher content of eugenol [54].

Cholinomimetic effect

Betle leaf rise in body temperature due to cholinergic responses. Aqueous and ethyl acetate extracts were evaluated for their cholinergic responses using isolated guinea-pig ileum15. It was observed that the spasmogenic activity was more in water than ethyl acetate extract. In isolated rabbit jejunum K+-induced contraction was inhibited by both extract, suggesting blockade in calcium channel. Thus, leaves contain cholinomimetic and possible calcium channel antagonist constituents which may provide the basis for several activities shown by this plant [55].

Hepato-protective activity

The antihepatotoxic effect of betle leaf extract was evaluated on ethanol and carbon tetrachloride (CCl4) induced liver injury in a rat model. Fibrosis and hepatic damage, as revealed by histology and the activities of aspartate amino transferase (AST) and alanine amino transferase (ALT) were induced in rats by CCl4. The extract significantly inhibited the elevated activities of AST and ALT and also attenuated total glutathione S-transferase (GST), which led to a rise in antioxidant enzymes such as superoxide dismutase (SOD) and Catalase (CAT). The histological examination showed that the betle leaf extract protected liver from the damage induced by CCl4 by decreasing alpha smooth muscle actin (alpha-sma) expression, inducing active matrix metalloproteinase-2(MMP2) expression through the Ras/Erkpathway, and inhibiting TIMP2 level that consequently attenuated the fibrosis of liver. These findings support a chemo preventive potential of betle leaf against liver fibrosis [56].

Anti-Photosensitizer

Inhibitory property of the *Piper betle* phenolics against photosensitization-induced biological damages: PB phenolics, allylpyrocatechol (APC) may play a role in protecting biological systems against damage by eliminating O2 generated from certain endogenous photosensitizers [57].

Radioprotective activity

Mammalian system if exposed to radiation can cause damaging effects leading to cell death and an increased risk of degenerative diseases. Recently the radioprotective property of ethanolic extract of *P. betle* leaves was studied as alternative low cost preventive medicine to synthetic radio protectants which are reported to be toxic. The capacity of the extract in preventing g-ray induced lipid peroxidation and DNA damage in rat liver mitochondria were accessed and evaluated to establish the mechanism of its Radioprotective action. The study revealed significant immunomodulatory and superior radical scavenging activities which may be due to the presence of phenolic bioactives such as chavibetol and allyl pyrocatechol. It suggests that the herb has a great potential not only it is cheap but also easily accessible natural radioprotectant to the common people [58].

Cytotoxicity / Anticancer Potential

Study evaluated an aqueous extract of leaves to cytotoxicity studies on Hep-2 cell line. The mean CTC50 was 96.25 ug/ml suggesting potent cytotoxicity and probable anticancer property [59].

Carcinogenicity

Study of rats on rats fed a dry powder of betle nuts, leaves and lime showed epidermal thickening in the upper digestive tracts in rats fed the betle nut mixed with lime and the betle leaves diet. A forestomach papilloma was seen in one rat on betle leaves diet. The epidermal changes were scarcely seen in rats on either betle nut or normal diet alone [60].

Therapeutic Properties and Its Uses

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been isolated from natural sources, many based on their use in traditional medicine. Various medicinal plants have been used for years in daily life to treat disease all over the world. One of the medicinal plant i.e. *Piper betle* is a source of great economic value in the Indian subcontinent.

Ethno botanical use

- Betle leaf has been described from ancient times an aromatic, stimulo-carminative [61] (katu), astringent and aphrodisiac.
- It has wound healing properties.
- The leaves were chewed by singers to improve their voice [62].
- Leaves considered being useful in treating bronchitis and dyspnea [63], stomach ailments, infections and as a general tonic.
- The Indian traditional system of medicine has identified that these leaves have digestive and pancreatic lipase stimulant activities [64-69].
- Known to be useful for the treatment of various ailments like bad breath, boils and abscesses, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, swelling of gum, rheumatism, cuts and injuries [70].
- The fruit of *Piper betle* employed with honey acts as a remedy for cough [71].
- Leaves are used in eye drops for eye injury/infection as a baby lotion for the new born, for coughs, asthma, constipation and to arrest milk secretion [72].
- The leaves affects fertility in male rats [73] and expresses anti motility effects on washed human spermatozoa [74]
- The users believe that chewing the *'paan'* improves their efficiency and stamina [75]. *Piper betle* showed hypotensive, cardio tonic, smooth and skeletal muscles relaxant actions [76-78].
- Essential oil from leaves of this plant has been used for the treatment of respiratory catarrhs and antiseptic [79, 80].
- In folk, the medicinal root is used as long lasting female oral contraceptive [81, 82].

Modern medicinal use

- Betle leaves are beneficial in pulmonary infection in childhood and old age. The leaves, soaked in mustard oil and warmed, may be applied to the chest to relive cough and difficulty in breathing [70].
- Local application of the leaves is effective in treating sore throat. The crushed fruit or berry should be mixed with honey and taken to relieve irritating cough [67].
- Betle leaves are useful in treatment of nervous pain, nervous exhaustion and debility. The juice of few betle leaves, with a teaspoon of honey, will serve as a good tonic [43].
- Applied locally, betle leaves are beneficial in the treatment of inflammation such as arthritis and orchitis i.e. inflammation of the testes [70].
- Betle leaves have analgesic and cooling properties [75].
- It is also a valuable remedy for boils. A leaf is gently warmed till it gets soft, and is then coated with a layer of castor oil. The oiled leaf is spread over the inflammation [73].
- A hot poultice of the leaves or their juice mixed with some bland oil such as refined coconut oil can be applied to the loins with beneficial results in lumbago [4].
- The leaves can be used to heal wounds. The juice of the leaves should be extracted and applied on the wounds [78].
- The application of leaves smeared with oil is said to promote secretion of milk when applied to the breast during lactation [80].
- According to Unani system the leaf has a sharp taste and good smell which helps improve appetite. It also acts as a tonic to brain, heart and liver [9].
- It helps to promote healthy teeth and skin [66].
- Helps in Treatment of Disorders in physiological function, Skin diseases, and Eye diseases [68].
- It also has a diuretic property. Betle leaf juice given with milk or honey helps in easing urination [30].
- Betle leaf is considered aphrodisiac i.e. an agent which stimulates sexual desire [67].

CONCLUSION

The glossy, heart shaped leaves of Piper betle has a tremendous potential as a potent source for novel herbal drugs. It contains active constituents mainly allylpyrocatechol, chavibetol, eugenol and hydroxychavicol; which has many therapeutic uses and supports the folklore. The pharmacological profile reveals it to be for its good antimicrobial activity, protective and healing activity, antidiabetic activity, gastroprotective activity, immunomodulatory activity, platelet inhibition activity, Antioxidant activity, antifertility activity, hepato-protective activity, anti-photosensitizer, cytotoxicity / Anticancer Potential , radioprotective activity etc. In future the standardization and stabilization studies on betle leaves extract can be carried out which can help in proving it to be a promising source in pharmaceutical as well as neutraceutical industry.

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