



## PIPER BETEL LINN: A BRIEF STUDY

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### ABSTRACT

Piper betel is glorified as evergreen and perennial plant that God designed and have given the shape of his own heart. The heart shaped of Piper betel leaves are initiate in ancient Sanskrit texts, include Charaka, Sushruta Samhita and Astanga Hridayam. Piper betel L. has been use in Chinese, Indian traditional medicine for centuries. Betel vine (Piper betel L.) belongs to genus Piper of the family Piperaceae. Leaves of Piper betel possesseveral bioactivities and are used in traditional medicinal systems. Many research studies on Piper betel has reported that it contains important chemical constituents and are acts to arouse action for its medicinal properties like anticancer, anti-allergic, anti-malaria, anti-filarial, antibacterial, antifungal study, insecticidal, antioxidant, anti-diabetic, gastro-protective, cyto-toxic, anti-platelet, wound healing activity, chlorophyllase activity, oral hygiene and anti-asthmatic effect. The present paper also focused on the chemical constituents of piper and diseases of betel vine and their various symptoms.

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## INTRODUCTION

The betel (piper betel) is the leaf of a vine belonging to the Piperaceae family which includes pepper and kava. Betel leaf mostly consumed in Asia, and elsewhere in the world by some Asian emigrants, as betel quid or in Paan, with Areca nut and or/ tobacco. In Sri Lanka and in the Indian states of Karnataka, Kerala, Tamil Nadu, Andhra Pradesh, Assam, West Bengal and Odisha a sheaf of betel leaves is traditionally offered as a mark of respect and auspicious beginnings. Occasions include, greeting elders at wedding ceremonies, New year, offering payment to Ayurvedic physicians and astrologers where usually money and /or areca nut kept on top of the sheaf of leaves and offered to the elders for their blessings.

The cheif Ayurvedic preparations of piper betel plamt are Lokantha Rasa, Puspadhava Rasa, Brhat sarwajwarahara lanha etc. In ayurvedic betel leaf juice is commonly utilized as an adjuvant and combined with different others medicines most likely for brtter effects beside its separate use as medicine. In Susrta Samhita, Tambool leaves have been described as aromatic, sharp, hot, acrid and valuable for voice, laxative, appetizer, beside this they soothe vata and aggravate pitta.

### P. Betle (Phytochemistry)

Polyphenols and alkaloids isolated from P. betle leaves were  $\beta$ -sitosterol, dotriacontanoic acid, tritriacontane, stearic acid, cepharadione and piperine 13. Other phenolic compounds were hydroxychavicol, chavibetol, chavibetol acetate and eugenol 14. Some 36 compounds representing 98% of the essential oil of P. betle leaves have been identified 15. Eugenol (36%), chavibetol acetate (17%), 4-allylphenyl acetate (9%) and 4-allylphenol (7%) were the main components. In the Philippines, major constituents of P. betle leaf oil were chavibetol (53%)

### Chemical Constituent

The piper betel leaf has been described to have Piperol-A, Piperol-B, methyl piper betol and they also have been isolated. The betel leaves have starch, sugars, diastases and an essential oil composing of terpinen-4-ol, saffrole, alkyl pyrocatechol monoacetate, eugenol ,eugenyl acetate, hydroxyl chavicol, eugenol and betol oil contains cadinene carvacrol, allyl catechol, chavicol, p-cymene, caryophyllene, chavibetol, cineole, estragol, etc. as the key components. and chavibetol acetate (16%).



Fig1 Piper Beetle Leaves



Fig2 Betel Quid



Fig3 Leaves And Fruits Of Piper Sarmentosum

Phytochemical analysis on leaves revealed the presence of alkaloids, Tannins, Carbohydrate, Amino acids and steroidal components. The chief component of the leaves is a volatile oil in the leaves from different countries, called Betle oil and contains 2 phenols, betle phenol (chavibetol and chavicol). Codinene has also been found.



Fig4 Leaves of Piper Sarmentosum

#### **Details about chemical constituents**

##### **Chavibetol**

Chavibetol is the natural chemical compound of the phenylpropanoid class. It is the most important component of the essential oil from the leaves of the piper beetle plant. It is an aromatic compound with a spicy odor and is an isomer of eugenol.[1,2]

##### **Eugenol**

Eugenol, one of the principal constituents of betle leaf, has also been shown to possess anti-inflammatory property in a variety of animal models of studies with various inflammogens. Antimicrobial, analgesic, anti-oxidant, antiviral and anticancer activity, other identified activities such as its anti-ulcerogenic potential and effect on osteoporosis and especially its effect on the CNS encompassing seizure control, Parkinson's disease, antidepressant effects etc.[3,4]

##### **Allylpyrocatechol**

The phenolic constituent allylpyrocatechol obtained from the leaves, shows action against obligate oral anaerobes responsible for halitosis. The leaf extract also has a stimulatory outcome on pancreatic lipase and antioxidant activity. Oral administration of APC at different

Doses accelerates the rate of remedial of gastric lesion induced by indomethacin due to its antioxidative and mucin defensive properties.[5,6]

##### **Hydroxychavicol(HC)**

The new, immature leaves contain various beneficial bioactive compounds, among which Hydroxychavicol is the most important phenolic compound which is reported to possess anticarcinogenic, antinitrosation, antimutagenic effects. Besides this, it has a considerable potency to act as an

antiinflammatory, antioxidant, antibacterial, anti-platelet and antithrombotic effects without impairing haemostatic function. In the aqueous extract of betle leaf it is reported to exhibit useful bioactivities – antimutagenic and anticarcinogenic activities, whereas isolated from the chloroform withdrawal from aqueous extract of *Piper betle* leaves show inhibitory action alongside oral cavity pathogens. 0.5% Hydroxychavicol inhibited the biofilm produced by anaerobes and biofilm produced in pooled saliva the use of Hydroxychavicol as an oral care agent. Hydroxychavicol show compelling anti-inflammatory action by considerably inhibits the phrase of the proinflammatory cytokine TNF- $\alpha$ . Methyl chavicol, a biogenic oxygenated aromatic compound, reported to have antioxidant activity. [7,8,9]

### Quercetin

Quercetin is one of the most important dietary flavonoids belong to a group of flavonols. It occurs chiefly as glycosides, but other derivatives of quercetin have been recognized as well. Joined substituent's changing the biochemical activity and bioavailability of molecules when compare to the aglycone. Quercetin has also been verified to exhibit the antiviral, antibacterial, anticarcinogenic and anti-inflammatory properties. The ant carcinogenic property of quercetin result from its important impact on an increase in the apoptosis of mutated cells, inhibition of DNA synthesis, inhibition of cancerous cell growth, decrease and alteration of cellular signal transduction pathways. Animal evidence suggest Quercetin's antioxidant effects provides protection of the brain, heart, and other tissues adjacent to ischemiareperfusion injury, toxic compounds, and other factors that can persuade oxidative stress.[10,11,12]

### $\beta$ -Caryophyllene

$\beta$ -Caryophyllene is a chief volatile compound establish in huge amounts in different spice and food plants.  $\beta$ -caryophyllene has shown to posses potent anti-inflammatory properties.  $\beta$ -caryophyllene is an FDA- approved food additive and it is apparently a non-toxic compound with no genotoxic or cytotoxic effect *in vivo*. Clinical studies prove its efficiency in treating endometriosis.  $\beta$ -caryophyllene exerts anti-inflammatory activity by acting as a potent, selective and nonpsychoactive full agonist for CB2 receptor *in vivo*. The *Piper betle* used as anti-depressant, CNS stimulant, Immunomodulator, antioxidant, antibacterial, antiulcer, cardiovascular, anti-diabetic, anti-infective. *Piper betle*, found to be safe in terms of hepatotoxicity, renotoxicity, hematotoxicity.[13,14]

### Traditional Uses

1. The paste of *Piper betle* leaves assorted with salt and hot water able to be administering for filariasis.
2. For curing obesity, one *Piper betle* leaf mix with *Piper nigrum* is prescribed for two months.
3. Juice of *Piper betle* with honey is accommodating to treat coughs, dyspnoea, and in indigestion, amongst children.
4. Leaves of *Piper betle* smeared with oil are useful on the breasts of lactating women; it is supposed to promote milk secretion.
5. A local application is recommended for inflammatory swelling such as orchitis, arthritis and mastitis.

6. For childhood and old people, leaves are mixed with mustard oil, warmed and are apply to the chest for treatment to reduce cough and dyspnoea.
7. Recovers bad breath, body odor and prevent tooth decay.
8. Prevents and treats vaginal ejection, and reduce itching of the vagina.
9. Stop bleeding in the nose.
10. It contains vitamins such as thiamine, niacin, riboflavin and carotene.
11. In India, leaves used for curing eczema, lymphangitis, asthma and rheumatism.
12. Paste of leaves is applied on cuts and wounds.
13. Roots with black pepper used to generate sterility in women.
14. Oil used for irritation in throat, larynx, bronchi, gargle and inhalation in diphtheria.
15. Juice of leaves is used as stomachic and febrifuge.

### Modern medicinal use

1. Betle leaves are advantageous in pulmonary infection in childhood and old age. The leaves, mixed in mustard oil warmed and applied to the chest to relive cough and intricacy in breathing.
2. Limited application of the leaves is efficient in procuring sore throat. The flattened fruit or berry should be mixed with honey and used to reduce irritating cough.
3. Betle leaves are helpful for the treatment of nervous pain, nervous exhaustion and debility. The extract of few betle leaves, with honey serve up as a good tonic.
4. On applied locally, betle leaves are valuable in the treatment of swelling such as arthritis and orchitis i.e. inflammation of the testes.
5. Betle leaves also shows analgesic and cooling properties.
6. It is also a priceless remedy for boils. A leaf is lightly warmed till it gets soft, and then coated with a layer of castor oil. The oiled leaf is placed over the inflammation.
7. A hot poultice of the leaves or their extract mixed with some bland oil as refined coconut oil which can be applied to the loins with beneficial results in lumbago.
8. The leaves can also be used to heal wounds. The juice of the leaves should be extracted and applied locally to the wounds.
9. The application of leaves coating with oil and said to encourage secretion of milk when applied over the breast during lactation.
10. According to Unani system, these leaves has a sharp taste and good smell which helps to improve appetite.
11. It also used as a tonic for brain, heart and liver.
12. It also helps to promote healthy teeth and skin.
13. It helps in procurement of Disorders in physiological function of body, Skin diseases, and several Eye diseases.
14. Betle leaf also contains diuretic property. Juice of leaves given with milk or honey helps in easing urination.
15. Betle leaf is used in aphrodisiac i.e. an agent that stimulates sexual desire.

16. The essential oils which contains in the leaves are antibacterial, antiprotozoal and antifungal properties. Therefore, the oil kills or inhibits expansion of outrageous bacteria causing typhoid, cholera, tuberculosis etc and helps in proper evaluation and exploitation.
17. The leaves are nutritive and hold considerable quantity of vitamins and minerals and therefore, six leaves with a small bit of slaked lime are said to be equivalent about 300 ml of cow milk mainly for the vitamin and mineral nutrition.
18. The leaves also hold the enzymes like diastase and catalase as well as major amount of all the essential amino acids except lysine, histidine, and arginine, which are found only in traces.

#### **Various proved activities of Piper betel**

##### **Anticancer activity**

Laboratory and clinical studies have confirmed that chronic Inflammation initiated many human diseases, including cancer And tumor [18,19,20]. The betel leaf was used as a common Household remedy for inflammation in oral cavity [21]. Oral Cancer was one of the ten most common cancers with nearly 90% of them being reported from the South East Asia region, where the habits of tobacco chewing and smoking are common. In one of the earliest studied Rao (1984) observed that topical application of betel leaf extract inhibited B(a) P induced oral tumorigenesis in hamsters [22]. The combination of betel leaf extract with turmeric was also observed to be effective between two dietary agents [23]. Anticancer and free radical scavenging potency of *Catharanthus roseus*, *Dendrophthoe pentandra*, *Piper betle* and *Curcuma mangga* extracts in breast cancer cell lines was investigated by Widowati *et al.*, 2013 [24,25]. Cancer preventive effects of *Piper betle* was reported by Rai *et al.*, 2011 [26]. Supplementation of *betle* leaf extract in drinking water significantly reduced the benzo (a) pyrene-induced forestomach neoplasia in a concentration dependent manner in mice [27]. Thus, the leaf extracts of *Piper betle* have anti proliferative and chemo preventive potential and can be used for the treatment of various ailments including human lung cancer [28].

##### **Anti-allergic activity**

Wirotesangthong *et al.*, 2008 worked on inhibitory effects of *Piper betle* on production of allergic mediators by bone marrow-derived cells and lung epithelial cells. The results suggested that *Piper betle* may offer a new therapeutic approach for the control of allergic diseases through inhibition of production of allergic mediators [29]. The goal of an antiseptic was to eliminated or reduced the number of microorganisms in the surgical field at the time of the surgery. Amalia *et al.*, 2009 tested the *Piper betle* leaf and successfully applied in pre surgery cataract patients [30]. Hajare *et al.*, 2011 applied the *Piper* leaf extract in guinea pig to evaluate the antihistaminic activity [31].

##### **Anti-malaria activity**

Essential oil of *Piper betle* provided better protection from biting of mosquitoes *Anopheles stephensi* and *Culex fatigans* compared to known mosquito repellent citronella oil. *Piper betle* oil provided more than 4 hrs protection against *Anopheles stephensi* and *Culex fatigans* when applied at the

rate of 20 µl /cm<sup>2</sup> where as citronella oil provided only 2.2 and 2.6 hrs protection respectively. Thus, mosquito repellent activity of pan were proved [32].

##### **Anti-filarial activity**

Singh *et al.*, 2009 investigated the anti-filarial activity of *Piper betle*. The report described the n-hexane and chloroform fractions of *Piper betle* L. Trigger different arms of immune responses in BALB/c mice and exhibit anti filarial activity against human lymphatic filarid *Brugia malayi* [33,25].

##### **Cyto-toxic activity**

Cyto-toxic activity of ethanolic extract of *Piper betle* leaves was evaluated using murine (Ehrlich Ascites Carcinoma and Melanoma B-16 cells) and human (Hela, Raji) cancer cell lines by employing MTT assay and Trypan-blue dye exclusion method were examined by Roy and Vijayalaxmi, 2013. The results suggested that there was a concentration-dependent cell death in various cultured cell lines. Even though *Piper betle* displayed cyto-toxicity towards both normal and tumor cell lines, the toxicity on tumor cells was far greater than that on normal cells indicating selective toxic effect of the plant extract on the tumor cells. Thus, the findings concluded that the IC<sub>50</sub> values for tumor cells were comparatively very low than their normal counterparts, while the percentage inhibition of tumor cells was higher than that of normal cells [34]. Phytochemical studies and in vitro cytotoxicity screening of *Piper betle* leaf extract were reported by Chaurasia *et al.*, 2010 [35]. Betel vine landraces genetic diversity were reported by Verma *et al.*, 2004 [36,37,38].

##### **Wound healing activity**

Evaluation of wound healing activity of *Piper betle* leaves and stem extract in experimental wistar rats were investigated by Nilugal *et al.*, 2014. Wounds were referred to as disruption of normal anatomic structure and function. Wound healing had a very complex, multifactor sequence of events involving several cellular and biochemical processes. The results showed wound healing and repair, accelerated by applying ointment formulation containing *Piper betle* leaves and stem extract, which was highlighted by the full thickness coverage of the wound area by an organized epidermis. The male albino rats treated with ointment formulation containing 10% *Piper betle* leaves and stem showed significant results when compared with diseased group and control group [39].

##### **Oral hygiene**

Bissa *et al.*, 2007 examined the oral hygiene and concluded that oral microbial population due to synergistic effect of the combination of betel leaf, cadamom and clove. Dental caries had a chronic endogenous infection caused by the normal oral commensally flora. The bacteria primarily responsible for dental decay in human are *Streptococcus mutans*. *Streptococci* belong to four species group: *mutan*, *salivarius*, *anginosus*, and *mitis*. In addition to *Streptococcus mutans*, *Lactobacillus acidophilus* bacteria probably play a minor role in acid production in the plaque [40]. Chu, 2001 investigated the effect of betel chewing on central and autonomic nervous systems [41]. Varunkumar *et al.*, 2014 tested the anticariogenic effect of crude extract of *Piper* by assessing its action on salivary pH [42].

### Anti-asthmatic effect

Misra *et al.*, 2014 worked on the anti-asthmatic effect of Piper betle in guinea pigs. Asthma was a hyper responsiveness of the tracheobronchial smooth muscle to a variety of stimuli. Bronchial asthma was an inflammatory condition. Free radical and superoxide may be responsible for bronchial asthma. Histamine may cause broncho-constriction. The effect of Bronchial asthma can be reduced significantly by Piper betle extract, though its action had less than that of di-phenyl hydramine. But in humans for asthma, other mediators like leukotriene plays an important role. Thus, effect of Piper betle L. on human asthma was not well known, but from that experiment it was concluded that Piper betle had the ability to reduce bronchial asthma in guinea pigs [43,25,44].

### Chlorophyllase activity

Gender based differences in response to low temperature stress in leaf chlorophyll (Chl) and carotenoids (Car) contents and chlorophyllase (Chlase) activity were monitored in male (Kapoori vellaikodi and Madras pan Kapoori) and female (Bangla mahoba, Desi bangla and Kaker) betel vine landraces. Although female plants contained nearly two fold more Chl than male counterparts, the low temperature induced Chl loss was comparable. Thus, male plants showed higher Chl a/b ratio than females. Chlase activity increased due to cold stress in all the landraces. Male plants always showed higher activities of Chlase, which may be one of the reasons for the rather low Chl contents in male plants [85]. Identification of sex specific DNA markers and RAPD analysis in betel vine have been worked by Ranade *et al.*, 2002 and Samantaray *et al.*, 2012[45,46]

### Betel leaf extract on thyroid function

Panda and Kar, 1998 examined that the effects of betel leaf extract (0.10, 0.40, 0.80, and 2.0 g kg<sup>-1</sup>day<sup>-1</sup>) for 15 days on the alterations in thyroid hormone concentrations, lipid peroxidation (LPO), superoxide dismutase (SOD) and catalase (CAT) were tested in male swiss mice. Administration of betel leaf extract exhibited a dual role, depending on the different doses. While the lowest dose decreased thyroxine (T4) and increased serum tri-iodothyronine (T3) concentrations, reverse effects were observed at two higher doses. Higher doses increased LPO with decrease in SOD and CAT activities. Thus, with the lowest dose effects were reversed. The findings suggested that betel leaf can be both stimulatory and inhibitory to thyroid function, mainly for T3 generation and lipid peroxidation in male mice, depending on the amount consumed[47,48,49]

**Anti-diabetic Activity:** The anti-diabetic activity of *P. betle* leaves was tested using normoglycaemic and streptozotocin (STZ)-induced diabetic rats by oral administration of aqueous and ethanol extracts. In normoglycaemic rats, both extracts significantly lowered the blood glucose level in a dose-dependent manner. The anti-diabetic activity of the aqueous extract was comparable to that of the ethanol extract. In the glucose tolerance test, both extracts markedly reduced external glucose load and blood glucose level. The ability of lowering blood glucose levels of STZ-induced diabetic rats suggested that the extracts have insulinomimetic activity. Another study evaluated the feasibility of using *P. betle* leaves for treating diabetes mellitus. Newly diagnosed Type-2 diabetic patients from either sex were selected ( $n = 50$  per group). Betel leaves were given to the patients for 30 days in comparison with

triphalala (an anti-diabetic herbal drug). Results showed that the blood glucose levels of betel-treated patients were significantly reduced by 22% and 25% at the end of the second and fourth week, respectively. The blood glucose levels of triphala-treated patients were significantly reduced by 14% and 24% over the same period. There were no toxic effects in terms of hepatotoxicity, renotoxicity and hematological parameters in both groups. The study showed that *P. betle* leaves can be used as a potential pharmaceutical for Type 2 diabetic patients.[49]

**Platelet Inhibition Activity:** Hydroxychavicol (HC), a component of *P. betle* leaves, was tested for its inhibition effect on platelet aggregation. Results showed that HC has the ability to inhibit cyclooxygenase activity of COX-1/COX-2, platelet calcium signalling, and thromboxan B2 production and aggregation, and to scavenge reactive oxygen. The study concluded that HC could be a potential therapeutic agent for the prevention and treatment of arteriosclerosis and other cardiovascular diseases through its anti-inflammatory and anti-platelet activities.[50]

**Radioprotective Activity:** The radioprotective activity of ethanol extract of *P. betle* leaves was evaluated using rat liver mitochondria and pBR 322 plasmid DNA as in vitro model systems. The extract effectively prevented gamma ray-induced lipid peroxidation assessed by measuring thiobarbituric acid reactive substrates, lipid hydroperoxide and conjugated diene. It also prevented radiation-induced DNA strand breaks in a concentration dependent manner. The radioprotective activity of the extract was attributed to its hydroxyl and superoxide radical scavenging ability along with its lympho-proliferative activity. Its radical scavenging capacity was probably due to its phenolic constituents comprising mainly of chevitbetol and allylpyrocatechol.[51]

**Neuroprotective Activity:** The protective effect of aqueous leaf extract of *P. betle* has been demonstrated in the brain of ethanol-treated rats. The brain of ethanol-treated rats exhibited increased levels of lipids, lipid peroxidation and disturbances in antioxidant defence. Subsequently, administration of 100, 200 and 300 mg/kg of extract for 30 days, resulted in significant reduction of lipid levels and lipid peroxidation. Extract dose of 300 mg/kg was the most effective.[52]

**Anti-dengue Activity:** The ethanol plant extract of *P. sarmentosum* possessed larvicidal effect on larvae of dengue mosquitoes of *Aedes aegypti* (LC50 of 4.06 ppm). Concurrently, the extract was also found to exert adulticidal activity (LC50 of 0.14  $\mu$ g) when tested against female *A. aegypti* mosquitoes. [53,54]

**Anti-tuberculosis Activity:** Of 78 methanol plant extracts from 70 Malaysian plant species screened for anti-tuberculosis activity against *Mycobacterium tuberculosis* using a colorimetric microplate-based assay, positive activity was found in *P. sarmentosum* with minimum inhibition concentration (MIC) of 800  $\mu$ g/ml. The amides isolated from fruits of *P. sarmentosum* displayed anti-tuberculosis activities against *Mycobacterium tuberculosis*. From the roots of *P. sarmentosum*, seven compounds exhibited anti-mycobacterial activity.[55,56,57]

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