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Traditional Use and Pharmacological Activity of Betel Leaf (*Piper betle* Linn.)



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ABSTRACT

Piper betle Linn. species of the Piperaceae family is an evergreen and perennial creeper, with glossy heart-shaped leaves that contain phenolic compounds with antiproliferative, anti-mutagenic, antibacterial and antioxidant properties. Phytochemical studies show that *Piper betle* contains a comprehensive variety of biologically active compounds whose concentration depends on the variety of the plant species. Many research studies on *Piper betle* has reported that it contains important chemical constituents such as chavibetol, chavibetol acetate, caryophyllene, allylpyrocatechol diacetate, campene, chavibetol methyl ether, eugenol, α -Pinene, β -Pinene, γ -Limonene, safrole, 1-8-cineol, and allylpyrocatechol monoacetate. These components containing a wide variety of medicinal properties like anti-fungal, anti-nociceptive, anti-cancer, immunomodulatory, antihalitosis, anti-diabetic, gastroprotective, anti-allergic, anti-fertility, antifilarial, anti-larvicidal, wound healing and anti-dermatophytic. The present review focus on various traditional uses as well as pharmacological reports on *Piper betle* L.



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INTRODUCTION:

The betel plant (*Piper betle* L.) is an evergreen; shade loving perennial root climber belongs to the family Piperaceae with glossy heart shaped leaves and white catkin ¹. It is extensively grown in Sri Lanka, India, Thailand, Taiwan and other Southeast Asian countries. This oil may be used as an industrial raw material for manufacturing medicines, perfumes, mouth fresheners, tonics, food additives etc. The leaves are nutritive and contain anti carcinogens showing promise for manufacturing of a blood cancer drug. Betel leaves are an integral component of the betel quid that consists of areca nut (*Areca catechu* L.), tobacco (*Nicotiana tabacum* L) and slaked lime ². Betel leaf is traditionally known to be useful for the treatment of various diseases like bad breath, boils and abscesses, conjunctivitis, constipation, learning and memory, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, anti-septic, swelling of gum, rheumatism, cuts and injuries ³. It is also used as a special item offered to the guests in order to show respect and for such traditional use of betel leaf in Indian society. Betel leaf cultivation has vast potential as it plays an important role in economics and livelihood of people in South Asia ^{4,5}.

Plant Profile:

Taxonomical Classification:

Kingdom : Plantae

Division : Magnoliophyta

Class : Magnolipsida

Order : Piperales

Family : Piperaceae

Genus : Piper

Species : Betel

Vernacular Names:

Sanskrit : Tambool, Mukhbhushan, Varnalata

Hindi : Paan



English : Betel, Betel pepper, Betel-vine

Telugu : Nagballi, Tamalapaku

Tamil : Vetrilai Gujarati : Nagarbael

Chemical constituents:

The leaf contains Water (85-90%), Proteins (3- 3.5%), Carbohydrates (0.5-6.1%), Minerals (2.3- 3.3%), Fat (0.4-1%), Fibre (2.3%), Essential oil (0.08-0.2%), Tannin (0.1-1.3%), Alkaloid (arakene). It also contains different vitamins like Vitamin-C (0.005-0.01%), Nicotinic acid (0.63- 0.89mg/100gms), Vitamin-A (1.9- 2.9mg/100gms), Thiamine (10-70µg/100gms), Riboflavin (1.9-30µg/100gms) beside this it contains minerals such as Calcium (0.2-0.5%), Iron (0.005-0.007), Iodine (3.4µg/100gms), Phosphorus (0.05-0.6%), Potassium (1.1- 4.6%). Leaves contain bitter compounds that are about (0.7-2.6%). The leaves contain specific strong pungent aromatic flavour is due to phenol and terpene like bodies⁶. The total phenol content is vary on gender. The male plant contains three fold higher total phenols content and two fold higher thiocyanate content as when compare to female plant. The quality of the leaf depends upon the phenolic content, i.e., more the phenolic content betters the leaf quality⁷. Recently many researches works shows the betel leaves contains starch, diastases, sugars and an essential oil composing of safrole, allyl pyrocatechol monoacetate, eugenol, terpinen-4-ol, eugenyl acetate, etc. as the major components^{8,9}. Phytochemical investigation on leaves revealed the presence of Alkaloids, Carbohydrate, Amino acids, Tannins and Steroidal components¹⁰. The middle part of the main vine contains largest quantity of Tannin. The terpenoids include 1, 8- cineole, cadinene, camphene, caryophyllene, limonene, pinene, Chavicol, ally pyrocatechol, carvacrol, safrole, eugenol and chavibetol are the major phenols found in betel leaf. Eugenol was identified as the antifungal principle in the oil. The fresh new leaves contain much more amount of essential oil diastase enzyme and sugar as compare to old leaves.

Traditional uses of Betel leaves:

Headache: Betel leaf is a popular home remedy for headache. The betel leaf has analgesic and cooling properties. It can be applied with beneficial results over the painful area to relieve intense headache.

Scanty or Obstructed Urination: Betel leaf juice is credited with diuretic properties. Its juice, mixed with dilute milk and sweetened slightly, helps in easing urination.

Weakness of Nerves: Betel leaves play a vital role in the treatment of nervous pains, nervous exhaustion and debility. The juice of a few betel leaves, with a teaspoon of honey, will serve as a good tonic. A teaspoon of this can be taken twice a day.

Sore Throat: Betel leaf is an excellent household remedy in the treatment of cough and sore throat. 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.

Respiratory Disorders: Betel leaves are useful in pulmonary affection in childhood and old age. The leaves, soaked in mustard oil and warmed, may be applied to the chest to relieve cough and difficulty in breathing.

Constipation: In the case of constipation in children, a suppository made of the stalk of betel leaf dipped in castor oil can be introduced in the rectum. This instantly relieves constipation.

Problem of Breast milk secretion: The application of leaves smeared with oil is said to promote secretion of milk when applied on the breasts during lactation ¹¹.

Inflammation: Applied locally, betel leaves are beneficial in the treatment of inflammation such as arthritis and orchitis that is inflammation of the testes.

Wounds: Betel leaves can be used to heal wounds. The juice of a few leaves should be extracted and applied on the wound. Then a betel leaf should be wrapped over and bandaged. The wound will heal up with a single application within 2 days.

Boils: Betel leaf is also an effective remedy for boils. A leaf is gently warmed till it gets softened and is then coated with a layer of castor oil. The oiled leaf is spread over the inflamed part. This leaf has to be replaced, every few hours. After a few applications, the boil will rupture draining all the purulent matter. The application can be made at night and removed in the morning.

Other medicinal uses¹²

In Unani system, it is used as an appetizer due to its sharp taste and good smell. For curing obesity, one *Piper betel* leaf mix with *Piper nigrum* is prescribed for two months. It recovers bad breath, body odor and prevent tooth decay. It contains vitamins such as thiamine, niacin,

riboflavin and carotene. The essential oils present in the leaves have antibacterial, antiprotozoal and antifungal properties. Therefore, the oil kills or inhibits expansion of outrageous bacteria causing typhoid, cholera and tuberculosis etc. and helps in proper evaluation and exploitation.

Pharmacological Activity:^{13,14,15}

A large number of natural products are being used in the treatment of many diseases as traditional medicine in several countries. *Piper betel* belongs to the family Piperaceae and has over 2000 species. The plant is indigenous to India. Extracts of *Piper betel* are used for the treatment of various ailments since ages due to its essential properties like anti-oxidant, anti-cancer, anti-allergic, etc.

Antimicrobial activity:

The betel shows the antimicrobial activity against *Streptococcus pyrogenes*, *Staphylococcus aureus*, *Proteus vulgaris*, *Escherichia coli* and *Pseudomonas aeruginosa*. Beside of this the leaf extract also possess bactericidal activity against the urinary tract pathogenic bacteria such as *Enterococcus faecalis*, *Citrobacter koseri*, *Citrobacter freundii* and *Klebsiella pneumoniae*^{16,17}. Dermatophytosis is a disease of the keratinized parts of the body (skin, hair, and nail) caused by athree genera of highly specialized fungi called the Dermatophytes¹⁸ is also cured by it. 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^{19,20}.

Antidiabetic activity:

The aqueous and ethanolic extracts of *Piper betel* leaves possess marked hypoglycaemic activity when tested in fasted normoglycaemic rats. In glucose tolerance test, the extract showed antihyperglycaemic activity in the external glucose level²¹.

Gastroprotective activity:

Mucus layer is considered to be important in mucosal defenses against endogenous aggressors, acids and also as an agent in facilitate the repair process. The higher dose of hot water extract does not cause significant inhibition in acidity or pH of gastric fluid ²². 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 faster healing. Allylpyrocatechol has shown a powerful antioxidant potential in various in-vitro models²³.

Immunomodulatory activity:

The decrease in antibody titer and increased suppression of inflammation suggests possible immunosuppressive effect of extract on cellular and humoral response in mice²⁴.

Platelet inhibition activity:

Hydroxychavicol (HC) was tested for its inhibition effect on platelet aggregation. The result showed hydroxychavicol to be a potent inhibitor for cyclooxygenase activity, reactive oxygen scavenger and inhibits platelet calcium signaling, thromboxan B2 production and aggregation. HC could be a potential therapeutic agent for prevention and treatment of atherosclerosis and other cardiovascular diseases through its anti-inflammatory and antiplatelet effects, without effects on homeostatic function²⁵.

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 carbohydrates²⁶. The bacteria primarily responsible for dental decay in man are *Streptococcus mutans*. This enzyme is considered to be of special importance in the establishment of dental plaque²⁷. So, it is best natural substance and its rating as second most popular daily consummation item in Asia, which contributes the best oral hygiene to oral cavity.

Antioxidant activity:

Oxidative damage is an important effect of ionizing radiation on biological membranes. It is a chain reaction of free radicals generated from the radiolytic decomposition of water can attack fatty acid chains of membrane lipid. Presence polyphenols compounds like catechol, allylpyrocatechol in betel 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 steps²⁸.

Anti-allergic activity:

The inhibitory effects of *Piper betel* on production of allergic mediators by bone marrow derived mast cells and lung epithelial cells were studied. The effects of *Piper betel* ethanolic extract on the production of histamine and granulocyte macrophage colony-stimulating factor (GMCSF) by murine bone marrow mast cells (BMMCs) and on the secretion of exotoxin and IL-8 by the human lung epithelial cell line, BEAS-2B, were investigated in vitro. The extracts significantly decreased histamine and GMCSF produced by an IgE mediated hypersensitivity reaction and inhibited exotoxin and IL-8 secretion in a TNF- α and IL-4-induced allergic reaction. The results suggest that *Piper betel* may control of allergic diseases through inhibition of production of allergic mediators²⁹.

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 betel*. The result shows no toxicity in all metabolically active tissue of mice and interestingly, the contraceptive efficacy emphasized reversible fertility after withdrawal of treatment³⁰.

Neuropharmacological profile:

Hydroalcoholic extract of betel leaves exhibited improvement in the discrimination index, potentiating the haloperidol induced catalepsy, reduction in basal as well as amphetamine induced increased locomotor activity and delay in sodium nitrite induced respiratory arrest. These results recommend promising facilitation of cholinergic spread and hanging-up of dopaminergic as well as noradrenergic transmission by the extract^{31,32}.

Pro-apoptotic Effect / Anti-Leishmaniasis:

In a comparative in vitro antileishmanial activity of methanolic extracts from two landraces of *Piper betel*. The efficacy mediated through apoptosis is probably due to higher content of eugenol.

Cholinomimetic effect:

Betel leaf rise body temperature due to cholinergic responses. The leaves contain cholinomimetic and possible calcium channel antagonist constituents which may provide the basis for several activities shown by this plant.

Hepatoprotective activity:

The examination showed that the betel 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/Erk pathway, and inhibiting TIMP2 level that consequently attenuated the fibrosis of liver. These findings support a chemopreventive potential of betel leaf against liver fibrosis.

Anticoagulant Activity:

The in vitro anticoagulant activity of *Piper betel* compound was obtained by column chromatography was studied. It has been found that the phenolic compound present in the *piper betel* was responsible for the anticoagulant activity³³.

Antiulcerogenic activity:

Pretreatment of an ethanolic extract of leaf of *Piper betel* Linn at a dose of 200mg/kg body weight, orally administered to rats for ten consecutive days, was found to possess a significant protective action against gastric lesions induced by indomethacin. The extract was also found to possess both superoxide and hydroxyl free radical scavenging action. Further investigation showed the protective activity of allyl pyrocatechol (APC), which is the major antioxidant constituent of *Piper betel* against the indomethacin-induced stomach ulceration in the rat model. It was found that the excellent healing activity of ethanolic extract of *Piper betel* play a major role of mucin protection and regeneration in the healing of non-steroidal anti-inflammatory drugs mediated stomach ulceration.

Anti-Photosensitizer:

Inhibitory property of the *Piper betel* 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 photosensitizers³⁴.

Anti-inflammatory activity:

Piper betel was evaluated for acute and chronic anti-inflammatory study at a dose of 300 mg/kg leaf powder. Diclofenac sodium was used as the standard drug. Carrageenan and

dextran models were studied for acute inflammation while cotton pellet induced granuloma was used for chronic inflammation study³⁵.

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 *Piper betel* 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. It suggests that the herb has a great potential not only it is cheap but also easily accessible natural radioprotectant to the common people.

Anti-larvicidal Activity:

Anti-larvicidal activity of *Piper betel* was observed by L.S. RArambewela et al., in the year 2011. The *piper betel* essential oil at different concentrations, i.e. 500, 100, 50, 25, 12.5 and 6.25 ppm concentrations were used, and motility was recorded between 1 to 24 h. Mortalities of 43% and 100% were observed for 100 and 500 ppm concentrations, respectively, within 1 h. The concentration of oil used was 1%, 0.8%, and 0.5% respectively and the mortality rate of 100% was observed in 1% betel oil solution within 1 h.

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 property³⁶.

CONCLUSION:

Since traditional times, *piper betel* is consumed frequently as mouth freshener. According to numerous research studies, the medicinal importance of the herb as discussed above evidently prove that betel leaf is one of the most promising commercial botanical. It has shown to possess a lot of therapeutic activities such as anticancer activity, anti-fungal activity, antinociceptive activity, immunomodulatory activity, anti-halitosis activity, anti-diabetic activity, gastroprotective activity, anti-allergic activity, antifertility activity, anti-filarial activity, anti-larvicidal activity, wound healing activity and antidermatophytic activity. In

consideration of the proven therapeutic values of *P. betel* proper characterization could be useful for long term research for drug development.

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