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REVIEW ON BETEL LEAF USED IN VARIOUS AILMENTS

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ABSTRACT: *Piper betel* Linn. an important species of the Piperaceae family is an evergreen and perennial creeper, with glossy heart-shaped leaves that are magnificent reservoirs of phenolic compounds with anti-proliferative, anti-mutagenic, antibacterial and antioxidant properties. Phytochemical studies show that *Piper betel* contains a wide variety of biologically active compounds whose concentration depends on the variety of the plant species. Many research studies on *Piper betel* has reported that it contains important chemical constituents such as chavibetol, chavibetol acetate, caryophyllene, allylpyrocatechol diacetate, camphene, chavibetol methyl ether, eugenol, α -Pinene, β -Pinene, γ -Limonene, safrole, 1-8-cineol, and allylpyrocatechol monoacetate. These components are valued as a stimulant for its medicinal properties like anti-fungal, anti-nociceptive, anti-cancer, immunomodulatory, anti-halitosis, anti-diabetic, gastroprotective, anti-allergic, anti-fertility, anti-filarial, anti-larvicidal, wound healing and anti-dermatophytic. The present review is an attempt to highlight various traditional uses as well as pharmacological reports on *Piper betel* L.

INTRODUCTION: The betel leaf is an evergreen and perennial, creeper, with glossy heart-shaped and white catkin. The genus *Piper* (Piperaceae) is largely distributed in tropical and subtropical regions of the world. *Piper betel* is cultivated in India, Sri Lanka, Malaysia, Indonesia, Philippines, Island, and East Africa. It has light yellow aromatic essential oil, with sharp taste. There are more than 90 varieties of betel vine in the world, of which about 45 are found in India and 30 varieties in West Bengal itself¹. It is grown in tropics and subtropics for its evergreen leaves that are used in pooja/religious events and as a chewing stimulant¹.

The leaves are chewed together in a wrapped package along with the areca nut (which, by association, is often inaccurately called the "betel nut") and mineral slaked lime (calcium hydroxide). Catechu called Kattha in Hindi and other flavoring substances and spices might be added. The lime acts to keep the active ingredient in its freebase.

Freebase or alkaline form, thus enabling it to enter the bloodstream *via* sublingual absorption². The areca nut contains the alkaloid arecoline, which promotes salivation (the saliva is stained red), and is itself a stimulant. This combination, known as a "betel quid", has been used for several thousand years. The plants of genus *Piper* are also used for many other purposes such as foods and spices, fish bait, fish poison, hallucinogens, insecticides, oils, ornaments, perfumes, *etc*^{3,4}. It is an effective anti-wormal agent and excellent anti-infectious agent because of its pungent taste.

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It helps in normalizing the digestive tract hence is very effective in maintaining the digestive system because of its light properties. Moreover, it helps in expelling out the mucus from the infusion prepared from the leaves and stems are supposed to be useful in treating indigestion, bronchitis, constipation, congestion, coughs, and asthma.

The leaf juice is given systemically to treat cough and indigestion in children. Many research investigations to date have given a lot of potential information about *Piper betel* and its activity such as anti-malarial activity, anti-bacterial activity, anti-fungal study, insecticidal activities, antioxidant activity, anti-diabetic activity, gastroprotective activity, anti-nociceptive activity, cytotoxic activity, anti-platelet, etc.

History: *Piper betel* is blessed as evergreen and perennial plant, that has God created and has given the shape of his own heart. Anthropologists have found traces of betel in the spirit caves in Northwest Thailand dating back as to 5500 - 7000 BC, which is even before systematic and organized agriculture came to be practiced.

There have been similar findings in Timor in Indonesia going back to 3000 BC and in the blacked teeth of a human skeleton in Palawan in the Philippines going back to 2600 BC. It had found a place in the most ancient Sri Lanka Historical Book “Mahawamsa” written in pali. Even today some hardened betel chewers in Thailand, Myanmar, and Indonesia were found with black teeth as result of long years of chewing. There is archaeological evidence that the betel leaves have been chewed along with the Areca nut since very ancient times is not known when these two different stimulant substances were first put together. Hence, it may difficult to clearly ascertain the period when the tradition of paan chewing was started.

However, its mention in the Vatsyayana’s Kamsutra and Kalidas’s Raghuvamsa in itself reflects the antiquity of this practice. Social status of paan can also be appreciated from the fact that it was considered to be a great honor to receive paan bida [A pair of leaves with churana (Lime), kattha (catechu) and supari (areca nut)] from kings and nobles that was the status of paan in ancient India.

During this period (Circa 600 AD) words like Tambuladhikara, Tambuladyaka, Tambuladayini and Tambulika, etc. used in different texts. Some of the common usages are mention in Kadamberi. Paan has been referred to in Sakta-tantra as one of the means of achieving siddhi. It was believed that without betel chewing and offering paan to Guru no siddhi can be gained³.

Ayurvedic Significance: *Piper betel* is a Vedic plant and its Vedic name is Saptasira and in Sanskrit known as Tambool, Nagvelleri, Nagani were used as a remedy against various diseases. Reference to Tambool occurs right from Vatsyayana’s Kamasutra & Panchatantra down to Kalhan’s Rajatarngni (which may perhaps be the last of the recognized old Sanskrit writing of historical significance).

Tambool has thus roughly referred across a period of about 2000 years. In Ayurveda medicine system, the properties of betel leaf described as given below:

Guna (Quality)	: Laghu, Ruksha, Tikshan
Rasa (Taste)	: Tikt
Vipak (Metabolism)	: Katu
Virya (Potency)	: Ushan
Prabhav (Impact)	: Hridya

In Ayurveda, betel leaf extract is frequently used as an adjuvant & mixed with different medicines possibly for better effects besides its independent use as medicine. In Sushruta Samhita tambool leaves have been described as aromatic, sharp, hot, acrid and beneficial for voice, laxative, appetizer, besides this they pacify Vata and aggravate pitta³.

Plant Profile:



FIG. 1: LEAVES OF PIPER BETEL

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

Varieties of Betel Leaf: Based on the morphological characters and essential oil content, betel vine varieties are divided into five main groups *viz*, Bangla, Desawari, Kapoori, Sanchi, and Meetha.

- Bangla is large thin leaves with nine main nerves and ovate lamina with cordate base.

Leaf apex is pointed and short, not curved. Petiolar sinus it is more prominent than other varieties.

- Desawari is large thin leaves and cordate lamina with seven to nine nerves. Leaf of Desawari is pinkish, and leaf apex is short, acuminate, and curved.
- Kapoori leaves are more elliptical, and lamina is thin with undulated margin. Leaf apex of Kapoori is acuminate, and petiolar sinus is inconspicuous.
- Leaves of Meetha are large, and lamina is cordate to broadly ovate and thick. Meetha leaf is waxy in texture with yellowish dots and three to five main nerves. Leaf apex of Meetha is short and pointed. It has a prominent joint in the petiole.
- Sanchi consists of a cordate leaf base with more elliptical lamina and long tapering apex. Normally seven nerves are seen in Sanchi^{6,7}.



FIG. 2: SANCHI



FIG. 3: BANGLA



FIG. 4: KAPOORI



FIG. 5: DESAWARI

Ayurvedic Uses:

- **Scanty or Obstructed Urination:** Betel leaf juice is credited with diuretic properties. Its juice, mixed with dilute milk and sweetened slightly, helps in easing the passage of urine.
- **Weakness of Nerves:** Betel leaves are beneficial in the treatment of nervous disorders. The juice of a few betel leaves, with a teaspoon of honey, serves as a good tonic. A teaspoon of this mixture can be taken twice a day.
- **Headaches:** The betel leaf has analgesic and cooling properties. It can be applied to relieve intense headaches.
- **Respiratory Disorders:** Betel leaves are useful in pulmonary afflictions suffered in childhood and old age. The leaves, soaked in mustard oil and warmed, may be applied to the chest to relieve a cough or 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.
- **Sore Throats:** 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 an irritating cough.
- **Wounds:** Betel leaves can be used to heal wounds. The juice of a few leaves should be extracted and applied to the wound. Then a betel leaf should be wrapped over it and bandaged. The wound will heal with just a single application within two days.
- **Boils:** The herb is also an effective remedy for boils. A leaf is gently warmed till it gets

softened and 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 out all the purulent matter. The application can be made at night and removed in the morning.

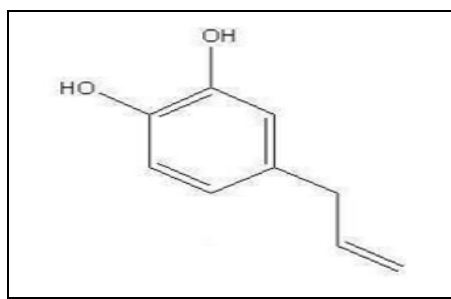
The Problem of Breast Milk Secretions: The application of leaves smeared with oil is said to promote the secretion of milk when applied on the breasts during lactation⁸.

Chemical Constituents: Leaves contain protein 3-3.5%, carbohydrate 0.5 - 6.10%, minerals 2.3-3.3%, and tannins 0.1 - 1.3%. It contains calcium, phosphorus, iron, iodine, potassium, vitamin B, vitamin C and vitamin A.

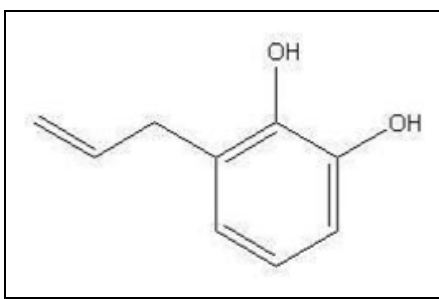
It also contains some aromatic compounds and stable oils like phenol and terpene. Besides, it contains eugenol, chavibetol a-pinene, f pinene, 1, 8 cineole and hydroxychavicol. Major constituents of common betel were found to be safrole (48.7%) and chavibetol acetate (15.5%). The presence of allylpyrocatechol, caryophyllene, anethole, stearic acid, carvacrol, polyphenol, alkaloids, saponin, are also found in *Piper betel*⁹.

TABLE 1: CHEMICAL CONSTITUENTS OF PIPER BETEL LEAF

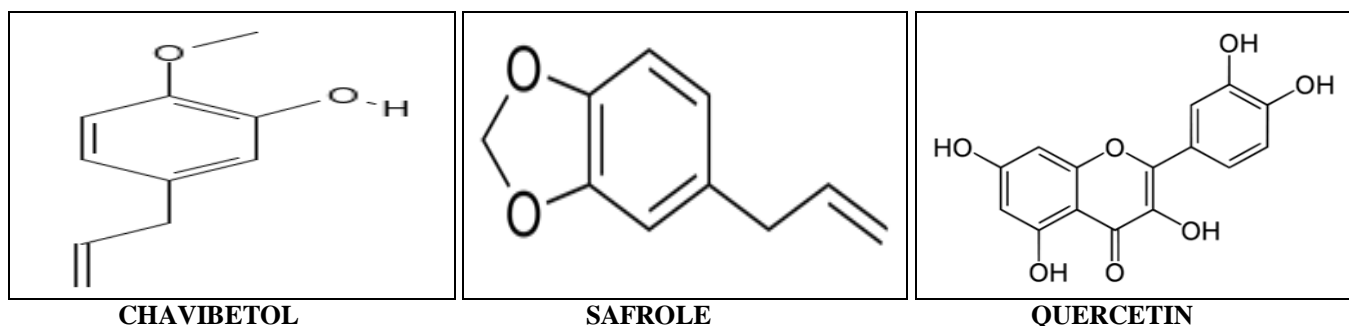
Chemical constituents	% of chemical constituents
Chavibetol	53.1
Chavibetol acetate	15.5
Caryophyllene	3.71
Allylpyrocatechol diacetate	0.71
Chavibetol methyl ether	0.48
Eugene	0.32
a-Pinene	0.21
f-Pinene	0.21
Safrole	48.7
1, 8-Cineol	0.04
Allylpyrocatechol Monoacetate	0.23
Tannins	0.1-1.3%



HYDROXYCHAVICOL ACETATE



ALLYLPYROCATECHOL



CHAVIBETOL

SAFROLE

QUERCETIN



FIG. 6: HEALTH BENEFITS OF BETEL LEAF



FIG. 7: BETEL LEAF OIL

Pharmacological Activity: 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. *Piper betel* leaves are shown to be effective against several human pathogens, although the mechanisms involved have not been elucidated. 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.

Anticancer Activity: Globally, breast cancer is the most common disease in women with new cases incidence of 1.38 million per year (Eccles, et al., 2013). The high mortality rate is usually due to the late prognosis of the disease, such as recently detected in the metastasis phase. This phase is characterized by high expression of matrix metalloproteinases (MMPs), cell migration, invasion and other phenomena associated with metastatic cascade. These conditions cannot be treated only with radiation therapy or by surgery, but rather need to be developed through chemotherapeutic drugs¹⁰. Zulharini M et al., 2018 used methanolic extract of red betel leaf to evaluate the cytotoxic and anti-migration activity towards metastatic breast cancer. Red betel leaves (*Piper crocatum* Ruiz dan Pav) has been known as herbal medicine containing biphenolic, such as apigenin

and luteolin derivatives which have cytotoxic activity toward cancer cells.

The study was intended to explore the inhibitory effect of *Piper crocatum* leaves methanolic extract (PCM) on cell proliferation and migration by using 4T1 cells as a model of metastatic breast cancer. By using MTT assay, PCM performed cytotoxic activity in a dose-dependent manner with IC₅₀ value of 120 µg/ml. Wound healing assay revealed that migration inhibitory activity of PCM on 4T1 cells at the concentration of 30 µg/ml. PCM performed cytotoxic effect and anti-migration activity towards metastatic breast cancer cells¹¹.

Anti-fungal Activity: Ali I et al., 2007 studied the *in-vitro* antifungal activity of hydroxychavicol isolated from *piper betel* leaf. The minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) were determined using broth microdilution method. Hydroxychavicol exhibited inhibitory effect on fungal species of clinical significance with MICs ranging from 15.62 to 500 µg/ml for yeasts, 125 to 500 µg/ml for *Aspergillus* species and 7.81 to 62.5 µg/ml for dermatophytes. The antifungal activity exhibited by this compound warrants its use as an anti-fungal agent particularly for treating topical infections as well as gargle mouthwash against oral *Candida* infections¹².

Gastroprotective Activity: Majumdar B *et al.*, 2003 studied the healing effect on treatment with ethanol extract of *P. betel* at a dose of 150 mg/kg body weight daily for 10 days, after induction of peptic ulcer by NSAID in albino rats. During the healing process, on treatment with extract of piper betel, antioxidant factor, *e.g.*, superoxide dismutase and catalase activity, mucus and total gastric tissue sulphahydril group were increased. Overall it can be suggested that the antioxidant or free radical scavenging activity of the plant extract may be responsible for its healing property¹³.

Further research was carried out by Arawwawala LD *et al.*, 2014 evaluated the gastroprotective activity of hot aqueous extract (HAE) and cold ethanolic extract (CEE) of *P. betel* against ethanol-induced gastric ulcers in rats. The parameters evaluated were (a) effects of HAE on mucus content adhering to the wall of the gastric mucosa, (b) acidity (total and free) (c) volume and (d) pH of the gastric juice. Oral administration of HAE and CEE provided marked dependent (HAE $r^2 = 0.97$; CEE $r^2 = 0.96$) and significant ($P \leq 0.05$) than that of misoprostol, the reference drug. The HAE significantly increased the mucus content adhering to the wall of gastric mucosa and inhibited the volume of gastric acid, and hence concluded that both HAE and CEE of *P. betel* leaves have a strong gastroprotective activity^{14, 15}.

Immunomodulatory Activity: Kanjwani DG *et al.*, 2008 evaluated immunomodulatory activity of methanolic extract of *Piper betel*. The MPB consisted of a mixture of phenols, flavonoids, tannins, and polysaccharides. Both *in-vitro* as well as *in- vivo* evaluation were carried out. The effects of MPB on lymphocyte proliferation, interferon- γ 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. *P. betel* significantly suppressed phytohaemagglutinin 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 the extract on cellular and humoral response in mice.

Thus, the MPB could be explored extensively as a therapeutic agent to treat various immune disorders, including autoimmune disorders¹⁶.

Anti-diabetic Activity: Arambewela LS *et al.*, 2005 investigated the anti-diabetic activities of aqueous and ethanolic extracts of *Piper betel* leaves in rats. This was tested in normoglycaemic and streptozotocin (STZ)-induced diabetic rats using oral administration of hot water extract (HWE) and cold ethanolic extract (CEE). In normoglycaemic rats, both HWE and CEE significantly lowered the blood glucose level in a dose-dependent manner. In glucose tolerance test, both extracts markedly reduced the external glucose load. The anti-diabetic activity of HWE is comparable to that of CEE. Moreover, HWE failed to inhibit the glucose absorption from the small intestine of rats. Both extracts were found to be non-toxic and well-tolerated after following chronic oral administration (no overt signs of toxicity, hepatotoxicity or renotoxicity). However, the weight of the spleen had increased in treated groups possibly indicating lymphoproliferative activity. In a nutshell it can be observed that HWE and CEE of *Piper betel* leaves possess safe and strong anti-diabetic activity¹⁷.

Anti-halitosis Activity: Anti-halitosis activity of *Piper betel* was done by Ramji N *et al.*, (2002). *Piper betel* L. (Piperaceae) leaves which are traditionally used in India and China in the prevention of oral malodor was examined by bioassay-guided fractionation to yield allylpyrocatechol (APC) as the major active principle which showed promising activity against obligate oral anaerobes responsible for halitosis.

The biological studies with allylpyrocatechol indicated that the potential to reduce methyl mercaptan and hydrogen sulfide was mainly due to the anti-microbial activity of allylpyrocatechol as established using dynamic *in-vitro* models¹⁸.

Siddeshappa ST *et al.*, 2018 compared the herbal mouth wash and chlorine dioxide mouthwash in the reduction of plaque and gingivitis. In a randomized clinical trial, forty patients were randomly selected and divided equally into two groups. After professional oral prophylaxis, the clinical parameters plaque index, gingival index, and

modified sulcular bleeding index were recorded at baseline, 7th day, 14th day and 21st day. The plaque samples were collected from gingival sulcus with an absorbent sterile paper point and were stored in a thioglycollate broth, then sent for microbiological examination.

The microbial colony-forming units were assessed at baseline, 7th day, 14th day and 21st day for *Streptococcus mutans*, *Tannerella forsythia*, and *Fusobacterium nucleatum*. A statistically significant reduction in both clinical and microbiological parameters was observed with the use of both the mouthwashes. However, herbal mouthwash was more effective in reducing plaque and gingivitis than chlorine dioxide mouthwash. It was thereby concluded that herbal mouth wash was statically efficacious in controlling plaque and gingivitis with potent anti-microbial activity^{19,20}.

Anti-allergic Activity: The inhibitory effects of *Piper betel* on the production of allergic mediators by bone marrow-derived mast cells and lung epithelial cells were studied by Wirotasangthong M et al., (2008). The effects of *Piper betel* ethanolic extract on the production of histamine and granulocyte macrophage colony-stimulating factor (GM-CSF) 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 GM-CSF 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 suggested that *Piper betel* may offer a new therapeutic approach for the control of allergic diseases through inhibition of production of allergic mediators²¹.

Anti-fertility Activity: Sharma JD et al., (2007) studied the anti-fertility efficacy of *Piper betel* Linn. (Petiole) in female Albino rats. Normal cyclic female Albino rats (*Rattus norvegicus*) of Wister strain weighing between 150-200 gm were treated with *Piper betel* (Petiole) ethanolic (50%) extract (100 mg/day/rat) for 30 days. The results revealed that *Piper betel* treatment caused a reduction in reproductive organ weights, circulating levels of estrogen, fertility, a number of litters, serum

glucose concentration, the enzyme activity of acid phosphates, SGOT, and SGPT as compared to control values. The concentration of cholesterol and ascorbic acid increased following *Piper betel* treatment, revealing non-utilization of cholesterol by the system and mobilization of ascorbic acid during phyto-drug treatment to overcome from induced stress condition. The estrus cycle was irregular and prolonged in the treated group of rats.

The data suggested that the *Piper betel* ethanolic extract exerted anti-fertility and anti-estrogenic effects in female rats, and effects brought by extract are non-toxic and transient. The alcoholic extract of the leaf-stalk showed significant anti-fertility effects in both male and female rats^{22,23}.

Anti-nociceptive Activity: Arambewela LS et al., in 2011 reported that *Piper betel* has anti-nociceptive activity. About 200 and 300 mg/kg doses of *Piper betel* extract markedly reduced the licking time in early and late phases of the formalin test in a bell-shaped dose-response curve. In the formalin test, the pain in the early phase is caused due to the direct stimulation of the sensory nerve fibers by formalin, while the pain in the late phase is due to the inflammatory mediators, like histamine, prostaglandin, serotonin, and bradykinin.

It was reported that NSAIDs reduce both phases of the formalin test. The betel extracts too induced interruptions in both phases of this test, suggesting possible impairments of sensory transmission and release of inflammatory mediators. The highest anti-nociceptive activity was evident with a 200 mg/kg dose of both HWE and CEE. As the anti-nociceptive activity of CEE was higher than that of HWE, CEE was used to investigate its anti-nociceptive mechanism²⁴.

Wound Healing Activity: Nilugal et al., 2014 investigated the wound healing capability of *Piper betel* leaves and stem extract. The enhanced rate of wound contraction and the drastic reduction in healing time in male albino rats, which might be due to enhanced epithelialization was observed. The results showed wound healing and repair, accelerated by applying ointment formulation containing *Piper betel* leaves and stem extract, which was highlighted by the full thickness

coverage of the wound area by an organized epidermis.

The animals treated with ointment formulation containing 10% *Piper betel* leaves and stem showed significant results when compared with providone iodine and control group. From this investigation, it can be concluded that *Piper betel* has the potential ability in wound healing²⁵.

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.

Betel solutions ranging in concentration from 1% to 4% were prepared using 1% Tween 80, sodium lauryl sulfate (0.05 gm/100 ml, as a stabilizer) and methylparaben (0.01 g/100 ml, as a preservative). The 4% and 3% preparations of the oil of betel were effective in killing 100% of the larvae of *C. megacephala* within 3 h, while betel oil at 2% concentration killed 97% of *C. megacephala* larvae within 4 h. This shows that betel oil is effective in the treatment of wound myiasis^{26,27}.

Anti-dermatophytic Activity: Anti-dermatophytic Activity of *Piper betel* cream was studied by Nopamart Chatchawanchonteera et al., in 2006. Crude ethanolic extracts of *Piper betel* leaves (Piperaceae), *Alpinia galangal* rhizomes (Zingiberaceae) and *Alliums ascalonicum* bulbs (Liliaceae) were previously tested against selected dermatophytes (*Microspore canis*, *Microsporum gypseum*, and *Trichophyton mentagrophyte*). The results suggested a promising anti-fungal property of *Piper betel* extracts than its counterparts. In a study conducted by for anti-dermatophytic activity 10% *Piper betel* cream was formulated, subjected to physical and microbial limit tests, and evaluated for its effect against dermatophytes *in-vitro*²⁸.

CONCLUSION: Since the 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, anti-nociceptive activity, immunomodulatory activity, anti-halitosis activity, anti-diabetic activity, gastroprotective activity, anti-allergic activity, anti-fertility activity, anti-filarial activity, anti-larvicidal activity, wound healing activity and anti-dermatophytic 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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