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## AN EVERGREEN BETEL PLANT (*PIPER BETLE* L): A REVIEW

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### ABSTRACT

A member of the Piperaceae family of plants, betel (*Piper betle*) has long been used as a mouth freshener, wound healer, stimulant and preventive against cataracts and bleeding. Ayurvedic doctors frequently employ betel leaf extract as an aphrodisiac, laxative, adjuvant and flavouring. In addition to avoiding fever, ulcers, nosebleeds and eye infections, it enhances taste and appetite. Saponins, flavonoids, polyphenols, triterpenoids, essential oils (carvacrol, eugenol, chavicol, chavibetol and estragole), sesquiterpenes, sugar and starch are among the chemicals found in betel. According to studies, piper betle possesses bioactivity as an antiproliferative, hepatoprotective, analgesic, antibacterial, antimicrobial, and anti-inflammatory chemical. It was found that the wonderful plant betel leaf (*Piper betle*), which is employed in many fields, has many uses and advantages. India's betel leaf growing industry is broad. Because of its antibacterial, antifungal, antioxidant and antiseptic qualities, betel leaves are used medicinally. Apart from its well-known medical applications, betel leaf has numerous other uses in both ancient and contemporary science.

### KEYWORDS

Betel (*Piper betle*), Piperaceae, Mouth freshener and Pharmacological activities.

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### INTRODUCTION

There are many different types of traditional medicinal herbs that Indonesians have been using for years. In traditional medicine, the betel plant-also referred to as piper betle-is utilised. The native plant of Indonesia, betel, creeps up or rests on other tree trunks. A common herb in Malay daily life and several family rituals is betel, a medicinal plant. In the province of the Riau archipelago in Indonesia, betel is a widely grown plant. The custom of utilising betel to cure a variety of ailments and consume it at welcoming ceremonies is highly valued by the people of the Riau Islands. But betel plants are widely distributed in Indonesia, whether

for practical purposes or aesthetic purposes. (Source:) Tens of metres can be reached by the piper betle plant, also referred to as betel. The stalk of the flat betel leaf is heart-shaped and relatively lengthy. The tree trunk has a light brownish-green tint with a rough, wrinkled skin surface; in contrast, the leaf surface is lustrous and green. The betel fruit, sometimes called the buni fruit, is a spherical, grayish-green fruit. Gather spherical, yellowish-brown tap roots<sup>1</sup>. Complex blooms with a house number of 1 or 2 and a gender number of 1 are produced by the betel plant. The bulb stands by itself at the end, facing the leaves. There is a range of 5 to 15cm for the grain length and 2 to 5cm for the grain width. The female ear measures 2.5 to 6cm in length and contains three to five white and yellowish green pistils. The male ear has two short stamens and is 1.5 to 3cm long<sup>2</sup>. Asia is home to the well-known medicinal plant known as betel leaf (Piper betel). It is a member of the family Piperaceae. Traditional remedies are made from plant leaves and are used to treat a wide range of illnesses. Its accessibility and affordability could encourage more research in the pharmaceutical and food sectors. Another name for betel leaf is betel vine. Chewing is a common habit in most nations, including India, to strengthen gums, prevent bad breath, and aid indigestion. In Indonesia, betel leaves are used as a vaginal douche and as a mouthwash in India. Betel leaf juice is utilised as a skin treatment in Sri Lanka. Because of their astringent flavour, betel leaves are also frequently boiled and used as a cough remedy<sup>3</sup>. Because of its astringent flavour, betel leaf is usually chewed in India after the beginning of a meal to aid in digestion. According to ancient classical Ayurvedic teachings like Bhojankutuhalam, consuming betel leaf after starting a meal is beneficial for improving digestion, reducing excessive coughing that has built up in the mouth, maintaining weight and clearing the throat. Tambul or Paan is the Ayurvedic term for a betel leaf mixed with medicinal plants. Ayurveda states that betel leaf has a strong, sweet, and bitter flavour and is hot, alkaline, and astringent. Because of its inherent aphrodisiac properties, it increases digestive fire, which kills worms and kindles the flame of love<sup>4</sup>. A 2017 study found phytochemicals with antibacterial,

antifungal, antiplatelet, anti-inflammatory, antioxidant, and thrombotic qualities in betel leaf. The phytochemicals present in betel leaf, including chavicol (69.46%), 4-Chromanol (24%), and eugenol (4.86%), have several uses, including as agents<sup>5</sup>. Betel leaf has long been used as a remedy for a variety of diseases and conditions. It can be applied to an injured region to provide treatment because it has cooling and analgesic qualities. Because betel leaf juice has a diuretic effect, it is used to relieve obstructed urine. At home, betel leaves can be used to cure sore throats and coughs. You can apply leaves soaked in mustard oil to your chest to ease coughing and breathing problems. Using betel leaves is essential when treating debility, nerve fatigue and pain<sup>6</sup>. There are about ninety different varieties of betel leaf worldwide, thirty of which are found in West Bengal and forty-five of which are found in India. Tellicher leaf is grown in tropical and subtropical regions. The leaves of the plant are used in cooking and spice production, as well as in the manufacture of oils, fragrances, insecticides and decorations<sup>7</sup>. Ayurveda outlines the ideal method for making and ingesting Tambul. Tambul is made using ingredients that have therapeutic value. Areca nut, camphor, cloves, nutmeg, Cutch tree leaves, tail pepper, and lime powder are among the main ingredients. Every component benefits the body in some way. Tambula boosts libido, pleasure, income and physical attractiveness<sup>4</sup>. The purpose of the study is to highlight the importance of regularly ingesting betel leaf to promote healthy sources of phytochemicals that boost immunity by lowering the growth of cancer cells, preventing damage to DNA and preventing other ailments. This may increase knowledge of the advantages of regularly ingesting betel leaf to strengthen immunity. Native to India, the Piperaceae family comprises over 2000 species of heart-shaped, deep green leaves with varied degrees of notoriety. Betel quids are often offered as a tongue refresher and moderate vitalizer on social, cultural, and religious occasions such as weddings, religious festivals, and sraddha ceremonies (religious services held after cremation). Most likely from Malaysia, the Piper betel vine is also produced in Bangladesh, Burma, India, Sri Lanka and Nepal. In India, between 15 and 20

million individuals eat piper betel leaves, often known as paan leaves. It is produced in India on roughly 55,000 hectares using traditional methods, and its annual production value is estimated to be Rs 9000 million. Approximately 66% of total production is produced on average in the state of West Bengal, where it is grown on 20,000 hectares approximately 4-5 lakh Boroj and employs almost the same number of agricultural families<sup>8,9</sup>. Potassium, protein, fats, minerals, vitamins, phytochemicals, and antioxidants are all rich in piper betel leaves. Halitosis, boils and abscesses, conjunctivitis, constipation, headache, hysteria, itching, mastitis, mastoiditis, leucorrhoea, otorrhoea, ringworm, swelling of the gums, rheumatism, abrasion, wounds, and bruises are just a few of the many ailments that it helps treat and prevent<sup>10</sup>. The vine is a dioecious perennial root climber with individual male and female plants that like shade. There are more than a hundred varieties of betel vines, of which about forty are native to India and thirty to West Bengal. The most plausible place for the origin of the betel vine is Malaysia. Even though they are identical, India has long had a greater reputation for the plant than any other country in the world<sup>11</sup>. These texts demonstrate the significance of leaves in relation to several facets of human existence, which is still highly relevant now, such as social, cultural, religious, and even daily living<sup>12</sup>. This edible leaf has gained prestige in human culture since the dawn of civilization. In countries like Bangladesh, Burma, Burkina Faso, China, India, Indonesia, Malaysia, Nepal, Pakistan, Philippines, South Africa, Sri Lanka and Thailand, in particular. Traditionally, the leaves were chewed in their raw, uncooked form along with sliced areca nuts, slaked lime, coriander, aniseed, clove, cardamom, sugar, coconut scrapings, jelly, peppermint, flavouring agent, and fruit pulp. There are numerous varieties of betel leaf; in India, the most popular varieties are the Bagerhati 4 and 6, as well as the Magadhi, Venmony, Mysore, Salem, Calcutta, Banarasi, Kauri, and Ghanagete varieties<sup>11,13</sup>. The piper betel vine is a tropical perennial evergreen that grows best in shade. It can rise to a height of ten to fifteen feet. High humidity is preferred by betel leaf piper. There are simple, alternating, entire, oval, cordate, acuminate or acute

leaves that are bright green in colour. This plant has broad, cylindrical male spikes and pendulum-shaped female spikes. The roots that each node develops aid in the plant's attachment to the host tree. Pepper betel has a polished upper surface and a colour that varies from yellowish green to dark green, with a distinct and pleasant scent. The betel leaves have a unique flavour that varies from sweet to spicy and a distinct aroma because of the essential oils that are present<sup>13,14</sup>. The Piperaceae family, popularly referred to as the Black Pepper family, includes the betel vine, scientifically known as Piper betel L. The plant is far more popular in India than it has been in any other country since antiquity, even though it is foreign. This would be shown by the numerous quotes from ancient literature, especially the Indian scriptures. These texts demonstrate how important leaves are to many facets of human existence, including social, cultural, religious, and even everyday existence, all of which are still highly significant in the modern era. It's also used as a special present to show guests that you appreciate them. The betel leaf is still unparalleled in modern times, owing to its lengthy history in Indian civilization<sup>15</sup>. It is thought that respiratory catarrhs can be treated with the essential oil that is collected from the leaves and used as an antiseptic<sup>16</sup>. There is no scientific evidence to back the claims made about piper betel's ability to improve memory and learning in Indian traditional medicine<sup>17</sup>. Shade is preferred by the evergreen perennial root climber known as piper betel L., or betel plant. It belongs to the family Piperaceae and bears white catkins and glossy, heart-shaped leaves<sup>18</sup>. It is extensively grown in Sri Lanka, India, Thailand, Taiwan, and other countries in Southeast Asia. Among other items, mouthwashes, tonics, scents, medications, and food additives can all be made with this oil as a raw ingredient. In addition to being nutrient-dense, the leaves have anti-carcinogens that may be utilised to create a blood cancer treatment. Betel leaves are an essential component of the betel quid, which also includes tobacco (*Nicotiana tabacum* L.), slaked lime, and areca nut (*Areca catechu* L.)<sup>19</sup>. Bad breath, boils and abscesses, conjunctivitis, constipation, memory loss, learning difficulties, headaches, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea,

antiseptic, gum swelling, rheumatism, wounds, and bruises are just a few of the conditions that betel leaf has long been associated with<sup>20</sup>. In observance of the traditional use of betel leaf in Indian culture, it is also used as a particular gift for visitors. Because betel leaf is so essential to South Asians' economy and way of life, betel leaf agriculture has enormous potential<sup>21,22</sup>.

## PLANT PROFILE

### Taxonomical Classification

Kingdom : Plantae  
Division : Magnoliophyta  
Class : Magnoliopsida  
Order : Piperales  
Family : Piperaceae  
Genus : Piper  
Species : Betel

### Vernacular Names

Sanskrit : Tambool, Mukhbhushan, Varnalata  
Hindi : Paan  
English : Betel, Betel pepper, Betel-vine  
Telugu : Nagavalli, Tamalapaku  
Tamil : Vetrilai Gujarati : Nagarbael

### AYURVEDIC SIGNIFICANCE

Vedic names for piper betel include Saptaswara<sup>23</sup> and Tambool, Nagvelleri and Nagani<sup>24</sup>. It was applied as a treatment for numerous illnesses. Most of these articles highlight different aspects of medicine. Texts including tambool include Kalhan's Rajatarangini (perhaps the last extant ancient Sanskrit work of historical relevance) and the Kamasutra and Panchatantra by Vatsyayana. Consequently, references to Tambool date back more than two millennia. The following is how the Ayurvedic medical system explains the therapeutic uses of betel leaf: <sup>25</sup>.

Guna (Quality): Laghu, Ruksha, Tikshan

Rasa (Taste): Tikta

Vipak (Metabolism): Katu

Virya (Potency): Ushan

Prabhav (Impact): Hridya

In addition to being used alone as medication, betel leaf extract is frequently utilised in Ayurveda as an adjuvant and in conjunction with other treatments for possible better benefits. Susruta Samhita (Ch 28-46, 279-280) describes tamabola leaves as laxative,

aromatic, pungent, spicy, acrid, good for the voice, and appetiser. They also aggravate pitta while pacifying vata. Moreover, chewing betel has been linked to sexual consequences in ancient writings. Additionally, pan is thought to strengthen the heart and control blood pressure. Usually, emphasis is placed on its anti-inflammatory and anti-microbial properties. In Ayurveda, it suppresses vata and kapha. Because of its hot power, it also helps to remove mucus from the respiratory system. According to the Yunani technique, the leaf's sharp flavour and pleasant aroma boost appetite and taste, are liver, heart, and brain tonics, reduce thirst, clear the throat, and purify the blood<sup>26</sup>. Secondary metabolites from the betel plant (*Piper betle*) can serve as a basis for traditional medicine. Native to central and eastern Malaysia, this plant was brought to the area around 2,500 years ago, along with tropical Asia, Madagascar, and East Africa. This kind of betel was brought to South India and South China by Europeans in the fourteenth century<sup>27</sup>. The leaves of the piper betle have been utilised for many years in India, China, and Thailand for a number of purposes, including as wound healing, improving digestion, stimulating pancreatic lipase, preventing cataracts and lung diseases, preventing secretion or bleeding and acting as aromatic stimulants and antifatulents. In addition, they are utilised to revive the mouth during meals<sup>28</sup>. Betel leaf extract is a common adjuvant in Ayurveda and it can be used alone or combined with other treatments for better results. Historically, betel leaf has been utilised as a laxative, fragrant, and health-promoting food. Moreover, aphrodisiac properties of eating betel are documented in ancient manuscripts. Betel is also supposed to strengthen the liver and regulate blood flow. Its antimicrobial and anti-inflammatory qualities are often emphasised. In Ayurveda, it suppresses Vata and Kapha. Betel leaf helps to clear mucus from the respiratory tract since it has the potential to produce heat. The Greek system describes it as having a flavorful and energising scent. Lowering taste, soothing the throat, increasing hunger, stimulating the liver, heart, and brain and purifying the blood<sup>29</sup>. The aim of the research was to determine the types of plants used as traditional medicine to treat women's health issues by the people in Masbangun Village, north

Kayong Regency, West Kalimantan Province, as well as how to prepare and use such plants. 2019's fieldwork took place in January and February. All gathered data were examined using electability level (Fidelity level, FL) and utilisation value (UVi). The general public is aware of sixteen different species of medicinal plants. A questionnaire was used to conduct interviews with 320 respondents who satisfied the criteria of being adults, residents with a permanent address, and at least 17 years old. The plant types turmeric, ginger, betel, and betel had the greatest use values (UVi). The therapeutic herbs with the highest Fidelity level (FL) value include banglai, gotu kola leaves, ginger (pre/postpartum), banana heart (breast feeding), majakani (vaginal discharge), singkil leaves (body odour), bean sprouts (female fertility), and coconut oil (black hair). The Masbangun people utilise betel leaf on a regular basis. Femininity-related issues in the village. There are reports that betel leaf can treat menstrual pain, vaginal discharge, postpartum depression, body smell and fertility. Betel leaf is a multipurpose plant that has antibacterial and cytotoxic phenolic chemicals<sup>30</sup>. Another way to stop nosebleeds is to use two fresh Piper betle leaf sheets, cleaned, rolled and put into the nostril. Additionally, piper betle is used medicinally, particularly for eye infections, wounds and fever<sup>31</sup>. Since more than 2,000 years ago, betel leaf has been utilised for medical purposes. Betel leaves can be used to treat the following illnesses.

#### **Headache**

A well-known natural headache treatment is betel leaf. The betel leaf has cooling and analgesic qualities. To treat a severe headache, it can be placed over the painful area with positive results.

#### **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 are essential in the treatment of debility, nervous weariness, and pain associated with the nervous system. A teaspoon of honey and the juice from a few betel leaves will make a wonderful tonic. This can be consumed twice daily with a teaspoon. Sore Throat: Cough and sore throat can both be effectively treated at home with betel

leaf. The leaves can effectively heal sore throats when applied locally. To cure an unpleasant cough, combine the crushed fruit or berry with honey.

#### **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**

A suppository produced from a betel leaf stalk bathed in castor oil can be inserted into the rectum in cases of pediatric constipation. Constipation is immediately relieved by this.

#### **Problem of Breast milk secretion**

When applied to the breasts during lactation, oil-covered leaves are thought to encourage milk secretion<sup>32</sup>.

#### **PHYTOCHEMICALS**

To extract betel leaf, ether (40-60°C), chloroform, ethanol, and water were utilised. All extracts produced phytosterol, with the exception of the water extract. While ethanol and water extracts contained water, sugars, tannins, and phenols, petroleum ether extracts did not contain any alkaloids. Whereas the ethanol extract contains flavonoids, the water extract solely contained essential oil. Phytosterols, alkaloids, water, tannins, phenols, flavonoids, and essential oils are all present in piper betle leaf extract. The leaf's essential oils contain carvacrol. Identification of fresh essential oils from Piper betle var. using eugenol methyl ether, allylcatechol, pcymentedan, cineol, estragole, caryophyllene and cardinene<sup>33</sup>. Deswari leaves were separated using a traditional three-hour Clevenger-style water distillation method using Piper betle and Bangla desi var. The derived essential oils have a v/w of 0.12% and 0.15, respectively. The oil is placed in a sterile tube and dried over anhydrous sodium sulphate before being kept in the refrigerator at 4°C. The Perkin-Elmer GC 8500, which has a flame ionisation detector, was used to analyse the essential oils using BP-1 (polydimethylsiloxane, 50mx 0.25mm). Twenty-five and 35 components were found in the essential oil samples after being analysed by GC and GC-MS, respectively. The largest component, accounting for 79.4% of the total, was eugenol

(50.29%), followed by -selinene (11.39%), -selinene (10.14%), germacrene D (2.82%), -farnesene (2.48%), hydroxyl chavicol (1.20%) and methyl eugenol (1.17%). Oil extracted from the bangladesi type of Piper betle leaves The primary ingredients found in Piper betle leaf oil of the deswari variety included methyl eugenol (1.46%), germacerene-D (0.91%), eugenyl acetate (1.72%), isosafrol (1.62%), and caryophyllene (1.14%). Eugenol, safrole, and selinene were also present<sup>34</sup>.

Using ethanol, methanol, butanolic, acetone, and water as solvents, the existence of secondary metabolites such as tannins, phytosterols, flavonoids, steroids, saponins and other substances was also ascertained. The findings showed that tannins, diterpenes and steroids were present in all betel extracts. Butanol and water extracts are the only sources of phenols and alkaloids. The acetone and water extracts contained coumarin and saponins, the butanol extract had emodin, and all extracts-aside from the methanol extract-contained flavonoids<sup>35</sup>. Previous studies have shown that betel leaf (Piper betle) water extract contains saponins and glycosides, whereas betel leaf ethanol extract contains tannins, phenolics and alkaloids<sup>36</sup>.

## PHARMACOLOGICAL ACTIVITIES

### Antibacterial

To assess the antibacterial activity of betel leaves (Piper betle), the leaves were first dried, then pulverised in a blender. After that, the leaves were extracted with water and heated to 90°C for 15 minutes. The bacteria used were *S. aureus*, *S. epidermidis*, and *E. coli* with ampicillin-sulbactam serving as a positive control. The findings show that both Gram-negative bacteria like *E. coli* and Gram-positive bacteria like *S. aureus* and *S. epidermidis* have a zone surrounding them that is inhibited by betel leaf (Piper betle). Betel leaf contains alkaloids, phenols, flavonoids, tannins, saponins, glycosides, terpenoids, steroids, and essential oils. The essential oil contains the following: eugenol (18.27%), 5-(2-propenyl)-1, 3-benzodioxole (25.67%) and 2-methoxy-4-(2-propenyl) acetate phenol (8.00%). Essential oils has antibacterial properties, particularly those that are oxygenated. While some hydrocarbons are usually inert, alcohol and phenolic terpenes are the most active terpenoids<sup>36</sup>.

Betel leaf (Piper betle) has been shown in previous research to have antibacterial properties against gram-positive (*Bacillus subtilis*, *Staphylococcus aureus* and *Micrococcus luteus*) as well as gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria. The Piper betle leaves are extracted using ethanol and water solvents. Proved that both extracts had antimicrobial properties. The significant antibacterial action may be due to the presence of several potent compounds, such as glycosides, phenolic molecules, tannins, and alkaloids<sup>37</sup>.

The betel leaf (Piper betle) methanol extract was macerated, refluxed, and then tested for antibacterial activity using the disc diffusion method, using the same methodology as the previous study. As the test organism, *Staphylococcus aureus* ATCC 25923 was used. The test solutions were generated in six (six) distinct concentrations: 0, 5, 10, 15 and 25%. Observations were made possible by calculating the inhibitory area's diameter (mm) throughout the course of three days<sup>38</sup>. The lowest inhibitory zone is displayed at a concentration of 5% betel leaf extract at 1.07mm and the largest inhibitory zone for macerated methanol extract is displayed at a concentration of 25% at 1.66mm. On the other hand, at zero concentration, it does not show an inhibitory zone. The refluxed methanol extract showed the largest inhibitory zone. It did not show an inhibition zone at 0% concentration; but, at 20% concentration, it did show one at 1.64mm and at 5% concentration, it showed one at 1.12mm<sup>39</sup>.

Many diverse countries use a variety of natural materials as traditional medicine to treat a wide range of illnesses. The family Piperaceae includes the piper betel, which has roughly 2000 species. The plant was originally found in India. Extracts of Piper betel have been used for millennia to cure a wide range of disorders because of its significant properties, which include antioxidant, anti-cancer, anti-allergic, etc<sup>40</sup>.

### PROTECTIVE AND HEALING ACTIVITY

The most recent study evaluated allylpyrocatechol's healing and protecting properties against indomethacin-induced stomach ulcers in rats. The results demonstrated that allylpyrocatechol's

antioxidative and mucin-protecting capabilities can prevent stomach ulcers caused by indomethacin<sup>41</sup>.

### **IMMUNOMODULATORY ACTIVITY**

A lot of today's ailments are caused by anomalies in the immune system. This necessitates the search for innovative, safer immunomodulators. The methanolic extract was used to assess lymphocyte proliferation, interferon- $\gamma$  receptors and nitric oxide production in vitro. Furthermore, the effects of different doses of the extract were investigated in vivo on the humoral and cellular immune responses in mice that had received sheep red blood cell vaccinations. The results demonstrated that it considerably and dose-dependently reduced the proliferation of peripheral blood lymphocytes activated by hemagglutinin. Reduced antibody titre and increased reduction of inflammation suggest that the extract may have an immunosuppressive effect on the cellular and humoral responses of the animals.

According to the literature, betle leaf is a fresh candidate for immunosuppressive activities. The substance in question could be further examined for its anticancer properties or as a potential therapy option for inflammatory diseases such rheumatoid arthritis, systemic lupus erythematosus, or emphysema<sup>42</sup>.

### **ANTIFERTILITY ACTIVITY**

With varying dosages of the Piper betle leaf stalk extract, male mice were used in a large-scale investigation to create an oral male contraceptive medication.

All of the mice's metabolically active tissue showed minimal damage as a result, and intriguingly, the contraceptive effectiveness highlighted reversible fertility after treatment withdrawal<sup>43</sup>.

### **RADIOPROTECTIVE ACTIVITY**

Mammals exposed to radiation may experience harmful effects such as cell death and an increased risk of degenerative diseases. Recently, the radioprotective qualities of a low-cost alternative to synthetic radioprotectants-which are supposedly harmful-have been investigated. The potential of the extract to prevent g-ray-induced lipid peroxidation and DNA damage in rat liver mitochondria was

investigated in order to identify the mechanism underlying its radioprotective effect. The significant immunomodulatory and superior radical scavenging properties of the study may be attributed to the presence of phenolic bioactives such as allyl pyrocatechol and chavibetol. Given that the herb is widely accessible and reasonably priced for the average person, it is implied to have great potential<sup>44</sup>.

### **PLATELET INHIBITION ACTIVITY**

It was investigated if hydroxychavicol (HC) could stop platelets from clumping together. The results showed that hydroxychavicol inhibits cyclooxygenase, scavenges reactive oxygen species and inhibits platelet aggregation and thromboxane B2 production. HC may be a useful therapeutic medication for the prevention and treatment of atherosclerosis and other cardiovascular disorders due to its anti-inflammatory and antiplatelet qualities<sup>45</sup>.

### **HEPATO-PROTECTIVE ACTIVITY**

A rat model of liver injury from ethanol and carbon tetrachloride (CCl<sub>4</sub>) was utilised to evaluate the antihepatotoxic properties of betle leaf extract. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and histology all showed signs of liver injury and fibrosis in rats exposed to CCl<sub>4</sub>. Antioxidant enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) were elevated when the extract significantly decreased high AST and ALT activity and decreased total glutathione Stransferase (GST).Catalase is CAT. According to the histological analysis, the betle leaf extract prevented the liver from being damaged by CCl<sub>4</sub> by inhibiting TIMP2, promoting the expression of active matrix metalloproteinase-2 (MMP2) via the Ras/Erk pathway and lowering the expression of alpha smooth muscle actin (alpha-sma), all of which attenuated the fibrosis of the liver. These results suggest that betle leaf may have chemopreventive properties against liver fibrosis.

### **Anti-Photosensitizer**

Piper betlephenolics' capacity to prevent photosensitization-induced cellular damage One method that PB phenolics, such as allylpyrocatechol

(APC), may help protect biological systems from injury is by removing O<sub>2</sub> generated by some endogenous photosensitizers<sup>46</sup>.

#### **ANTI-HISTAMINIC ACTIVITY**

Hajare *et al.*, (2011) investigated the antihistaminic activity of Piper betle Linn. leaves. The study, P. betle Linn. ethanolic extract and essential oil extract's antihistaminic effectiveness. Pharmacological studies have been conducted on guinea pigs' leaves. When preparing the tracheal chain in guinea pigs, the histamine dose response curve (DRC) was moved to the right. Substituting with chlorpheniramine maleate Furthermore, the whole guinea pig is induced to bronchoconstriction by P. betel disrupted histamine aerosol extracts, with essential oil having a greater effect than ethanolic extract in this regard. They concluded that the essential oil and ethanolic extract of P. betel Linn exhibit antihistaminic properties<sup>47</sup>.

#### **ANTI-ULCER ACTIVITY**

Vyawahare *et al.*, (2010) investigated the antiulcer activity of the hydroalcoholic extract of Piper betel (HEPB) leaves in rats by inducing experimental stomach ulcers by the use of pylorus ligation, acute stress and HCl-ethanol. Pre-treatment with Piper betel extract resulted in a considerable increase in stomach pH and a decrease in gastric fluid volume in all of the experimental models, along with an ulcer-protective effect. The hydroalcoholic extract of Piper betel leaves' likely mode of action is what gives it its antiulcer properties<sup>48</sup>.

#### **ANTIBACTERIAL ACTIVITY**

The four varieties of Piper betel that are grown in India are Jaleswar, Bangladeshi, Desi, and Desawar. 2012 The dried leaves of all four varieties of Piper betel were assessed by Agarwal *et al.* in cold aqueous, methanolic, ethanolic, and ethyl acetate extracts at a final Hazardous bacteria such *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* were assessed against a 500mg/ml concentration using the agar well diffusion method<sup>49</sup>.

#### **ANTIFUNGAL ACTIVITY**

Ali *et al.*, (2010) conducted an examination of the antifungal activity of hydroxychavicol, which was derived from the chloroform extraction of the aqueous leaf extract of Piper betle L. (Piperaceae), against 124 strains of selected fungi. The MICs for yeasts ranged from 15.62 to 500g/ml, *Aspergillus* species from 125 to 500g/ml, and dermatophytes from 7.81 to 62.5g/ml. However, the MFCs were found to be either two times bigger than the MICs or equivalent to them. On fungal species, hydroxychavicol showed inhibitory effects that were clinically significant. Up to 8 MIC, both *Candida glabrata* and *Candida albicans* were eliminated in a concentration-dependent manner. In addition, hydroxychavicol reduced the development of mutants of the investigated fungi at 2 MIC to 8 MIC concentration and had a prolonged post-antifungal impact of 6.25 to 8.70 h at 4 MIC for *Candida* species. They concluded that because of this compound's antifungal activity, it can be used as a mouthwash to gargle against oral *Candida* infections and as an antifungal medication, specifically for treating topical infections<sup>50</sup>.

#### **ANTI-HAEMOLYTIC ACTIVITY**

Chakraborty *et al.*, (2011) investigated the anti-haemolytic efficacy of piper betel leaf extracts using erythrocytes as a model. They also assessed the amount of lipid peroxidation in the extracts<sup>51</sup>. Because of their high polyunsaturated fatty acid content, erythrocyte membranes are susceptible to peroxidation. Because of their continuous exposure to high oxygen concentrations, the oxidation may be catalysed by the haemoglobin they carry. The oxidative damage to cellular membranes can be well modelled by the oxidation of erythrocytes. It has been found that certain compounds that can create radicals specifically target the erythrocyte membrane. This damages the membrane and causes hemolysis by starting a chain reaction that oxidises proteins and lipids. When red blood cells were treated with betel leaf extract and H<sub>2</sub>O<sub>2</sub>, a significant decrease in hemolysis was discovered<sup>52</sup>.

#### **ANTIMICROBIAL**

The antibacterial activity of the betel leaf ethanol extract was tested using the disc diffusion method.



Phytochemical investigations on betel leaf powder (Piper betle) have revealed the presence of total antioxidants, alkaloids, phenolic compounds, proteins, flavonoids, and carbohydrates. The ethanol extract demonstrated antioxidant activity using the DPPH method. The significant antibacterial activity of these extracts against all tested microbes (*Klebsiella pneumonia*, *Proteus vulgaris*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*) demonstrates the antimicrobial properties of the antioxidants found in medicinal plants<sup>53</sup>.

According to additional investigations, four distinct Piper betle leaf extracts tested against four different pathogenic bacteria (*Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus* and *Streptococcus pyogenes*) demonstrated a clear zone of inhibition against all microorganisms. Water, methanol, ethyl acetate, and petroleum ether make up these extracts. This is as a result of the betel extract's high sterol activity content. Furthermore, betel extract contains the fatty acids palmitic acid, stearic acid, and hydroxy ester fatty acids, which have potent antibacterial qualities against a range of pathogenic microorganisms<sup>54</sup>.

The disc diffusion method also shown reduction of the antibacterial activity of fresh Piper betle Linn leaf extract against gram-positive and gram-negative bacterial trains. The results showed that all extracts had excellent inhibitory effect against *S. aureus*. It was determined that the ether extract outperformed ordinary penicillin. It was also shown that the aqueous extract had a significantly higher potency against *Bacillus* and *P. aeruginosa* than ordinary penicillin<sup>55</sup>.

The antibacterial activity of an aqueous and methanol extract of the leaves of *Terminalia catappa L.*, *Manilkarazapota L* and *Piper betel L* was examined by Nair and Chanda (2008) against ten strains of Gramme positive, twelve strains of Gramme negative, and one strain of *Candida tropicalis*. Gentamicin and piperacillin were used as standards for the antibacterial test, whereas fluconazole was used as the standard for the antifungal assay. Different levels of activity were demonstrated by the three plants against the tested microorganisms.

The methanolic extract substantially outperformed the aqueous extract in inhibiting the tested microbial strains. Plantain piper betel Nair and Chanda (2008) state that an investigation was conducted on the antibacterial activity of the leaves of *Terminalia catappa L.*, *Manilkarazapota L* and *Piper betel L* against ten strains of Gramme positive, twelve strains of Gramme negative and one strain of *Candida tropicalis*. Fluconazole was the standard for the antibacterial assay, and piperacillin and gentamicin were the standard for the antifungal assay. The three plants showed varying degrees of effectiveness against the tested microorganisms. The methanolic extract significantly outperformed the aqueous extract in terms of inhibiting the tested microbial strains. Plant Piper betel<sup>56</sup>.

The four varieties of Piper betel; namely Desawar, Desi, Bangladeshi and Jaleswar, are cultivated in India. Agarwal *et al*, (2012) evaluated that the cold aqueous, methanolic, ethanolic, and ethyl acetate extracts of dried leaves of all the four varieties of Piper betel at a final<sup>57</sup>.

#### ANALGESIC AND ANTIINFLAMMATORY

Following the use of the Soxhlet equipment to extract the hydroalcoholic extract of betel leaf (HEPBL), a phytochemical analysis was conducted. Wistar rats weighing 150-220g (aged 8-12 weeks) and Swiss albino mice of both sexes, measuring 22-25g, were the experimental animals employed in this investigation. The tail-flick and acetic acid induction methods were employed to assess analgesic activity, while cotton pellet granuloma and carrageenan-induced paw edoema models were used to investigate anti-inflammatory activity. HEPBL demonstrated significant analgesic efficacy at dosages of 100mg/kg and 200mg/kg, as well as significant anti-inflammatory effects at dosages of 50mg/kg, 100mg/kg and 200mg/kg. The subtherapeutic dose of HEPBL at 50mg/kg also reinforces the subtherapeutic effect of the typical analgesic dosage. P. betle's analgesic and anti-inflammatory qualities are attributed to phytochemicals such as flavonoids, tannins, phenols, and glycosides<sup>58</sup>. Desawar, Desi, Bangladeshi, and Jaleswar are the four varieties of Piper betel that are farmed in India. Agarwal *et al*.

(2012) evaluated the cold aqueous, methanolic, ethanolic, and ethyl acetate extracts of dried leaves of all four varieties of Piper betel at a final level. Research on acute inflammation used dextran models, while studies on chronic inflammation used cotton pellet-induced granuloma<sup>59</sup>.

### ANTIOXIDANTS

The mean IC<sub>50</sub> (g/ml) for the DPPH ascorbic acid radical in the ethanol extract of betel leaf was determined to be 3.128. The ethanol extract's mean IC<sub>50</sub> (g/ml) value was discovered to be 9,362. Piper betel L. leaf ethanolic extract had a negligible impact on the DPPH radical<sup>60</sup>.

Experiments using rabbits as experimental animals revealed that the ethanol extract of betel leaf (Piper betel) in various concentrations (5%, 10%, and 15%) has an antioxidant effect.

After shaving, the rabbits' backs were heated to the point where the dermis and the tissue underneath it ruptured, leaving the skin covered in blisters. To guarantee even distribution, the therapy was given once a day for seven days. Subsequently examined the rabbit's back wound under a microscope to see how it was healing. Bioplacenton was utilised as the positive control. At doses of 5%, 10% and 15%, ethanol extract from betel leaves can be used to treat burns on the back skin of rabbits (*Oryctolagus cuniculus*). The bioactive ingredients in betel leaf, including tannins, flavonoids, phenols, essential oils, and saponins, are what cause the faster healing process<sup>61</sup>. Compared to Piper betel leaf extract with water, methanol, and hexane, proliferation (IC<sub>50</sub> = 65 g/ml) was inhibited. With the addition of certain additives, RPMI 1640 culture media was used to grow and maintain MCF-7 cells. Cell viability (MTT technique), enzyme antioxidant activity test, Catalase test (CAT), superoxide dismutase test (SOD), and glutathione peroxidase test (GPx) were among the test parameters employed<sup>62</sup>.

Ionizing radiation harms cellular membranes by causing oxidative damage, which is a significant consequence. A series of free radicals produced by the radiolytic breakdown of water can damage the fatty acid chains in membrane lipids. The radiation-induced lipid peroxidation process was substantially prevented by the presence of polyphenol

components like charcoal and allylpyrocatechol in betel leaf extract. This might be explained by its capacity to scavenge free radicals implicated in the stages of initiation and propagation<sup>63</sup>.

### ANTIDIABETIC

*Ex vivo* studies have shown that crude betel leaf (Piper betel) flower extract is useful in reducing glucose generation. Gallic acid equivalents in the methanol extract of the sample extract were determined to be 0.39 and 0.05mg/ml, whereas the ethanol extract exhibited a high DPPH radical scavenging activity of 92.0 and 0.68%. Antioxidants can lessen the amount of glucose that cortisol-induced chicken hepatocytes release. In contrast to the glucose produced by dry 5% ethanol extract of Piper betel leaf powder in cortisol-induced chicken hepatocytes, treatment with 15% methanol extract of fresh betel leaf shown an increase in the first hour and a drop to a maximum of 60 minutes. The rate of 5% ethanol extract of dried, powdered piper betel leaves and fresh piper betel blooms decreased gradually when hepatocytes were treated with a 15% methanol extract of a gluconeogenic chemical. The methanol extract showed a noticeably higher reduction in gluconeogenesis in comparison to the ethanol extract. At quantities of 10, 20, 30, 40 and 50 l, the MTT test showed that the sample extract was not harmful after incubating hepatocytes for a full day<sup>64</sup>.

In 2005, Arambewela et al. used streptozotocin (STZ)-induced diabetic rats and normoglycemic rats to test the anti-diabetic effects of Piper betel leaves by administering hot water extract (HWE) and cold ethanolic extract (CEE) orally. HWE and CEE both markedly reduced blood glucose levels in normoglycemic rats in a dose-dependent manner. Both extracts significantly decreased the external glucose load during the glucose tolerance test. HWE has an anti-diabetic action, just like CEE. Following a prolonged oral treatment period, both extracts proved to be safe and well tolerated (no overt symptoms of toxicity, hepatotoxicity, or neurotoxicity). However, the therapy groups' spleens were bigger, which might be a sign of lymphocyte proliferation<sup>65</sup>. The aqueous and ethanolic extracts of Piper betel leaves showed a

strong hypoglycemic effect when tested on fasting normoglycemic rats. During the glucose tolerance test, the extract showed an antihyperglycemic impact in the external glucose level<sup>65</sup>.

### ANTIPROLIFERATION

An ethyl acetate extract of Piper betle leaves on MCF-7 human breast cancer cells showed the highest inhibitory impact. In vivo studies were carried out by employing GCMS to analyse the metabolites of betel leaf (Piper betle) extracts in ethanol and water. Five of the fourteen metabolites found in Piper betle leaves were new. Alanine and beta-sitosterol are the two primary amino acids and sterols. Stable and palmitic acids are the primary fatty acids. Meanwhile, the potential to obstruct -glucosidase was evaluated. Spectrophotometrically using an Ascent Multiskan plate reader from Thermo Electron Corporation, based on the reaction with PNP-] G. The absorbance was determined at 400nm, and three independent tests were carried out in duplicate. The outcomes were compared with those of an acarbose (positive control) test that was conducted under identical circumstances. With IC50 values of 0.069 and 0.257mg/mL, respectively, the ethanol and water extracts of P. betle leaves demonstrated a high ability to inhibit - glucosidase in a concentration-dependent manner<sup>66</sup>.

### HEPATOPROTECTIVE

Hepatoprotectors are substances that help to protect the liver. The folate antagonist methotrexate (MTX) is currently the first-line treatment for autoimmune diseases such as psoriasis and rheumatoid arthritis. However, their use is limited due to the possibility of hepatotoxicity or liver poisoning. The ethanol extract of betel leaf (Piper betle) can reduce hepatotoxicity in rats given methotrexate (MTX). Mice treated with extra betel leaf ethanol at doses of 50 or 100mg kg-1 bw did not exhibit the same hepatoprotective properties as mice received a single intraperitoneal dosage of 20mg kg-1 bw of MTX. At a dose greater than folic acid, 1mg kg-1 bb, ip<sup>67</sup>.

### BIO-ACTIVE COMPONENTS

The two primary components of Piper betel are chavibetol (53.1%) and chavibetol acetate (15.5%).

Moreover, there was eugenol (0.32%), chavibetol methyl ester (0.48%), camphene (0.48%), safrole (0.11%), 1, 8-cineole (0.04%), allylpyrocatecholdiacetate (0.71%), and a-limonene (0.14%). The hexane portion of leaf stalks produced four pure aliphatic compounds: pentadecyl 6-hydroxy tetradecanoate, pentatriacontane, methyl hexacos-7-enoate and 6, 9-heptacosadiene. It was found that the primary chemical components of piper betel were vitamin C and polyphenols such as eugenol, chavicol, carvacrol, chavibetol, catechol and allyl pyrocatechol that exhibited significant antioxidant activity. Furthermore, by altering our immune systems and efficiently scavenging free radicals, these polyphenols contribute to our protection<sup>68</sup>.

### THERAPEUTIC IMPORTANCE

The anticancer, antimutagenic, anti-amoebic, anti-inflammatory, mosquito larvicidal, immunomodulatory, antiulcerogenic, radioprotective, and antifungal activity<sup>17</sup> are among the pharmacological actions of piper betel. The leaf extract has also been shown to have radioprotective, antibacterial, antifungal, anti-inflammatory and antioxidant properties. Piper betel leaf has been used traditionally to treat a wide range of conditions, such as rheumatism, abrasion, cuts, and injuries; bad breath, boils and abscesses, conjunctivitis, constipation, headache, hysteria, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, ringworm, and swelling of the gums<sup>69,70</sup>.

#### Leaf

The leaf juice is administered systemically to treat cough and indigestion in children, as well as for its anti-malarial, antibacterial, antifungal, insecticidal, antioxidant, anti-diabetic, gastroprotective, antinociceptive, cytotoxic, and antiplatelet properties.

#### Stem

Asthma, bronchitis, constipation, asthma and indigestion are all claimed to be helped by stems.

#### Whole Plant

Due to their pungent flavor, plants in the genus Piper are also used for a variety of other things, including as food and spice, fish bait, fish poison, hallucinogen, insecticide, oil, adornment, and perfume. Because of its light qualities, it helps to

normalize the digestive tract and is therefore particularly useful in maintaining the digestive system. Use of modern medicine<sup>71</sup>.

Betle leaves are helpful in treating lung infections in both children and the elderly. The leaves can be applied to the chest to relieve coughing and breathing difficulties after being warmed up and soaked in mustard oil.

Using the leaves locally to cure a sore throat is beneficial. To treat a bothersome cough, combine the crushed fruit or berry with honey.

Betle leaves can be used to alleviate debility, nervous weariness, and pain associated with anxiety. A teaspoon of honey and the juice from a few betle leaves will make a nice tonic.

When used locally, betle leaves are effective in treating inflammatory conditions like arthritis and orchitis, or inflammation of the testicles.

Betle leaves have cooling and analgesic qualities.

Additionally, it works well on boils. A leaf is given a gentle warming till it becomes soft and castor oil is then applied on top. The leaf is covered in oil and applied to the inflammation.

The loins can benefit from a heated poultice made of the leaves or their juice combined with some bland oil, such as refined coconut oil.

A heated poultice consisting of the leaves or their juice mixed with some bland oil, like refined coconut oil, can be beneficial for the loins.

When applied to the breast during lactation, leaves rubbed with oil are supposed to encourage milk secretion.

The leaf has a strong flavor and pleasant aroma, which, in accordance with the Unani system, serves to increase hunger. Additionally, it strengthens the liver, heart and brain.

It supports the maintenance of healthy skin and teeth.

## CONCLUSION

In the future, a detailed investigation of the nutritional analysis and shelf life of betle leaf may be conducted. P. betel is known to have therapeutic benefits, therefore thorough characterisation may be helpful for long-term drug development studies. All around the world, piper betel is a well-known and popular mouth refresher. Many individuals are unaware of the significant concentration of

minerals, antioxidants, phytochemicals, and various nutraceutical qualities found in these leaves. It is possible to enhance the medicinal qualities of "Paan" by substituting cardamom-infused leaves for the tobacco, areca nut, betel nut, and other ingredients. The paper's main focus is on the advantages of Piper betel plants. Since ancient times, it has been used as a herb with therapeutic properties. We have to keep using it to treat illnesses as a result. Piper betel has been used as a mouth refresher since ancient times. Because of the herb's previously noted medical potential, betel leaf has been identified by numerous studies as one of the most promising commercial botanicals. Research has demonstrated that it possesses anti-halitosis, anti-diabetic, anti-allergic, anti-fertility, anti-filarial, anti-larvicidal, wound healing, immunomodulatory, anticancer, antifungal, antinociceptive, and antidermatophytic properties. P. betel is known to have therapeutic benefits, therefore thorough characterisation may be helpful for long-term drug development studies.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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