

## A Review on *Piper betle* L.: Nature's Promising Medicinal Reservoir.

V.P.B. Rekha\*<sup>1</sup>, Manideep Kollipara<sup>1</sup>, B.R.S.S. Srinivasa Gupta<sup>1</sup>, Y. Bharath<sup>1</sup> and Krishna Kanth Pulicherla<sup>2</sup>

<sup>1</sup>R.V.R. & J.C. College of Engineering; Guntur; Andhra Pradesh, India

<sup>2</sup>CBST, VIT University, Tamilnadu, India

### ABSTRACT

*Piper betle* 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 antiproliferative, antimutagenic, antibacterial and antioxidant properties. Phytochemical studies show that *Piper betle* contains a wide 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,  $\alpha$ -Pinene,  $\beta$ -Pinene,  $\gamma$ -Limonene, Saprobe, 1-8-cineol and Allylpyrocatechol monoacetate. These components are valued as a stimulant for its medicinal properties like antiplatelet, anti-inflammatory effects as well as immunomodulatory, gastroprotective and antidiabetic activity. This review is focused on emphasizing the varied pharmacological properties of *Piper betle* Linn. and its future prospects for improved usage in treating numerous conditions.

**Keywords-** *Piper betle*, Chemical constituents, Pharmacological profile, Medicinal properties.

### INTRODUCTION

Medicinal plants are of proven value as potential therapeutics with the increase of resistant pathogens to commonly used antibiotics and the emergence of new infectious diseases. Extracts of the *Piper betle* leaf are shown to be effective against several human pathogens, although the mechanisms involved have not been elucidated. A large numbers of natural

products are being used in the treatment of many diseases as a traditional medicine in several countries. Extracts of *Piper betle* are used for the treatment of various ailments since ages due to its essential properties like antioxidant, anticancer, anti-allergic etc., *Piper betle* belongs to the family Piperaceae and has over 2000 species. The plant is indigenous to India.<sup>1</sup>

The *Piper betle* leaf is known is Paan in Assamese/Urdu/Hindi/Odia/Bengali, and Tambula and Nagavalli in Sanskrit.

Some of the names in the regions in which it is consumed are:

Vettilai - Tamil  
 Tamalapaku - Telugu  
 Vidyache pan - Marathi  
 Veeleyada yele - Kannada  
 Vettila - Malayalam.<sup>2</sup>

The scientific classification of *Piper betle* Linn. is as follows:

<b>Kingdom:</b>	<i>Plantae</i>
<b>Order:</b>	<i>Piper ales</i>
<b>Family:</b>	<i>Piperaceae</i>
<b>Genus:</b>	<i>Piper</i>
<b>Species:</b>	<i>Piper betle</i> . <sup>3</sup>

### Family

Botanical – *Piperaceae*

Ayurvedic – *pippali kul*

Six cultivars of *Piper betle* Linn. namely, Galdalu, Mahamaneru, Kudamaneru, Ratadalu, Nagawalli and Malabulath, were used in the investigation of *Piper betle* grown in Srilanka. The betel leaf is cultivated in most areas of South and Southeast Asia. Since it is a creeper, it needs a compatible tree or a long pole for support. It is generally found in hot and moist climatic condition. In India it is found in Bihar, Bengal, Orissa, Tamilnadu and Karnataka. It is also seen in Sri Lanka.<sup>4</sup>

Paan cultivation is a special type of agriculture. Highland and especially fertile soil are best for *betel*. Waterlogged, saline and alkali soils are unsuitable for its cultivation. In Bangladesh, farmers prepare a garden called a barouj in which to grow betel. The barouj is fenced with bamboo sticks and coconut leaves, and on top it is also covered by paddy leaves. The land is dug well and laid out into furrows of 10–15

m length, 75 cm width and 75 cm depth. Oil cakes, cow dung, rotten farmyard manure and leaves are thoroughly incorporated with the topsoil of the furrows and wood ash. The creeper cuttings are planted after proper dressing in the months of May and June, at the beginning of the monsoon season. The plants are neatly arranged in parallel rows about two feet apart, and the saplings are twined around upright sticks of split bamboo and reeds.<sup>5</sup>

Proper shade and irrigation are essential for the successful cultivation of this crop. The plants are regularly watered in the hot months. The leaves of the plant become ready for plucking after one year of planting and the production of the barouj lasts for several years from the date of planting. Betel needs constantly moist soil, but there should not be excessive moisture. Hence, frequent light irrigations are given. The quantity of irrigation water should be such that the standing water should not remain for more than half an hour in the bed. If water logging by heavy rains or excess irrigation occurs, drainage should be arranged immediately. The best time for irrigation is morning or evening.<sup>5</sup>

*Piper* species have been used in a variety of traditional medicine such as Traditional Chinese Medicine, Ayurvedic system and folklore medicine of Latin America and West Indies. 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.<sup>1</sup> It is an effective anti wormal agent because of its pungent taste. It is an excellent anti-infectious agent again because of its pungent taste. It helps in normalizing the digestive tract hence is very effective in maintaining the digestive system because of its light properties. It also 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 till date have given a lot of potential information about *Piper betle* and its activity like such as Anti-malarial Activity, Antibacterial activity, Antifungal study, Insecticidal Activities, Antioxidant Activity, Anti-diabetic Activity, Gastro protective Activity, Antinociceptive Activity, Cytotoxic activity, Anti-platelet etc.<sup>7</sup> Solvents such as ethanol, methanol, chloroform, n-hexane, ethyl acetate, dichloromethane, acetone, petroleum ether, benzene and water were used for the extraction of various plant parts of *Piper betle*.<sup>8</sup>

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 and potassium, it is also contains 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 and hydroxychavicol. Major constituents of common betel were found to be safrole (48.7%) and chavibetol acetate (12.5%). Malabulath does not contain these two compounds. The major compound in Malabulath oil is allylpyrocatechol diacetate (34.0%), which is the third major compound in common betel oil (11.3%). Further, *p*-cymene, 4-terpineol, safrole, eugenol,  $\beta$ caryophellene and chavibetol acetate detected in common betel leaf oil were not detected in Malabulath leaf olive. The presence of hydroxychavicol acetate, allylpyrocatechol piperbetol, isoeugenol, anethole, stearic acid, methyl eugenol, carvacrol, polyphenol, alkaloids, saponin, tannin, steroids and other compounds like chavicol, allylpyrocatechol, are also found in *Piper betle*.<sup>6</sup>

The work on *Piper betle* Linn. In early 70's were investigated by Mishra and Gaur from Bhabha atomic Research Center,

Bombay, India. Their investigations were on "Role of Petiole in the protein metabolism of senescing *Betel (Piper betle L.)* Leaves" In normal petiole leaves, the level of chlorophyll and proteins and extent of protein synthesis declined, while the protease activity registered man fold increase with the advancement of senescence. All of these changes were delayed by depetiolation de-midribbing treatments, through without affecting the general pattern of senescence. Thus, the presence of petiole seems to expedite protein degradation.

#### Chemical constituents of *Piper betle* L.<sup>10</sup>

Components	% of components
Chavibetol	53.1
Chavibetol acetate	15.5
Caryophyllene	3.71
Allylpyrocatechol Diacetate	0.71
Campene	0.48
Chavibetol methyl ether	0.48
Eugenol	0.32
a-Pinene	0.21
f-Pinene	0.21
u-Limonene	0.14
Saprobe	0.11
1,8-Cineol	0.04
Allylpyrocatechol Monoacetate	0.23

In the year 1994 Chen *et al.*, investigated the *Piper betle* florescence extracts and found that it contained eugenol (6.2%) and safrole (78.9%). Intravenous injections of water extracts of *Piper betle* in

rats induced hypotensive and bradycardia effects due to the presence of eugenol and safrole. Moreover, the effects of intravenous injections of *Piper betle* extracts were reversed or inhibited by the pretreatment with atropine (1mg/kg, i.p.) and capsaicin (100 mg/kg, s.c.). Eugenol and safrole induced the same pattern on blood pressure and heart rate changes as *Piper betle* extracts in rats after various treatments. This report suggests that acute administration of betle inflorescence extracts by different routes may activate C-fiber evoked parasympathetic and sympathetic cardiovascular reflexes in rats.<sup>11</sup>

Bhattacharya *et al.*, (2006) investigated the inhibitory property of *Piper betle* extract against photosensitization-induced damages to lipids and proteins. The protective activity of *Piper betle* ethanolic extract against the photosensitization-induced damage to lipids and proteins of rat liver mitochondria was studied and it was found that *Piper betle* ethanolic extract could effectively prevent lipid per oxidation, as assessed by measuring thiobarbituric acid reactive substances, lipid hydro peroxide and conjugated diene. In addition, it prevented photo-induced oxidation of proteins in a concentration dependent manner. Furthermore, its preventive capacity against iron-mediated lipid per oxidation was also confirmed. The protective activity of *Piper betle* ethanolic extract could be attributed to its free radical and singlet oxygen scavenging properties. The activity of the *Piper betle* extract was primarily due to its phenolic constituents, which were identified as chavibetol and 4-allylpyrocatechol.<sup>12</sup>

Shun *et al* first examined the effect of *Piper betle* extract on the activity of Glutathione S-transferase (GST) iso-forms, and found that *Piper betle* inhibited total GST and the a class of GST (GSTA), but not the p class of GST (GSTP), and the l class of GST (GSTM), activity in Hep G2 cells. RT-

PCR results verified a reduction in the expression of GSTA1. Next, Shun *et al* examined whether *Piper betle* extract could increase the sensitivity of Hep G2 cells to anti-cancer drugs. These data showed that the cytotoxicity of cisplatin was significantly enhanced by the presence of *Piper betle* extract, accompanied by a reduction in the expression of multidrug resistance protein 2 (MRP2). These effects of *Piper betle* extract were attributed to its major constituent eugenol. Although eugenol decreased MRP2 level more effectively than *Piper betle* extract, it exhibited less sensitizing effect. It is also observed that *Piper betle* extract was able to increase the sensitivity of Hep G2 cells to cisplatin via at least two mechanisms, reducing the expression of MRP2 and inhibiting the activity of total GST and the expression of GSTA<sup>13</sup>. They also observed the increased sensitivity of Hep G2 cells towards the cytotoxicity of cisplatin by the treatment of *Piper betle* leaf.

Further, they evaluated the anti-hepatotoxic effect of *Piper betle* extract on the carbon tetrachloride (CCl<sub>4</sub>) induced liver injury in a rat model. Fibrosis and hepatic damage, as revealed by histology and the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were induced in rats by an administration of CCl<sub>4</sub> (8%, 1 ml/kg body weight) thrice a week for 4 weeks. *Piper betle* extract significantly inhibited the elevated AST and ALT activities caused by CCl<sub>4</sub> intoxication. The histological examination showed the *Piper betle* extract protected liver from the damage induced by CCl<sub>4</sub> by decreasing  $\alpha$ -smooth muscle actin ( $\alpha$ -sma) expression, inducing active matrix metalloproteinase-2 (MMP2) expression, though Ras/Erk pathway, and inhibiting TIMP2 level that consequently attenuated the fibrosis of the liver. The data of this study support a preventive potential of *Piper betle* against liver fibrosis.

### Anti-fertility activity

Sharma *et al.*, (2007) studied the antifertility efficacy of *Piper betle* 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 betle* (Petiole) ethanolic (50%) extract (100 mg/day/rat) for 30 days. The results revealed that *Piper betle* treatment caused a reduction in reproductive organ weights, circulating levels of estrogen, fertility, number of litters, serum glucose concentration, enzyme activity of acid phosphates, SGOT and SGPT as compared to control values. The concentration of cholesterol and ascorbic acid increased following *Piper betle* 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 indicative of an estrus condition, which resulted in infertility.

The hematological parameters remained within normal range. Withdrawal of Phyto-drug for 30 days restored complete/partially decreased reproductive organ weights, circulating levels of estrogen, fertility, number of litters, the concentration of glucose and enzyme activity of acid phosphates SGOT and SGPT to control values. The cholesterol and vitamin C concentration was also restored to control level. The data suggest that the *Piper betle* ethanolic extract exerted anti-fertility and anti-estrogenic effects in female rats. The effects brought by *Piper betle* extract are non-toxic and transient. The alcoholic extract of the leaf-stalk showed significant anti-fertility effects in both male and female rats.<sup>14</sup>

### Antiulcer property

S Bhattacharya *et al.*, (2007) studied the Anti-ulcerative property of the *Piper betle* against indomethacin-induced stomach ulceration and its mechanism of action. They also evaluated the protective activity of allylpyrocatechol (APC), the major antioxidant constituent of *Piper betle*, against the indomethacin-induced stomach ulceration in threat model and correlated the data obtained with its anti-oxidative and mucus protecting properties. The models used were Male Sprague-Dawley rats. The study revealed that the treatment with APC (2 mg/kg body weight per day) and misoprostol (1.43 µg/kg body weight per day) for 7 days could effectively heal the stomach ulceration as revealed from the ulcer index and histo-pathological studies.<sup>15</sup>

### Anti-allergic activity

The inhibitory effects of *Piper betle* on production of allergic mediators by bone marrow derived mast cells and lung epithelial cells were studied by Mali Wirotasangthong *et al.*, (2007). The effects of *Piper betle* 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- $\alpha$  and IL-4-induced allergic reaction. The results suggest that *Piper betle* may offer a new therapeutic approach for the control of allergic diseases through inhibition of production of allergic mediators.<sup>16</sup>

### Anti-filarial activity

In the year 2009, Meghana *et al.*, investigated the Anti-filarial activity of



*Piper betle*. The n-hexane and chloroform fractions of *Piper betle L.* trigger different arms of immune responses in BALB/c mice and exhibit ant filarial activity against human lymphatic filarid *Brugia malayi*. Modulation of immune functions by using herbal plants and their products has become a fundamental regime of therapeutic approach. It was reported that the anti-filarial and anti-leishmanial efficacy in the leaf extract of Bangla Mahoba landrace of *Piper betle* which is a female plant. The report describes the in vivo immunomodulatory efficacy of the crude Methanolic extract and its n-hexane, chloroform, n-butanol fractions of the female plant at various dose levels ranging between 0.3 and 500 mg/kg in BALB/c. Attempts were made to observe ant filarial activity of the active extracts and correlate it with the antigen specific immune responses in another rodent *Mastomys coucha* infected with human lymphatic filarial parasite *Brugia malayi*.<sup>17</sup>

#### Anti-halitosis activity

Anti-halitosis activity of *Piper betle* was done by Niranjan Ramji *et al* (2002). *Piper betle 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 as established using dynamic in vitro models.<sup>19</sup>

#### Antibacterial activity

T. Nalina *et al* investigated the antibacterial effect of *Piper betle* in 2007. The antimicrobial influence of crude aqueous extract of *Piper betle L.* on

*Streptococcus mutans* was investigated. The focus of the antimicrobial effects includes the ultra-structure and acid producing properties of *S. mutans*. From the micrographs of the transmission electron, it was found that the crude extract of *Piper betle L.* leaves causes plasma cell Membrane damage and coagulation of the nucleoid.<sup>20</sup> The extract was found to significantly reduce acid producing properties of the bacteria. Chemical analysis of the extract showed that hydroxychavicol, fatty acids (stearic and palmitic) and hydroxyl fatty acid esters (stearic, palmitic and myristic) as the main components. From the results obtained by T. Nalina *et al* it was concluded that the crude extract of *Piper betle L.* leaves may exert anti-cariogenic activities that are related to decrease in acid production and changes to the ultrastructure of *S. mutans*. Recent studies in Srilanka infer that *Piper betle* inhibit the growth of microorganism namely *Escherichia. Coli*, *Streptococcus. Pyogenes* and *Staphylococcus aureus* at lower activity.

Rajat Ghosh *et al* (2014) conducted studies on piper species and observed some species exhibiting antimicrobial activity. Studies on antimicrobial activity are done by using extracts of the *Piper* using n-hexane as solvent was done. It was found that compound 3-(4'-Methoxyphenyl) propanoyl pyrrole of *Piper lolot* showed antibacterial activity. Orjala J *et al.* reported the petroleum ether extract of leaves of *Piper gibbilimum* had antibacterial activity against *Staphylococcus epidermidis* and *Bacillus cereus*.<sup>1</sup> The Antimicrobial Activity, Mosquito Larvicidal Activity, Antioxidant Property and Tyrosinase Inhibition of *Piper betle* was studied with Li-Ching *et al.*, in 2009. The essential oil and methanolic and aqueous extracts of *Piper betle L.* were assayed for their antimicrobial activity, mosquito Larvicidal activity, antioxidant property and mushroom Tyrosinase inhibition. The methanolic and

aqueous extracts showed strong activity against the yeasts: *C. albicans*, and *M. pachydermatous*. The crude essential oil exhibited a broad-spectrum strong antimicrobial activity against all test organisms. The strongest activity was observed against *C. albicans*, followed by *S. aureus* and *M. pachydermatis*. The chemical composition of the essential oil and its fractions was analyzed by GC/MS analysis. Eugenol (36.2%), chavibetol acetate (16.9%), 4-allylphenyl acetate (9.4%) and 4-allylphenol (7.2%) were the main components, comprising 69.7% of the oil. The fractionation of the essential oil gave two fractions. Fraction I was rich in eugenol (71.3%) and fraction II in eugenol (46.4%), chavibetol acetate (19.4%) and 4-allylphenyl acetate (11.8%). The essential oil exhibited the mosquito Larvicidal activity with 2 h and 24 h LD50 value of 86 and 48 ppm, respectively.<sup>18</sup>

### Insecticidal activities

Insecticidal activities of essential oil from *Piper betle* against storage insect pests were studied by Ma. Cristina *et al.*, in 2009. The insecticidal activity of essential oil extracted from the leaves of *Piper betle* Linn, was evaluated against the bean weevil (*Callosobruchus maculatus* F.), corn weevil (*Sitophilus zeamais* Motchulsky) and lesser grain borer (*Rhizopertha dominica* F.) using aged grain assay. The efficacy of treatments was assessed by determining the acute toxicity on adult insects and the extent of preventing or suppressing the production of progenies. The volatile oil in 30% dust formulation exhibited toxicity against adult *C. maculatus*, *S. zeamais* and *R. Dominica* at varying application rates, such as 0.2g/100g, 1.75g/100g and 2.0g/100g, respectively. Survival of adult *C. maculatus* was prevented until six months by 52%, while the treatment allowed six months protection of corn against *S. zeamais* and *R. Dominica*. Although eggs were visible in the

treated mung bean, the treatment prevented them to develop further.<sup>21</sup>

The research results of Ma. Cristina *et al* disclosed that the biologically active component of *Piper betle* leaf oil may possess ovicidal properties that inhibited the development of eggs of *C. maculatus* into larvae, thus prevented the emergence of the adult stage. Meanwhile, the absence of eggs of both *S. zeamais* and *R. dominica* was prominent in treating corn. The treatments were able to inhibit entirely the emergence of progenies. No living progenies were observed in treated samples until six months while progenies were abundant in two control samples, check and untreated. The data revealed that *Piper betle* leaf oil is a fecundity-reducing agent to adult *S. zeamais* and *R. dominica*. Likewise, the oil's ovicidal effect cannot be discounted. It was suggested that the essential oil from *Piper betle* leaves is a promising grain protectant.

### Anti-larvicidal activity

Anti-larvicidal activity of *Piper betle* was observed by L. S. RArambewela *et al.*, in the year 2011. Arambewela *et al* introduced the *piper betle* essential oil at different concentrations, i.e. 500, 100, 50, 25, 12.5, 6.25 ppm concentrations, and motility was recorded between 1 to 24 hours. Mortalities of 43% and 100% were observed for 100 and 500 ppm concentrations, respectively, within 1 hour. Compared to the control, significant mortality was observed even at lower concentrations, 25 and 50 ppm, after 24 hours. 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 hour. 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 methyl paraben (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 hours, while betel oil at 2% concentration killed 97% of *C. megacephala* larvae within 4 hours. The positive control, mineral turpentine, also killed the larvae within 4 hours. This shows that betel oil is effective in the treatment of wound myiasis.<sup>22</sup>

Studies were also carried out to estimate the efficiency of essential oil from *Piper betle* against the larvae of *Chrysomya bezziana* *in vitro* conditions with 4% betel oil, all the 1st instar larvae were killed within 2 hours, and the 2nd instar larvae were killed within 4 hours<sup>23</sup>. The positive control showed no mortality until 4 hours, but all larvae were weak - for first 30 minutes. Betel oil at 3% killed all the 1st instar larvae within 150 minutes; and 74% of the 2nd instar larvae, within 4 hours. These results indicated that betel oil extracted from the *Piper sp.* with nativity of Sri Lanka proved to be an effective larvicide.

#### Antioxidant activity

Antioxidant activities of *Piper betle* Linn, extracts with different solvents and extraction times were done by Pitchaon Maisuthisakul in 2007. Total phenolic content was evaluated according to the Folin-Ciocalteu procedure. The polarity of the plant extract from various solvents was assessed by determining the oil-water partition coefficient by high-performance liquid chromatography (HPLC). The extract showed the highest antioxidant activities, total phenolic content and yield. *Piper betle* leaf phenolics were found to have less polarity than other phenolic antioxidants due to their high value of oil-water partition coefficient. The results indicated that the extraction solvent and time are important for the preparation of the betle leaf extract for use as a natural antioxidant.<sup>24</sup>

*Piper betle* induces phase I & II genes through the Nrf2/ARE signalling

pathway in mouse embryonic fibroblasts derived from wild type and Nrf2 knockout cells was reported by Wan Hasan *et al.* in 2014<sup>20</sup>. Nuclear factor-erythroid 2 p45 related factor 2 (Nrf2) is a primary transcription factor, protecting cells from oxidative stress by regulating a number of antioxidants and phase II detoxifying enzymes. Dietary components such as sulforaphane in broccoli and quercetin in onions have been shown to be inducers of Nrf2. *Piper betle* grows well in tropical climate and the leaves are used in a number of traditional remedies for the treatment of stomach ailments and infections among Asians.<sup>25</sup>

#### Gastro protective activity

The Arambewela LSR *et al* (2004) study evaluated the gastro protective activity of HWE and CEE of *Piper betle* leaves in rats.<sup>26,27</sup> To determine the gastro protective activity two components Hot water extract (HWE) and Cold ethanolic extract (CEE) with three different concentrations (200, 300 and 500 mg/kg) were fed to rats to induce ulcer. Oral administration of HWE and CEE gave information about an activity which is dependent on dose-age and significant protection against gastric damage caused by absolute ethanol. The HWE significantly increased the mucus content (by 49%) adhering to the wall of the gastric mucosa. Mucus layer is considered to be important in the mucosal defence against endogenous aggressors, e.g., acids, and also as an agent in facilitating its repair. It is generally believed that enhanced acid secretion is the most important factor for the induction of gastric lesions. In this study, the highest dose of HWE did not cause significant inhibition in acidity (both total and free) or pH of gastric fluid. From the investigation, it was concluded that the gastro protective effect of *Piper betle* was not mediated *via* inhibition of acid secretion in the gastric mucosa but by increasing its mucus content.



### Anticancer activity

Anticancer and free radical scavenging potency of *Catharanthus roseus*, *Dendrophthoe pentandra*, *Piper betle* and *Curcuma mangga* extracts in breast cancer cell lines was reported by Wahyu Widowati *et al* in the year 2013. Research was conducted to identify the anticancer and antioxidant activity of *Catharanthus roseus* [L.] G. Don, *Dendrophthoe pentandra* L., *Piper betle* L and *Curcuma mangga* Val aqueous extracts in T47D human ductal breast epithelial tumor cell line. The anticancer potency was determined via the MTS (3-(4, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay while the apoptotic activity was determined with Sub-G1 flow cytometric analysis. The antioxidant activity was determined by using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity.<sup>28</sup>

### Antinociceptive activity

L.S.R Arambewela *et al.*, in 2011 reported that *Piper betle* has Antinociceptive activity. About 200 and 300 mg/kg doses of *Piper betle* 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 is 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 antinociceptive activity was evident with 200 mg/kg dose of both HWE and CEE. As the antinociceptive activity of CEE was higher than that of HWE, CEE was used

to investigate its antinociceptive mechanism.<sup>29</sup>

### Antidermatophytic activity

Antidermatophytic Activity of *Piper betle* cream was studied by Nopamart Chatchawanchonteeera *et al.*, in 2006. Crude ethanolic extracts of *Piper betle* 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 antifungal property of *Piper betle* extracts than its counterparts. In a study conducted by Nopamart Chatchawanchonteeera for anti-dermatophytic activity 10% *Piper betle* cream was formulated, subjected to physical and microbial limit tests, and evaluated for its effect against dermatophytes *in vitro*. The freshly prepared *Piper betle* cream (pH~5.0) was dark green with a pungent odor of *Piper betle* leaves. After repeated freeze-thawing, the cream was darkening and markedly thickening. Its pH also increased significantly no bacterial or fungal contamination was detected from the *Piper betle* cream samples.<sup>30</sup>

### Antihypercholesterolemic activity

Karuppasamy Venkadeswaran in 2014 demonstrated the Anti-hypercholesterolemic and Antioxidative potential activity of *Piper betle*. Hypercholesterolemia is a dominant risk factor for atherosclerosis and cardiovascular diseases. In this study the putative anti-hypercholesterolemic and anti-oxidative properties of an ethanolic extract of *Piper betle* and of its active constituent, eugenol, were evaluated in experimental hypercholesterolemia induced by a single intraperitoneal injection of Triton WR-1339 (300 mg/kg b.wt) in Wistar rats. Hypercholesterolemic rats receiving the

*Piper betle* extract (500 mg/kg b.wt) or eugenol (5 mg/kg b.wt) for seven days orally, all these parameters were significantly better than those in saline-treated hypercholesterolemic rats. The hypercholesterolemia-ameliorating effect was better defined in eugenol-treated than in *Piper betle* extract-treated rats, being as effective as that of the standard lipid-lowering drug, lovastatin (10 mg/kg b.wt). These results suggest that eugenol, an active constituent of the *Piper betle* extract, possesses anti-hypercholesterolemic and other activities in experimental hypercholesterolemic Wistar rats. Results indicated that blood glucose level in hypercholesterolemic, saline treated (group II) rats was significantly higher than that in control (group I) rats. In hypercholesterolemic rats treated with lovastatin (group III), *Piper betle* extract (group IV), or eugenol (group V). Significantly lower mean blood glucose levels were observed when compared to that in saline treated hypercholesterolemic rats though the levels were still higher than that in the control rats. The mean blood glucose level was higher in *Piper betle* extract treated hypercholesterolemic rats than that in lovastatin-treated or eugenol treated hypercholesterolemic rats.<sup>31</sup>

#### Anti-diabetic activity

Reports of M. Kaleem *et al.* 2004 suggested that *Piper betle* also can be used effectively in the treatment of diabetes. The anti-diabetic properties of some plants like Bitter gourd (*Momordica charantia*), Neem (*Azadirachta Indica*), Tulsi (*Ocimum Sanctum*), and Garlic (*Allium Sativum*) are well known in India. In Piperaceae family *Piper sarmentosum*, *Piper longum*, *Piper nigrum* and *Piper betle* are identified as potential antidiabetic agents. Oral administration of the water extract from the whole plant of *Piper sarmentosum* Roxb. (Chaplu) at doses of 0.125 and 0.25 g/kg

significantly lowered the plasma glucose levels in healthy rats. In contrast, the repeated oral administration of the water extract at a dose of 0.125 g/kg for 7 days produced a hypoglycemic effect in the diabetic rats.<sup>32</sup> The aqueous extract of *Piper nigrum* seeds were administered orally to alloxan induced diabetic rats once a day for 4 weeks. These treatments lead to significant lowering of blood sugar level and reduction in serum lipids. The levels of antioxidant enzymes, catalase and glutathione peroxidase decreased in alloxan induced diabetic rats, however these levels returned to normal in insulin and *Piper nigrum* treated rats. These results suggest that oxidative stress plays a key role in diabetes, and treatment with *Piper nigrum* are useful in controlling not only the glucose and lipid levels but these components may also be helpful in strengthening the antioxidant potential.

Recent Investigations on *Piper betle* grown in Sri Lanka show that both HWE and CEE of *Piper betle* leaves have marked hypoglycemic activity (tested in fasted normoglycemic rats). In glucose tolerance test, HWE, CEE and tolbutamide lowered the external glucose level in a similar manner. Further, HWE significantly reduced the blood glucose level of rats with STZ induced diabetes treated with a dose (50 mg/kg) which is known to irreversibly damage the insulin-secreting  $\beta$  cells of the pancreas. The ability of lowering the blood glucose levels of rats with STZ-induced diabetes also suggests that *Piper betle* extracts have insulin omimetic activity. The increased glycogenesis may result from enhanced glucose uptake from the liver and skeletal muscle by sensitization of insulin receptors and/or inducing the activity of enzymes involved in glycogen synthesis and concluded that *Piper betle* has better antidiabetic activity.<sup>22</sup>

### Immunomodulatory activity

D. G. Kanjwani *et al.*, (2008) studied the efficiency of methanolic extract of *Piper betle* for its novel candidature in immunosuppressive activity. The animal studies were carried out to evaluate the effect of methanolic extract of *Piper betle* on T- and B-cell mediated immune response. In vivo studies in mice showed suppression of cell- and antibody-mediated immune response in a dose-dependent manner. The methanolic extract of *Piper betle* at various concentrations produces suppression of mitogenicity induced by Phytohaemagglutinin. Interferon-c is an anti-inflammatory cytokine secreted by lymphocytes in response to external stimuli. In the presence of immunosuppressive substance the level of IFN c is reduced. Obtained results showed that the crude methanolic extract decreased antibody titer. The methanolic extract of *Piper betle* at different concentrations on delayed type of hypersensitivity reaction was measured from T-cell mediated immunity. DTH is characterized by a large influx of non-specific inflammatory cells, mainly macrophages. It is developed when antigen activates sensitized TH cells. The Methanolic Extract of *Piper betle* at 500 mg/kg dose produced immunosuppression that was almost equivalent to that produced by the well-known immunosuppressive drug cyclophosphamide (2 mg/kg). Research by D. G. Kanjwani *et al.*, concluded that *Piper betle* a potential candidate for immunomodulatory drug.<sup>33</sup>

### Anti-asthmatic effect

Antioxidant and Anti-inflammatory, Antihistaminic activities of *Piper betle* effect wide range diseases.<sup>34-37</sup> Misra *et al.* 2014 evaluated the Anti-Asthmatic effect of *Piper betle* in guinea pigs. Asthma is hyper responsiveness of the tracheobronchial smooth muscle to a variety of stimuli. Bronchial asthma is an inflammatory

condition, Free radical and superoxide may be responsible for bronchial asthma. Histamine may cause bronchoconstriction. The effect of Bronchial asthma can be reduced significantly by *Piper betle* extract, though its action is less than that of diphenhydramine. But in humans for asthma, other mediators like Leukotriene plays an important role. Although effect of *Piper betle* Linn. on human asthma is not known well, but from the studies conducted by Misra *et al.* it was concluded that *Piper betle* Linn. has the ability to reduce bronchial asthma in guinea pigs.<sup>38</sup>

### Wound healing activity

Nilugal *et al.*, 2014 investigated the wound healing capability of *Piper betle* leaves and stem extract. Wounds are referred to as a disruption of normal anatomic structure and function. Wound healing is a very complex, multifactor sequence of events involving several cellular and biochemical processes. Nilugal *et al* investigated the enhanced rate of wound contraction and drastic reduction in healing time in male albino rats, which might be due to enhanced epithelialization. The results showed wound healing and repair, accelerated by applying ointment formulation containing *Piper betle* leaves and stem extract, which was highlighted by the full thickness coverage of the wound area by an organized epidermis. The animals treated with ointment formulation containing 10% *Piper betle* leaves and stem showed significant results when compared with providone iodine and control group. From Nilugal *et al.* investigations concluded that *Piper betle* has the potential ability in wound healing.<sup>39</sup>

### CONCLUSION

This review suggests that the leaves of *Piper betle* have a tremendous potential as a potent source for novel therapeutic

usage. The pharmacological profile reveals it to be fit for its future usage as a promising source for treating various conditions. Therefore, in the near future the standardization and stabilization studies on the leaf extract can be carried out which can help in improving its usage for varied medicinal usage.

## REFERENCES

1. Rajat Ghosh, Katon Darin, Payel Nath, Panchali, An Overview of Various Piper Species for Their Biological Activities. *International Journal of Pharma Research & Review* Jan 2014; 3(1):67-75.
2. Satish A Bhalerao1\*, Deepa R Verma2, Rohan V Gavankar2, Nikhil C Teli2, Yatin Y Rane3, Vinod kumar S Didwana2 and Ashwin Trikannad2. Phytochemistry, Pharmacological Profile and Therapeutic Uses of *Piper betle* Linn.-An Overview. Research and Reviews: *Journal of Pharmacognosy and Phytochemistry*; Volume 1 | Issue 2 | October-December, 2013.
3. L.D. Pradhan, Dr. K. A. Suri, Dr. D. K. Pradhan and P. Biswasroy; Golden Heart of the Nature: *Piper betle*; *Journal of Pharmacognosy and Phytochemistry*; Vol. 1 No. 6 2013; 147.
4. Arambewela L, Kumaratunga KG, Dias K. Studies on *Piper betle* of Srilanka. *Nath Sci. Foundation Sri Lanka*. 2005; 33:133-9.
5. Nikhil Kumar; Betel vine (*Piper betle* L.) Cultivation: A unique case of plant establishment under anthropogenically regulated microclimatic conditions. *Indian Journal of History of Science*, 34(1), 1999.
6. Lakshmi Arambewela, K.G.A. Kumaratunga and Kalyani Dias. Studies on *Piper betle*; *J. Natn. Sci. Foundation Sri Lanka* 2005 33(2): 133-139.
7. Arawwala L, Arambewela L, Ratnasooriya W. Gastro protective effect of *Piper betle* Linn. Leaves grown in Srilanka. *J Ayurveda Integr Med*. 2014, 5:38-42.
8. Kambham Venkateswarlu, N.Devanna; Pharmacological Evaluations (Analgesic Activity) of '*Piper betle*'; *International Journal of Pharmamedix India*; 2014, 2(2), 688-93.
9. K. Ghosh and T. K. Bhattacharya; Chemical Constituents of *Piper betle* Linn. (Piperaceae) roots; *Molecules* 2005, 10, 798-802.
10. Misra KH, Kodanda Ramu B., Ranjita N. and Bandyopadhyay M. Evaluation of anti-asthmatic effect of ethanol Extract of *Piper betle* Linn. Against histamine induced Bronchospasm in guinea pigs. *International Journal of Basic and Applied Chemical Sciences*, ISSN: 2277-2073, 2014 Vol. 4 (1) January-March, pp.67-73.
11. Chen SJ, WO BN, Yeh JL, Lo YC, Chen IS, Chen IJ. C-fiber evoked autonomic cardiovascular effect of after injection of *Piper betle* inflorescence extracts. *Journal of Ethnopharmacology*. 1995; 43: 183-8.
12. Bhattacharya S., S. Mula, S. Gamre, J.P. Kamat, S.K. Bandyopadhyay and S. Chattopadhyay (2006). Inhibitory property of *Piper betle* extract against photosensitization-induced damages to lipids and protein. *Food Chem*. Pages 1474–1480.
13. Shun-Chieh Young, Chau-Jong Wang, Jeng-Dong Hsu, Jui-Ling Hsu, Fen- Pi Chou. Increased sensitivity of Hep G2 cells toward the cytotoxicity of cisplatin by the treatment of *Piper betle* leaf extract. *Archives of Toxicology* (2006), 80, 319-327.
14. J.D. Sharma, Lalita Sharma and Poonam Yadav. Antifertility Efficacy of *Piper betle* Linn. (Petiole) on Female Albino Rats. *Asian J. Exp. Sci.*, Vol. 21, No.1, 2007, 145-150.
15. S Bhattacharya *et al* , D Banerjee, AK Bauri, S Chattopadhyay, and SK Bandyopadhyay . Healing property of the *Piper betle* phenol, allylpyrocatechol against indomethacin-induced stomach ulceration and mechanism of action. *World J Gastroenterol*. 2007 Jul 21; 13(27):3705-13.
16. Mali Wirotasangthong, Naoki Inagaki, Hiroyuki Tanaka, and Witchuda Thanakijcharoenpatha, Hiroichi Nagai. Inhibitory effects of *Piper betle* on production of allergic mediators by bone marrow-derived mast cells and lung epithelial cells. *International*



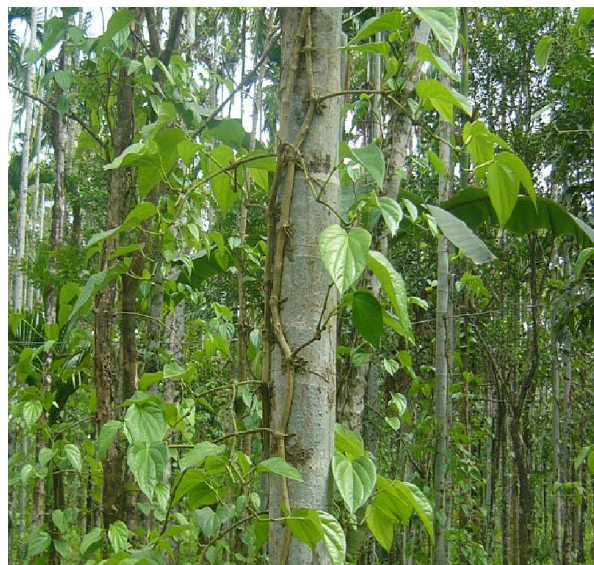
- Immunopharmacology*. Volume 8, Issue 3, March 2008, Pages 453–457.
17. Meghna Singh, Shilpy Shakya, Vishal Kumar Soni, Anil Dangi, Nikhil Kumar, Shailja-Misra Bhattacharya. The n-hexane and chloroform fractions of *Piper betle* L. trigger different arms of immune responses in BALB/c mice and exhibit ant filarial activity against human lymphatic filarid *Brugia malayi*. *International* 2009; 9(6):716-28.DOI: 10.1016/j.intimp.2009.02.012.
  18. Li-Ching Morgan Rowa and Jiau-Ching Hob. The Antimicrobial Activity, Mosquito Larvicidal Activity, Antioxidant Property and Tyrosinase Inhibition of *Piper betle* *Journal of the Chinese Chemical Society* Volume 56, Issue 3, pages 653–658, June 2009. DOI: 10.1002/jccs.200900097.
  19. Niranjana Ramji, Nivedita Ramji, Ritu Iyer, and S. Chandra sekaran. Phenolic antibacterials from *Piper betle* in the prevention of halitosis. *Journal of Ethnopharmacology* 12/2002; 83(1-2):149-52.DOI: 10.1016/S03788741 (02)00194-0.
  20. T. Nalina and Z.H.A. Rahim. The Crude Aqueous Extract of *Piper betle* L. and its Antibacterial Effect towards *Streptococcus mutans*. *American Journal of Biotechnology and Biochemistry* 3 (1): 10-15, 2007. ISSN 1553-3468.
  21. Ma. Cristina B. Gragasini, Agnes M. Wy, Bernie P. Roderos, Miriam A. Acda, Aida D. Solsoloy Insecticidal Activities of Essential Oil from *Piper betle* Linn. Against Storage Insect Pests the Philippine agricultural scientist Vol. 89 No. 3, 212-216 September 2006. ISSN 0031-7454.
  22. L.S.R Arambewela, L.D.A.M Arawwawala, KG Kumaratunga, DS Dissanayake, WD Ratnasooriya, SP Kumarasingha. Investigations on *Piper betle* grown in Sri Lanka *Pharmacogn Rev.* 2011 Jul; 5(10):159-63. DOI: 10.4103/0973-7847.91111.
  23. Kumarasingha, SP, Ihalamulla RL, Arambewela LSR, Dissanayake DS. Larvicidal effects of mineral turpentine, low aromatic white spirits, aqueous extracts of *Cassia alata* and aqueous extracts, ethanolic extracts and essential oil of betel leaf (*Piper betle*) on *Chrysomya megacephala*. *Int J Dermatol* 2002; 41:877-80.
  24. Nabasree Dasgupta, Bratati De. Antioxidant activity of *Piper betle* L. Leaf extracts in vitro *Food Chemistry* 88(2):219 (2004). DOI: 10.1016/j. Food chem. 2004.01.036.
  25. Pitchaon Maisuthisakul. Phenolic Constituents and Antioxidant Properties of some Thai Plants. *Phytochemicals – A Global Perspective of Their Role in Nutrition and Health* <http://cdn.intechopen.com/pdfs-wm/32944.pdf>.
  26. Wan Nuraini Wan Hasan, Mi-Kyoung Kwak, Suzana Makpol, Wan Zurinah Wan Ngah and Yasmin Anum Mohd Yusof. *Piper betle* induces phase I & II genes through Nrf2/ARE signaling pathway in mouse embryonic fibroblasts derived from wild type and Nrf2 knockout cells. *BMC Complementary and Alternative Medicine* 2014, 14:72 doi: 10.1186/1472-6882-14-72.
  27. Arambewela LSR, Arawwawala LDAM, Ratnasooriya WD. Gastro protective activities of Sri Lankan *Piper betle* leaf extracts in rats. SLAAS. 60<sup>th</sup> Annual Session. 2004. p. 117.
  28. Wahyu Widowati, Tjandrawati Mozef, Chandra Risdian, Yellianty. Anticancer and free radical scavenging potency of *Catharanthus roseus*, *Dendrophthoe petandra*, *Piper betle* and *Curcuma mangga* extracts in breast cancer cell lines. *Oxid Antioxid Med Sci.* 2013; 2(2): 137-142.
  29. Arambewela LSR, Arawwawala LDAM, Ratnasooriya WD. Antidiabetic activities of aqueous and ethanolic extracts of *Piper betle* leaves in rats. *J Ethnopharmacol* 2005; 102:239-45.
  30. Nopamart Trakranrungsie, Arinee Chatchawanchonteera, Watcharee Khunkitti. Antidermatophytic Activity of *Piper betle* Cream. *Thai J Pharmacol*; Vol 28:No.3, 2006.
  31. Karuppasamy Venkadeswaran, Arumugam Ramachandran Muralidharan, Thangaraj Annadurai, Vasanthakumar, Vasantha Ruban, Mahalingam Sundararajan, Ramalingam Anandhi, Philip A.Thomas, and Pitchairaj Geraldine. Antihypercholesterolemic and Antioxidative Potential of an Extract of the Plant, *Piper betle*, and



- Its Active Constituent, Eugenol, in Triton WR-1339-Induced Hypercholesterolemia in Experimental Rats Evidence-Based Complementary and Alternative Medicine Volume 2014 (2014), Article ID 478973.
32. Kaleem M, Sheema, Sarmad H, Bano B. Protective effects of piper nigrum and vinca rosea in alloxan induced diabetic rats. *Indian J Physiol Pharmacol* 2005, 49(1):65-71. *PubMed Abstract*.
  33. D. G. Kanjwani, T. P. Marathe, S. V. Chiplunkar & S. S. Sathaye. Evaluation of Immunomodulatory Activity of Methanolic Extract of *Piper betle*. *Scandinavian Journal of Immunology* (2008) 67, 589–593 doi: 10.1111/j.1365-3083.2008.02110.x.
  34. Sudipto Ganguly, Soumyaditya Mula, Subrata Chattopadhyay and Mitali Chatterjee (2007). An ethanol extract of *Piper betle* linn. Mediates its anti-inflammatory activity via down-regulation of nitric oxide. *Journal of Pharmacy and Pharmacology* 59 1-8.
  35. Srimani P *et al.*, (2009). Antioxidant effect of *Piper betle* Linn. (Paan) on erythrocytes from patients with HbE-beta thalassemia. *Indian Journal of Biochemistry & Biophysics* 46 241–46.
  36. Rathee JS, Patro BS, Mula S, Gamre S and Chattopadhyay S. Antioxidant activity of *Piper betle* leaf extract and its constituents. *Journal of Agricultural and Food Chemistry* 2006, 54 9046–9054.
  37. Rahul Hajare, Darvhekar VM, Ashish Shewale and Vijay Patil. Evaluation of antihistaminic activity of *Piper betle* leaf in guinea pig. *African Journal of Pharmacy and Pharmacology* 2011, 5(2) 113-117.
  38. Misra KH, Kodanda Ramu B., Ranjita N. and Bandyopadhyay M. Evaluation of anti-asthmatic effect of ethanol Extract of *Piper betle* linn. Against histamine induced Bronchospasm in guinea pigs. *International Journal of Basic and Applied Chemical Sciences* 2014 Vol. 4 (1) January-March, pp.67-73/Misra *et al.* ISSN: 2277-2073.
  39. Kiran C Nilugal, Komathi Perumal, Ugander R E, Asif iqbal chittor. Evaluation of Wound Healing Activity of *Piper betle* Leaves and Stem Extract in Experimental Wistar Rats. *Am. J. Pharm Tech Res.* 2014; 4(3).



**Figure 1.** *Piper betle* Leaf



**Figure 2.** *Piper betle* creeping onto a bamboo tree