



***Piper betel* - Not Just a Mouth Freshener But Also a Miraculous Herb for Healing: A Review**

Nivedita Panda ^{a*} and Arpita Panda ^b

^a Department of Environmental Science, Fakir Mohan University, Vyasa Vihar, Balasore-756089, India.

^b Department of Geography, Central University of Jharkhand, Ranchi, Jharkhand-835222, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOB/2023/v18i2340

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/99410>

Review Article

Received: 24/02/2023

Accepted: 27/04/2023

Published: 10/05/2023

ABSTRACT

Piper betel L., often known as betel vine, is a member of the Piperaceae family and is a significant cash crop for both economic and therapeutic purposes. The betel vine is most likely from Malaysia, while it is also grown in India, Sri Lanka, Bangladesh, Myanmar, and Nepal. It is grown in the districts of Balasore, Jagatsinghpur, Puri, Khordha, and Ganjam along Odisha's coast. With tremendous potential for creating jobs and improving the socioeconomic situations of rural people in India and other Asian nations, betel vine has enormous economic, medical, and nutraceutical value. However, there are still a number of significant elements of these plants that have not received enough consideration. Over a million people in Odisha use paan, yet most are not aware of its superior nutritional value. The most common chewing combinations for *Piper betel* include sliced areca nut, slaked lime, coriander, aniseed, clove, cardamom, sweetener, and coconut scrapings. Along with its traditional uses, *Piper betel's* therapeutic characteristics have the power to treat a variety of illnesses and lessen mouth cancer, which is actually brought on by sliced areca

*Corresponding author: E-mail: niveditapanda13@gmail.com;

nuts and slaked lime rather than betel leaves. Betel leaves are a great source of vitamins, minerals, phytochemicals, antioxidants, protein, lipids, fibre, calcium, iron, and many other nutrients. Many research studies on *Piper betle* have reported that it contains important chemical constituents such as chavibetol, chavibetol acetate, caryophyllene, allylpyrocatechol diacetate, camphene, chavibetol methyl ether, eugenol, α -Pinene, β -Pinene, γ -Limonene, saporin, 1-8-cineol, allylpyrocatechol monoacetate etc. Betel leaf is one of nature's best medicines and is thought to be superior to medications. Additionally, the leaves retain an essential oil (EO) with a high eugenol content (1-3%), which is a popular ingredient in medicines, stimulants, antiseptics, tonics, and other ayurvedic formulations. The demand for its goods, such as herbal medications, treatments, and natural herbal formulations, has grown recently. Additionally, *Piper betle* aids in the treatment of a wide range of illnesses, including rheumatism, diabetes, hypertension, halitosis, boils and abscesses, obesity, voice issues, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, ringworm, gum swelling, and many others. The botanical description, geographic distribution, economic worth, cultivation, and ethnobotanical use of *P. betle* are all succinctly summarised in the current paper. According to the research, *P. betle* is a naturally occurring, safe, and orally active drug with significant therapeutic potential for treating a range of human medical disorders. To better understand its underlying molecular mechanisms of action, clinical features, structure-activity connections, bioavailability, and synergistic interactions with other medications, more research is still required.

Keywords: *Piper betel*; nutrients; phytochemical; antioxidants; nutraceutical.

1. INTRODUCTION

The perennial, evergreen creeper known as "Paan" is the betel leaf, which belongs to the Piperaceae family. It is a significant herb with documented therapeutic and recreational benefits. It also offers lots of conventional advantages [1,6]. In Southeast Asia, it is grown. Although betel originated in Malaysia, it is now grown in Sri Lanka, India, Bangladesh, and a number of other countries [57]. *Piper betel* is recognised for its traditional uses in medicine. Due to its extraordinary medical qualities, many people have been aware of its use for ages [14-18]. Betel leaf significance has been discussed in regard to every aspect of human life, including social, cultural, and religious spheres, and it is still highly important today [26]. In several Asian countries, betel has traditionally been chewed with areca nut, slaked lime, cardamom, and clove [76]. Betel leaf has a number of beneficial qualities, such as radioprotection, immunomodulation, anti-inflammatory, antifilarial, antibacterial, antifertility, and anti-hyperglycemia [46]. Betel leaf has been referred to as an aromatic stimulo-carminative, astringent, and aphrodisiac since ancient times [43,45,48]. An extract from betel leaves has a significant deal of potential to be employed in the creation of commercial products, according to scientific studies on this plant's leaf [28,37,42]. The best tropical rain forests, including those in Indonesia, Malaysia, the Philippines, Thailand, Cambodia,

Vietnam, and India, provide cool shade, significant humidity, and a sufficient supply of soil moisture for betel vine production.

After meals, *Piper betel* L. is frequently used for refreshment. Betel leaves are used in a variety of ways in the Indian medical and health systems. Betel leaf is frequently used as an antibacterial and topically applied to wounds and lesions in Indian folk medicine to promote healing [20,24,27]. Betel leaf essential oil can be utilised as a raw material in the production of pharmaceuticals, fragrances, mouthwashes, tonics, and food additives, among other products [26].

In this review, many therapeutic effects of the various bioactive components of betel leaf are discussed. These effects include antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, cardioprotective, radioprotective, anticancer, antidiabetic, and analgesic characteristics.

2. PLANT PROFILE

The scientific classification of *Piper betel* Linn.

Kingdom - Plantae
Division - Magnoliophyta
Class - Magnolipsida
Family - Piperaceae
Genus - *Piper*
Species - *Piper betel*



Fig. 1. *Piper betle* leaf

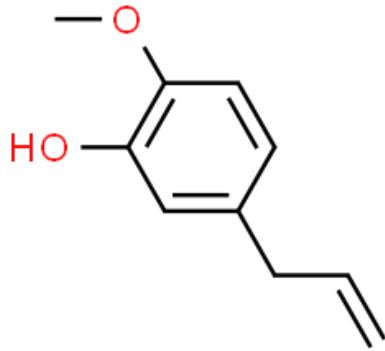


Fig. 2. *Piper betle* plant in the betel vine yard (locally known as “Pana Baraja”)

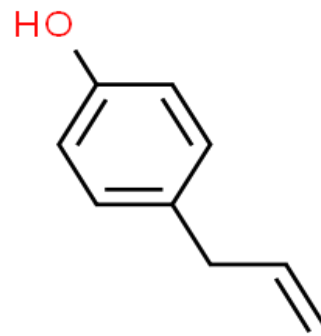
3. CONTENTS OF BETEL LEAF

Terpene, Phenol, P-cymene, carvacrol, chavicol and its derivatives, allyl catechol, eugenol, estragol, oxalic acid, malic acid, amino acids etc. are found to be present in the betel leaves. The particular strong aromatic flavour of betel leaves is mostly caused by phenol and terpene compounds [7]. The phenol content differs from plants to plants on the basis of their sexes. The total phenol content of the male plants is three times higher than that of the female plants. Even the quality of the leaf is affected by the phenol concentration. The glossier the leaf, the higher the phenol concentration [13 and 55]. Betel leaves also contain good amounts of vitamins,

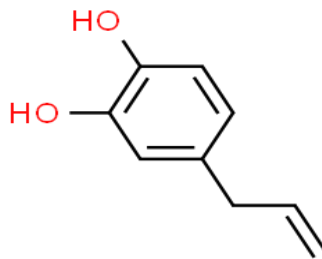
including nicotinic acid, ascorbic acid, and carotene. Aside from lysine, histidine, and arginine, betel leaves contain significant amounts of all other essential amino acids. Its aromatic flavour comes from the essential oil. The essential oil has a strong, scorching taste and an aromatic light-yellow liquid appearance. It contains chavicol, a phenol with powerful antiseptic properties. The root contains β -sitosterol [32]. The mid-region of the midrib of the vine possesses the highest of tannin. The highest amount of tannin is found in the mid region of the midrib of the vine. Betel leaves are very nutritious and rich in essential oil (EO), proteins, enzymes, vitamins and minerals [50].



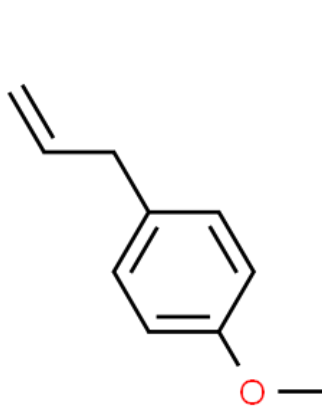
Chavibetol



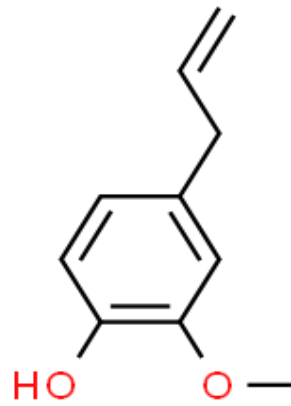
Chavicol



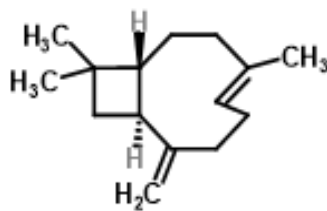
Hydroxychavicol



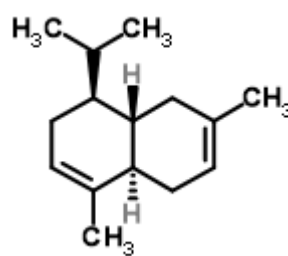
Estragole



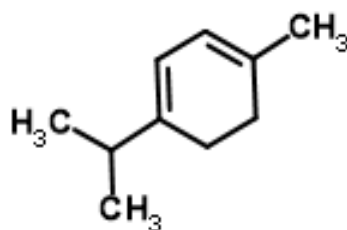
Eugenol



Caryophyllene



Cadinene



Terpinene

Fig. 3. Structure of some of the constituents of the plant

4. TRADITIONAL ETHNOBOTANICAL USES OF *Piper betel*

The therapeutic powers of pan were recognized during 600 A D when the Ayurveda medical system came into practice. One of the grandmother's remedies is betel leaf, which is prescribed as traditional medicine by experienced, older family members. The following illnesses can be healed using betel leaves. Such as: -

4.1 Respiratory Disorders

Betel leaves are beneficial in treating pulmonary diseases in childhood and old age. The leaves, soaked in mustard oil and warmed, can be applied to the chest to relieve cough and breathing difficulties [39].

4.2 Sore Throat

Cough and sore throat can both be effectively treated at home with betel leaf. The leaves can be applied locally to soothe sore throats. The crushed fruit or berry should be mixed with honey and taken to treat irritating cough [59].

4.3 Weakness of Nerves

Betel leaves are essential in the treatment of nervous pains, nervous exhaustion and debility. A teaspoon of honey and the juice of a few betel leaves make a potent tonic. This can be taken twice daily with a teaspoon for best benefits.

4.4 Inflammation

Applying betel leaves locally can help treat inflammatory conditions like arthritis and testicular inflammation (orchitis).

4.5 Headache

A popular home remedy for headache is betel leaf. The betel leaf has cooling and analgesic qualities. To treat a severe headache, it can be applied over the painful area with positive results [25].

4.6 Boils

Boils can be effectively treated with betel leaf as well. A leaf is gently warmed until it becomes soft and is then coated with a layer of castor oil. Over the inflamed area, the oiled leaf is applied. In every couple of hours, this leaf needs to be replaced. After a few applications, the boil will rupture draining all the pus-filled material. The application can be made at night and removed in the morning.

4.7 Wounds

Disruption of normal anatomical structure and function is referred to as a wound[53]. The process of healing a wound is an extremely complicated one that involves several cellular and biochemical processes [53]. Wounds can be treated with betel leaves [49]. The juice of a few leaves should be extracted and applied on the wound. Then the area should be bandaged and wrapped in a betel leaf. The wound will heal up with a single application within two days.

4.8 Problem of Breast Milk Secretion

The application of betel leaves smeared with oil is said to help in secretion of milk when applied on the breasts during lactation.

4.9 Scanty or Obstructed Urination

Juice made from betel leaves is said to have diuretic qualities. Its juice, when combined with diluted milk and slightly sweetened, helps in easing urination [26].

4.10 Constipation

A suppository made of the stalk of betel leaf dipped in castor oil can be inserted into the rectum, in case of constipation in children. This immediately relieves constipation [59].

4.11 Filariasis

Filariasis can be treated with a paste made from *Piper betel* leaves, salt, and warm (but not very hot) water.

4.12 Obesity

When one *Piper betel* leaf is combined with *Piper nigrum* and used for two months, it also aids in the treatment of obesity.

4.13 Piles

This plant's leaves have proven to be a very effective treatment for piles. The leaves are first warmed. They are covered with a layer of castor oil after they become pliable. Now, this oily leaf produces superior outcomes when applied to the inflammatory area [5 and 26].

5. MODERN MEDICINAL USES

5.1 Antibacterial Activity

Leaf extract from *Piper betel* Linn. promotes salivation in the mouth. As a result, salivary peroxidases, antibodies, and lysozyme levels rise, acting to inhibit oral bacterial development [40]. Certain significant phenolic components and essential oils found in its leaf extracts have antibacterial activity against numerous microorganisms in the oral cavity. Additionally, it is effective against the *Vibrio cholera* bacteria. Additionally, its leaf extract slows and kills harmful bacteria that cause typhoid, tuberculosis, and other diseases [23]. Research based studies indicate that *Piper betel* is effective against the following bacterial strains: *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Streptococcus pyogenes*,

Streptococcus mutans, *Enterococcus faecalis*, *Fusobacteriumnucleatum*, and *Prevotella intermedia* [10].

5.2 Prevention of Halitosis

Oral malodour or poor breath is what is referred to as halitosis. It is brought on by salivary protein, amino acid, and peptide breakdown, gingival cervical fluid, and occasionally food that has been left on the teeth due to improper brushing. Halitosis has long been treated traditionally with *Piper betel* leaves. It has been demonstrated through research-based study that it aids in breath freshening and the prevention of foul breath. Its leaves are chewed for this purpose either on their own or in combination with other spices like clove, cardamom, cinnamon, and areca nut [58].

5.3 Antidiabetic Activity

Nowadays, diabetes disorder is becoming more prevalent in human beings. It is a heterogeneous and metabolic disorder of carbohydrate, lipid and protein metabolism characterized by high blood glucose levels due to the absolute lack of insulin. Due to this deficiency, body cells do not respond properly to insulin. Thus, several anti-diabetic drugs, as a medicine, are used to control the increased blood glucose level in the body. According to some researchers, the oral administration of betel leaf suspension at 75 and 150 mg/kg of body weight for 30 consecutive days to streptozotocin-induced diabetic rats caused a significant reduction in blood glucose and glycosylated hemoglobin level. Administering betel leaf to diabetic animals is also reported and, in this report, it was found that glucose 6-phosphatase and fructose-1, 6-bisphosphatase levels drop in the liver with an increase in hexokinase levels [39]. Arambewela et al. (2005) examined the antidiabetic property of *Piper betle* leaves [5].

5.4 Gastro Protective Activity

Since a long time ago, *Piper betel* Linn. has been utilised to treat stomach ulcers. gastrointestinal protection. The balance between exposure to aggravating stimuli that harm the mucosal lining and gastro protective mechanisms that prevent further injury determines the complex pathogenesis of gastroduodenal ulcers [81]. Exogenous variables that enhance the production of ROS include NSAIDs and

Helicobacter pylori infections, while endogenous factors include conditions that cause excessive stomach output [81]. The gastroprotective mechanism contains elements that affect an ulcer's potential to heal and the production of protective mucus with a buffering effect [36]. By scavenging oxygen radicals, antioxidant activity also plays a protective role [36]. NSAIDs are frequently used to create stomach ulcers in lab animals. The extent of protein oxidation, the amount of lipid peroxidation, and the drop in DNA tissue concentration are all indicators of tissue damage in NSAID-induced stomach ulcers [12]. Histological examination can be used to quantify the size and quantity of ulcer formations, as well as mucus production and antioxidant levels using Alcian blue binding protein [12]. When ethanolic extracts of *P. betle*, *Embllica officinalis*, *Terminalia bellerica*, and *Terminalia chebula* were compared, *P. betle* was found to have the highest potential for healing ulcers caused by indomethacin gastroduodenal injection [12]. Following ten days of therapy with *P. betle* leaf extract, another trial conducted on albino rats demonstrated healing effects. When compared to the untreated group, the histological analysis revealed that the number of ulcers had decreased according to the length of the treatment [41]. Following *P. betle* therapy, lipid peroxidation, protein oxidation, and DNA damage were decreased [12]. Following treatment with *P. betle* extract, the activity of antioxidant enzymes including SOD and catalase increased. When indomethacin-induced stomach ulcers were treated with allylpyrocatechol, similar results were obtained [8]. As a result, allylpyrocatechol is the *P. betle* compound that most likely exerts the gastroprotective effect.

5.5 Antiallergic Activity

Ethanolic extracts from *Piper betel* exhibit strong anti-allergic properties. According to research, it has an impact on histamine and granulocyte macrophage-colony-stimulating factor (GM-CSF) production. These are created by murine BMMCs, or bone marrow mast cells. The generation of GM-CSF and histamine has been significantly reduced by betel extracts through an IgE-mediated hypersensitivity response. So, it is proven that betel offers excellent control of allergic illnesses. It prevents the synthesis of allergy mediators [79].

5.6 Antihypercholesterolemic Effects

On hypercholesterolemia, *Piper betel* has exceptional results. Hypercholesterolemia or

hyperlipidaemia are terms used to describe elevated amounts of lipids or cholesterol in the blood. The probability of having cardiovascular (CVS) illnesses is greatly increased. The outcome is atherosclerosis, which is followed by numerous CVS issues. Betel extract was administered orally to hypercholesterolemic rats for up to seven days, and the results revealed improvement in cholesterol and other associated parameters. These rats' blood glucose, triglyceride, low density lipoprotein (LDL), and total cholesterol levels were greater. The results therefore showed that the *Piper betel* extract has anticholesterolemic effects [74].

5.7 Anti-inflammatory Activity

Inflammation is considered as a part of the complicated biological response of vascular tissues to potentially harmful stimuli like pathogens, damaged cells, etc. Anti-inflammatory is the activity that aids in the treatment of inflammation or swelling. Betel leaf has a significant role in the anti-inflammatory action which has been used as a household treatment for the oral cavity inflammation. Eugenol, the main component of betel leaf, also has anti-inflammatory properties in several animal models of research with various inflammogens.

5.8 Antimicrobial Activity

Antimicrobial activity is the process of killing or inhibiting the pathogenic microbes. Antimicrobial may be antibacterial, antifungal or antiviral. Betel leaf contains chavibetol, chavibetol acetate, chavicol, allylpyrocatechol, and allylpyrocatechol diacetate etc. Presence of these bioactive components is the primary cause for its antimicrobial effectiveness. A recent study by Roy and Guha (2018) reported the antimicrobial effectiveness, where nano emulsion made with betel leaf essential oil showed in-vitro inhibition of many foodborne pathogens, including *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* [61]. The EO, extracted from betel leaves, holds strong antimicrobial properties that lessen the adhesion of bacteria that cause early dental plaque [56]. Eugenol, a significant component extracted from *Piper betel* has strong antifungal activity against *Aspergillus flavus*. The extracts of the betel vine parts (stalks and stems) and the EO extracted from the leaves also shown potent anti-fungal action and found to be effective at 450 µg/ml concentration

[8]. Additionally, the aqueous and methanolic *Piper betle* L. leaf extract were selected to analyse the antibacterial activity against some selected microorganisms (Antimicrobial activity using 10 gram positive, 12-gram negative bacteria and one fungal strain, *Candida tropicalis*) and the methanolic extract was found to be more effective at inhibiting the microbial strains [47]. Trakranungsie et al. (2008) investigated the antimicrobial efficacy of crude ethanolic extracts of betel leaves against several zoonotic dermatophytes, including *Microsporum canis*, *Microsporum gypseum* and *Trichophyton mentagrophyte* and the yeast-like *Candida albicans* [73]. The findings of that anti-microbial activity examination revealed that betel leaves extract shown more potent antifungal activities, with an antioxidant activity with an average IC₅₀ values that ranged from 110.44 to 119.00 lg/ml. Using the disk diffusion method, Row and Ho (2009) investigated the antimicrobial activity of *P. betle*'s EO and solvent extract (methanolic and aqueous extracts) against the selected yeasts including *C. chromatography-mass* and *M. pachydermatis* [60]. Together with EO, the methanolic and aqueous extracts exhibited strong activity against the yeasts.

Four varieties of pan (Desawari, Desi, Bangladeshi and Jaleswar) were studied and reported [2]. The findings described that the cold aqueous, methanolic, ethanolic and ethyl acetate extracts of dried leaves of all four varieties of *Piper betle* at concentration of 500mg/ml were tested against pathogenic microorganisms like *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* using the agar well diffusion method and discussed the antimicrobial screening on leaves of *Piper betle*. Because of the high concentration of sterols, the results showed that all the extracts exhibited a clear zone of inhibition against all the bacteria. Moreover, the crude ethanol extract of *Piper betle* showed strong antimicrobial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Staphylococcus aureus* [22]. (Khan and Kumar 2011) assessed the antibacterial efficacy of *Piper betle* leaf extracts (ethanolic and methanolic) against pathogenic bacteria including *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [34]. The methanolic extract was found to be more efficient than ethanolic extract against the pathogens studied. Also, three gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, and *Micrococcus luteus*), and two gram-negative

bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) were carefully chosen for the antibacterial activity of aqueous and ethanol betel leaf extracts. Ethanol extract exhibited more significant and effective antibacterial action than aqueous ones due to the presence of alkaloids, tannins, phenolic substances, and glycosides, etc. [33]. Also, the antibacterial effects of various dried betel leaves (Desawari, Desi, Bangladeshi, and Jaleswar) extracts were assessed against pathogenic bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* using the agar well diffusion method. The dried leaf extracts were obtained by cold aqueous, methanol (80%), ethanol (70%), and ethyl acetate (80%) solvent extraction technique. The findings discovered that Bangladeshi and Jaleswar varieties of betel leaf extract were an effective and good source of herbal medicines with strong antibacterial activity [2]. Ali et al. (2010) have demonstrated that the Hydroxychavicol, extracted from the chloroform extraction of the aqueous leaf extract of *Piper betle* L., was examined for its antifungal activity against 124 strains of selected fungi [4].

5.9 Antifungal Activity

Piper betle exhibits an antifungal action against *Candida albicans* [67]. The methanolic and aqueous extracts of *Piper betle* leaves are highly effective against the yeasts *Candida albicans* and *Malassezia pachydermatis* [66]. Because it contains non-polar chemical components, the *Piper betle* chloroform extract is more effective than the methanol fraction against dermatophytes (*Trichophyton*, *Microsporum*, and *Epidermophyton*) [67]. The antifungal properties of the *Piper betle* extract's hydroxychavicol showed fungicidal effects against all of the tested fungal species, including *Trichophyton rubrum*, *Candida* species, and *Aspergillus* species. The fungi *Candida albicans*, *Candida parapsilosis*, and *Candida tropicalis* displayed a reduced amount of adhesin synthesis when treated with betel crude aqueous extract [67]. These adhesins are essential because they enable the fungi to attach to host tissues and colonise a variety of substrates. A crude essential oil was found to have a wide range of antibacterial activity against the tested pathogens, most notably *Candida albicans*, *Staphylococcus aureus*, and *Malassezia pachydermatis* [67]. As it improves the permeability of fungal membranes, phenols (carvacrol) and phenylpropan (eugenol and chavicol) from *Piper betle* are demonstrated to display antifungal action [67].

5.10 Antioxidant Action

Antioxidants are molecules that protect our body from free radicals. Free radicals are the compounds that harm our body if their levels become too high. They are connected to numerous diseases, including diabetes, heart disease and cancer. Free radical reactions happening in the body are associated with neurological diseases and pulmonary diseases also. These free radicals have a major role in the aging process. The antioxidant activity is another significant property of betel leaf. A large number of researchers have reported on it. It has been demonstrated that the aqueous extract of the inflorescence of *Piper betle* extract was effective in scavenging H₂O₂, superoxide radical and hydroxyl radical [38]. It has also been demonstrated that the ethanol extracts of the Bangla, sweet, and Mysore varieties of betel leaf were effective in scavenging DPPH radicals in vitro, with best effects being detected with the Bangla variety [59]. Moreover, studies have revealed that the hydroalcoholic extract of the betel leaf has an in vitro nitrogen oxide scavenging activity [30]. Moreover, it can help fight oxidative stress and eradicates free radicals by which it can prevent cancer [57]. Ascorbic acid, as a powerful antioxidant, is very advantageous in lessening the levels of free radicals in the body and thus preventing cancer. Shah et al. (2016) also described that betel leaf extracts showed free radical scavenging activity [68].

5.11 Hepatoprotective Action

Cadmium, ethanol, and carbon tetrachloride are just a few of the models that have been used to cause hepatotoxicity in test animals [54]. These xenobiotics' hepatotoxicity stimulates Kupffer cells, which then generate ROS [29]. Numerous cytochrome P450 isoforms, including CYP2E1, which contributes to the production of ROS, are also expressed in the liver [21]. The mitochondria's oxidative phosphorylation is decoupled by xenobiotics, which increases lipid peroxidation, damages DNA, and changes calcium homeostasis. Treatment with *P. betle* extract considerably decreased the levels of conjugated diene, TBARS, LOOH, protein carbonyl contents, and other lipid peroxidation products [54]. It has been noted that *P. betle* extract increases the antioxidant level of catalase, SOD, and GSH. It was hypothesised that allylpyrocatechol played a role in hepatoprotective activity.

5.12 Cardioprotective Action

The imbalance between increased oxygen demand and decreased blood supply, which results in prolonged ischemia, leads to Cardial infarction [71]. The formation of ROS during ischemia worsens the heart's damage. As a result, increasing the antioxidant content may prevent additional infarction from developing. Pre-treatment with *P. betle* improved hemodynamic and ventricular function measures in rats with iso-proterenol (ISP)-induced myocardial infarction [71]. It improved the levels of SOD, CAT, GSH, and GPx, decreased the heart's lipid peroxidation, and as a result, less CK-MB isoenzyme and LDH leaked into the blood. Cardiovascular disorders are mostly caused by platelet hyperactivity, which results in intravascular thrombosis. Piperbetol, ethylpiperbetol, piperol A, and piperol B, which were extracted from the leaves of *P. betle*, demonstrated specific action in suppressing platelet aggregation brought on by platelet activating factor (PAF).

5.13 Radioprotective Action

The cornerstone of cancer treatment, which tries to eradicate cancer cells, is radiotherapy. However, it is impossible to avoid the detrimental effect on normal tissue [75]. Ionising radiation exposure boosts the generation of mitochondria-dependent ROS, which boosts lipid peroxidation [75]. Treatment with *P. betle* reduces lipid peroxidation as shown by the levels of TBARS, lipid hydroperoxide, and conjugated diene [12]. *P. betle*'s phenolic constituents, such as chavibetol and allylpyrocatechol, which have been reported to have radical-scavenging properties, contribute to this protective effect.

5.14 As an Anticancer Agent

Betel vine has reported cancer preventive effects [35, 44 and 19]. An abundant source of calcium, vitamin C, niacin, thiamine, carotene, and riboflavin, [80], betel leaves are undoubtedly related with nutritive benefits. Other betel phytochemicals include allyl pyrocatechol (APC; 2-hydroxychavicol), 4-hydroxycatechol, b-caryophyllene, methyl eugenol, carotenes, starch, diastases, and an essential oil containing hydroxychavicol [70]. Hydroxychavicol, a phenolic component quantitatively present at about 26% in betel leaves, has antiproliferative action on prostate cancer [52]. Hydroxychavicol has also been demonstrated to obstruct cell-cycle progression of prostate cancer and oral KB

carcinoma cells [52]. Some other research indicates that hydroxychavicol, also known as APC has antiulcerogenic property and has been shown to treat indomethacin-induced stomach ulceration leading to gastric cancer [11]. Chlorogenic acid (ChA), another active component extracted from betel leaves, has been testified to eradicate cancerous cells without harming normal cells, unlike most conventional chemotherapeutic [26]. Mouth cancer is one of the ten most common cancers, with 90% of cases occurring in Southeast Asia, where cigarette and smoking behaviors are common [31]. One of the earliest experiments discovered that topical treatment with leaf extracts inhibited pinene- induced mouth cancer in hamsters [72]. It was also found that combining leaf extracts and turmeric into the dietary supplements was very helpful. The leaf extracts have both anti- proliferative and preventative chemical properties and can therefore be applied to treat several conditions including human lung cancer [9].

5.15 Analgesic Action

According to their mode of action, analgesics can be classified as peripherally acting medications that affect the anti-inflammatory response or centrally acting medications that affect the central nervous system [51]. Hot plates were frequently utilised in animal research to evaluate centrally acting analgesics [3]. While the generation of pain mediators such as prostaglandin and bradykinin are inhibited during the acetic acid-induced writhing test, which is frequently used to evaluate substances with peripheral action. The formalin test is a biphasic pain model with two peaks of pain response [69]. Narcotic analgesics influence both phases equally while anti-inflammatory analgesics primarily effect the second phase. It was discovered that there was a considerable latency to pain response in the hot plate test after *P. betle* extract administration at 100 and 200 mg/kg body weight, compared to the control group [3]. In the acetic acid-induced writhing test, treatment with *P. betle* extract also markedly decreased the number of writhing movements. Following administration of *P. betle* extract in the formalin test, a strong analgesic effect was noted in both the early and late phases [65,77,78]. According to these pain models, *P. betle* has analgesic properties that work both centrally and peripherally. *P. betle* has a high alkaloid content. As a result, it was suggested that opioid receptors were implicated in its central analgesic impact.

Naloxone, an opioid antagonist, was administered concurrently with *P. betle* and diminished its analgesic efficacy [5]. As a result, it can be said that the opiate receptors contribute to the central activity, while its anti-inflammatory effect contributes to the peripheral action.

6. CONCLUSION AND FUTURE PROSPECTS

The betel plant's diverse pharmacological effects are caused by a variety of physiologically active chemicals. It may be possible to do additional research to elucidate the precise mechanisms through which betel leaves affect various human metabolic processes. The selection of future elite landraces and their improvement plans may benefit from the identification of constituents in various landraces using contemporary gas chromatographic techniques. The majority of the landraces that are now available should be characterised in order to solve the synonym problem and properly authenticate them. Proper characterization could be helpful for long-term study for drug development in light of the *P. betle*'s demonstrated therapeutic efficacy [62-64]. To get potential landraces with high eugenol and chavibetol content, efforts must be stepped up. In addition to its bioactivity research, consideration may also be given to correct landrace authentication and their preservation for ongoing supply. Studying the impact of abiotic factors on the production and quality of betel vine is essential since soil and environmental factors always affect plant secondary metabolites. Prior to clinical trials and extensive commercial production, additional standardisation of parameters for quality and quantity of betel vine essential oil and extracts may be the focus of future research. The use of biotechnology has created new opportunities for genetic advancement, accurate authentication, and identification of elite chemotypes of this economically and medicinally significant cash crop. Therefore, more in-depth research on leaf extract should be required to enhance its applications in the creation of diverse medicines. As a result, investigations on the standardisation and stabilisation of the leaf extract can be conducted soon, which will serve to improve its application for a variety of medical applications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Abraham NN, Kanthimathi MS, Abdul Aziz A. Piper betle shows antioxidant activities, inhibits MCF-7 cell proliferation and increases activities of catalase and superoxide dismutase. BMC. Comp. Alt. Med. 2012;12(1):220.
2. Agarwal T, Singh R, Shukla AD, Waris I, Gujrati A. Comparative analysis of antibacterial activity of four Piper betle varieties. Adv. App. Sci.Res. 2012;3: 698-705.
3. Alam B, Akter F, Parvin N. Antioxidant, analgesic and anti-inflammatory activities of the methanolic extract of Piper betle leaves. Avic. J. Phyto. 2013;3(2):112.
4. Ali I, Khan FG, Suri KA, Gupta BD, Satti NK, Dutt P, Khan I. In vitro antifungal activity of hydroxychavicol isolated from *P. betle* L. Ann. Cli. Mic. Ant. 2010;9(7):01–09.
5. Arambewala LSR, Arawwawala LDAM, Ratansooriya WD. Antinoceptive activities of aqueous and ethanol extract of Piper betle leaves in rats. J. Ethnopharm. 2005; 102(2):239- 245.
6. Arawwawala LDAM, Arambewala LSR, Ratnasooriya WD. Gastroprotective effect of *Piper betle* Linn. leaves grown in Sri Lanka. J. Ayurve. Integ. Med. 2014;5:38.
7. Bajpai V, Sharma D, Kumar B, Madhusudan KP. Profiling of Piper betle Linn. cultivars by direct analysis in real time mass spectrometric technique. Biomedical Chromatography. 2010;24(12): 1283-1286.
8. Banerjee D, Bhattacharya S, Bandyopadhyay SK, Chattopadhyay S. Biochemical mechanism of healing activity of the natural phenolic, allylpyrocatechol against indomethacin induced gastric ulceration in mice. Digest. Dis. Sci. 2008;53(11):2868-2877.
9. Banerjee D, Shah B. Anti proliferative activity of *Piper betel* leaf extracts on human lung cancer cell line (A549), Inter. J. Pharma. Pharmac. Sci. 2014;6(1): 432-435.
10. Bangash FA, Hashmi AN, Mahboob A, Zahid M, Hamid B, Muhammad SA, Shah ZU, Afzaal H. In-vitro antibacterial activity of *Piper betel* leaf extracts. J. App.Pharm. 2012;3:639- 646.
11. Bhattacharya S, Subramanian M, Roy, chowdhury S, Bauri AK, Kamat JP, Chattopadhyay S. Radioprotective property of the ethanolic extract of *Piper betel* Leaf. J Radiat Res. 2005; 46:165–171.
12. Bhattacharya S, Mula S, Gamre S, Kamat JP, Bandyopadhyay SK, Chattopadhyay S. Inhibitory property of Piper betle extract against photosensitization-induced damages to lipids and protein. Food Chem. 2006; 1474-1480.
13. Bissa S, Songara D, Bohra A. Traditions in oral hygiene: Chewing of betel (*Piper betel*L.) leaves. Curr Sci. 2007;92(1): 26-28.
14. Chakraborty. Devjani, Shah. Barkha. Antimicrobial, antioxidative and anti-haemolytic activity of *Piper betel* leaf extracts. Int. J. Pharm. Pharm. Sci. 2011; 3,192-199.
15. Chakraborty JB, Mahato SK, Joshi K. Hydroxychavicol, a Piper betle leaf component, induces apoptosis of CML cells through mitochondrial reactive oxygen species dependent JNK and endothelial nitric oxide synthase activation and overrides imatinib resistance. Canc. Sci. 2012; 103(1):88- 99.
16. Chang MC, Uang BJ, Wu HL. Inducing the cell cycle arrest and apoptosis of oral KB carcinoma cells by hydroxychavicol: roles of glutathione and reactive oxygen species. Br. J. Pharmacol. 2002; 135(3):619-630.
17. Chauhan ES, Aishwarya J, Singh A, Tiwari A. A review: Nutraceuticals properties of *Piper betel* (Paan). Am. J. Phytomed. Clin. Ther. 2016;4:28-41.
18. Choudhary D, Kale RK. Antioxidant and non-toxic properties of Piper betle leaf extract: in vitro and in vivo studies. Phytotherapy. Res. 2002;16(5):461-466.
19. Chowdhury CR, Markus AF. Level of oral cancer awareness among Indian rural population: A possible research model using knowledge, attitude and practice (KAP) intervention and its utilisation in low resource settings of LMICs. - J. Oral Biol. Craniofacial Res.2022;12(1):154-160.
20. Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. Free. Rad. Biol. Med. 2010; 48(6):749-762.
21. Cullen JM. Mechanistic classification of liver injury. Toxicol. Pathol. 2005;33(1): 6-9.
22. Datta. Arani, Ghoshdastidar. Shreya, Singh. Mukesh. Antimicrobial property of *Piper betel*leaf against clinical isolates of

- bacteria. Int. J. Pharm. Sci. Res. 2011; 2(3):104-109.
23. Dwivedi V, Tripathi S. Review study on potential activity of Piper betle. J.Pharmacogn. Phytochem. 2014;3:93-98.
 24. Ganguly S, Mula S, Chattopadhyay S. An ethanol extract of Piper betle Linn. mediates its anti-inflammatory activity via downregulation of nitric oxide. J. Pharma. Pharmaco. 2007;59(5):711-718.
 25. Guha P. Commercial exploitation of oil from betel leaves. IIT, Kharagpur, India: Agricultural and Food Engineering Department. 2000;56-57.
 26. Guha P. Betel leaf: The neglected Green Gold of India. J. Hum. Ecol. 2006;19(2): 87- 93.
 27. Gundala SR, Yang C, Mukkavilli R. Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis. Toxicol. App. Pharmacol. 2014; 280(1): 86-96.
 28. Hertog MG, Feskens EJ, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. The. Lancet. 1992; 342(8878):1007-1011.
 29. Jaeschke H, Gores GJ, Cederbaum AI. Mechanisms of hepatotoxicity. Toxicol. Sci. 2003; 65(2):166-176.
 30. Jagetia GC, Baliga MS. The evaluation of nitric oxide scavenging activity of certain Indian medicinal plants in vitro: A preliminary study. Journ. Med. Food. 2004; 7(3):343–348.
 31. Jiang X, Wu J, Wang J, Huang R. Tobacco and oral squamous cell carcinoma: A review of carcinogenic pathways. Tobacco Induced Diseases. 2019;17-29.
 32. Joshi SG. Medicinal plants. Oxford IBH Publishing Co. Pvt. Ltd. New Delhi. 2009;307.
 33. Kaveti B, Tan L, SarnniaKuan TS, Baig M. Antibacterial activity of *Piper betel* leaves. Int. Journal. Pharma. Teach. Prac. 2011; 2:129–132.
 34. Khan JA, Kumar N. Evaluation of antibacterial properties of extracts of *Piper betel* leaf. Journ. Pharma.Bio. Sci. 2011; 11:01–03.
 35. Kudva AK, Rao S, Rao P, Periera R, Bhandari G, Mathew JM, Baliga MS. Piper betle Linn. in Cancer: Past, present, and future. In: Akhtar M.S, and M.K. Swamy (eds.) Anticancer Plants: Properties and Application. 2018;327-347.
 36. Kumar N, Misra P, Dube A, Bhattacharya S, Dikshit M, Ranade S. *Piper betle* Linn. A maligned pan-Asiatic plant with an array of pharmacological activities and prospects for drug discovery. Curr. Sci. 2010; 99(7):922-932.
 37. Kundu S, Bala A, Ghosh P. Attenuation of oxidative stress by allylpyrocatechol synovial cellular infiltrate of patients with rheumatoid arthritis. Free. Rad. Res. 2011;45(5):518-526.
 38. Lei D, Chan CP, Wang YJ. Antioxidative and antiplatelet effects of aqueous inflorescence *Piper betel* extract. J Agric Food Chem. 2003;26,2083-2088.
 39. Madan A, Balan N, Barma RD. Reducing postharvest losses of betel (*Piper betle*L.) leaves by various preservation techniques. J. Agri. 2014;1(4):251-256.
 40. Madhumita M, Guha P, Nag A. Bio-actives of betel leaf (*Piper betle* L.): A comprehensive review on extraction, isolation, characterization, and biological activity. Phyto. Res. 2020;34:2609-2627.
 41. Majumdar B, Chaudhuri SGR, Ray A. Effect of ethanol extract of piper betle linn. leaf on healing of NSAID-induced experimental ulcer-A novel role of free radical scavenging action. Ind. J. Exp. Biol. 2003;41(4):311-315.
 42. Md.Pisar, Mazura. Hashim, Nuziah. Ali RM. Evaluation of *Piper betle* on platelet activating factor (PAF) receptor binding activities. Malays. J. Sci. 2007;26.
 43. Mahfuzul M, Shemona HRM. Asaduzzaman S, Bari ML, Inatsu Y, Kawamoto S. Antibacterial activity of ethanol extract of betel leaf (*Piper betle* L.) Against Some Food Borne Pathogens. Bang. J. Microbiol. 2011;28(2):58-63.
 44. Malkani N, Kazmi S, Rashid MU. Epidemiological assessment of oral cancer burden in Pakistan. Cancer Investigation. 2021;39(10):842-853.
 45. Morimoto K, ShirataN, Taketomi Y. Prostaglandin E2–EP3 signalling induces inflammatory swelling by mast cell activation. J. Immuno. 2014;192(3): 1130-1137.
 46. Nagori K, Singh MK, Alexander A, Kumar T, Dewangan D, Badwaik H. *Piper betle* L.: A review on its ethnobotany, phytochemistry, pharmacological profile and profiling by new hyphenated technique DART-MS (Direct Analysis in Real Time Mass Spectrometry). J. Pharm. Res. 2011; 4(9):2991-2997.

47. Nair R, Chanda, Sumitra. Antimicrobial activity of *Terminalia catappa*, *Manilkara zapota* and *Piper betel* leaf extract. Ind. Journ. Pharma. Sci. 2008;70(3):390– 393.
48. Nalina T, Rahim ZHA. The crude aqueous extract of *Piper betle* L. & its antibacterial effects towards *Streptococcus mutans*. Am. J. Biotechnol. Biochem. 2007;3(1): 10-15.
49. Nilugal KC, Perumal K, Ugander RE, Chittor AI. Evaluation of wound healing activity of *Piper betle* leaves and stem extract in experimental wistar rats. Americ J Pharm Tech Res. 2014; 4(3).
50. Nayaka NMDMW, Sasadara MMV, Sanjaya DA, Yuda PESK, Dewi NLKAA, Cahyaningsih E, Hartati R. *Piper betle* (L): Recent review of antibacterial and antifungal properties, safety profiles, and commercial applications. Molecules. 2021; 26(8):2321.
51. Olesen AE, Andresen T, Stahl C. Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. Pharmac. Rev. 2012;64(3):722-779.
52. Paranjpe R, Gundala SR, Lakshminarayana N, Sagwal A, Asif G, Pandey A. *Piper betel* leaf extract: anticancer benefits and bio-guided fractionation to identify active principles for prostate cancer management. Carcinogenesis.2013;34:1558–66.
53. Patra B, Das MT, Dey SK. A review on *Piper betle* L. J. Med. Pl. Stud. 2016; 4(6):185-192.
54. Prabhu SM, Muthumani M, Shagirtha K. Protective effect of *Piper betle* leaf extract against cadmium-induced oxidative stress and hepatic dysfunction in rats. Saud. J. Biol. Sci. 2012; 19:229-239.
55. Pradhan D, Suri KA, Pradhan DK, Biswasroy P. Golden heart of the nature: *Piper betle* L. Journ. Pharmac. Phyto. 2013;1(6):147–167.
56. Punuri JB, Sharma P, Sibyala S, Tamuli R, Utpal B. *Piper betle* mediated green synthesis of biocompatible gold nanoparticles. Int. Na. Let. 2012;2:01–09.
57. Rai MP, Thilakchand KR, Palatty PL, Rao P, Rao S, Bhat HP, Baliga MS. *Piper betel* Linn (betel vine);the maligned Southeast Asian medicinal plant possesses cancer preventive effects: Time to reconsider the wronged opinion. Asian. Pac. J. Cancer. Prev. 2011;12:2149-2156.
58. Ramji N, Iyer R, Chandrasekaran S. Phenolic antibacterial from *Piper betle* in the prevention of halitosis. J. Ethnopharm. 2002;83:149-152.
59. Rathee JS, Patro BS, Mula S. Antioxidant activity of *Piper betel* leaf extract and its constituents. J. Agri. Food. Chem. 2006; 54(24):9046-54.
60. Row LM, Ho J. The antimicrobial activity, mosquito larvicidal activity, antioxidant property and tyrosinase inhibition of *Piper betle*. Journ. Chi. Chem. Soc. 2009; 56(3):653–658.
61. Roy A, Guha P. Formulation and characterization of betel leaf (*Piper betel*L.) essential oil based nanoemulsion and its in vitro antibacterial efficacy against selected food pathogens. J FoodProcesPreserv. 2018; e13617.
62. Sarkar D, Saha P, Gamre S. Anti-inflammatory effect of allylpyrocatechol in LPS-induced macrophages is mediated by suppression of iNOS and COX-2 via the NF-κB pathway. Int. Immune. 2008;8(9): 1264-1271.
63. Sarkar D, Kundu S, De S, Hariharan C, Saha P, Manna A, Chatterjee M. The antioxidant activity of allylpyrocatechol is mediated via decreased generation of free radicals along with escalation of antioxidant mechanisms. Phyto. Res. 2013;27(3):324-329.
64. Sazwi NN, Nalina T, Rahim ZHA. Antioxidant and cytoprotective activities of *Piper betle*, *Areca catechu*, *Uncaria gambir* and betel quid with and without calcium hydroxide. BMC. Comp. Alt. Med. 2013; 13(1):351.
65. Serhan CN, Ward PA, Gilroy DW. Fundamental of inflammation. New York: Camb. Univ. Press. 2010;1-39.
66. Shalini Goyat, Grewal, Anita. Singh, Devendra. Katiyar, R. Tewari, Shri. Nainwal, Rakesh Bindu K. Evaluation of genetic diversity of *Piper betle* cultivars using ISSR markers. Int. J. Adv. Res. 2016;4:571-579.
67. Sharma S, Khan IA, Ali I. Evaluation of the antimicrobial, antioxidant, and anti-inflammatory activities of hydroxychavicol for its potential use as an oral care agent. Antimicrob. Agen. Chemother. 2009;53(1): 216–222.
68. Shah Sk, Garg G, Jhade D, Patel N. *Piper betle*: phytochemical, pharmacological and nutritional value in health management. Int. Journ. Pharma. Sci. Rev.Res. 2016; 38:181-189.

69. Shibata M, Ohkubo T, Takahash H. Modified formalin test: characteristic biphasic pain response. 1989;38(3): 347-352.
70. Singla R, Ganguli A, Ghosh M, Sohal S. Evaluation of sanitizing efficacy of acetic acid on Piper betle leaves and its effect on antioxidant properties. Int J Food Sci Nutr. 2009;7:297–307.
71. Smilowitz NR, Naoulou B, Sedlis SP. Diagnosis and management of type ii myocardial infarction: increased demand for a limited supply of evidence. Curr. Athero. Rep. 2015; 17(2):1-7.
72. Toprani R, Patel D. Betel leaf: Revisiting the benefits of an ancient Indian herb. South Asian J. Cancer. 2013;2(3):140-141.
73. Trakranrungsie N, Chatchawanchonteera A, Khunkitti W. Ethnoveterinary study for antidermatophytic activity of *Piper betle*, *Alpinia galanga* and *Allium ascalonicum* extracts sin vitro. Res. Vet. Sci. 2008; 84(1):80–84.
74. Venkadeswaran K, Muralidharan AR, Annadurai T, Ruban VV, Sundararajan M, Anandhi R, Thomas PA, Geraldine P. Antihypercholestrolemic 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. Evid. Comple. Alt. Med.; 2014.
75. Verma A, Kumar N, Ranade S. Genetic diversity amongst landraces of a dioecious vegetatively propagated plant, betel vine (*Piper betle* L.). J. Biosc. 2004;29: 319–328.
76. Walter TM, Sofia HN. Effect of consumption of thamboolam (conventional betel chewing) trad. Sid. Med; 2007.
77. Waris G, Ahsan H. Reactive oxygen species: role in the development of cancer and various chronic conditions. J. Carcino. 2006;5(1)14.
78. Widowati W, Wijaya L, Wargasetia TL. Antioxidant, anticancer, and apoptosis-inducing effects of Piper extracts in HeLa cells. J. Exp. Integ. Med. 2010;3(3):225-30.
79. Wirotasangthong M, Inagaki N, Tanaka H, Thanakijcharoenpath W, Nagai H. Inhibitory effects of Piper betle on production of allergic mediators by bone marrow-derived mast cells and lung epithelial cells. Int. Immune. 2008;8: 453-457.
80. Yin Y, Huang XZ, Wang J, Dai JH, Liang H, Dai Y. Studies on the chemical constituents of the stems of Piper betle. Zhong Yao Cai. 2009;32:887–890.
81. Zakaria ZA, Balan T, Suppaiah V. Mechanism (s) of action involved in the gastroprotective activity of *Muntingia calabura*. J. Ethnopharmaco. 2014;151(3): 11.

© 2023 Panda and Panda; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<https://www.sdiarticle5.com/review-history/99410>