# Piper betle Linn: A Review of Medicinal Properties and Future Prospects

Dr. Nirbhay Kumar[1*], Shyamla Srivastava[1], Dr. Ankita Kumari[1], Dr. Archana[1], Dr. Bipin Kumar[2]and Dr. Kaushal Kumar[3]

## Abstract

Piper betle (L) is a popular medicinal plant in Asia. Plant leaves have been used as a traditional medicine to treat various health conditions. It is highly abundant and inexpensive, therefore promotion of further research and industrial development, including in the food and pharmaceutical industries is needed. Many reviews published in recent past shown recent updates on the pharmacological properties including antibacterial and antifungal properties of betel leaves. This current review showed that betel leaves extract, essential oil, preparations, and isolates could inhibit microbial growth and kill various Gram-negative and Gram-positive bacteria as well as fungal species, including those that are multidrug-resistant and cause serious infectious diseases. P. betle leaves displayed high efficiency on Gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa, Gram-positive bacteria such as Staphylococcus aureus, and Candida albicans. The ratio of MBC/MIC indicated bactericidal and bacteriostatic potential of P. betle leaves, while MFC/MIC values showed fungicidal and fungistatic effects. This review also provides a list of phytochemical compounds in betel leaves extracts and essential oils, safety profiles, and value-added products of betel leaves. Some studies also showed that the combination of betel leaves extract and essential oil with antibiotics (streptomycin, chloramphenicol and gentamicin) could provide potentiating antibacterial properties. Moreover, this review delivers a scientific resume for researchers in respective areas and manufacturers who want to develop betel leaves-based products.

Keywords: Antibacterial, Antifungal, Betel leaves, Piper betle.

## Introduction

Piper betle Linn. commonly known as betel vine belongs to the genus Piper of plant family Piperaceae. In traditional medicine practices, betel leaves are used as a gargle mouthwash in India and Thailand (Chowdhury and Baruah, 2020), as a treatment for dental problems, headaches, arthritis, and joint pain in Malaysia (Fazal et al., 2014), and for vaginal douching in Indonesia (Joesoef et al., 1996). In Srilanka, the betel leaf juice is used to treat skin ailments (Arambewela et al., 2010). Although betel vine has been cultivated in Sri Lanka for centuries, very few research activities have been carried out on it, except studies on antiaphrodisiac activity (Ratnasooriya and Premakumara, 1996) antifertility effects on male rats (Ratnasooriya and Premakumara, 1997) and antimotility effects on washed human spermatozoa (Ratnasooriya et al., 1990) However, P. betle grown in other countries has been shown to possess antimicrobial (Nair and Chanda, 2008) gastroprotective (Majumdar et al., 2003) wound healing (Santhanam and Nagarajan, 1990) hepatoprotective (Saravanan et al., 2002) and antioxidant (Dasgupta and De, 2004) activities. Traditional applications of betel leaves are related to their antibacterial and antifungal properties.

The essential oil of betel leaves possess anti-bacterial, anti-protozoan and anti-fungal properties. From the study, it is known that the aqueous extract of betel vine reduces the adherence of early dental plaque bacteria (Punuri et al., 2012). It is also found that betel has significant anti proliferative activity in vitro and in vivo prostate cancer models (Paranjpe et al., 2013). Betel leaves consist of the most abundant phytochemicals i.e. hydroxychavicol which contributes to the antiproliferative efficacy of betel leaf extract (Gundala et al., 2014). This phenolic compound of betel leaf inhibits prostate cancer through ROS driven DNA damage and apoptosis (Gundala et al., 2014).

In this paper, a review of the literature was conducted to display recent studies on the medicinal properties of betel leaf extract (BLE), essential oil (BLEO), preparations, and isolates. In addition, the phytochemical constituents, safety profiles, and Future prospects of betel leaves are also provided.

✉ Dr. Nirbhay Kumar
drnkvet@gmail.com
1. Department of Veterinary Pharmacology & Toxicology, Bihar Veterinary College,Patna
2. Department of Veterinary Medicine, Bihar Veterinary College, Patna
3. Department of Veterinary Pathology , Bihar Veterinary College, Patna

## Phytochemicals of Betle Leaves

### Betel Leaves Extract (BLE)

A preliminary phytochemical analysis of betel leaves from Malaysia showed that alkaloids, tannins, glycosides, reducing sugars and saponins were found in the water extract of betel leaves (Kaveti et al., 2011) Moreover, a study determined the total content of phenol, flavonoid and tannin in water, ethanol, ethyl acetate, acetone, and dichloromethane extracts of betel leaves from Mauritius (Taukoorah et al., 2016). The highest total phenol, flavonoid, and tannin were found in the acetone, dichloromethane, and ethanol extracts, respectively.

A study on the sample of betel leaves collected from Tamilnadu, India determines that it contain steroids, tannins, proteins, amino acids, flavonoids, terpenoids, mucilage, volatile oil, saponin, carbohydrates, and fixed oil, but an absence of alkaloids (Periyanayagam et al., 2012). Furthermore, some studies have effectively isolated bioactive compounds from BLE such as phytol, acyclic diterpene alcohol, 4-chromanol, hydroxychavicol or 4-allylpyrocatechol, and allylpyrocatechols (Srinivasan et al., 2016; Teanpaisan et al., 2017; Ali et al., 2018; Kurnia et al., 2020).

### Betel Leaves Essential Oil (BLEO)

Betel leaves contain 0.15% to 0.2% essential oil which are classified as monoterpenes, sesquiterpenes, phenylpropanoids, and aldehydes.GC-MS analysis of BLEO from different places in India showed that phenylpropanoid groups such as acetyl eugenol, eugenol, chavicol, and safrole were the major components (Karak et al, 2018). The study also revealed that BLEO contained eugenol (40%) and a combination of carvacrol and chavicol (up to 40%) with chavibetol as a marker compound. Meanwhile, another study found additional main compounds including estragole, linalool, -copaene, anethole, and caryophyllene -terpinene, p-cymene, 1,8-cineole, β-caryophyllene, -humulene, allyl pyrocatechol, allylcatechol, methyl eugenol, estragol (methyl chavicol), chavibetol, chavibetol acetate, safrol, 4-allyl-2- methoxy-phenolacetate, and 3-allyl-6-methoxyphenol (Prakash et al., 2010; Salehi et al., 2019; Madhumita et al., 2019).

## Therapeutic and Biological Activities of Piper Betle

The objective here is to reveal the potential effect of this plant against different diseases. Along with its traditional medicinal uses which signify its tremendous potential, it is also used towards cure of many antimicrobial ailments of great concern. The leaf extract and purified compounds are found to play a vital role and are of immense benefits in oral hygiene, anti-diabetic, cardiovascular, anti-inflammatory, and anti-ulcer. The active compounds isolated from leaf and other parts have great therapeutic role.

### Antibacterial activity

The extract, essential oil, preparation, and isolated compounds of betel leaves are effective against numerous Gram-negative and Gram-positive bacteria. A study showed that the ethanol extract of betel leaves was more effective than the water extract with greater inhibition zones. The ethanol extract at 50-100 µg/mL had the maximum inhibition zones (8.9–11.0 mm) on E. coli and moderate inhibition was observed on P. aeruginosa (<7.2mm). Meanwhile, the water extract at 50 µg/mL did not actively inhibit bacterial growth (Kaveti et al., 2011). Another investigation using the agar well diffusion method showed that the ethanol extract of betel leaves showed greater inhibition zones on Gram-negative than Gram-positive bacteria (Teanpaisan et al., 2017). Acetone and ethyl acetate extracts demonstrated the most remarkable activity against the six bacteria tested, with S. aureus being the most susceptible one. Moreover, the antibacterial property of BLEs was related to their phenol and flavonoid contents (Taukoorah et al., 2016). Other than the inhibition zone, the antibacterial activity was also presented as minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). MIC is defined as the lowest concentration of samples that inhibits microbial growth. Meanwhile, MBC is the lowest sample concentration at which 99.9% of the bacteria are killed (Mogana et al., 2020). For easier comparison, the MIC and MBC values from published articles were recalculated from µg/mL, mg/mL, and µg/µL to percentage (w/v or v/v).

The most frequently studied Gram-negative bacteria were laboratory strains of E. coli and P. aeruginosa with MIC range from 0.03 to 0.4% and 0.05–0.4%, respectively (Tan and Chan, 2014; Aumeeruddy-Elalfi et al., 2015; Valle et al., 2015; Rashida et al., 2016; Roy and Guha, 2018; Mogana et al., 2020; Yoonus et al., 2020). Meanwhile, the lowest MIC (0.0156%) among Gram-negative bacteria was documented for clinical isolates of P. aeruginosa MβL (+) 3, A. baumannii MβL(+) 2, and P. aeruginosa MβL(+) 3 (Valle et al., 2016). Additionally, S. aureus was the most commonly used Gram-negative bacteria to screen the antibacterial effect of betel leaves with MIC range from 0.00025 to 0.15% (Roy and Guha, 2018; Valle et al., 2015; Yoonus et al., 2020). The lowest MIC among Gram-positive bacteria was recorded for an oral pathogen Streptococcus gordonii DMST 38731 (0.00005%) (Phumat et al., 2017).

In this review, the MBC/MIC ratio was also measured to show the bacteriostatic and bactericidal effects of betel leaves. If the ratio is 2, the samples are considered to be bactericidal agents. The

bacteriostatic mode of action is reflected when the ratio is  4 (Abdi and Kerro Dego, 2019). BLEO showed only a bactericidal effect and BLE was found to be bacteriostatic and bactericidal. The bactericidal action was reported against Gram-negative and Gram-positive bacteria, including those classified as MDR bacteria such as ESβL-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE), Metallo-β-lactamase (MβL)-producing P. aeruginosa and A. baumannii, MRSA, and VRE. On the other hand, a bacteriostatic effect was only observed against Gram-positive bacteria Streptococcus gordonii.

A previous study proved the promising antibacterial effect of BLE against oral pathogens including Gram-positive cariogenic bacteria and Gram-negative periodontal pathogenic bacteria. The study also found that 4-chromanol was the compound responsible for the antibacterial and antibiofilm properties of BLE (Teanpaisan et al., 2017). Another study discovered the ability of BLE to control biofilm formation of Vibrio harveyi (Srinivasan et al., 2017). The antibacterial effect of BLE was dose-dependent. BLE was also found to be effective in reducing biofilm formation and extracellular polymeric substance production caused by P. aeruginosa and bacterial consortium without increasing the selective pressure for the growth of microorganisms (Siddiqui et al., 2012). Additionally, the ethyl acetate extract of betel leaves could act as antibiofilm agents against the nosocomial pathogen Serratia marcescens through the inhibition of quorum sensing mediated virulence factors production such as protease and lipase (Srinivasan et al., 2016). Piper betle was the only plant that showed potent bactericidal activity against all the bacteria tested with an MBC/MIC ratio between 1 to 2 (Valle et al., 2015).

The study also revealed that ethyl acetate fraction showed the strongest antimicrobial activity compared to hexane and ethanol fractions and crude ethanol extract. Further, the ethyl acetate fraction showed higher inhibition zones and MIC against Streptococcus gordonii than the positive control (chlorhexidine solution) (Phumat et al., 2017).

The synergistic effect was found in a combination of ethyl acetate or acetone extract of betel leaves and streptomycin and chloramphenicol against P. aeruginosa, S. aureus, Propionibacterium acnes, Staphylococcus epidermidis, and Streptococcus pyrogens. The highest synergy was observed when the acetone extract and chloramphenicol combination (70:30) was used against P. aeruginosa.

The antibacterial activity of silver-BLE nanoparticles was found to be similar to standard drug (Norfloxacin) against S. aureus. The nanoparticles also exhibited a bacteriostatic effect on Salmonella typhi, E. coli, and P. aeruginosa. Moreover, the previous study concluded that Gram-positive bacteria are more susceptible to silver-BLE nanoparticles rather than Gram-negative bacteria (Rashida et al., 2016). Another study also developed the green synthesis of CaO nanoparticles using the water extract of betel leaves. It showed maximum and minimum activity against E. coli and Streptococcus mutans, respectively (Yoonus et al., 2020). Additionally, BLEO based nanoemulsion was observed to be effective against five strains of foodborne pathogens and can be used as a promising natural antibacterial agent in the food system (Roy and Guha, 2018). The isolated phenolic compound of BLE, namely hydroxychavicol or allylpyrocatechols, were tested against Streptococcus sanguinis, a Gram-positive bacterium that contributes to caries (Kurnia et al., 2020). The compound was a moderate antibacterial agent that functioned by blocking MurA that causes bacterial cell wall disruption. The result exhibited the potential of betel leaves as an alternative effective and efficient treatment for mechanical plaque removal through inhibition of bacterial growth. The isolate could also kill Streptococcus intermedius and S. mutans by a similar mechanism mentioned above. The study showed that the killing kinetic of 4-allylpyrocatechol was dose and pathogen dependent (Phumat et al., 2020). The overgrowth of these bacteria develops many serious oral infections and are the major cause of caries, gingivitis, and chronic periodontitis (Faran Ali and Tanwir, 2012).

## Anti-fungal activity

Numerous methods have been applied to test the antifungal properties of betel leaves. MFC/MIC ratio to determine fungicidal and fungistatic effects, were also conducted. Candida albicans was the most screened fungal species with MIC ranging from 0.01% to 0.07% (Ali et al., 2010; Aumeeruddy-Elalfi  et al., 2015; Phumat et al., 2017; Kaypetch and Thaweboon, 2018; Sivareddy et al., 2019].

Meanwhile, the fungistatic effect was only recorded from hexane and ethyl acetate extract of betel leaves against C. albicans, and its isolate, hyroxychavicol, against C. krusei. Ethanol and ethyl acetate extracts of betel leaves were found to be effective against C. albicans isolated from oral thrush patients. The ethyl acetate extract demonstrated the highest inhibition zone compared to extracts from another plant (Ocimum sanctum) and a standard drug (fluconazole) (Sivareddy et al., 2019). Other studies have also demonstrated the greater antifungal activity of ethyl acetate extract compared to hexane and ethanol extracts of betel leaves (Pawar et al., 2017; Phumat et al., 2017). The killing kinetic study revealed that the fungistatic activity of the ethyl acetate extract was concentration-dependent.

Furthermore, other research showed the anticandidal action of water extract from betel leaves. This effect was possibly related to its ability to reduce the cell surface hydrophobicity of several Candida species. Hydrophobic domains in fungal surface proteins which consist of non-polar amino acids are a major factor involved in fungal adhesion. Thus a deviation in hydrophobic affinity produced by P. betle extract may influence the adherence mechanism of the fungal cell (Nordin et al., 2013).

Some research investigated the antifungal activity of BLEO. A study showed that antifungal and aflatoxin suppressor actions of BLEO are related to its main components such as eugenol (Karak et al., 2018; Aiemsaard and Punareewattana, 2017). Eugenol contains a hydroxyl group that could form hydrogen bonds

with the active site on fungal enzymes that are responsible for aflatoxin secretion and later causes denaturation (Bluma et al., 2008). Eugenol was also reported to induce fungal morphological abnormalities by changing or disrupting fungal cell wall structure, increasing cell membrane fluidity and permeability, and interfering with important regulator function (De Oliveira Pereira et al., 2013).

The study revealed that BLEO was the strongest fungicidal agent with the lowest MIC against all the ATCC strains and clinical isolates fungi tested (Aumeeruddy-Elalfi et al., 2015). A formula of BLEO based microemulsion showed tremendous fungi toxic activity against a selected mold in raw apple juice at low concentration (<0.5µlit./ml). Meanwhile, spore inactivation of A. flavus and P.expansum by BLEO was found at a greater concentration (15microlit./ml).

Hydroxychavicol or 4-allylpyrocatechol isolated from betel leaves was also reported to be effective against various fungi species. The killing ability of hydroxychavicol against C. albicans and C. glabrata was dose-dependent. Hydrochavicol demonstrated fungicidal effects against other clinical isolates fungi, with the MICs ranging from 7.81 to 62.5 µg/mL for dermatophytes, 15.62 to 500 µg/mL for yeasts, and 125 to 500 µg/mL for Aspergillus species, while the MFCs were found to be equal or two-fold higher than the MICs (Ali et al., 2010). Moreover, it could prevent biofilm formation and promote biofilm eradication (Ali et al., 2010; Plumat et al., 2020). The development of a biofilm, which is a network of microbial cells tightly adsorbed at the mucosal surface, is linked to a severe infection (Pozo, 2018).

## Anti-diabetic activity

The aqueous extract of betel leaves possess marked hypoglycaemic activity when tested in fasted normoglycaemic rat (Chandra et al., 2011). In glucose tolrence test, both extracts markedly reduced the external glucose load. The leaf suspension, significantly reduces the blood glucose level, glycosylated haemoglobin and decreased activities of liver glucose-6-phosphatase and fructose-1, 6- bisphosphatase, whereas liver hexokinase increased in Streptozocin (STZ) diabetic rats compared with untreated diabetic rats. The ability of lowering blood glucose level of Streptozocin (STZ) induced diabetic rat gives a suggestion that the extract have the insulinomimetic activity (Ramji et al., 2002; Arambewela et al., 2005).

Study evaluated the possibility of P. betle as a neutraceutical for diabetes mellitus patients. Patients were treated with either P. betle or triphala (an herbal antidiabetic drug). Results demonstrated the ability of P. betle capsules made from spray dried powder of betel hot water extract as a potential treatment for type 2 diabetes patients (Bhattacharya et al., 2005).

## Gastro-protective activity

The hot water extract significantly increased the mucus content adhering to the wall of the gastric mucosa. Mucus layer is considered to be important in mucosal defences against endogenous aggressors, e.g., acids, and also as an agent in facilitate the repair process. It is generally believed that enhanced acid secretion is the most important factor for the induction of gastric lesions. The higher dose of hot water extract does not cause significant inhibition in acidity or pH of gastric fluid. Therefore, gastroprotective effect of piper betel was not mediated via inhibition of acid secretion in the gastric mucosa but by increasing its mucus content. The gastroprotective activities of the higher dose of hot water extract significantly greater than Misoprostol (Rahmatullah et al., 2009). The extensive research has been proven that anti-oxidants might be effective mechanism not only in protecting against gastric mucosal injury, but also inhibiting progression of gastric ulceration. Ulceration progression is caused by free radical-induced chain process. Consequently, its arrest by radical scavengers helps in the faster healing (Majumdar et al., 2003; Arambewela et al., 2004). Allylpyrocatacol has shown a powerful anti-oxidant potential in various in-vitro models. Treatment with Allylpyrocatacol significantly accelerated the ulcer-healing process, which increases the mucus production usually assist the healing process by protecting the ulcer crater against irritant stomach secretion (HCl and Pepsin) thereby enhancing the rate of local healing process (Bhattacharya et al., 2007).

## Antioxidant activity

Oxidative damage is an important effect of ionizing radiation on biological membranes. It is a chain reaction (Verma et al., 2010). Free radicals generated from the radiolytic decomposition of water can attack fatty acid chains of membrane lipid. A free radical that has sufficient energy to abstract an allylic hydrogen from the methylene carbon of polyunsaturated fatty acids can initiate the per oxidative process. Here the presence polyphenols compounds like chatecol, allylpyrocatecol etc. in betel leaf extract inhibited the radiation induced lipid peroxidation process effectively. This could be attributed to its ability to scavenge free radicals involved in initiation and propagation steps (Parillon, 2006). The extracts reduced most of the Fe3+ ions and possess strong reductive ability (Manigauha and Maheshwari, 2009). The extract also showed strong hydroxyl radical and superoxide anion radical scavenging property when compared with different standards such as ascorbic acid and BHT (Rathee et al., 2006; Dasgupta and De, 2004; Arambewela et al., 2006; Pin et al., 2010).

## Safety Profile of Piper Betle

An acute toxicity study in both male and female ICR mice showed the safety of the methanol extract of betel leaves orally. The median lethal dose (LD50) of the extract was higher than 5000 mg/kg body weight (Al-Adhroey et al., 2010). There was also an evaluation of oral acute and sub-acute toxicity (28 days) and genotoxicity of an herbal formulation containing betel leaves alcoholic extract in rats and cellular models. This study revealed the absence of major adverse reactions (Sengupta et al., 2012). Moreover, betel leaves were considered safe in terms of hematotoxicity, hepatotoxicity, genotoxicity, weights of organs, gross morphology, stress, or aversive behaviors in rats (Arambewela et al., 2011). Another study discovered the nontoxicity of the ethanol extract of betel leaves on normal human dermal fibroblasts (HDFn) (Valle et al., 2016).

Neither extract significantly changed any of the serum parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine] and hematological [red blood cell (RBC) counts, white blood cell (WBC) counts and haemoglobin (Hb) concentration] parameters investigated. All the tested organs (liver, kidneys, testes, adrenal glands, heart, spleen, vasa differentia, prostate glands, seminal vesicles together with coagulating glands and caput plus corpus epididymis) appeared normal in all treated rats.

There were no significant changes in the organ weights between the treated groups except for the spleen. Compared to the control, in both treated groups significant increase in weight of the spleen was evident (CEE- 217.4%; HWE- 234.8%). Gastric lesions were not observed in any of the treated rats showed normal food intake, water intake, and their percentage weight gain significantly reduced. The consistencies of feces and color of urine in CEE and HWE treated rats were essentially similar to those of therefore future herbal drug preparations and development. This hitherto untapped vast potential of betel grown in Sri Lanka, if properly harnessed, will safeguard the betel industry of Sri Lanka, enhance the livelihood of a large number of villagers depending on betel industry and introduce novel herbal products and drug preparations into the market.

## Conclusion

The medicinal importance of the herb as discussed above evidently prove that betel leaf is one of the most promising commercial botanical with earlier reported to possess a lot of therapeutic values. The leaf has the great potency to act as natural antioxidant. The anti-oxidant property is correlated with different biological activities like hepatoprotective, antidiabetic, antiarthritis, anti-stroke and anticancer properties, since free radicals are involved in all these diseases. The leaf possesses the broad spectrum antimicrobial activity against various bacterial strains including Bacillus cereus, Pseudomonas Aeruginosa, Escherichia coli, Micrococcus luteus, Staphylococcus aureus, Aeromonas hydrophila, etc.

The leaf extract shows the gastro-protective activity by enhancing the mucus rather than decrease the acid production. Chewing of betel leaf not only accelerating the salivation but also enhances the gastric juice, pancreatic lipase secretion which aids in digestion process. This may the reason for which traditionally pan was chewed after eating.

Chewing of betel leaf increases salivation which increases the contents of peroxidase, lysozyme and antibodies to combat bacterial growth in the oral cavity. It is the best choice for oral hygiene because while chewing bio-active phytochemicals are released into the oral cavity. The betel leaves are also reported to possess anti-mutagenic and anticarcinogenic properties particularly against the tobacco carcinogens due to presence of phytoconstituents like hydroxychavicol and chlorogenic acid. The aqueous leaf suspension has significant reduction in blood glucose level, act same as insulinomimetic.

Considering the above properties, it can be concluded that betel leaf places its position in nature same as our heart in our body and play the role, same with lots of biological activities and has a tremendous strength to come out as a future green medicine, hence Piper betle L. leaf is regard as “Golden heart of Nature”.

The antibacterial and antifungal properties and safety profiles of betel leaves firmly support their application in the development of various products, especially in the food and pharmaceutical industries. The utilization of betel leaves in producing modern-commercial goods could increase the economy of local farmers, specifically in Asia. A good agricultural process should be applied to the farm to yield standardized raw material and should be followed by a good manufacturing process in industries to form high-quality final products. Additionally, clinical studies should be conducted to support the use of betel leaves in medical fields. Researcher, government, and manufacturer collaboration could facilitate this necessary task.

## Future Prospects

Piper betle is a good candidate for future herbal drug preparations and development. In recent years, multiple drug resistance has developed due to indiscriminate use of existing antimicrobial drugs in the treatment of infectious diseases. These problems stress a transformed attempt to find the antimicrobial agents effective against the pathogenic microorganisms’ resistant to current antibiotics. Therefore, there is an extensive requirement to establish alternative antibacterial molecules for the treatment of infectious diseases from other sources. From this review, it can be concluded that phenolic antibacterials from betel leaf cause suppression of bacterial activity in the oral cavity and prevents halitosis. Activity-directed purification led to the identification of allylpyrocatechol (APC) possessing antimicrobial activity against oral bacteria, Staphylococcus aureus. Crude aqueous extract of P. betel was found effective against other oral microbes, which causes changes in the ultra-structure and its acid-producing properties like Streptococci, Lactobacilli, Staphylococci, Corynebacteria, Porphyromonas gingivalis and Treponema denticola. Gram positive bacterial strains were

found to be more susceptible. It may be due to that cell wall of gram positive bacteria is less complex and lack natural sieve effect against large molecules due to small pores in their cell envelope.

Essential oil obtained from leaf extract may be commercialized by used as active pharmaceutical ingredient in different oral care product like toothpaste, mouthwash, mouth fresheners to get maximum result against dental pathogens. Due to high phenolic content in the leaf, the plant poses high antioxidant activity. Other pharmacological activities like antiulcer, antidiabetic, immunomodulatory, cardiovascular and anticancer were demonstrated in last two decades. P. betel also offers a possibility for use in drug delivery though buccal mucosa by passing the gastric route, where drug has to endure gastric acidic pH. This route of administration may be beneficial for those pharmaceutical drugs which acid labile i.e., degrading in the acidic medium.

The betel leaf may enhance the bioavailability of a drug because of its nature as described by “Bhabaprakash” (Virya: Ushan). It supposed to elevate the temperature of plasma fluid which may ultimately fasten the drug absorption, hence the betel leaf may be used as natural bio enhancer. The leaves are very nutritive and contain substantial amount of vitamins and minerals. The leaves also contain the enzymes like diastase and catalase besides a significant amount of all the essential amino acids except lysine, histidine and arginine, which are found only in traces; hence it has great potency to entry to the nutraceuticals industry as food additives.

The utilization of betel leaves in producing modern-commercial goods could increase the economy of local farmers, specifically in Asia. Hence, further critical studies on leaf extract should be necessary for improving its uses for various medicine production. During cultivation, betel vine affected by some diseases that causes great loss to farmers. So, disease identification must be necessary at an early stage and preventive action can be taken before the disease starts to spread.

## Refrences


Abdi, R.D. and Kerro Dego, O. (2019). Antimicrobial activity of Persicaria pensylvanica extract against Staphylococcus aureus. European Journal of Integrative Medicine. 29: 100921.

Aiemsaard, J. and Punareewattana, K. (2017). Antifungal activities of essential oils of Syzygium aromaticum, Piper betle, and Ocimum sanctum against clinical isolates of canine dermatophytes. Science Asia. 43: 223.

Al-Adhroey, A.H., Nor, Z.M., Al-Mekhlafi, H.M., Amran, A.A.and Mahmud, R. (2010) Antimalarial Activity of Methanolic Leaf Extract of Piper betle L. Molecules. 16: 107–118.

Ali, A., Lim, X.Y. and Wahida, P.F. (2018). The fundamental study of antimicrobial activity of Piper betle extract in commercial toothpastes. Journal of Herbal Medicine. 14: 29–34.

Ali, I., Khan, F.G., Suri, K.A., Gupta, B.D., Satti, N.K., Dutt, P., Afrin, F., Qazi, G.N. and Khan, I.A. (2010). In vitro antifungal activity of hydroxychavicol isolated from Piper betle L. Annals of Clinical Microbiology and Antimicrobials. 9: 7.

Arambewela L., Arawwawala M and Rajapaksa D.(2006). “Piper betle: a potential natural antioxidant. International Journal of Food Science and Technology. 41:10–14.

Arambewela L.S., Arawwawala L.D. and Ratnasooriya W D. (2005) “Antidiabetic activity of aqueous and ethanolic extract of Piper betle”. Journal of Ethanopharmacology. 102: 239-45.

Arambewela, L., Arawwawala, M., Withanage, D. and Kulatunga, S. (2010). Efficacy of Betel cream on skin ailments. Journal of Complementary Integrative Medicine. 7 (1): 48.

Arambewela, L.S.R., Arawwawala, L.D.A.M and Ratnasooriya, W.D. (2004) “Gastro protective activities of Sri Lankan Piper betle leaf extracts in rats”, SLAAS, 60th Annual Session, 2004, pp. 117.

Arambewela, L.S.R., Arawwawala, L.D.A.M., Kumaratunga, K.G., Dissanayake, D.S., Ratnasooriya, W.D. and Kumarasingha, S.P. (2011). Investigations on Piper betle grown in Sri Lanka. Pharmacological Reviews. 5: 159-163.

Aumeeruddy-Elalfi, Z., Gurib-Fakim, A. and Mahomoodally, F. (2015). Antimicrobial, antibiotic potentiating activity and phytochemical profile of essential oils from exotic and endemic medicinal plants of Mauritius. Industrial Crops and Products. 71: 197-204.

Bhattacharya S., Subramanian M., Bauri A. and Kamat J.P. (2005). Radioprotecting property of the ethonolic extract of the Piper betel leaf. Journal of Radiation Research. 46:165-171.

Bhattacharya, S., Banerjee, D., Bauri, A.K., Chattopadhyay, S. and Bandyopadhyay, S.K. (2007). “Healing property of the Piper betel phenol, allylpyrocatechol against Indomethacininduced stomach ulceration and mechanism of action”. World Journal of Gastroenterology.13:3705-3713.

Bluma, R., Amaiden, M.R. and Etcheverry, M. (2008). Screening of argentine Plant extracts: Impact on growth parameters and aflatoxin B1 accumulation by Aspergillus section flavi. International Journal of Food Microbiology. 122: 114-125.

Chandra, V., Tripathi, S., Verma N.K., Singh D.P., Chaudhary S.K. and Roshan A. (2011) “Piper betel: phytochemistry, traditional use & pharmacological activity-a review”, International Journal of Pharmacological Research and Development. 4:216 -223.

Chowdhury, U. and Baruah, P. K. (2020). Betel vine (Piper betle L.): A Potential Source for Oral Care. Current Botany. 87 - 92.

Dasgupta, N. and De, B. (2004). Antioxidant activity of Piper betle L. leaf extract in vitro. Food Chemistry. 88: 219-24.

De Oliveira Pereira, F., Mendes, J.M. and De Oliveira Lima, E. (2013). Investigation on mechanism of antifungal activity of eugenol against Trichophyton rubrum. Medical Mycology. 51: 507-513.
Faran Ali, S.M. and Tanwir, F. (2012). Oral microbial habitat: A dynamic entity. Journal of Oral Biology Craniofacial Research. 2: 181-187.
Fazal, F., Mane, P.P., Rai, M.P., Thilakchand, K.R., Bhat, H.P., Kamble, P.S., Palatty, P.L. and Baliga, M.S. (2014). The Phytochemistry, traditional uses and pharmacology of Piper betel. Linn (Betel leaf): A Pan-Asiatic medicinal plant. Chinese Journal of Integrative Medicine. doi: 10.1007/s11655-013-1334-1
Gundala, S.R., Yang, C., Mukkavilli, R., Paranjpe, R., Brahmbhatt, M., Pannu, V., Cheng, A., Reid, M. D. and Aneja, R. (2014). Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis. Toxicology and Applied Pharmacology. 280(1): 86-96.
Joesoef, M. R., Sumampouw, H., Linnan, M., Schmid, S., Idajadi, A. and St. Louis, M.E. (1996). Douching and sexually transmitted diseases in pregnant women in Surabaya, Indonesia. American Journal of Obstetrics and Gynecology. 174: 115 - 119.
Karak, S., Acharya, J., Begum, S., Mazumdar, I., Kundu, R. and De, B. (2018). Essential oil of Piper betle L. leaves: Chemical composition, anti-acetylcholinesterase, anti-β-glucuronidase and cytotoxic properties. Journal of Applied Research on Medicinal and Aromatic Plants. 10: 85-92.
Kaveti, B., Tan, L., Sarnnia, Kuan, T.S. and Baig, M. (2011). Antibacterial activity of Piper betel leaves. International Journal of Pharmacy Teaching & Practices. 2: 129-132.
Kaypetch, R. and Thaweboon, S. (2018). Antifungal property of Piper betle leaf oil against oral candida species. Matec Web Conference. 242: 01021.
Kurnia, D., Hutabarat, G.S., Windaryanti, D., Herlina, T., Herdiyati, Y. and Satari, M.H. (2020). Potential allylpyrocatechol derivatives as antibacterial agent against oral pathogen of S. sanguinis ATCC 10, 556 and as inhibitor of MurA enzymes: in vitro and in silico study. Drug Design Development. 14: 2977-2985.
Madhumita, M., Guha, P. and Nag, A. (2019). Extraction of Betel leaves (Piper betle L.) essential oil and its bio-actives identification: process optimization, GC-MS analysis and anti-microbial activity. Industrial Crops Production. 138: 111578.
Majumdar, B., Chaudhuri, S.G., Ray, A. and Bandyopadhyay, S.K. (2003). Effect of ethanol extract of Piper betle Linn leaf on healing of NSAID - induced experimental ulcer - A novel role of free radical scavenging action. Indian Journal of Experimental Biology. 41: 311-5.
Manigauha A., Ali H and Maheshwari M. U. (2009). “Antioxidant activity of ethanolic extract of Piper betel leaves”. Journal of Pharmacy Research. 2:194-95.
Mogana, R., Adhikari, A., Tzar, M.N., Ramliza, R. and Wiart, C. (2020). Antibacterial activities of the extracts, fractions and isolated compounds from Canarium patentinervium Miq. against bacterial clinical isolates. BMC Complementary Medicine and Therapies. 20: 55.
Nair, R. and Chanda, S. (2008). Antimicrobial activity of Terminalia catappa, Manilkara zapota and Piper betle leaf extract. Indian Journal of Pharmaceutical Sciences. 70: 390-3.
Nordin, M.A.F., Wan Harun, W.H.A. and Abdul Razak, F. (2013). An in vitro study on the anti-adherence effect of Brucea javanica and Piper betle extracts towards oral Candida. Archives of Oral Biology. 58: 1335–1342.
Paranjpe, R., Gundala, S.R., Lakshminarayana, N., Sagwal, A., Asif, G., Pandey, A. and Aneja, R. (2013). Piper betel leaf extract: Anticancer benefits and bio-guided fractionation to identify active principles for prostate cancer management. Carcinogenesis. 34: 1558-1566.
Parillon, H.E.F. (2006). Antimicrobial Activity of Psidium Guajava and Piper Betle Extracts on Selected Foodborne Bacteria. Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia.
Pawar, S., Kalyankar, V., Dhamangaonkar, B., Dagade, S., Waghmode, S. and Cukkemane, A. (2017). Biochemical profiling of antifungal activity of betel leaf (Piper betle L.) extract and its significance in traditional medicine. Journal of Advanced Research in Biotechnology. 2: 1-4.
Periyanayagam, K., Jagadeesan, M., Kavimani, S. and Vetriselvan, T. (2012). Pharmacognostical and phyto-physicochemical profile of the leaves of Piper betle L. var Pachaikodi (Piperaceae) - Valuable Assessment of Its Quality. Asian Pacific Journal of Tropical Biomedicine. 2 (2): S506-S510.
Phumat, P., Khongkhunthian, S., Wanachantararak, P. and Okonogi, S. (2017). Potential of Piper betle extracts on inhibition of oral pathogens. Drug Discovery. 11: 307-315.
Phumat, P., Khongkhunthian, S., Wanachantararak, P. and Okonogi, S. (2020). Comparative inhibitory effects of 4-allylpyrocatechol isolated from Piper betle on Streptococcus intermedius, Streptococcus mutans, and Candida albicans. Archives of Oral Biology. 113: 104690.
Pin K.Y., Chuah A. L., Rashih A. A., Mazura, M.P., Fadzureena1 J., Vimala S. and Rasadah M.A.(2010). “Antioxidant and anti-inflammatory activities of Extracts of betel leaves (Piper betle) from solvents with different polarities”. Journal of Tropical Forest Science. 22:448– 455.
Pozo, J.L.D. (2018). Biofilm-related disease. Expert Review of Anti-Infective Therapy. 16: 51-65.
Prakash, B., Shukla, R., Singh, P., Kumar, A., Mishra, P.K. and Dubey, N.K. (2010). Efficacy of chemically characterized Piper betle L. Essential oil against fungal and aflatoxin contamination of some edible commodities and its antioxidant activity. International Journal of Food Microbiology. 142: 114-119.
Punuri, J.B., Sharma, P., Sibyala, S., Tamuli, R. and Utpal, B. (2012). Piper betle mediated green synthesis of biocompatible gold nanoparticles. International Nano Letters. 2: 18.
Rahmatullah, M., Mukti I.J., Haque, A.K.M.F., Mollik Md.A.H., Kanta P., Jahan R., Chowdhury M.H. and Taufiq R. (2009). “An Ethnobotanical Survey and Pharmacological Evaluation of Medicinal Plants used by the

Garo Tribal Community living in Netrakona district, Bangladesh". Advances in Natural and Applied Sciences. 3: 402-418
Ramji N., Ramji N., Iyer R. and Chandrasekaran S. (2002). "Phenolic antibacterial from Piper betle in the prevention of halitosis". Journal of Ethonpharmacology. 83:149-152.
Rashida, M., Islam, I., Haque, A., Rahman, A., Hossain, T. and Hamid, A. (2016). Antibacterial activity of polyaniline coated silver nanoparticles synthesized from Piper betle leaves extract. Iranian Journal of Pharmaceutical Research. 15: 591-597.
Rathee J. S., Patro B.S., Mula S., Gamre S., and Chattopadhyay S.,(2006). "Antioxidant Activity of Piper betel Leaf Extract and Its Constituents". Journal of Agriculture Food Chemistry. 54: 9046–9054.
Ratnasooriya, W.D. and Premakumara, G.A. (1996). Piper betle leaves impairs masculine sexual behavior of rats. Medical Science Research. 24: 303-6.
Ratnasooriya, W.D. and Premakumara, G.A. (1997). Piper betle leaves reversibly inhibits fertility of male rats. Vidyodaya Jounal of Science. 7: 15-21.
Ratnasooriya, W.D., Jayawardena, K.G. and Premakumara, G.A. (1990). Antimotility effects of Piper betle (L) leaf extract on washed human spermatozoa. Journal of the National Science Foundation of Sri Lanka 18: 53-60.
Roy, A. and Guha, P. (2018). Formulation and characterization of Betel leaf (Piper betle L.) essential oil based nanoemulsion and its in vitro antibacterial efficacy against selected food pathogens. Journal of Food Processing and Preservation. 42: 13617.
Salehi, B., Zakaria, Z.A., Gyawali, R., Ibrahim, S.A., Rajkovic, J., Shinwari, Z.K., Khan, T., Sharifi-Rad, J., Ozleyen, A. and Turkdonmez, E. (2019). Piper species: A comprehensive review on their phytochemistry, biological activities and applications. Molecules. 24: 1364.
Santhanam, G. and Nagarajan, S. (1990). Wound healing activity of Curcuma aromatica and Piper betle. Fitoterapia. 61: 458-9.
Saravanan, R., Prakasam, A., Ramesh, B. and Pugalendi, K.V. (2002). Influence of Piper betle on hepatic marker enzymes and tissue antioxidant status in ethanol - treated Wistar rats. Journal of Medicinal Food. 5: 197-204.
Sengupta, K.,Mishra, A.T., Rao, M.K., Sarma, K.V.,Krishnaraju, A.V. and Trimurtulu, G.(2012). Efficacy of an Herbal Formulation LI10903F Containing Dolichos biflorus and Piper betle Extracts on Weight Management. Lipids Health and Disease. 11: 176.
Siddiqui, M.F., Sakinah, M., Ismail, A.F., Matsuura, T. and Zularisam, A.W. (2012). The anti-biofouling effect of Piper betle extract against Pseudomonas aeruginosa and bacterial consortium. Desalination. 288: 24–30.
Sivareddy, B., Reginald, B.A., Sireesha, D., Samatha, M., Reddy, K.H. and Subrahamanyam, G. (2019). Antifungal activity of solvent extracts of Piper betle and Ocimum sanctum Linn on Candida albicans: An in vitro comparative study. Journal of Oral Maxillofacial Pathology. 23: 333-337.
Srinivasan, R., Devi, K.R., Kannappan, A., Pandian, S.K. and Ravi, A.V. (2016). Piper betle and its bioactive metabolite phytol mitigates quorum sensing mediated virulence factors and biofilm of nosocomial pathogen Serratia marcescens in vitro. Journal of Ethnopharmacology. 193: 592-603.
Srinivasan, R., Santhakumari, S. and Ravi, A.V. (2017). In vitro antibiofilm efficacy of Piper betle against quorum sensing mediated biofilm formation of luminescent Vibrio harveyi. Microbial Pathogenesis. 110: 232-239.
Tan, Y.P. and Chan, E.W.C. (2014). Antioxidant, antityrosinase and antibacterial properties of Fresh and processed leaves of Anacardium occidentale and Piper betle. Food Bioscience. 6: 17–23.
Taukoorah, U., Lall, N. and Mahomoodally, F. (2016). Piper betle L. (Betel quid) shows bacteriostatic, additive, and synergistic antimicrobial action when combined with conventional antibiotics. South African Journal of Botany. 105: 133–140.
Teanpaisan, R., Kawsud, P., Pahumunto, N. and Puripattanavong, J. (2017). Screening for antibacterial and antibiofilm activity in Thai medicinal plant extracts against oral microorganisms. Journal of Traditional and Complementary Medicine. 7: 172-177.
Valle, D.L., Andrade, J.I., Puzon, J.J.M., Cabrera, E.C. and Rivera, W.L. (2015). Antibacterial activities of ethanol extracts of Philippine medicinal plants against multidrug-resistant bacteria. Asian Pacific Journal of Tropical Biomedicine. 5: 532-540.
Valle, D.L., Cabrera, E.C., Puzon, J.J.M. and Rivera, W.L. (2016). Antimicrobial activities of methanol, ethanol and supercritical $CO_2$ extracts of Philippine Piper betle L. on clinical isolates of Gram positive and Gram negative bacteria with transferable multiple drug resistance. Plos One. 11: 0146349.
Verma S., Gupta M.L., Dutta A., Sankhwar S., Shukla S.K., and Flora S.J. (2010). "Modulation of ionizing radiation induced oxidative imbalance by semi-fractionated extract of Piper betle: an in vitro and in vivo assessment". Oxidative Medicine and Cellular Longevity. 3: 44-52.
Yoonus, J., Resmi., R. and Beena, B. (2020). Greener nanoscience: Piper betel leaf extract mediated synthesis of CaO nanoparticles and evaluation of its antibacterial and anticancer activity. Materials Today Proceedings. 41: 535-540.

* * * * *