Pharmacogn. Res., 2025; 17(4):1077-1097.
https://www.phcogres.com

Review Article

Therapeutic Potentials of *Piper betle* Leaf: Insights into Its Medicinal Uses and Bioactive Compounds

Ruchi Tiwari[1,*], Shivam Verma[1], Pranshul Sethi[2,3], Pijush Dutta[4], Rajesh Devarai[5]

[1]PSIT-Pranveer Singh Institute of Technology (Pharmacy), Kalpi Road, Bhauti, Kanpur, Uttar Pradesh, INDIA.
[2]Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, INDIA.
[3]Department of Pharmacology, College of Pharmacy, Shri Venkateshwara University, Gajraula, Uttar Pradesh, INDIA.
[4]Department of Electronics and Communication Engineering, Greater Kolkata College of Engineering and Management, Baruipur, West Bengal, INDIA.
[5]Department of Botany, SRNK Government Degree College Autonomous Banswada, Kamareddy, (Affiliated to Telangana University Dichpally), Nizamabad, Telangana, INDIA.

ABSTRACT

Plant extracts, composed of bioactive non-nutrient phytochemicals, have historically stood out as a primary reservoir for the development of new leads in anticancer drug research. *Piper betel* (L.), a widely cultivated plant in Asia, particularly renowned for its medicinal properties, has been traditionally employed in treating various health ailments. *Piper betel* L., commonly known as Pan and belonging to the *Piperaceae* family, flourishes in regions like Sri Lanka, India, Thailand, Taiwan, and other Southeast Asian countries. Remarkably, *P. betel* leaves have shown significant effectiveness against various bacteria, including *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans*. The oil extracted from betel leaves holds potential as a raw material in the production of medicines, perfumes, mouth fresheners, tonics, and food additives. Rich in nutrients and possessing anti-carcinogenic properties, betel leaves present a promising avenue for the development of drugs targeting blood cancer. This comprehensive review serves as a scientific compendium for researchers and manufacturers engaged in the development of products derived from betel leaves. Widely dubbed as "Green Gold," betel leaves serve various purposes including stimulation, antiseptic action, and breath freshening. Their diverse properties encompass anti-fungal, anti-bacterial, anti-inflammatory, antimicrobial, antioxidant, antimutagenic, anti-haemolytic, anti-diabetic, and anti-ulcer effects. This review not only furnishes fundamental insights into the manifold effects of betel leaves but also delineates the phytochemical compounds found in their extracts and essential oils, safety profiles, and value-added products.

Keywords: History of betel leaf, Chemical properties, Physical properties, Therapeutic activities.

Correspondence:
Dr. Ruchi Tiwari
Professor, PSIT-Pranveer Singh Institute of Technology (Pharmacy), Kalpi Road, Bhauti, Kanpur-208020, Uttar Pradesh, INDIA.
Email: tiwaridrruchi@gmail.com
ORCID: 0000-0001-6897-3472

Received: 12-04-2025;
Revised: 09-06-2025;
Accepted: 22-08-2025.

INTRODUCTION

Piper betle (L.), commonly referred to as betel vine, is a member of the Piperaceae family, also known as the black pepper family. The term "betel" originates from the Malayalam word "vettila" via Portuguese influence.[1-4] The leaf of the betel vine is the most extensively utilized and researched component. This perennial and evergreen creeper, known as "Paan" and "Nagvalli," holds profound cultural, social, religious, and practical significance, aspects that remain highly relevant in contemporary times. The betel leaf is a perennial and evergreen creeper that has glossy, white, heart-shaped catkins. *Piper betel* is grown in India, Sri Lanka, Malaysia, Indonesia, the Philippines, the Islands, and East Africa. Its yellow aromatic essential oil imbues it with a pungent flavor.[5-8] Betel leaf boasts a multitude of properties, encompassing antioxidant, antifungal, antiulcerogenic, antiplatelet, antidiabetic, immunomodulatory, antileishmanial, antiamoebic, anti-inflammatory, antifilarial, antimicrobial, antifertility, antihyperglycemic, antidermatophytic, and radioprotective attributes (Figure 1). In addition to being utilized for food and spices, the plants in the genus Piper are also used for insecticides, fish poison, hallucinogens, oils, decorations, and perfumes.[9] The plant's leaf has been shown to have a variety of advantageous bioactivities by scientists, and an extract from betel leaves has a lot of promise for application in the creation of manufactured goods. Due to the numerous benefits, betel vines are grown for its leaves.[10] *Piper betel* L. leaves are extensively utilized as a post-meal mouth freshener. This plant is cultivated extensively in Bangladesh, India, Sri Lanka, Malaysia, Thailand, Taiwan, and various other Southeast Asian countries. Blessed are the evergreen and perennial *Piper betel* plants, which bear the

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/pres.20252107

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

imprint of God's heart. In the spirit caves of Northwest Thailand, anthropologists have discovered betel residues that date as far back as 5500-7000 BC—well before the advent of organized and systematic agriculture.[11] The blackened teeth of a human skeleton from Palawan, the Philippines, dating back to 2600 BC, and Timor, Indonesia, dating back to 3000 BC, have both produced comparable discoveries. It was mentioned in the Palli version of the oldest historical book in Sri Lanka, the Mahavamsa. Betel Leaf (BL) has held significant cultural significance in India since ancient times, with its usage dating back to 400 BC.[12] Ancient writings including the Ayurveda, Charka, Sushruta Samhitas, and Kashyapa Bhojanakalpa state that between 75 and 300 AD, the custom of chewing BL after meals spread. By the thirteenth century, European explorer Marco Polo had recorded that Indian monarch and noble chewed betel.[13-19]

Ayurvedic Significance

Piper betel holds a revered status in Vedic literature, where it is referred to as Saptasira, and in Sanskrit, it goes by names such as Tambool, Nagvelleri, and Nagani, valued for its therapeutic properties against diverse ailments. References to Tambool span from ancient texts like Vatsyayana's Kamasutra and Panchatantra to Kalhan's Rajatarngni, spanning approximately 2000 years, making it a consistent subject across significant historical Sanskrit writings.[20-24] In Ayurveda medicine system, the properties of betel leaf described as given below:

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

In Ayurveda, betel leaf extract is commonly employed as an adjunct, often combined with various medicines to potentially enhance their efficacy, in addition to being utilized independently as a remedy. The Sushruta Samhita describes tambool leaves as aromatic, possessing sharp, hot, and acrid properties, beneficial for voice, acting as a laxative and appetizer. Furthermore, they are noted to pacify Vata and aggravate Pitta.[25]

Varieties of betel leaf

The betel vine has multiple variations based on the morphological characteristics, essential oil concentration, leaf blade form, size, brittleness, and flavor (Table 1).

Chemical constituents of *Piper betle*

About 3 to 3.5% protein, 0.5-6.10% carbohydrates, 2.3-3.3% minerals, and 0.1-1.3% tannins are present in the leaves (Figure 2). They are high in potassium, iodine, calcium, phosphorus, iron, and vitamins B, C, and A (Figure 3). They also contain stable oils like terpene and phenol, as well as aromatic chemicals (Table 2).[26] Moreover, there is hydroxychavicol, 1,8-cineole, α-pinene, β-pinene, chavibetol, and eugenol. The main ingredients in common betel are chavibetol acetate (15.5%) and safrole (48.7%). *Piper betel* is also known to include allylpyrocatechol, caryophyllene, anethole, stearic acid, carvacrol, polyphenol, alkaloids, and saponin.[27-31]

The roots were discovered to possess ursonic acid and 3β-acetyl ursolic acid in another study. It was once believed that women would use *P. betle* roots along with black pepper as a kind of birth control. Root of *P. betle* also contain some major constituents like aristololactam A-11, 4-allyl resorcinol, diketosteroid contain stigmast-4-en-3,6-dione (Table 3).[32-39]

Character of *Piper betel* leaf

A verdant leafy vine, exhibiting growth characteristics akin to pepper, serves as ground cover or a modest climber. *Piper betel* leaf, a perennial and dioecious creeper belonging to the dicot family Piperaceae, manifests as robust male vines reaching heights of up to 20 m, with stem diameters ranging from 15 to 20 cm. Thriving in warm, humid climates, this plant prefers environments conducive to growth, albeit it can withstand moderate drought conditions.[40,41] Typically, it thrives within tropical regions, as it is too delicate for cultivation outside such climates. The semi-woody stems of the plant are green or pinkish-green, cylindrical, or bilaterally compressed with dimorphic branching. Betel leaf finds its place in numerous traditional remedies, offering relief from stomach ailments, infections, and serving as a general tonic.[26,40]

Ideal for: well-drained soil and suitable for light (sandy), medium (loamy), and heavy (clay) soils.

Appropriate pH: soils that are somewhat alkaline, neutral, basic, and acidic.

It grows in both semi-shaded (light forest) and full shade (deep woodland). It likes soil that is damp.

THERAPEUTIC EFFECT OF BETEL LEAF

Many natural ingredients have been used as traditional remedies to treat a wide range of illnesses in different cultures. *Piper betel* leaves boast a plethora of pharmacological activities that prove effective against various human pathogens (Table 4). Extracts derived from *Piper betel* have been employed for centuries in the treatment of diverse conditions owing to their intrinsic properties.[41]

Anti-fungal Activity

The creation of natural solutions appropriate for therapeutic use is required to address the negative effects of commercial products and manage candida infections. With the growing recognition of medicinal herbs as a source of antimicrobial agents, natural products have become viable substitutes for synthetic chemical

agents. A tropical plant closely related to pepper, *Piper betle* is commonly grown in Thailand, Malaysia, and India, among other nations in Southeast Asia.[62] *Candida albicans* is the prevalent fungal infection that causes oral candidiasis. Recent evidence of Candida species' resistance to numerous synthetic medications has brought attention to the need for innovative antifungal medications with fewer side effects for the effective treatment of candidiasis. Numerous studies suggest that some plant species may contain compounds with promising antibacterial qualities. The ethanolic extract of leaves and essential oils shown potential antifungal activity against the fungal mycelia of Aspergillus flavus, *Candida tropicalis*, and *Candida albicans*.[63] Methanolic and aqueous leaf extracts, along with betel essential oil, demonstrated significant antifungal efficacy against Malassezia pachydermatis and *Candida albicans*. Furthermore, the hydro distillation-obtained leaf extract showed antifungal efficacy against Saccharomyces cerevisiae and *Candida albicans*. It has also been discovered that adding betel essential oil to tomato paste and apple juice at a safe concentration increases their antioxidant activity and inhibits the growth of microorganisms like *Aspergillus flavus* and *Penicillium expansum*, extending their shelf life in refrigerated environments.[64]

Some Examples of Anti-fungal activity experiments are as follows:

Piper betle's Improved Antifungal Activity Against *Candida albicans* Infection and *in silico* Analysis with its Virulent Protein

The widespread use of synthetic chemical medications frequently results in the evolution of drug resistance in clinical pathogens and increases the likelihood of undesirable side effects in humans. *Candida albicans*, a common pathogen, particularly in oral candidiasis, is a significant concern. This study aims to explore novel natural compounds from the medicinal plant *Piper betle* against *C. albicans*. Bioactive chemicals were extracted from betel leaves with a variety of solvents. The standard medicine, fluconazole, was used to evaluate *P. betle's* anticandidal activity against *C. albicans*. Furthermore, the plant extracts were evaluated using antioxidant and scavenging assays.[65] The biocompounds were identified using gas chromatography-mass spectrometry, followed by molecular docking investigations. Methanol and ethanol extracts outperformed the control medication in terms of antifungal, antioxidant, and scavenging activity against *C. albicans*. *P. betle's* methanol extract contained twenty-seven bioactive components. These molecules were docked with candidapepsin-1, a pathogenic *C. albicans* enzyme, and compared to fluconazole (-7.8 kcal/mol). An effective interaction was reported with a particular bioactive molecule, 4-hydroxy-5-imino-3,4-dimethyl-1-(4-nitrophenyl)-2-imidazolidinone (-7.5 kcal/mol). According to the study, methanol and ethanol extracts of *P. betle* could be used as natural antioxidants with free radical scavenging activities. These findings offer promise for the development of novel medications that target antimicrobial biocompounds to treat candidiasis and other clinically relevant infections.[24,66]

Piper betle leaf oil has antifungal properties against oral Candida species

Fungal infections provide substantial clinical issues due to the extensive use of broad-spectrum antibiotics and immunosuppressive therapy, with candida species being among the most common pathogens. *Piper betle* Linn., a tropical plant closely related to pepper, has long been used as a traditional herb in many Asian nations. The purpose of this study was to determine the antibacterial effectiveness of essential oil derived from fresh *P. betle* leaves against several candida species, such as *C. albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. pseudotropicalis,* and *C. stellatoidia*. Inhibitory activity was first evaluated using the Kirby-Bauer disk diffusion method, and the Minimum Inhibitory Concentration (MIC) was determined using the agar dilution method. Areca nut oil showed antibacterial activity against all yeast species, with an inhibition zone ranging from 32 to 33 mm and MIC values ranging from 0.039 to 0.078% v/v. The results of this study indicate the possibility of using the fruit's oil in the design and production of drugs to treat Candida infections. However, more research is needed to understand the anti-inflammatory properties of this oil and conduct clinical trials in patients.[26,67]

Palladium nanoparticles: A one-step plant-mediated green chemical approach using *Piper betle* leaf broth and anti-fungal investigations

The goal of this research is to use green chemical techniques for the production of metal nanoparticles, which have innovative

Table 1: Regional *Piper betel* Leaf Varieties in India.

Andhra Pradesh
Karapaku, tellaku, bangla, chennor, and kallipatti
Assam
Assam patti, awani pam, bangla and khasi pan
Bihar
Desi pan, Calcutta, paton, maghai and bangla
Karnataka
Kariyale, mysoreale and Ambadiale
Odisha
Godi bangla, nova cuttak, sanchi and birkoli
Madhya Pradesh
Desi bangl, Calcutta and deswari
Maharashtra
Kallipatti, kapoori and bangla (Ramtek)
West Bengal
Bangla, sanchi, mitha, kali bangla and simurali bangla

applications in optical, catalytic, hydrogen storage, bio-imaging, and electrochemical domains. To produce stable Pd0 nanoparticles, a solution of 1 mM $PdCl_2$ and *Piper betle* leaf broth (10:1) is used. UV-vis, XRD, and FTIR spectroscopy are used to evaluate the structural properties of the produced nanoparticles. Additionally, the shape, particle distribution, and size of the palladium nanoparticles are investigated using TEM and SAED techniques. The bioactivity of the produced PdNPs suggests that they could be used clinically as antifungal medications.[28,68]

Anti-Diabetic Activity

Diabetes occurs when insulin-producing β-cells in the pancreas become destroyed, leading to insufficient insulin production and consequently elevated glucose levels in the blood. Glucose, a sugar molecule produced during carbohydrate digestion, is regulated by the hormone insulin. This study looks at the effect of *Piper betel* juice on hyperglycemic blood glucose levels by comparing the hepatoprotective Serum Glutamate Oxaloacetate Transaminase (SGOT) activities in alloxan-induced diabetic mice to those treated with metformin. The study also examines the hypolipidemic effects on Total Cholesterol (TC), Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), and Triglyceride (TG) levels. The extract's antidiabetic effect *in vitro* is measured by inhibiting α-glucosidase enzyme activity. *Piper betel* ethanol has strong antibacterial properties against Gram-positive bacteria, including vancomycin-resistant Enterococcus and methicillin-resistant *Staphylococcus aureus*. The effects of *Piper betel* juice on blood glucose levels are further investigated in hyperglycemic conditions and compared to the hypolipidemic effects and hepatoprotective activities observed in alloxan-induced diabetic mice, in conjunction with metformin treatment.[15,69]

Some Examples of Antidiabetic or anti-hyperlipidemic experiments are as follows:

In STZ-induced diabetic rats, *Piper longum* root aqueous extract exhibited antidiabetic and antihyperlipidemic effects

Existing diabetes medications such as insulin or oral hypoglycemic drugs often have one or more side effects. It is difficult to find new antidiabetic drugs from medicinal plants with minimal or no side effects according to World Health Organization standards. In this context, this study attempted to determine the hypoglycemic and hypolipidemic effects of *Piper longum* root aqueous extract (PlrAqe) on Streptozotocin (STZ)-induced diabetic rats. (STZ) (50 mg/kg.b.w) intraperitoneally. Measure Fasting Blood Glucose (FBG) levels using glucose oxidase and peroxidase antibodies. Various blood chemicals including glycated heme (HbA1c), Total Fat (TC), Triglycerides (TG), Very Low Lipoprotein (VLDL), low-density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) Cholesterol are measured. Liver and kidney function tests were evaluated. Statistical analysis was performed by Student's t test and one-way Analysis of Variance (ANOVA) followed by DMRT. Important exhibits in preventing diabetes. Additionally, administration of the same dose of aqueous extract for 30 days in STZ-induced diabetic rats resulted in a decrease in FBG levels and improvement in diabetic dyslipidemia compared to untreated diabetic rats. In addition, liver function and kidney function were

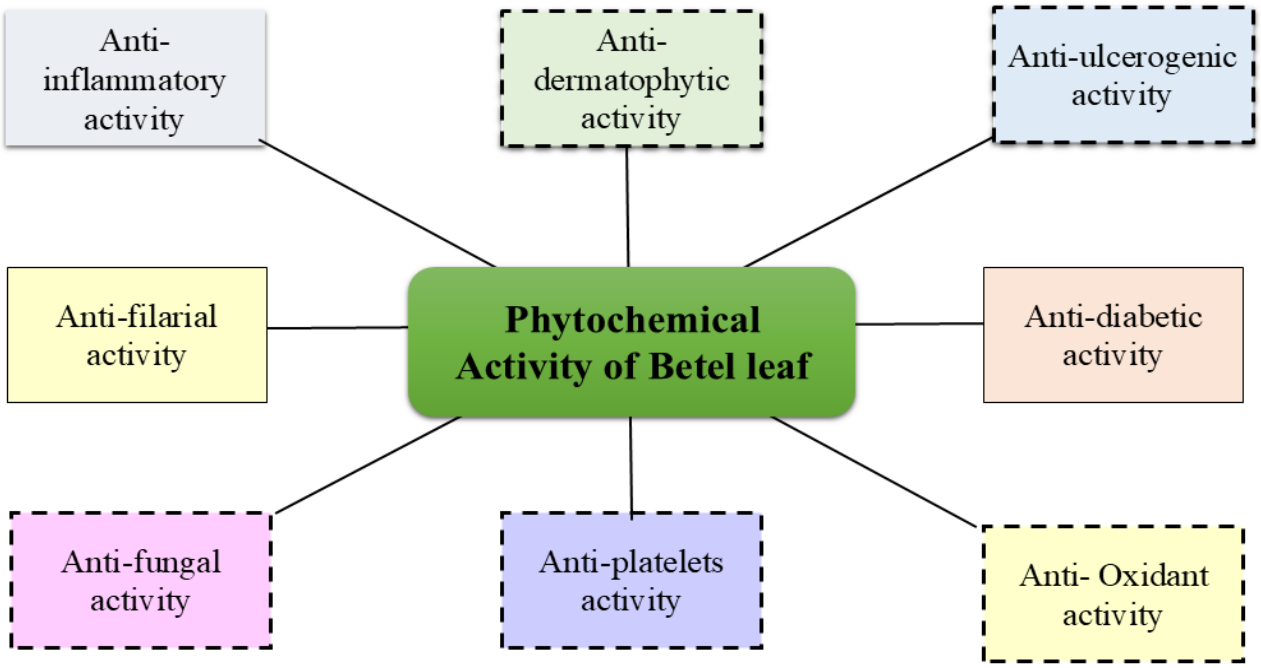

Figure 1: Phytochemical Activity of *betle* leaf.

Table 2: Chemical constituents of *Piper betle* leaf and their uses.

Compound	Molecular formula	Molecular weight	Uses
α-Pinene	$C_{10}H_{16}$	136.23	Both anti-inflammatory and antibiotic.
Camphene	$C_{10}H_{16}$	136.24	Making perfumes and food additives to add flavor.
Sabinene	$C_{10}H_{16}$	136.24	Antimicrobial activity
Myrcene	$C_{10}H_{16}$	136.24	Making food additives and scents.
B-Phellandrene	$C_{10}H_{16}$	136.23	Cleaning supplies, personal hygiene, and cosmetics industries.
B-Ocimene	$C_{10}H_{16}$	136.23	Perfumery
Terpinolene	$C_{10}H_{16}$	136.26	Perfumery and food additive
Cis-sabinene	$C_{10}H_{16}$	136.23	Anti-Infective Agents
Terpineol-4	$C_{10}H_{18}O$	154.25	Fragrance combinations in home goods, polishes, and disinfectants.
Safrole	$C_3H_5C_6H_3O_2CH_2$	162.19	Making drinks and candies
Eugenol	$C_{10}H_{12}O_2$	164.22	In dentistry, antiseptic and anesthetic.
Iso-safrole	$C_3H_5C_6H_3O_2CH_2$	162.19	Fragrance industry
B-Bourbonene	$C_{15}H_{24}$	204.3511	As both Flavour and fragrance agents.
B-Elemene	$C_{15}H_{24}$	204.35628000	Antiproliferative properties; utilized in cancer chemotherapy.
Methyl Eugenol	$C_{11}H_{14}O_2$	178.22	Fragrance component found in detergents, toiletries, and fragrances.
Caryophyllene	$C_{15}H_{24}$	204.35	Anti-inflammatory, anti-cancer, antioxidant, and local anesthetic.
Aromadendrene	$C_{15}H_{24}$	204.35	Both Antioxidants and anti ageing.
B-Farnesene	$C_{15}H_{24}$	204.35	Natural insect repellent
A-humulene	$C_{15}H_{24}$	204.39	Beneficial in lowering platelet activating factor and anti-inflammatory.
Methyl isoeugenol	$C_{11}H_{14}O_2$	178.23	Flavour and fragrance agents
Germacerene-D	$C_{15}H_{24}$	204.4	Both Analgesic and anti-inflammatory properties.
B-Selinene	$C_{15}H_{24}$	204.35628000	Utilized in aromatherapy and having antimicrobial qualities.
A-Selinene	$C_{15}H_{24}$	204.3511	Aroma active compound
A-Farnesene	$C_{15}H_{24}$	204.3511	Plant defence, biofuel precursor.
Hydroxychavicol	$C_9H_{10}O_2$	150.1745	Antimutagenic effect
Eugenyl acetate	$C_{12}H_{14}O_3$	206.24	Anti-virulence potential
A-Cadinene	$C_{15}H_{24}$	204.36	Anticancer activity
Germacerene-B	$C_{15}H_{24}$	204.356	Antimicrobial and insecticidal properties.
E-Nerolidol	$C_{15}H_{26}O$	222.37	Flavouring agent and in perfumery.
Spathulenol	$C_{15}H_{26}O$	220.4	Antibacterial activity
Chavibetol	$C_{10}H_{12}O_2$	164.2	Aromatic compound with a spicy odour.
Allylpyrocatechol Diacetate	$C_{13}H_{14}O_4$	234.25	Antibacterial action on several types of obligatory oral anaerobes.
1,8-Cineol	$C_{10}H_{18}O$	154.28	Used in treatment of inflammatory diseases.

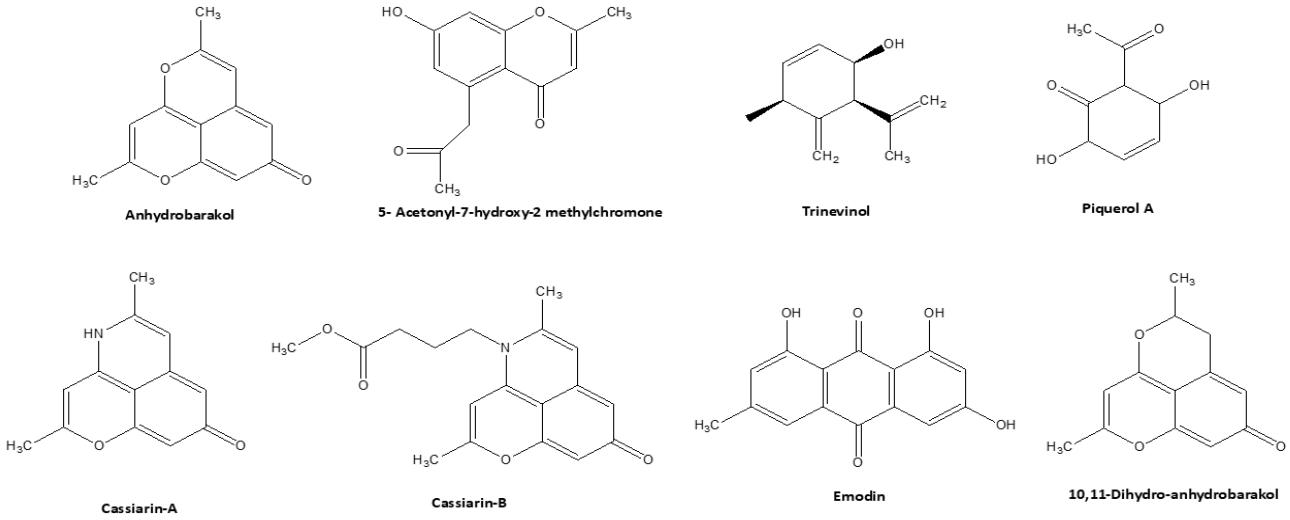

Figure 2: Chemical Structure of some chemical constituents found in *Piper betle leaf.*

Table 3: Chemical constituents on different parts of the *Piper betle* leaf.

Parts of *P. betle*	Chemical constituents
Root	aristololactam A-11 4-allyl resorcinol, diketosteroid contain stigmast-4-en-3,6-dione.
Leaves	1 n dodecanyloxy resorcinol(H1) desmethylenesqualenyl deoxy-cepharadione-A(H4)
Stem	6 beta-hydroxy stigmast-4-ene-3 one beta-sitosterol stigmasterol oleanolic acid 23-hydroxyursan-12-ene-28 oic acid beta-sitosterol-3-O-beta-D glucoside-6'-O-palmitate beta-daucosterol (25)-4'hydroxy-2,3-dihydroflavone 7-O-beta-D glucoside alpha-ethyl glucoside

reduced in diabetic rats compared with non-diabetic rats; This showed that the liquid extract was able to prevent liver and kidney damage while still being non-toxic. It can be concluded that this herb has good potential in the treatment of hyperglycemia and diabetic complications in STZ-induced diabetic rats. Therefore, this plant can be considered as a useful resource for the development of new oral hypoglycemic drugs.[70]

In rats, aqueous and ethanolic extracts of *Piper betle* leaves exhibited antidiabetic activity

The leaves of *Piper betle* (Piperaceae) have many bioactivities and are hired in traditional clinical systems. but, its anti-diabetic pastime has yet to be thoroughly explored. The cause of this study changed into to discover the antidiabetic interest of *Piper betle* leaves. This becomes investigated in normoglycemic and Streptozotocin (STZ)-caused diabetic rats through oral administration of Hot Water Extract (HWE) and Cold Ethanolic Extract (CEE). In normoglycemic rats, both HWE and CEE dramatically decreased blood glucose tiers in a dose-structured way. During the glucose tolerance check, each extract significantly lowered the external glucose load. HWE has antidiabetic impact similar to CEE. Moreover, HWE did now not inhibit glucose absorption from the rats' small gut. Each extract had been proven to be non-poisonous and properly tolerated after prolonged oral remedy (no apparent symptoms of toxicity, hepatotoxicity, or renotoxicity). However, the load of the spleen rose in dealt with agencies, that may indicate lymphoproliferative hobby. Its miles installed that HWE and CEE from *Piper betle* leaves have safe and effective antidiabetic homes.[71]

Piper betle leaf exhibits antihyperglycemic action in streptozotocin-induced diabetic mice

Piper betle, a medicinal plant with a strong reputation in traditional medicine systems like Siddha and Ayurveda, is particularly prominent in rural southern India. This study aimed to investigate the effects of *P. betle* on glucose metabolism, given its common use as betel-quid after meals. Researchers measured plasma levels of glucose and glycosylated hemoglobin, along with the activities of liver hexokinase and gluconeogenic enzymes such as glucose-6-phosphatase and fructose-1,6-bisphosphatase, in both control and Streptozotocin (STZ) diabetic rats. After 30

Table 4: Table showing research on various activities of *P. betle* leaf.

Sl. No.	Objective	Results	Conclusion	References
1.	In patients with conjunctivitis, the antibacterial activity of *betle* leaf extract which inhibits *Staphylococcus aureus*.	By agar well diffusion method and Kruskal-Wallis test. Standard 10% DMSO solution was used to treat negative control group (P-), and ceftriaxone was used to treat the positive control group (P+). The clear zone diameters around the well were examined using the Kruskal-Wallis test. The results that indicated there is no smaller significant difference between concentrations of 1% and 1.5%, 1.5% and 2%, 2% and 2.5%, and 2.5% and 3%, but between concentrations of 0.5% and 1%, 0.5% and 1.5%, 0.5% and 2%, 0.5% and 2.5%, and 0.5% and 3%, 1% and 2%, 1% and 2.5%, 1% and 3%, 1.5% and 2.5%; 1.5% and 3%; 2% and 3%, 1.5% and 2.5%, and 1.5% and 2% and 3%.	*Staphylococcus aureus* growth is significantly inhibited by the leaf extract of *Piper betle* L. In conclusion, *Piper betle* L. leaf extract has a great deal of promise for use as an antibacterial agent.	[42]
2.	*P. betle* extract's antibacterial and antibiofilm properties were evaluated using isolates of *S. pseudointermedius* and Methicillin-Resistant *Staphylococcus pseudintermedius* (MRSP).	By using Broth microdilution, time-kill assays, Polymerase Chain Reaction (PCR), molecular docking. Using time-kill tests and broth microdilution, the antibacterial properties of *P. betle's* ethanol leaf extract was examined with respect to *S. pseudintermedius* and MRSP. Assays for biofilm development and inhibition were used to assess the effects of antibiofilm and biofilm eradication, respectively. Real-time PCR was used to further investigate the expression of genes linked to biofilms (PCR). Using molecular docking, the potential interaction between IcaA and important *P. betle* chemicals was examined.	The antibacterial, antibiofilm, and biofilm-removal properties of *P. betle* extract were exhibited against *S. pseudointermedius* and MRSP. The extract may have affected the formation of biofilms via downregulating the expression of the icaA gene and through protein interactions. As a substitute therapy for *S. pseudointermedius* infections, particularly those linked to biofilm and resistant to existing medications, this extract demonstrated potential.	[43]
3.	Leaf extracts from *Piper betle* L. hinder *Vibrio harveyi*, a shrimp pathogen, from sensing quorum, and shield *Penaeus vannamei* postlarvae from bacterial infection.	This process requires extraction of Crude Extract (CE) and Crude Alkaloids (CA) of *Piper betel* leaves. Rotary evaporation of 800 g of dry *betle* leaves (approximately 10% moisture content) in 6 L of 100% ethanol leads to a yield of 145 g CE or 18.12% (=181.2 mg/g). Phytochemical tests revealed that CEs contained alkaloids, glycosides, sterols, triterpenes, saponins, and tannins.	The development of QS- induced biofilm and bioluminescence in Vibrio spp. and was prevented at low concentrations by the Crude Extract (CE) and Crude Alkaloids (CA) from the *Piper betle* L., without affecting the organism' growth.	[44]
4.	The study examined the antimicrobial properties of Philippine *Piper betle* L. methanol, ethanol, and supercritical CO_2 extracts in clinical isolates of both Gram Positive and Gram-Negative bacteria that exhibited transferable multiple drug resistance.	Plant materials are collected, and ethanol and methanol plant extract are prepared. The 150 g of powdered plant material were steeped in 500 mL of each of absolute ethanol and methanol are separately for seven days, stirring occasionally, before being filtered using Whatman filter paper no.1. A rotating evaporator operated at 50°C and reduced pressure was used to concentrate the filtrate. After being collected, the crude extract was let to dry fully at room temperature. The dried extract was dissolved in 0.2% DMSO at a concentration of 100 mg/mL to create the stock solution. Therefore, using the disc diffusion assay, the 0.2% DMSO was initially evaluated on reference strains of *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853. Disk diffusion method and Broth Microdilution Method are used for antibacterial susceptibility test.	The antibacterial, antibiofilm, and biofilm-removal properties of *P. betle* extract were exhibited against *S. pseudointermedius* and MRSP. The extract may have affected the formation of biofilms via downregulating the expression of the icaA gene and through protein interactions. As a substitute therapy for *S. pseudointermedius infections*, particularly those linked to biofilm and resistant to existing medications, this extract demonstrated potential.	[45]

Sl. No.	Objective	Results	Conclusion	References
5.	*Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aspergillus parasiticus, Candida glabrata, Candida krusei, Candida neoformans, Candida parapsilosis, Candida tropicalis, Epidermophyton floccosum, Trichophyton mentagrophytes, Trichophyton rubrum, Microsporum canis,* and *Microsporum gypseum* have all been studied in relation to the fungicidal effects of betel leaf extract against a variety of fungal species.	Microdilution of broth and well-diffusion Solid dilution and Disk Diffusion.	It has been shown that hydroxychavicol, also known as 4-allylpyrocatechol, which is extracted from betel leaves, is efficient against a variety of fungus species. At as low as 400 μg/mL, this chemical was able to eradicate *C. albicans* entirely.	[46]
6.	Sought to investigate the processes underlying the stem of the *Piper betle* anti-cancer benefits.	In this study, the anti-inflammatory properties of the root extract were evaluated on human oral squamous cell carcinoma cell lines Cal-27 and Ca9-22. Tests include MTT testing, cell morphology measurements, and flow cytometry. Additionally, Western blotting was also performed to examine the effects of apoptotic molecular pathways and cell growth.	The process of apoptotic cell death involves mitochondrial inactivation, which resulted in an upregulation of Bax and Bad expressions and a downregulation of Bcl-2 and Bcl-xl expressions. In addition, the *P. betle* stem extract-induced apoptosis in oral cancer cells involves the activation of p38MAPK and the inhibition of ErbB2 and ErbB3 proteins.	[47]
7.	Impact of *Piper betle* L. extract on cultured umbilical cord cells and possible application in the management of cutaneous wounds.	Isolation of UC-MSCs from Wharton's jelly; Establishment of growth curves and population determination using the automated cell count system, Countess; Immunophenotype analysis; Evaluation of the impact of *Piper betle* L. extract on fibroblasts; Analyzing the effectiveness of *Piper betle* L. extract in scratch experiments on fibroblasts and UC-MSCs to promote wound healing; cDNA synthesis, RNA extraction, and real-time quantitative PCR analysis.	To furnish scientific insights into the properties inherent in betel leaves and to formulate natural pharmaceutical products for treating open wounds. This study investigates the potential of *Piper betle* extract to induce cell line proliferation via in vitro scratch assays.	[48]
8.	Age-related changes in betel leaf (*Piper betle* L.) essential oil output and quality: antioxidant activity, GC-MS, and SEM analysis.	Plant data were collected and selected with emphasis on *betle* leaf samples of Meetha cultivar collected from the field of Kaktiya village near Mecheda village in East Midnapur, West Bengal, India (22°42'N, 87°87'E). The essential oil derived from leaves of varying ages underwent analysis and was tabulated. Oil extraction was conducted from leaves aged 15, 30, 45, and 60 days, utilizing various leaf-to-water ratios ranging from 1:1 to 1:3. The extraction process employed a maximum temperature of 100°C. The findings indicated that the leaf-to-water ratio exerted the most substantial influence on oil yield.	Researchers have examined the effects of varying betel leaf ages on the yield content and chemical and physical characteristics of the essential oil produced by the hydro-distillation process. The results showed that whereas older leaves (≥ 60 days) showed lesser amount of essential oils, younger leaves (15 days) were better suited for higher generation of betel leaf essential oil yield (0.65%) with less antioxidant qualities (84.05%).	[49]

Sl. No.	Objective	Results	Conclusion	References
9.	Examining the effectiveness of *Piper betle* L. leaf extract against Streptococcus mutans ATCC 25175 using scanning electron microscopy.	Six different brain infusion media were tested to enable S. mutans to adhere to glass beads: sucrose-free, sucrose-containing extract (2 mg mL-1 and 4 mg mL-1), and sucrose-containing extracts (2 mg mL-1 and 4 mg). mL-1). Hexidine (0.12%) was used as a positive control. Glass beads were processed and then examined using SEM. SEM was used to measure the number, appearance, and cell area of S. Proteins bind to glass beads. Additionally, glucosyltransferase activity with and without extract was also measured. Therefore, one-way ANOVA and two-way ANOVA were used.	It was discovered that sucrose enhanced S. mutans' adhesion and cell surface area (p<0.001). Streptococcus mutans adhering to 100 μm2 glass surfaces with or without sucrose showed a decrease in cell area, a puffy extracellular appearance, and a decrease in cell numbers in the presence of betel leaf extract. Furthermore, glucosyltransferase activity was shown to be reduced by the extract; at 2.5 mg mL-1, this inhibition matched that of 0.12% chlorhexidine. Even though the glucosyltransferase activity was negligible at 4 mg mL-1 of the extract, the bacterial cells were still able to cling to one another.	[50]
10.	Expression of senescence-related genes in senescent human diploid fibroblasts is modulated by *Piper betle* L.	This study used quantitative PCR to determine the expression of genes to examine the effects of PB aqueous extracts on replicative senescent Human Diploid Fibroblasts (HDF). Our results showed that 0.4 mg/mL PB extract promoted cell growth in young (143%), pre-aged (127.3%), and aged (157.3%) HDFs. It was demonstrated that, in contrast to youthful and/or pre senescent HDFs, senescent HDFs expressed greater levels of PRDX6, TP53, CDKN2A, PAK2, and MAPK14. Senescent HDFs' altered transcriptional profiles are modulated by treatment with PB extracts. In contrast, PB-treated senescent HDFs showed higher levels of SOD1, while GPX1, PRDX6, TP53, CDKN2A, PAK2, and MAPK14 showed lower expressions when compared to untreated senescent HDFs. This work concludes by showing that replicative senescent HDFs' expression of senescence-associated genes is modulated by PB extracts.	During the replicative senescence of HDFs, *Piper betle* extracts control the expression of genes linked to antioxidant defense (SOD1, GPX1, and PRDX6), DNA damage, and cell cycle arrest (TP53, CDKN2A, PAK2, and MAPK14) signaling pathways. In order to clarify the functional functions of these genes in mediating *Piper betle's* actions during HDF replicative senescence and to discover the active chemicals in *Piper betle* extracts responsible for gene regulation during this process, more research is needed.	[51]
11.	The hypoglycemic effects of *Piper sanctum, Tilia americana, Borago officinalis*, and *Chenopodium nuttalliae* on Wistar rats.	Soxhlet extraction was used to produce methanolic extracts of the studied plants. Artemia was used for toxicity testing and its antioxidant capacity was evaluated by the DPPH method. Alloxan (120 mg/kg)-induced diabetic Wistar rats were used to evaluate hypoglycemic potential at doses of 250 and 500 mg/kg. *B. officinalis* and *O. Sainttum* was nontoxic to *A. salina*, while *T. americana* and *C. nuttlliae* showed mild and high toxicity, respectively. *T. americanavar mexicana* extract was found to exhibit antioxidant activity. Three plants showing hypoglycemic effects in the study were *Tilia americana* (p = 0.0142), Borage (p = 0.0112) and *P. sainttum* (p = 0.0078).	Out of the three plants examined, *P. sanctum* had the biggest drop in glucose levels at a lower dosage. All three plants exhibited hypoglycemic action. The presence of flavonoids and alkaloids that have already been linked to hypoglycemic activity may be related to this effect. For the first time, hypoglycemic action of this plant has been documented; at the doses tested, it did not exhibit toxicity for *A. salina. T. americana* var. mexicana's methanolic extract demonstrated mild toxicity and antioxidant efficacy. To determine which metabolites are responsible for the biological activity of the plants under evaluation, more investigation is required.	[52]

Sl. No.	Objective	Results	Conclusion	References
12.	Effect of betel leaf extract on antibacterial properties of sago starch-based bioplastics.	Various ingredients were used in this study, including distilled water, ethanol, sago starch, glycerin, gallic acid, quercetin, Bacillus cereus, and black yeast starter culture. The betel leaves were obtained from the Medan market. Equipment used included measuring instruments, glass containers, petri dishes, rotary evaporators, hot plates, magnetic stirrers, ovens, stirrers, ultrasonic baths, 50-mesh sieves, and Whatman No. 2. 41 filters and Fourier Transform Infrared (FTIR) spectrometer. Various steps were taken as follows, preparation of *Piper betle* leaf extract, preparation of bioplastic, FTIR analysis, density of bioplastics, water absorption of bioplastic, antimicrobial activity analysis etc.	The bioplastic with the highest content of betel leaf extract demonstrated the highest density. The bioplastic with the maximum water absorption value (0% betel leaf extract) was produced without the addition of betel leaf extract. According to the antibacterial analysis, every bioplastic sample has the ability to stop *Bacillus cereus* from growing. According to the antifungal analysis, *Aspergillus niger* growth is not inhibited by any of the bioplastic variations. Because of its excessive dilution, the 2% concentration of betel leaf extract is unable to stop *Aspergillus niger* from growing. Thus, more research is required to determine the minimal inhibitory concentration of betel leaf extract for *Aspergillus niger* species.	[53]
13.	*In vitro* in silicon method was used to study the antibacterial, antifungal and antioxidant properties of *betle* leaf extract of Bacillus gaemokensis MW067143 isolated from dental caries.	This study used techniques such as isolating, purifying, and characterizing the bacterial flora from caries samples. Furthermore, *P. betle* extract was analyzed using FTIR (Fourier Transform Infrared), TLC (Thin Layer Chromatography), and GC-MS (Gas Chromatography-Mass Spectrometry). Minimum Inhibitory Concentration (MIC) assays were performed, followed by isolation as well as purification of bioactive compounds from *P. betle* extract. Scanning electron microscopy was also utilized, among other methods.	This study demonstrates *P. betle* chloroform extract's anti-biofilm and, for the first time, antibacterial capabilities against B. gaemokensis. Additionally, it is crucial to look into new bioactive substances that are non-toxic and effective that are produced from natural sources. The creation of herbal remedies and formulations to treat human ailments may benefit greatly from this, but particular attention should be paid to the identification, characterization, and elucidation of the mechanism of action of each active phytocompound.	[54]
14.	Acute toxicity and antilithiasic activity of *Piper amalago* (Piperaceae) essential oil were determined through chemical analysis using rapid-scanning quadrupole mass spectrometry (GC×GC/qMS) in conjunction with comprehensive two-dimensional gas chromatography.	Hydrodistillation was used for extraction, while two-dimensional gas chromatography combined with rapid-scanning quadrupole mass spectrometry (GC×GC/qMS) was used for chemical characterisation. The impact of the EOs on the in vitro crystallization of calcium oxalate was used to assess their antilithiasic efficacy. As an estimation of the activity, the number of crystals that formed and the turbidity index were calculated. The effects of a single oral dose of the EOs in Wistar rats were ascertained using the acute toxicity assay. Mortality, side effects, and general behavior were identified.	322 chemicals in all were found in the EOs. Sesquiterpenes, which included δ-cadinene and bicyclogermacrene, had the largest contribution to leaf EOs. The biggest contribution of sesquiterpenes and oxygenated sesquiterpenes, such as α-cadinol and bicyclogermacrene, was seen in the essential oils extracted from stems. The EOs showed a great deal of effectiveness in inhibiting the formation of the crystals, and the oral dose that was evaluated did not significantly alter the parameters for acute toxicity. The considerable chemical complexity of the oils and the variations in their compositions may account for the observed variations in antilithiasic action. The results validate the folk medicine's usage of this plant to treat kidney ailments.	[55]

Sl. No.	Objective	Results	Conclusion	References
15.	Extraction of essential oil from betel leaves (*Piper betle* L.) and identification of its bioactive ingredients: process streamlining, GC-MS analysis, and antimicrobial activity.	The Box-Behnken design includes technological solutions to enhance independent variables including liquid-to-solid ratio (30:1 to 50:1 mL/g), extraction length (5 to 7 hr), and particle size (0 -20 mesh). The study found that the quadratic polynomial model with a ratio of 40:1 was significant ($p<0.05$) for EO production from fresh and pickled *P. leaf* with yields of 0.18%±0.01% and 0.22%±0.02., based on %. Gas Chromatography Mass Spectrometry (GC-MS) study found 30 volatile compounds accounting for 98.41% and 97.34% of the EO of ideal fresh and pickled leaves, respectively. This substance has many biological activities and use for industrial purpose also.	Using a response surface methodology with Box-Behnken design, the effects of ideal extraction parameters (liquid-to-solid ratio, extraction period, and particle size) on response yields (fresh and cured betel leaf essential oil yield) were fully investigated. It was determined that a liquid-to-solid ratio of 40:1 mL/g, extraction duration of 6 hr, and particle size of 10 mesh were the optimal conditions for achieving the maximum yields of Fresh Betel Leaf Essential Oil (FLEO) at 0.18±0.01% and Cured Betel Leaf Essential Oil (CLEO) at 0.22±0.02%. The composition of the extracted oils was determined by gas chromatography-mass spectrometry analysis.	[56]
16.	In addition to having antioxidant properties, *Piper betle* also suppresses the growth of MCF-7 cells and boosts the activity of superoxide dismutase and catalase.	*P. betle* leaves were extracted using a variety of polarity-varying solvents, such as hexane, methanol, water, and ethyl acetate. To determine the amount of flavonoids and phenolic compounds in the leaves, colorimetric tests were used. Utilizing High-Performance Liquid Chromatography (HPLC), the phenolic content was described. DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging, superoxide anion scavenging, nitric oxide scavenging, and hydroxyl radical scavenging tests were among the assays used to measure antioxidant activity. Using MTT assay and antioxidant enzyme assays (catalase, superoxide dismutase, and glutathione peroxidase) in MCF-7 cells, the biological activities of the extracts were assessed.	Overall, the ethyl acetate extract showed the strongest ferric reducing and radical scavenging activities against DPPH, superoxide anion, and nitric oxide radicals. Additionally, this extract had the highest phenolic content, suggesting that phenolics may have contributed to the antioxidant effects. The leaves contained quercetin, morin, and catechins, according to HPLC analysis. Additionally, the ethyl acetate extract (IC_{50}=65 µg/mL) had the most inhibitory impact against MCF-7 cell proliferation. The plant extract treatment boosted the activities of superoxide dismutase and catalase in MCF-7 cells.	[57]
17.	Comparative antibacterial activity of *Piper sarmentosum* and *Garcinia cowa* extracts against *Escherichia coli* and *Staphylococcus aureus* using batch tests, material characterizations, and disc diffusion assay studies	Researchers used a disc diffusion experiment, batch investigations, adsorption isotherms, adsorption kinetics, and desorption trials to see how successfully materials eliminated germs. Synthetic bead materials (GCB and PSB), ethanol extraction (EGC and EPS), and leaf powders of *G. cowa* and *P. sarmentosum* (GCP and PSP) were produced.	GCB has a higher surface area than PSB, but its material and pore size are smaller. GCP and PSP have different shapes, while GCB and PSB have rough and jagged shapes. According to the results of paper disks (EGC and EPS) and bead data (GCB and PSB), *G. cowa* (EGC) and *P. sarmentosum* (EPS) extracts were resistant to S. *Staphylococcus aureus* and *Escherichia coli*. However, EGC and GCB were found to have excellent antibacterial properties against both strains compared to EPS and PSB. In one batch study, the negative GCB concentration for nearly 100% bacterial removal was found to be 0.3 g, 6 hr, pH 7, 106 CFU/mL for S. aureus and 0.3 g, 3 hr, pH 7, 106 CFU/mL for *E. coli*.	[58]

Sl. No.	Objective	Results	Conclusion	References
18.	Green production of biocompatible gold nanoparticles mediated by *Piper Beetle*.	In Guwahati, India, *P. betel* was sourced from a local market. Analytical quality reagents were obtained from Merck or Sisco Research Laboratories in Mumbai, India. The compound 3,4,5-Dimethylthiazol-2-yl-2-5-diphenyltetrazolium bromide (MTT) was acquired from Hi Media in Bangalore, India. The *P. betel* leaves were cleaned with deionized water to remove any absorbed dirt, then cut into small (2 x 2 cm) pieces and air-dried in the shade at room temperature (25°C). The dried leaves were ground using a mixer grinder (Bajaj Model GX 11, Mumbai, India). The leaf extract was made by diluting five grams of powdered leaves in 50 mL of ethanol. The leaf extract was then kept for a week at 4°C. Insect leaf extract (PLE) was filtered using Whatman filter paper (50 mm; Sigma, Bangalore, India) and the filter was stored at 4°C for further studies. UV-vis spectrophotometric measurements of the produced AuNPs were performed using a Cary 100 BIO UV-vis spectrophotometer (Varian, Palo Alto, CA, USA).	The synthesis process of AuNPs presented here has the benefit of being quick, using biocompatible biomaterial (PLE), and, most importantly, producing AuNPs that are biocompatible. At a concentration of 100 μM, the produced AuNPs exhibit negligible toxicity, suggesting that they may find great use in medication delivery and other biomedical fields.	[59]
19.	Analyzing the antibacterial and anthelmintic properties of *Piper betel* leaves using their total phenolic content.	To determine the antibacterial and antifungal properties of the extracts, we tested five different Gram-positive and Gram-negative strains of *Pheritima posthuma* to measure the duration of paralysis and death using the Folin-Ciocalteau Method to determine the total phenolic content of the extracts.	The extract showed significant (p<0.01) zone of inhibitions against Gram positive *Staphylococcus aureus* [(6.77±0.25) mm], Gram negative *Escherichia coli* [(8.53±0.25) mm], Salmonella typhi [(5.20±0.26) mm], and Shigella dysenteriae [(11.20±0.26) mm] in comparison to the positive control drug, azithromycin (ranging from 20.10±0.17 to 25.20±0.35 mm). However, neither the extract nor the standard drug showed any zone inhibitory activity against Gram positive *Bacillus cereus*. In addition, the extract exhibited strong anthelmintic action, needing a shorter period of time to cause paralysis and death than the prescribed medication, albendazole (10 mg/mL). At 10, 20, 40, 60, and 80 mg/mL, the leaf extract demonstrated paralysis at 9.83±0.60, 8.50±0.29, 6.60±0.17, 6.20±0.44 and 4.16±0.60 min; death occurred at 11.33±0.88, 9.67±0.33, 7.83±0.17, 7.16±0.60, and 5.16±0.72 min, correspondingly. On the other hand, paralysis and death were observed at 19.33±0.71 and 51.00±0.23 min, respectively, using the usual medication. When analyzed for total phenolic components, the extract verified the greater quantity of phenolic contents (124.42±0.14 mg of GAE /g of extract).	[60]

Sl. No.	Objective	Results	Conclusion	References
20.	Eugenol's antioxidant properties in *Piper betel* leaf extract.	To assess piper betel's antioxidant potential, assay methods for hydroxyl radical, nitric oxide, and reducing power were employed.	The antioxidant activity was tested at 1000 to 62.5µg/mL for nitric oxide, hydroxyl radical, and reducing power assays. In the Reducing Power Assay (RPA), eugenol demonstrated an IC_{50} value of 306.44± 5.28 and 114.34± 0.46 for hydroxyl radical and nitric oxide, respectively, while the antioxidant activity of *Piper betel* leaf extract demonstrated an IC_{50} value of >1000. The RPA values for both Extract and Eugenol ranged from 0.44-0.08 and 0.53-0.12.	[61]

days of oral administration of *P. betle* leaf suspension at doses of 75 and 150 mg/kg body weight, there was a significant reduction in blood glucose levels (from 205.00±10.80 mg/dL to 151.30±6.53 mg/dL) and glycosylated hemoglobin. Additionally, the activity of liver glucose-6-phosphatase and fructose-1,6-bisphosphatase decreased. STZ diabetic rats exhibited higher liver hexokinase activity ($p<0.05$) compared to untreated diabetic rats. Notably, a dose of 75 mg/kg body weight of *P. betle* was more effective at reducing sugar levels than a dose of 150 mg/kg. Furthermore, diabetic animals were protected from body weight loss. The effects of *P. betle* were compared to the conventional medication, glibenclamide. This study conclusively demonstrates the beneficial impact of *P. betle* intake on glucose metabolism.[72]

Anti-Ulcer Activity

Ulcers, a common gastrointestinal ailment, cause significant discomfort for sufferers, disrupting their everyday lives and inflicting emotional suffering. Peptic ulcers are caused by damage to the mucous membrane, which normally protects the esophagus, stomach, and duodenum from gastric acid (HCl) and pepsin. Currently, several synthetic anti-ulcer medications are available, including misoprostol, which is used to prevent or treat NSAID-induced stomach ulcers. The incidence of NSAID-induced stomach ulcers is increasing, accounting for approximately 25% of all gastric ulcer occurrences, in addition to stress, hunger, and *H. pylori* invasion. *P. betel* leaves are known in traditional Indian medicine for their digestive and pancreatic lipase stimulating properties. One of the ulcerogenic chemicals is ethanol, which causes significant damage to the stomach mucosa by interrupting mucosal microcirculation, producing ischemia, generating free radicals, releasing endothelin, activating mast cell degranulation, suppressing prostaglandins, and decreasing gastric mucus production. The gastroprotective action of *P. betle* extracts may involve improving gastrointestinal mucosal defense mechanisms, such as boosting mucus and bicarbonate secretion, decreasing gastric acid secretion, or decreasing gastric acidity.[73]

In the current study, it was found that the hydroalcoholic extract of *P. betle* considerably increases gastric mucus secretion while decreasing gastric juice volume in rats. Phytochemical analysis of *P. betle* indicated the presence of alkaloids, flavonoids, steroids, saponins, and tannins that have antiulcerogenic activities due to their protein-precipitating and vasoconstricting effects. Notably, the greatest dose of hydroalcoholic extract had no significant influence on gastric fluid acidity or pH, showing that *P. betle's* gastroprotective activity does not include acidity inhibition in gastric juice. Finally, these findings demonstrate the gastroprotective activity and mode of action of Sri Lankan *P. betle* leaves for the first time, emphasizing their therapeutic potential as a low-cost, effective, and safe herbal gastroprotective medication.[74]

Some Examples of Anti-ulcer activity experiments are as follows:

To assess the gastroprotective activity of *P. betle*'s Hot Aqueous Extract (HAE) and Cold Ethanolic Extract (CEE) using rats as an experimental model

Both extracts were tested for gastroprotective effect against ethanol-induced stomach ulcers in rats at three different doses (200, 300, and 500 mg/kg/bw). The parameters studied were (a) the effects of HAE on gastric mucosa wall mucus content, (b) acidity levels (total and free), (c) gastric juice volume, and (d) gastric juice pH. Oral administration of both HAE and CEE showed considerable, dose-dependent protection against stomach injury caused by absolute ethanol, with marked dosage dependency (HAE: $r^2 = 0.97$; CEE: $r^2 = 0.96$) and statistical significance ($p<0.05$). CEE and HAE had similar gastroprotective effects. Furthermore, the highest dose of both extracts showed considerably higher gastroprotective action ($p<0.05$) than misoprostol, the reference medicine. HAE significantly enhanced the mucus content sticking to the gastric mucosa wall and decreased gastric acid volume, although acidity levels (total and free) and gastric juice pH were unaltered.[75]

Ethanol extract of the leaves of *Piper betle* Linn. has potent antiulcerogenic action through an antioxidant mechanism

Pre-administration of an ethanolic extract produced from *Piper betle* Linn. leaves, at a dosage of 200 mg/kg body weight, orally delivered to rats for ten consecutive days, showed considerable protection against indomethacin-induced stomach lesions. The extract pretreatment significantly increased the activity of

Superoxide Dismutase (SOD) and Catalase (CAT), as well as the levels of mucus, hexosamine, and total thiols. In contrast, levels of oxidatively damaged proteins and peroxidized lipids were much lower than those in the untreated ulcerated control group. Additionally, the extract exhibited scavenging capabilities against both superoxide and hydroxyl free radicals. These data convincingly confirm the extract's efficacy in preventing experimentally produced peptic ulcers caused by indomethacin, with its antioxidant characteristics playing a major role in exerting cytoprotective action in the experimental paradigm.[76]

The gastroprotective effect of a standardized leaf extract of Argyreia speciosa on experimental stomach ulcers in rats

The butanol fraction of *Argyreia speciosa* leaf (ASE), administered orally at doses of 50, 100, and 200 mg/kg body weight twice daily for 5 days, was evaluated for its ulcer-preventive effects Against Aspirin (ASP), Ethanol (EtOH), Cold-Restraint Stress (CRS), and Pylorus Ligation (PL). In the CRS-induced ulcer model, the activity of antioxidant enzymes was assessed, while in the PL-induced ulcer model, parameters such as gastric juice volume, acid production, and pH were measured. ASE demonstrated dose-dependent ulcer protection against ASP (23.64-58.76%; $p<0.01$ to $p<0.001$), EtOH (15.45-58.45%; $p<0.001$), CRS (19.39-78.36%; $p<0.001$), and PL (19.67-69.04%; $p<0.05$ to $p<0.01$). Ranitidine, a conventional medication, showed a protective effect of 77.77-84.32% ($p<0.01$ to $p<0.001$) in gastric ulcer models. ASE significantly increased stomach wall mucus production ($p<0.001$), enhancing its first line of defense against EtOH-induced gastric ulcers, thereby demonstrating cytoprotective properties. Additionally, ASE modestly reduced gastric juice volume, acid pepsin content, and output. ASE also reduced the ulcer index with a significant decrease in Lipid Peroxidation (LPO) and Superoxide Dismutase (SOD) levels ($p<0.01$ to $p<0.001$) compared to the CRS-induced group. At doses of 100 and 200 mg/kg, Catalase (CAT) activity significantly increased ($p<0.01$ to $p<0.001$). These results suggest that ASE exhibits strong dose-dependent gastroprotective effects, likely due to its free radical scavenging ability.[77]

HCl extract of *Piper betle* leaf has anti-ulcer activity in experimental animals

The primary goal of this study is to determine the anti-ulcer properties of a hydroalcoholic extract derived from *Piper betle* leaves in experimental animals, building on previously established attributes such as antioxidant, antihistaminic, and antimicrobial properties of the leaves. The leaves were collected, air-dried, and extracted using a Soxhlet apparatus with 70% ethanol. The extract's anti-ulcer capability was examined in albino Wistar rats using pyloric ligation and stress-induced antiulcer models, with ranitidine serving as the standard medication in both. The activity's significance was assessed using one-way ANOVA, followed by Dunnett's post-parametric test. In the pyloric ligation model, the untreated control group had an acidity level of 4.3 mEq/l, whereas the ranitidine-treated group had a lowered acidity level of 2 mEq/l, and the *P. betle*-treated group had an acidity level of 2.5 mEq/l. In the stress-induced antiulcer model, the efficacy was greater, with the untreated control group showing 26 ulcer sores, the standard group showing only one ulcer sore, and the *P. betle* treated group showing four ulcer sores. The current investigation demonstrates that *P. betle* has strong antiulcer potential, comparable to that of the conventional medicine ranitidine and superior to the untreated control. These findings provide support for betel leaf's traditional usage as a digestive or gastroprotective agent.[78]

Anti-Inflammatory and Antioxidant Activity

Cells generally maintain a balance of antioxidants and free radicals, but nutrition, pollution, radiation, lifestyle choices, and immune system activity can all disrupt this balance, resulting in oxidative stress. Prolonged oxidative stress can cause damage to DNA, proteins, and cells, hastening the aging process. Furthermore, persistent inflammation can result from oxidative damage, which accelerates the aging process. In reaction to damage, sickness, or infection, the body produces inflammation as a natural healing mechanism controlled by the immune system. Inflammation can be classified as acute or chronic. Chronic inflammation, in particular, is connected to brain diseases and can lead to ailments such as diabetes, cardiovascular disease, and arthritis.[79]

Some Examples of Anti-inflammatory and antioxidant activity experiments are as follows:

Piper betle exhibits antioxidant properties, inhibits the proliferation of MCF-7 cells, and enhances the activities of catalase and superoxide dismutase

Breast cancer is the most common type of cancer, leading a recent shift in attention to investigate natural compounds as potential chemotherapeutic treatments. *Piper betle*, a medicinal herb known for its various biological properties, shows promise in this respect. However, there is little research on its anti-cancer properties on breast cancer. Given the current interest in using natural antioxidants to treat breast cancer, we conducted a study to investigate the antioxidant capabilities of *P. betle* leaves as well as their inhibitory effect on the proliferation of MCF-7, a breast cancer cell line. *P. betle* leaves were extracted using solvents of varying polarity (water, methanol, ethyl acetate, and hexane), and their phenolic and flavonoid content was measured using colorimetric assays. The phenolic content was further analyzed using HPLC, and antioxidant properties were evaluated through FRAP, DPPH, superoxide anion, nitric oxide, and hydroxyl radical scavenging assays. The extracts' biological activity was then assessed using the MTT assay and antioxidant enzyme assays (catalase, superoxide dismutase, glutathione peroxidase) in MCF-7 cells.[80]

Overall, the ethyl acetate extract demonstrated superior ferric reducing and radical scavenging activity against DPPH, superoxide anion, and nitric oxide radicals. This extract also had the highest phenolic content, suggesting that phenolics contribute significantly to its antioxidant activity. HPLC analysis identified catechin, morin, and quercetin in the leaves. Additionally, the ethyl acetate extract exhibited the strongest inhibitory effect on MCF-7 cell proliferation (IC_{50}=65 μg/mL). Treatment with this extract enhanced catalase and superoxide dismutase activity in MCF-7 cells, thereby modifying the antioxidant defense system and contributing to its anti-proliferative effects. Our findings support the ethyl acetate extract of *P. betle* leaf as a promising source of natural antioxidants and a potential therapeutic agent for cancer treatment.[81]

The methanol extract of *Piper betle* Linn. (*Piper betle* L.) leaves and stems inhibits the NF-κB/MAPK/Nrf2 signaling pathways in RAW 264.7 macrophages, leading to significant anti-inflammatory and antioxidant effects.

Plant extracts have showed promise in avoiding and alleviating the harmful effects of oxidative stress and chronic inflammation, which are linked to a variety of disorders. *Piper betle Linn.* is a widely distributed plant in the Piperaceae family, having edible leaves that provide several health advantages. The purpose of this study was to investigate the anti-inflammatory and antioxidant activities of a methanol extract from *Piper betle L.* leaves and stems (MPBLLS). The 2,2-diphenyl-1-picrylhydrazyl (DPPH) experiment demonstrated that MPBLLS scavenged radicals in a dose-dependent manner. Additionally, it decreased the expression of inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenase-2 (COX-2) in RAW 264.7 macrophages, inhibiting LPS-induced Nitric Oxide (NO) and Prostaglandin E2 (PGE2) synthesis while maintaining cell viability. MPBLLS inhibited the Nuclear Factor-κB (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) signaling pathways in LPS-treated RAW 264.7 macrophages, thereby reducing the levels of pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6). Both MPBLLS and hydroxychavicol inhibited the LPS-induced translocation of NF-κB p65 from the cytoplasm to the nucleus. Notably, MPBLLS increased nuclear factor erythroid 2-related factor 2 (Nrf2) protein levels and Nrf2 target gene transcription in a dose-dependent manner. Given its capacity to reduce oxidative and inflammatory stress, these findings suggest that MPBLLS has the potential to serve as a foundation for developing innovative orally delivered medicines.[82]

Antioxidant and antiplatelet properties of aqueous inflorescence *Piper betle* extract

Piper betle, a member of the Piperaceae family, is a tropical plant commonly known as Betel Quid (BQ) in Taiwan and other South and Southeast Asian countries. Despite its popularity, the biochemical properties of inflorescence *Piper betle* (IPB), particularly concerning Reactive Oxygen Species (ROS) and platelet activities, are not well understood. In this study, an aqueous IPB extract demonstrated scavenging abilities against H_2O_2, superoxide radical, and hydroxyl radical, with IC_{50} values of approximately 80, 28, and 73 μg/mL, respectively. Additionally, the IPB extract inhibited hydroxyl radical-induced breakage in PUC18 plasmid DNA at concentrations above 40 μg/mL. Given the role of ROS in platelet aggregation, the effects of IPB extract on arachidonic acid (AA)-induced and collagen-induced platelet aggregation were investigated. The results showed significant suppression of both AA-induced and collagen-induced platelet aggregation, with IC_{50} values of 207 and 335 μg/mL, respectively. Moreover, the IPB extract significantly reduced AA-, collagen-, and thrombin-induced thromboxane B(2) (TXB(2)) generation by over 90%. Although the IPB extract had a minimal effect on thrombin-induced aggregation, our data suggest that its aqueous components possess ROS scavenging properties and may reduce platelet aggregation either by scavenging ROS or by reducing TXB(2) synthesis.[83]

The aqueous extract of two fractions of *Piper betle* leaves: their phytochemical content, β-glucuronidase inhibition, and antioxidant activities

This work aims to find active components against β-glucuronidase using chemometric analysis and examine the phytochemical composition of chloroform and ethyl acetate fractions derived from aqueous extracts of eight kinds of *P. betle* leaves. The solvent fractions contained twenty-four phenolic chemicals as well as other organic acids, fatty acids, amino acids, sugars, and polyols. The extracts showed that the β-glucuronidase enzyme was inhibited, and the most active component was piceatannol, which exhibited activity that was 12 times greater than silymarin. Additionally, β-glucuronidase was significantly inhibited by chlorogenic acid (with an activity 4.4 times higher than silymarin). Furthermore, both *P. betle* leaf extract fractions from the eight types showed substantial scavenging activity against superoxide and 2,2'-diphenyl-1-picrylhydrazyl free radicals, indicating their great antioxidant potential. These results validate the therapeutic qualities of *P. betle* leaves.[84]

Potential for antioxidant and antibacterial properties in specific *Piper betle* L. (betel leaf) cultivars

This study investigates the antibacterial and antioxidant properties of *Piper betle* L., a perennial creeper from the Piperaceae family with various therapeutic applications. Extracts were prepared using distilled water, hexane, acetone, and ethanol from two types of betel leaves: Meetha paan and Banarasi paan. The study included antioxidant activity tests (DPPH radical scavenging activity, total phenolics, ascorbic acid, and reducing

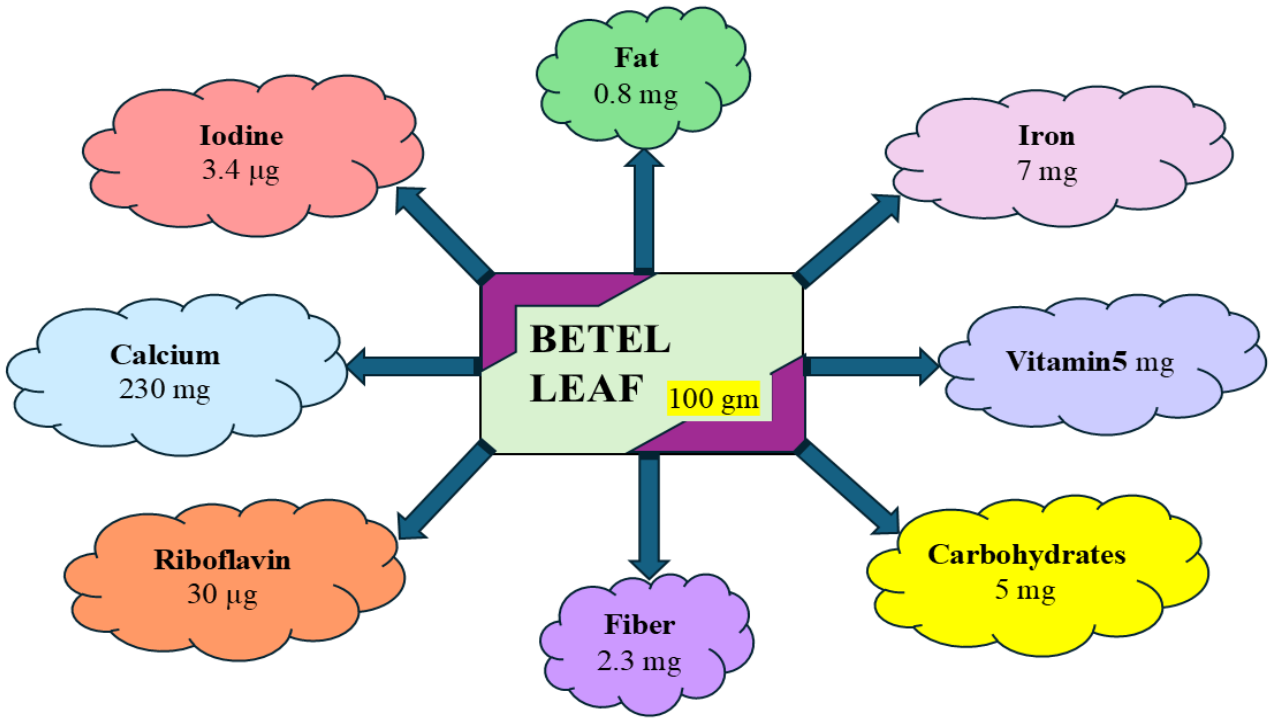

Figure 3: Several types of chemical constituents in 100g of betel leaf.

power), antimicrobial susceptibility tests against four pathogens (*B. subtilis, E. coli, A. niger*, and *S. cerevisiae*), and proximate analysis measuring moisture, ash, protein, lipids, and minerals like sodium and potassium. The ethanolic extract exhibited the highest antioxidant activity (89.46% inhibition), while the aqueous extract showed the lowest (62.03% inhibition). Increased reducing power was associated with leaf extract concentrations of 5, 10, 25, and 50 µg/mL. The ascorbic acid content in Meetha paan (5.20 mg/100 g) and Banarasi paan (5.21 mg/100 g) was found to be non-significant. Banarasi paan leaves contained phytosterols, which likely contributed to the maximum antibacterial activity observed in the ethanolic extract. This comprehensive analysis of the antioxidant and antibacterial properties of betel leaf supports its medicinal use and contributes to the development of a detailed database.[85]

Antibacterial Activity

All living things require access to clean water because it is a necessary component of life. However, a number of human activities, including home use, industrial processes, transportation, and agriculture, can lead to bacterial contamination of water. Gram-positive and Gram-negative bacteria are the two basic categories into which bacteria are often divided. *Staphylococcus aureus*, is a gram-positive bacterium that is widely used in antibacterial research and is recognized for its ability to cause infections in people. Conversely, *Escherichia coli*, often known as *E. coli*, is a common Gram-negative bacterium that is recognized as a pathogenic microorganism that can cause infections in humans, especially when it is present in contaminated water sources. It is also utilized as an indicator of water quality.[86]

Soft rot disease-causing bacteria have been the focus of extensive research due to their significant negative impact on various crops. Erwinia Carotovora subsp. Carotovora (ECC), a Gram-negative pectolytic bacterium belonging to the Pectobacteriaceae family, is known to induce soft rot disease. This pathogen spreads through various means, including manual transmission, sprinkler irrigation, and drainage water. ECC is challenging to control and eradicate as it can persist for extended periods on field weeds and plant debris, and it can also spread during the storage and transportation of crops. Through wounds and stomata, among other natural openings, ECC enters plant tissues and creates a variety of enzymes that break down plant cell walls.[87] These enzymes, which include pectate lyase, protease, cellulase, and pectin-methylesterase, cause interior plant tissues to soften, moisten, and eventually break down. Some Examples of Antibacterial activity experiments are as follows:

The mode of action and *in vitro* antibacterial activity of *Piper betle* extracts against bacteria that cause soft rot disease

Soft rot disease poses a significant threat to various crops both in the field and during transportation and storage, leading to substantial losses in yield and negative economic consequences. This research aimed to assess the *in vitro* antibacterial properties and mechanism of action of *Piper betle* extracts against Erwinia Carotovora subsp. Carotovora (ECC), the bacterium responsible

for soft rot disease. Dried leaves of *P. betle* were subjected to extraction using water, ethanol, and hexane solvents, and their antibacterial efficacy was evaluated.[72] With Minimum Inhibitory Concentrations (MICs) of 1.562, 6.25, and more than 12.50 mg/mL, respectively, the ethanol extract had the strongest antibacterial action against ECC, whereas the hexane and water extracts showed the lowest antibacterial activity. The time-kill experiment demonstrated a bactericidal mode of action, with ECC growth eliminated 6 and 8 hr after treatment with the ethanol extract at 4-fold MIC and 2-fold MIC, respectively. These findings highlight the promising antibacterial activity of the ethanol extract of *P. betle* against ECC, suggesting the plant's potential as an innovative alternative therapy for controlling phytobacteria.[73,74]

The study examined the characteristics and antibacterial properties of composite films made from passion fruit peel pectin and chitosan that included extract from *Piper betle* L. leaves to preserve purple eggplants.

This study aimed to create biodegradable films by combining a bioactive extract from *Piper betle* L. leaves with crosslinked passion fruit peel Pectin and Chitosan (P/CH). The objective was to analyze the morphological, mechanical, optical, water vapor permeability, and antibacterial properties of these films. The content of *Piper betle* extract (PB) in the P/CH blend films increased with their thickness and water vapor permeability. Compared to P/CH films, the tensile strength of P/CH/PB films was significantly lower, decreasing by 42.89%. Morphological analysis confirmed that the resulting blend films had a well-structured, homogeneous composition free of cracks. Additionally, higher concentrations of PB in the films enhanced antibacterial activity against *Pseudomonas aeruginosa, Bacillus cereus, Klebsiella pneumoniae*, and *Staphylococcus aureus*. These findings suggest that P/CH/PB blend films could be useful in food packaging.[75-78]

Phytochemicals in Helicobacter pylori Infections

This comprehensive review delves into plant-derived sources that exhibit notable antibacterial properties against Helicobacter pylori infections. It meticulously examines the intrinsic bioactive compounds accountable for these effects and elucidates their specific mechanisms of action. Beyond their traditional applications as herbal remedies, the review critically assesses both *in vitro* and *in vivo* studies centered on plant extracts and isolated bioactive compounds displaying anti-H. pylori activity. Additionally, considerable attention is dedicated to plant extracts showcasing urease inhibitory effects, with a focus on the underlying mechanisms of action.[79,80]

Phytochemical analysis, identification, and quantification of antibacterial active compounds in methanolic extract of betel leaves (*Piper betle*).

The conventional approach to addressing bacterial infections in aquaculture has involved the administration of antibiotics. Nonetheless, research into medicinal plants and herbs as possible substitutes for traditional antibiotics is gaining traction. The current study looked at the methanolic extract of *Piper betle*, a native herb, and its phytochemical makeup, antibacterial capabilities, and composition of antibacterial active components. Using a methanolic extract of *P. betle* leaves, putative active components were first identified using qualitative phytochemical analysis. Then, using a TLC-bioautography agar overlay test, the antibacterial activity of the main constituents in this extract were assessed against nine fish pathogenic bacteria, and their amounts were concurrently ascertained by HPLC.[81] The use of methanol as an extracting solvent proved successful in extracting numerous bioactive compounds, including antibacterial agents. Two substances, hydroxychavicol and eugenol, were discovered to have inhibitory effects in the TLC-bioautography experiment, while β-caryophyllene had no effect against any of the tested bacterial species. The results showed that the extract contained 374.72±2.79 mg g-1 of hydroxychavicol and 49.67±0.16 mg g-1 of eugenol. These results imply that the main substances responsible for the encouraging antibacterial activity of the methanolic extract of *P. betle* leaves are hydroxychavicol and eugenol. It was discovered that there was a strong correlation between the concentration of these chemicals in the extract and their inhibitory action. The *P. betle* leaf extract or any of its constituent chemicals have the potential to be used as a substitute source of strong natural antibacterial agents for the treatment of illnesses in aquaculture.[82]

FUTURE PERSPECTIVES

Further investigation and advancement focused on various betel leaf species will elucidate the mechanisms of their bioactive constituents and their diverse roles, including antioxidant, Free Radical Scavenging (FRC), antiallergic, anti-inflammatory, antimutagenic, and antitumor-promoting properties, in combating a range of degenerative and chronic human diseases. Additional research is also needed to determine the role of nutraceutical foods and products in cancer treatment.[83] The phytochemicals found in different betel leaf varieties have demonstrated new benefits, enhanced nutritional applications, and potential uses in the food and pharmaceutical industries. The food industry could benefit from the biological properties and bioactive compounds of betel leaf, which include antimicrobial, antioxidant, scavenging capabilities, estragole, anethole, iso-eugenol, and terphenyl acetate. *P. nigrum* stands out as the most significant species in this genus because of piperine, its potent principal component, and its widespread use as a culinary flavoring. Since spices and their essential oils are regarded as GRAS, the Piper species has a bright future as a food preservative to prevent many types of food spoiling and harmful microbes.[84] To acquire consumer acceptance, it is therefore necessary to carefully select the right

concentrations of this extract in relation to the sensory and compositional status of the food system to which it is applied. As a result, fresh research and technological advancements are required to improve food safety and quality without altering the food's organoleptic characteristics.[85] Piper species have demonstrated their biological effects in a variety of *in vivo, in vitro*, and clinical investigations. Globally, neurodegenerative disorders and chronic illnesses are the leading causes of death and disability. Piper species' antiproliferative, anti-inflammatory, and neuropharmacological properties have shown them to have therapeutic and preventative promise against several chronic illnesses. All things considered; research conducted on Piper species suggests that these plants may be useful in the treatment of illnesses characterized by inflammation.[86,87] Because of their widespread use, more efforts should be undertaken to research standardized Piper plants using carefully planned experiments. Furthermore, a plethora of opportunities exists for the creation of functional meals derived from Piper species. The anti-*H. pylori* activity of *Piper betel* extracts supports traditional medicine practitioners' assertions regarding their potential anti-ulcerative qualities. Few of them, meanwhile, have been tested for their capacity to block urease activity or for effectiveness in animal models. Extensive research is necessary to investigate the effectiveness of the treatment in animal models, clarify the mechanisms of action that work (such as urease inhibition), and conduct human clinical trials.[88]

Southeast Asian nations have long used *Piper betle* Linn., sometimes known as paan or betel vine, as an essential component of their traditional and folk medicines. The most valuable plant parts are betel leaves, which are frequently chewing agents and have been shown to guard against halitosis. Betel vine leaves are used medicinally for a variety of conditions, including cough, bronchitis, constipation, congestion, and indigestion. The main use of betel vine leaves is as part of betel quid, a mixture of tobacco (*Nicotiana tabacum* Linn.), areca nut (*Areca catechu* Linn.), and slaked lime that has strong carcinogenic effects. Regular betel quid use has been linked to oral cancer. Scientific assessments have also linked tobacco and areca nut to carcinogenesis, and slaked lime to carcinogenesis promotion.[89] Modern gas chromatographic techniques for the identification of ingredients in various landraces may prove beneficial for the selection of elite landraces in the future and their enhancement initiatives. Simultaneously, the majority of the landraces that are now accessible should be characterized in order to solve the synonym problem and ensure correct authentication. Given the established medicinal benefit of *P. betle*, accurate characterization may prove beneficial for long-term drug development research.[90] The pursuit of acquiring promising landraces with elevated levels of eugenol and chavibetol is to be escalated. Apart from the bioactivity tests, proper verification of a specific landrace and its conservation for ongoing supply should also be addressed. Studying the impact of abiotic factors on betelvine production and quality is crucial since soil and environmental factors always affect plant secondary metabolites. Prior to clinical trials and extensive commercial production, further standardization of the parameters governing the quality and amount of betelvine essential oil and extracts may be the future study focus. Current biotechnological instruments such as NMR, chromatography, and functional genomics approaches could be investigated to identify novel compounds with promising properties from this undiscovered plant species.[91] Chlorophyllase activity needs more research in order to increase the long-term storage and export potential of betelvine leaves. To generate new and improved varieties of betelvine, special attention must be paid to the management of pests and diseases. Assessing genetic diversity with molecular markers should be expanded to include as many landraces as possible. Essentially, biotechnological intervention has created new opportunities for elite chemotype identification, correct authentication, and genetic improvement of this critically important cash crop for both medicine and the economy.[92] Another future perspective of *Piper betle* is Hydroxychavicol present in the *Piper betle* leaf which is maybe useful for the treatment of cancer. However, frequent pathways that are targeted by HC include the eNOS, MAPK, and JNK signaling pathways. Caspases 3 and PARP are two examples of the proteins in apoptotic pathways that HC may modify to have an anticancer effect. All things considered, it seems that HC's ability to fight cancer depends on ROS building up inside cancer cells, which ultimately causes apoptosis. Additionally, the lack of studies utilizing animal models has left uncertainty regarding the adsorption of HC and the proper dosage. Thus, in order to guarantee the safety and bioavailability of HC in humans, *in vivo* experimentation should be the primary focus of future study. Moreover, it may be possible to test the viability of mixing HC with other chemotherapeutics to see if a synergistic positive interaction takes place that makes cancer cells more susceptible to chemotherapy or aids in their death.[93]

CONCLUSION

A well-known medicinal plant, *Piper betle* leaf has a wide range of pharmacological qualities that make it a promising therapeutic option. Antioxidant, anti-inflammatory, antibacterial, anticancer, antidiabetic, and gastroprotective properties are among its many bioactive components, which include polyphenols, flavonoids, alkaloids, and essential oils. Both conventional and contemporary studies demonstrate its effectiveness in treating a range of conditions, such as diabetes, inflammatory disorders, cardiovascular illnesses, and oral infections. Further clinical research and sophisticated pharmacological analyses are needed to confirm its safety, effectiveness, and ideal dose for therapeutic uses, despite its encouraging medical effects. Its potential for incorporation into contemporary medicine will be increased through formulation development and standardisation of bioactive components. The leaf of the *Piper betle* plant, with

its extensive ethnomedicinal history, has significant potential as a natural therapeutic agent and merits further investigation in pharmaceutical and nutraceutical applications.

ACKNOWLEDGEMENT

The authors would like to express their sincere gratitude to PSIT-Pranveer Singh Institute of Technology (Pharmacy) for valuable support. Additionally, we appreciate the contributions of peer reviewers whose comments helped improve the quality of this manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

***A. salina*:** *Artemia salina*; **AgNPs:** Silver nanoparticles; **ANOVA:** Analysis of Variance; **ASP:** Aspirin; **ATCC:** American type culture collection; ***B. officinalis*:** *Borago officinalis*; **Bax:** Bcl-2-associated protein x; **Bcl xl:** B-cell lymphoma-extra-large; ***C. albicans*:** *Candida albicans*; ***C. nuttalliae*:** *Chenopodium nuttalliae*; **Cal 27:** Carcinoma cell line 27; **CAT:** Catalase; **CDKN2A:** Cyclin-dependent kinase inhibitor 2A; **cDNA:** Complementary DNA; **CEE:** Cold ethanolic extract; **CFU/mL:** Colony form unit per millilitre; **CLEO:** Cured betle leaf essential oil; **CRS:** Cold-resistance extract; **DMRT:** Duncan's Multiple Range test; **DMSO:** Dimethyl sulfoxide DPPH 2,2-diphenyl-1-picrylhydrazyl; ***E. coli*:** *Escherichia coli*; **ERBB:** Erythroblastic leukemia viral oncogene homologue receptors; **EtOH:** Ethanol; **FBG:** Fasting blood glucose; **FLEO:** Fresh betle leaf essential oil; **FRAP:** Fluorescence recovery after photobleaching; **FTIR:** Fourier Transform Infrared; ***G. cowa*:** *Garcinia cowa*; **GC-MS:** Gas chromatography-mass spectrometry; **GCB:** Germinal center B-cell; **GPX1:** Glutathione peroxidase 1; ***H. pylori*:** *Helicobacter pylori*; **HAE:** Hot aqueous extract; **HCL:** Hydrochloric Acid; **HDFs:** Human diploid fibroblasts; **HDL:** High-density lipoprotein; **HPLC:** High performance liquid chromatography; **HWE:** Hot water extract; **ica A gene:** Intercellular adhesion (ica) locus; **IPB:** Inflorescence *Piper betle*; **LDL:** Low-density lipoprotein; **MAPK:** Mitogen-activated protein kinase; **MAPK14:** Mitogen-activated protein kinase 14; **MAPKs:** Mitogen-activated protein kinases; **MCF7:** Michigan Cancer Foundation-7; **MIC:** Minimum inhibitory concentration; **MRSP:** Methicillin-resistant *Staphylococcus pseudintermedius*; **MTT:** 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide); **NSAID:** Non-steroidal anti-inflammatory drugs; ***O. sanctum*:** *Ocimum sanctum*; **P. betle:** *Piper betle*; **PB extract:** Peanut Butter; **PCR:** Polymerase chain reaction; **PL:** Pylorus ligation; **PLE:** Protein-losing enteropathy; **PlrAqe:** *Piper longum* root aqueous extract; **PRDX6:** Peroxiredoxin-6; **RNA:** Ribonucleic acid; **RPA:** Reducing power assay; ***S. mutants*:** *Streptococcus mutans*; **SAED:** Selected area electron diffraction; **SEM:** Scanning electron microscopy; **SGOT:** Serum glutamate oxaloacetate transaminase; **SOD1:** Superoxide dismutase type 1; **STZ:** Streptozotocin; ***T. americana*:** *Tilia americana*; **TC:** Total cholesterol; **TEM:** Transmission electron microscopy; **TG:** Triglyceride; **TLC:** Thin layer chromatography; **TP53:** Tumor protein p53; **UC-MSCs:** Umbilical cord-derived mesenchymal stem/stromal cells; **VLDL:** Very low-density lipoprotein; **WHO:** World health organization; **XRD:** X-ray diffraction.

REFERENCES

1. Bakthavatchalam YD, Rao SV, Isaac B, Manesh A, Nambi S, Swaminathan S, *et al.* A comparative assessment of clinical, pharmacological and antimicrobial profile of novel anti-methicillin-resistant *Staphylococcus aureus* agent levonadifloxacin: therapeutic role in nosocomial and community infections. Indian J Med Microbiol. 2019; 37(4): 478-87. doi: 10.4103/ijmm.IJMM_20_34, PMID 32436868.
2. Jantorn P, Tipmanee V, Wanna W, Prapasarakul N, Visutthi M, Sotthibandhu DS. Potential natural antimicrobial and antibiofilm properties of *Piper betle* L. against *Staphylococcus pseudintermedius* and methicillin-resistant strains. J Ethnopharmacol. 2023; 317: 116820. doi: 10.1016/j.jep.2023.116820, PMID 37369337.
3. Guzman JP, Yatip P, Soowannayan C, Maningas MB. *Piper betle* L. leaf extracts inhibit quorum sensing of shrimp pathogen *Vibrio harveyi* and protect *Penaeus vannamei postlarvae* against bacterial infection. Aquac. 2022; 547: 737452.
4. Valle Jr DL, Cabrera EC, Puzon JJ, Rivera WL. Antimicrobial activities of methanol, ethanol and supercritical CO2 extracts of Philippine *Piper betle* L. PLOS One. 2016; 11(1): e0146349. doi: 10.1371/journal.pone.0146349, PMID 26741962.
5. Nayaka NM, Sasadara MM, Sanjaya DA, Yuda PE, Dewi NL, Cahyaningsih E, et al. *Piper betle* (L): Recent Review of Antibacterial and Antifungal Properties, Safety Profiles, and Commercial Applications. Molecules. 2021; 26(8): 2321. doi: 10.3390/molecules 26082321, PMID 33923576.
6. Lee MT, Chang CI, Lin JJ, Wu YJ. *Piper betle* stem extract induces apoptosis through mitochondria inactivation, p38MAPK activation and ErB2/ErbB3 suppression on oral squamous cell carcinoma cells. Phytomed Plus. 2022; 2(3): 100295. doi: 10.1016/j.phyplu.2022.100295.
7. Thị CH, Nguyễn HĐ, Lê Hoàng DM. Influence of *Piper betle* L. extract on umbilical cord cells *in vitro* and potential treating cutaneous wound. Heliyon. 2021; 7(3).
8. Biswas P, Anand U, Saha SC, Kant N, Mishra T, Masih H, *et al.* Betelvine (*Piper betle* L.): a comprehensive insight into its ethnopharmacology, phytochemistry, and pharmacological, biomedical and therapeutic attributes [*Piper betle* L]. J Cell Mol Med. 2022; 26(11): 3083-119. doi: 10.1111/jcmm.17323, PMID 35502487.
9. Khatun MM, Sapon MA, Hossain MS, Islam MR. Antidiabetic activity of *Piper betle* in alloxan induced type 1 diabetic model rats. Int J Pharm Sci. 2016; 7(2): 675-80.
10. Seo J, Lee U, Seo S, Wibowo AE, Pongtuluran OB, Lee K, *et al.* Anti-inflammatory and antioxidant activities of methanol extract of *Piper betle* Linn. (*Piper betle* L.) leaves and stems by inhibiting NF-κB/MAPK/Nrf2 signaling pathways in RAW 264.7 macrophages. Biomed Pharmacother. 2022; 155: 113734. doi: 10.1016/j.biopha.2022.113734, PMID 36152408.
11. Nabi SA, Kasetti RB, Sirasanagandla S, Tilak TK, Kumar MV, Rao CA. Antidiabetic and antihyperlipidemic activity of *Piper longum* root aqueous extract in STZ induced diabetic rats. BMC Complement Altern Med. 2013; 13: 37. doi: 10.1186/1472-6882-13-37, PMID 23414307.
12. Charirak P, Prajantasan R, Premprayoon K, Srikacha N, Ratananikom K. *In vitro* antibacterial activity and Mode of Action of *Piper betle* Extracts against Soft Rot Disease-Causing Bacteria. Sci. 2023; 2023(1): 5806841. doi: 10.1155/2023/5806841, PMID 37766936.
13. Abrahim 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 Complement Altern Med. 2012; 12: 220. doi: 10.1186/1472-6882-12-220, PMID 23153283.
14. Nguyen TT, Le TQ, Nguyen TT, Nguyen LT, Nguyen DT, Van Tran TV. Characterizations and antibacterial activities of passion fruit peel pectin/chitosan composite films incorporated *Piper betle* L. leaf extract for preservation of purple eggplants. Heliyon. 2022; 8(8): e10096. doi: 10.1016/j.heliyon.2022.e10096, PMID 36016528.
15. Santhakumari P, Prakasam A, Pugalendi KV. Antihyperglycemic activity of *Piper betle* leaf on streptozotocin-induced diabetic rats. J Med Food. 2006; 9(1): 108-12. doi: 10.1089/jmf.2006.9.108, PMID 16579737.
16. Arambewela LS, Arawwawala LD, Ratnasooriya WD. Antidiabetic activities of aqueous and ethanolic extracts of *Piper betle* leaves in rats. J Ethnopharmacol. 2005; 102(2): 239-45. doi: 10.1016/j.jep.2005.06.016, PMID 16055288.
17. Arawwawala LD, Arambewela LS, Ratnasooriya WD. Gastroprotective effect of *Piper betle* Linn. leaves grown in Sri Lanka. J Ayurveda Integr Med. 2014; 5(1): 38-42. doi: 10.4103/0975-9476.128855, PMID 24812474.
18. Ngamsurach P, Praipipat P. Antibacterial activities against *Staphylococcus aureus* and *Escherichia coli* of extracted *Piper betle* leaf materials by disc diffusion assay and

batch experiments. RSC Adv. 2022; 12(40): 26435-54. doi: 10.1039/d2ra04611c, PMID 36275084.

19. Rahim ZH, Thurairajah N. Scanning electron microscopic study of *Piper betle* L. leaves extract effect against *Streptococcus mutans* ATCC 25175. J Appl Oral Sci. 2011; 19(2): 137-46. doi: 10.1590/s1678-77572011000200010, PMID 21552715.
20. Durani LW, Khor SC, Tan JK, Chua KH, Mohd Yusof YA, Makpol S. *Piper betle* L. BioMed Res Int. 2017; 2017: 6894026. doi: 10.1155/2017/6894026, PMID 28596968.
21. Rodríguez-Magaña MP, Cordero-Pérez P, Rivas-Morales C, Oranday-Cárdenas MA, Moreno-Peña DP, García-Hernández DG, *et al.* Hypoglycemic activity of *Tilia americana, Borago officinalis, Chenopodium nuttalliae*, and *Piper sanctum* on Wistar rats. J Diabetes Res. 2019; 2019(1): 7836820. doi: 10.1155/2019/7836820, PMID 31179342.
22. Sivareddy B, Reginald BA, Sireesha D, Samatha M, Reddy KH, Subrahamanyam G. Antifungal activity of solvent extracts of*Piper betle* and*Ocimum sanctum* Linn. on*Candida albicans*: an*in vitro* comparative study. J Oral Maxillofac Pathol. 2019; 23(3): 333-7. doi: 10.4103/jomfp.JOMFP_167_19, PMID 31942110.
23. Salehi B, Zakaria ZA, Gyawali R, Ibrahim SA, Rajkovic J, Shinwari ZK, *et al.* Piper species: A Comprehensive Review on Their Phytochemistry, Biological Activities and Applications. Molecules. 2019; 24(7): 1364. doi: 10.3390/molecules24071364, PMID 30959974.
24. Mallikarjuna K, Sushma NJ, Reddy BS, Narasimha G, Raju BD. Palladium nanoparticles: single-step plant-mediated green chemical procedure using *Piper betle* leaves broth and their anti-fungal studies. Int J Ana. 2013; 4(1): 14-8.
25. Jalil V, Khan M, Haider SZ, Shamim S. Investigation of the antibacterial, Anti-Biofilm, and antioxidative Effect of*Piper betle* Leaf Extract against Bacillus gaemokensis MW067143 Isolated from Dental Caries, an. Microorganisms. 2022; 10(12): 2485. doi: 10.3390/microorganisms10122485, PMID 36557738.
26. Gupta RK, Guha P, Srivastav PP. Phytochemical and biological studies of betel leaf (*Piper betle* L.): review on paradigm and its potential benefits in human health. Acta Ecol Sin. 2023; 43(5): 721-32. doi: 10.1016/j.chnaes.2022.09.006.
27. McFerren MA, Rodriguez E. Piscicidal properties of piperovatine from *Piper piscatorum* (Piperaceae). J Ethnopharmacol. 1998; 60(2): 183-7. doi: 10.1016/s0378-8741(97)00154-2, PMID 9582010.
28. Kumar S, Malhotra S, Prasad AK, Van der Eycken EV, Bracke ME, Stetler-Stevenson WG, *et al.* Anti-inflammatory and antioxidant properties of Piper species: a perspective from screening to molecular mechanisms. Curr Top Med Chem. 2015; 15(9): 886-93. doi: 10.2174/1568026615666150220120651, PMID 25697561.
29. Dos Santos AL, Novaes AD, Polidoro AD, de Barros ME, Mota JS, Lima DB, *et al.* Chemical characterisation of *Piper amalago* (Piperaceae) essential oil by comprehensive two-dimensional gas chromatography coupled with rapid-scanning quadrupole mass spectrometry (GC×GC/qMS) and their antilithiasic activity and acute toxicity. Phytochem Anal. 2018; 29(5): 432-45. doi: 10.1002/pca.2747, PMID 29479742.
30. Souto RN, Harada AY, Andrade EH, Maia JG. Insecticidal activity of Piper essential oils from the Amazon against the fire ant *Solenopsis saevissima* (Smith) (*Hymenoptera*: *Formicidae*). Neotrop Entomol. 2012; 41(6): 510-7. doi: 10.1007/s13744-012-0080-6, PMID 23949677.
31. Da Silva JK, Da Trindade R, Alves NS, Figueiredo PL, Maia JG, Setzer WN. Essential oils from Neotropical Piper species and their biological activities. Int J Mol Sci. 2017; 18(12): 2571. doi: 10.3390/ijms18122571, PMID 29240662.
32. Salehi B, Sharopov F, Martorell M, Rajkovic J, Ademiluyi AO, Sharifi-Rad M, *et al.* Phytochemicals in Helicobacter pylori infections: what are we doing now? Int J Mol Sci. 2018; 19(8): 2361. doi: 10.3390/ijms19082361, PMID 30103451.
33. Madhumita M, Guha P, Nag A. Extraction of betel leaves (*Piper betle* L.) essential oil and its bio-actives identification: process optimization, GC-MS analysis and anti-microbial activity. Ind Crops Prod. 2019; 138: 111578. doi: 10.1016/j.indcrop.2019.111578.
34. Bajpai V, Sharma D, Kumar B, Madhusudanan KP. Profiling of *Piper betle* Linn. cultivars by direct analysis in real time mass spectrometric technique. Biomed Chromatogr. 2010; 24(12): 1283-6. doi: 10.1002/bmc.1437, PMID 21077247.
35. Anand U, Jacobo-Herrera N, Altemimi A, Lakhssassi N. A comprehensive review on medicinal plants as antimicrobial therapeutics: potential avenues of biocompatible drug discovery. Metabolites. 2019; 9(11): 258. doi: 10.3390/metabo9110258, PMID 31683833.
36. Roy A, Guha P. Development of a novel cup cake with unique properties of essential oil of betel leaf (*Piper betle* L.) for sustainable entrepreneurship. J Food Sci Technol. 2015; 52(8): 4885-94. doi: 10.1007/s13197-014-1540-2, PMID 26243908.
37. Arambewela LS, Arawwawala LD, Kumaratunga KG, Dissanayake DS, Ratnasooriya WD, Kumarasingha SP. Investigations on *Piper betle* grown in Sri Lanka. Pharmacogn Rev. 2011; 5(10): 159-63. doi: 10.4103/0973-7847.91111, PMID 22279373.
38. Wang YH, Morris-Natschke SL, Yang J, Niu HM, Long CL, Lee KH. Anticancer principles from medicinal piper (hú jiāo) plants [hú jiāo]. J Tradit Complement Med. 2014; 4(1): 8-16. doi: 10.4103/2225-4110.124811, PMID 24872928.
39. Verma A, Kumar N, Ranade SA. Genetic diversity amongst landraces of a dioecious vegetatively propagated plant, betelvine (*Piper betle* L.). J Biosci. 2004; 29(3): 319-28. doi: 10.1007/BF02702614, PMID 15381853.
40. Das S, Parida R, Sriram Sandeep I, Nayak S, Mohanty S. Biotechnological intervention in betelvine (*Piper betle* L.): a review on recent advances and future prospects. Asian Pac J Trop Med. 2016; 9(10): 938-46. doi: 10.1016/j.apjtm.2016.07.029, PMID 27794386.
41. Jeng JH, Chen SY, Liao CH, Tung YY, Lin BR, Hahn LJ, *et al.* Modulation of platelet aggregation by areca nut and betel leaf ingredients: roles of reactive oxygen species and cyclooxygenase. Free Radic Biol Med. 2002; 32(9): 860-71. doi: 10.1016/s0891-5849(02)00749-9, PMID 11978487.
42. Lei D, Chan CP, Wang YJ, Wang TM, Lin BR, Huang CH, *et al.* Antioxidative and antiplatelet effects of aqueous inflorescence *Piper betle* extract. J Agric Food Chem. 2003; 51(7): 2083-8. doi: 10.1021/jf0210223, PMID 12643677.
43. Rajedadram A, Pin KY, Ling SK, Yan SW, Looi ML. Hydroxychavicol, a polyphenol from*Piper betle* leaf extract, induces cell cycle arrest and apoptosis in TP53-resistant HT-29 colon cancer cells. J Zhejiang Univ Sci B. 2021; 22(2): 112-22. doi: 10.1631/jzus.B2000446, PMID 33615752.
44. Abrahim 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 Complement Altern Med. 2012; 12: 220. doi: 10.1186/1472-6882-12-220, PMID 23153283.
45. Bhattacharya S, Subramanian M, Roychowdhury S, Bauri AK, Kamat JP, Chattopadhyay S, *et al.* Radioprotective property of the ethanolic extract of *Piper betel* Leaf. J Radiat Res. 2005; 46(2): 165-71. doi: 10.1269/jrr.46.165, PMID 15988134.
46. Toprani R, Patel D. Betel leaf: revisiting the benefits of an ancient Indian herb. S Asian J Cancer. 2013; 2(3): 140-1. doi: 10.4103/2278-330X.114120, PMID 24455591.
47. Garg SC, Jain R. Volatile constituents of the essential oil of *Piper betle* L. (Cultiver Sagar Bangla). Indian J Chem B Organ Chem. 1996; 35(8): 874-5.
48. Ngamsurach P, Praipipat P. Comparative antibacterial activities of*Garcinia cowa* and*Piper sarmentosum* extracts against*Staphylococcus aureus* and*Escherichia coli* with studying on disc diffusion assay, material characterizations, and batch experiments. Heliyon. 2022; 8(11): e11704. doi: 10.1016/j.heliyon.2022.e11704, PMID 36439749.
49. Haslan H, Suhaimi FH, Thent ZC, Das S. The underlying mechanism of action for various medicinal properties of *Piper betle* (betel). Clin Ter. 2015; 166(5): 208-14. doi: 10.7417/CT.2015.1880, PMID 26550811.
50. Karak S, Das S, Biswas M, Choudhury A, Dutta M, Chaudhury K, *et al.* Phytochemical composition, β-glucuronidase inhibition, and antioxidant properties of two fractions of *Piper betle* leaf aqueous extract. J Food Biochem. 2019; 43(12): e13048. doi: 10.1111/jfbc.13048, PMID 31581322.
51. Syahidah A, Saad CR, Hassan MD, Rukayadi Y, Norazian MH, Kamarudin MS. Phytochemical Analysis, Identification and Quantification of antibacterial Active compounds in Betel Leaves, *Piper betle* methanolic Extract. Pak J Biol Sci. 2017; 20(2): 70-81. doi: 10.3923/pjbs.2017.70.81, PMID 29022997.
52. Mohamad NA, Rahman AA. Sheikh Abdul Kadir SH. Hydroxychavicol as a potential anticancer agent. Oncol Lett. 2022; 25(1): 34.
53. Punuri JB, Sharma P, Sibyala S, Tamuli R, Bora U. *Piper betle*-mediated green synthesis of biocompatible gold nanoparticles. Int Nano Lett. 2012; 2: 1-9.
54. Majumdar B, Chaudhuri SR, Ray A, Bandyopadhyay SK. Potent antiulcerogenic activity of ethanol extract of leaf of *Piper betle* Linn. by antioxidative mechanism. Indian J Clin Biochem. 2002; 17(1): 49-57. doi: 10.1007/BF02867942, PMID 23105337.
55. Choudhary D, Kale RK. Antioxidant and non-toxic properties of *Piper betle* leaf extract: *in vitro* and *in vivo* studies. Phytother Res. 2002; 16(5): 461-6. doi: 10.1002/ptr.1015, PMID 12203268.
56. Saravanan R, Rajendra Prasad N, Pugalendi KV. Effect of *Piper betle* leaf extract on alcoholic toxicity in the rat brain. J Med Food. 2003; 6(3): 261-5. doi: 10.1089/109662003360716689, PMID 14585193.
57. Jaiswal SK, Rao CV, Sharma B, Mishra P, Das S, Dubey MK. Gastroprotective effect of standardized leaf extract from *Argyreia speciosa* on experimental gastric ulcers in rats. J Ethnopharmacol. 2011; 137(1): 341-4. doi: 10.1016/j.jep.2011.05.028, PMID 21658440.
58. Sarkar UR, Saha A, Majumdar MR. Antiulcer activity of hydroalcoholic extract of *Piper betle* leaf on experimental animals. Asian J Pharm Clin Res. 2019; 12(7): 226-9.
59. Aara A, Chappidi V, Ramadas MN. Antioxidant activity of eugenol in *Piper betel* leaf extract. J Fam Med Prim Care. 2020; 9(1): 327-31. doi: 10.4103/jfmpc.jfmpc_809_19, PMID 32110613.
60. Gundala SR, Aneja R. *Piper betel* leaf: a reservoir of potential xenohormetic nutraceuticals with cancer-fighting properties. Cancer Prev Res (Phila). 2014; 7(5): 477-86. doi: 10.1158/1940-6207.CAPR-13-0355, PMID 24449055.
61. Madhumita M, Guha P, Nag A. Bio-actives of betel leaf (*Piper betle* L.): a comprehensive review on extraction, isolation, characterization, and biological activity [*Piper betle* L]. Phytother Res. 2020; 34(10): 2609-27. doi: 10.1002/ptr.6715, PMID 32524688.
62. Paranjpe R, Gundala SR, Lakshminarayana N, Sagwal A, Asif G, Pandey A, et al. *Piper betel* leaf extract: anticancer benefits and bio-guided fractionation to identify active principles for prostate cancer management. Carcinogenesis. 2013; 34(7): 1558-66. doi: 10.1093/carcin/bgt066, PMID 23430955.
63. Gundala SR, Yang C, Mukkavilli R, Paranjpe R, Brahmbhatt M, Pannu V, *et al.* Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis. Toxicol Appl Pharmacol. 2014; 280(1): 86-96. doi: 10.1016/j.taap.2014.07.012, PMID 25064160.
64. Guha Majumdar A, Subramanian M. Hydroxychavicol from *Piper betle* induces apoptosis, cell cycle arrest, and inhibits epithelial-mesenchymal transition in pancreatic cancer cells. Biochem Pharmacol. 2019; 166: 274-91. doi: 10.1016/j.bcp.2019.05.025, PMID 31154000.

65. Patra AP, Mukherjee AK, Acharya L. Comparative study of RAPD and ISSR markers to assess the genetic diversity of betel vine (*Piper betle* L.) in Orissa, India. Am J Biochem Mol Biol. 2011; 1(2): 200-11. doi: 10.3923/ajbmb.2011.200.211.
66. Rawat AK, Tripathi RD, Khan AJ, Balasubrahmanyam VR. Essential oil components as markers for identification of *Piper betle* L. cultivars. Biochem Syst Ecol. 1989; 17(1): 35-8. doi: 10.1016/0305-1978(89)90039-2.
67. Harun WH, Zulaila CO, Fahim A, Allah NU. The synergistic effects of hydroxychavicol and amphotericin B towards yeast-hyphae transition and the germination of *Candida albicans*. J Taibah Univ Med Sci. 2023; 18(5): 967-75. doi: 10.1016/j.jtumed.2023.02.004, PMID 36866244.
68. Savsani H, Srivastava A, Gupta S, Patel K. Strengthening antioxidant defense & cardio protection by*Piper betle*: an *in vitro* study. Heliyon. 2020; 6(1): e03041. doi: 10.1016/j.heliyon.2019.e03041, PMID 31909246.
69. Bhattacharya S, Subramanian M, Roychowdhury S, Bauri AK, Kamat JP, Chattopadhyay S, *et al.* Radioprotective property of the ethanolic extract of *Piper betel* Leaf. J Radiat Res. 2005; 46(2): 165-71. doi: 10.1269/jrr.46.165, PMID 15988134.
70. Verma S, Gupta ML, Dutta A, Sankhwar S, Shukla SK, Flora SJ. Modulation of Ionizing Radiation Induced Oxidative Imbalance by Semi-Fractionated Extract of *Piper betle*: an *in vitro* and *in vivo* assessment. Oxid Med Cell Longev. 2010; 3(1): 44-52. doi: 10.4161/oxim.3.1.10349, PMID 20716927.
71. Rao AR, Sinha A, Selvan RS. Inhibitory action of *Piper betle* on the initiation of 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in rats. Cancer Lett. 1985; 26(2): 207-14. doi: 10.1016/0304-3835(85)90028-x, PMID 3919938.
72. Panda N, Panda A. *Piper betel*-not just a mouth freshener but also a miraculous herb for healing: a review. Asian J Biol. 2023; 18(2): 20-33. doi: 10.9734/ajob/2023/v18i2340.
73. 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: 922-32.
74. Amonkar AJ, Nagabhushan M, D'Souza AV, Bhide SV. Hydroxychavicol: a new phenolic antimutagen from betel leaf. Food Chem Toxicol. 1986; 24(12): 1321-4. doi: 10.1016/0278-6915(86)90065-7, PMID 3100406.
75. Saeed SA, Farnaz S, Simjee RU, Malik A. Triterpenes and b-sitosterol from *Piper betle*: isolation, antiplatelet and anti-inflammatory effects. Biochem Soc Trans. 1993; 21(4): 462S. doi: 10.1042/bst021462s, PMID 8132030.
76. Ghosh K, Bhattacharya TK. Chemical constituents of *Piper betle* Linn. (Piperaceae) roots. Molecules. 2005; 10(7): 798-802. doi: 10.3390/10070798, PMID 18007349.
77. Nalina T, Rahim ZH. The Crude Aqueous Extract of *Piper betle* L. and its Antibacterial Effect Towards *Streptococcus mutans*. Am J Biotechnol Biochem. 2007; 3(1): 10-5. doi: 10.3844/ajbbsp.2007.10.15.
78. Trakranrungsie N, Chatchawanchonteera A, Khunkitti W. Ethnoveterinary study for antidermatophytic activity of *Piper betle, Alpinia galanga* and *Allium ascalonicum* extracts *in vitro*. Res Vet Sci. 2008; 84(1): 80-4. doi: 10.1016/j.rvsc.2007.03.006, PMID 17482221.
79. Ali I, Khan FG, Suri KA, Gupta BD, Satti NK, Dutt P, et al. *In vitro* antifungal activity of hydroxychavicol isolated from *Piper betle* L. Ann Clin Microbiol Antimicrob. 2010; 9: 7. doi: 10.1186/1476-0711-9-7, PMID 20128889.
80. Kumarasinghe SP, Karunaweera ND, Ihalamulla RL, Arambewela LS, Dissanayake RD. Larvicidal effects of mineral turpentine, low aromatic white spirits, aqueous extracts of *Cassia alata*, and aqueous extracts, ethanolic extracts and essential oil of betel leaf (*Piper betle*) on Chrysomya megacephala. Int J Dermatol. 2002; 41(12): 877-80. doi: 10.1046/j.1365-4362.2002.01660.x, PMID 12492975.
81. Sarkar A, Sen R, Saha P, Ganguly S, Mandal G, Chatterjee M. An ethanolic extract of leaves of *Piper betle* (Paan) Linn. mediates its antileishmanial activity via apoptosis. Parasitol Res. 2008; 102(6): 1249-55. doi: 10.1007/s00436-008-0902-y, PMID 18273645.
82. Al-Adhroey AH, Nor ZM, Al-Mekhlafi HM, Amran AA, Mahmud R. Antimalarial activity of methanolic leaf extract of *Piper betle* L. Molecules. 2010; 16(1): 107-18. doi: 10.3390/molecules16010107, PMID 21189459.
83. Singh M, Shakya S, Soni VK, Dangi A, Kumar N, Bhattacharya SM. The n-hexane and chloroform fractions of *Piper betle* L. trigger different arms of immune responses in BALB/c mice and exhibit antifilarial activity against human lymphatic filarid *Brugia malayi*. Int Immunopharmacol. 2009; 9(6): 716-28. doi: 10.1016/j.intimp.2009.02.012, PMID 19281872.
84. Wirotesangthong 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 Immunopharmacol. 2008; 8(3): 453-7. doi: 10.1016/j.intimp.2007.11.005, PMID 18279799.
85. Saravanan R, Prakasam A, Ramesh B, Pugalendi KV. Influence of *Piper betle* on hepatic marker enzymes and tissue antioxidant status in ethanol-treated Wistar rats. J Med Food. 2002; 5(4): 197-204. doi: 10.1089/109662002763003348, PMID 12639394.
86. Young SC, Wang CJ, Lin JJ, Peng PL, Hsu JL, Chou FP. Protection effect of *Piper betel* leaf extract against carbon tetrachloride-induced liver fibrosis in rats. Arch Toxicol. 2007; 81(1): 45-55. doi: 10.1007/s00204-006-0106-0, PMID 16676162.
87. Pushpavalli G, Veeramani C, Pugalendi KV. Influence of *Piper betle* on hepatic marker enzymes and tissue antioxidant status in D-galactosamine-induced hepatotoxic rats. J Basic Clin Physiol Pharmacol. 2008; 19(2): 131-50. doi: 10.1515/jbcpp.2008.19.2.131, PMID 19024930.
88. Bhattacharya S, Banerjee D, Bauri AK, Chattopadhyay S, Bandyopadhyay SK. Healing property of the *Piper betel* phenol, allylpyrocatechol against indomethacin-induced stomach ulceration and mechanism of action. World J Gastroenterol. 2007; 13(27): 3705-13. doi: 10.3748/wjg.v13.i27.3705, PMID 17659730.
89. Panda S, Kar A. Dual role of betel leaf extract on thyroid function in male mice. Pharmacol Res. 1998; 38(6): 493-6. doi: 10.1006/phrs.1998.0398, PMID 9990660.
90. Vasantha-Srinivasan P, Senthil-Nathan S, Ponsankar A, Thanigaivel A, Edwin ES, Selin-Rani S, *et al.* Comparative analysis of mosquito (Diptera: Culicidae: *Aedes aegypti* Liston) responses to the insecticide temephos and plant derived essential oil derived from *Piper betle* L. Ecotoxicol Environ Saf. 2017; 139: 439-46. doi: 10.1016/j.ecoenv.2017.01.026, PMID 28213320.
91. Vasantha-Srinivasan P, Senthil-Nathan S, Thanigaivel A, Edwin ES, Ponsankar A, Selin-Rani S, *et al.* Developmental response of *Spodoptera litura* Fab. to treatments of crude volatile oil from *Piper betle* L. and evaluation of toxicity to earthworm, *Eudrilus eugeniae* Kinb. Chemosphere. 2016; 155: 336-47. doi: 10.1016/j.chemosphere.2016.03.139, PMID 27135695.
92. Arambewela L, Arawwawala M, Rajapaksa D. *Piper betle*: a potential natural antioxidant. Int J Food Sci Technol. 2006; 41(s1):10-4. doi: 10.1111/j.1365-2621.2006.01227.x.
93. Govind AS, Madhusudana NV. A molecular theory of smectic C liquid crystals made of rod-like molecules. Eur Phys J E Soft Matter. 2002; 9(2): 107-26. doi: 10.1140/epje/i2002-10060-x, PMID 15015110.

Cite this article: Tiwari R, Verma S, Sethi P, Dutta P, Devarai R. Therapeutic Potentials of *Piper betle* Leaf: Insights into Its Medicinal Uses and Bioactive Compounds. Pharmacog Res. 2025;17(4):1077-97.