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Review Article

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Piper betle: Deep Insights into the Pharmacognostic and Pharmacological Perspectives

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ABSTRACT

Piper betle L., belonging to Piperaceae family, referred to as a standard herbal medicinal plant and used for several health benefits in Asian countries. Currently, demand for its products like herbal drugs, medicines, and natural herbal formulations have increased. The beneficial effects of betel leaves and its products have traditionally exploited for the treatment of several diseases like bad breath, cuts, injuries, inflammations, cold cough, indigestion, etc. Till now, a broad range of bioactive compounds including polyphenols, terpenes, etc., has been identified from the extracts and volatile oil (EO) of betel leaves. Most of the health-related benefits of betel leaves are related to their bioactive phenolic compounds. The extract of this highly perishable product are often utilized in organic synthesis, food, and beverage industry, pharmaceuticals, etc., to the environmental issues. The present review provides information on pharmacognostic aspects, bioactive compounds, and their biological activities of *Piper betle* L.

Keywords: *Piper betle*, Leaves, Pharmacology, Therapeutics, Phytochemicals, Antimicrobial

INTRODUCTION

The bacterial infections mainly occur with the injuries or ulcers or after the surgical treatments. Antibacterial substances help to inhibit or kill bacterial cells Infectious diseases are an increasingly greater extent in recent years. Furthermore, antibiotic-resistant becomes a major therapeutic problem. The infectious diseases killing 50,000 people every day, and now, this is a world-leading cause for premature death. Natural products of higher plants may possess a new source of an antimicrobial agent with a possible novel mechanism of action. The researchers reported the antimicrobial activity of many plants and secondary metabolites of plants such as alkaloids, tannins, terpenoids, and flavonoids mainly responsible for these activities. Medicinal plants used for the antimicrobial treatment started in ancient times[1].

Several medicinal plant extracts and its phytochemicals have shown activity against all types of microorganisms including both Gram-negative and Gram-positive bacteria. Plants have the immense potential for the management and treatment of microbial infections. A large number of plants are used by tribal and folklore in many countries for the treatment of various types of infections such as antibacterial, antifungals, etc. These phytomedicine are not only cheap and affordable but are also safe. The presence of various life-sustaining constituents in plants has urged scientist to examine these plants with a view to determine potential antimicrobial properties[2].

Antibacterial activity is that the ability of a substance to inhibit or kill bacterial cells, differing types of antibiotics and chemotherapeutic agents are getting used within the treatment of 1 sort of disease or the opposite. Most of those antibiotics were originally derived from micro-organisms while the chemotherapeutic agents are from plants. However, nowadays these antibiotics and chemotherapeutic agents are obtained by various synthetic processes. India is richly blessed forests containing arrays of various herbs, shrubs and trees. The leaves, stems, bark and roots of those plants are getting used by the local populace and other people with thin income for incurring differing types of ailments due to the inadequate medical facilities across the country[3].

TRADITIONAL MEDICINE

Herbal medicine, also called phytotherapy or phytomedicine, refers to the utilization of any plant's seeds, berries, roots,

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leaves, bark, or flowers for medicinal purposes. Long practiced outside of conventional medicine, herbalism is becoming more mainstream as up-to-date analysis and research show their value within the treatment and prevention of disease. Plants had been used for medicinal purposes long before recorded history. Indigenous cultures (African and Native American) used herbs in their healing rituals, while others developed traditional medical systems (Ayurveda and Traditional Chinese Medicine) during which herbal therapies were used systematically[4]. Scientists found that folks in several parts of the world intended to use an equivalent or similar plants for an equivalent purposes. Recently, World Health Organization (WHO) estimated that 80% of individuals worldwide believe herbal medicines for a few aspect of their primary healthcare, for many herbs, the precise ingredient that causes a therapeutic effect isn't known. Whole herbs contain many ingredients, and it's likely that they work together to supply the specified medicinal effect. Herbalists prefer using whole plants instead of extracting single components from them. Whole plant extracts have many components. These components work together to supply therapeutic effects and also to reduce the probabilities of side effects from anybody component. Several herbs are often used together to reinforce effectiveness and synergistic actions and to scale back toxicity[5]. Traditional medicine is a crucial source of probably useful new compounds for the event of chemotherapeutic agents, the primary step towards this goal is that the screening of plants utilized in popular medicine. Thus, antimicrobial research is geared towards the invention and development of novel antibacterial and antifungal agents. Plant drugs are frequently considered to be less toxic and freer from side effects than the synthetic ones. Along side other dosage forms, herbal drugs also are formulated within the sort of ointment. An ointment may be a viscous semisolid preparation used topically on a spread of body surfaces. These include the skin and therefore the mucus membranes of the attention, vagina, anus, and nose[6]. An ointment may or might not be medicated. Medicated ointments contain a medicament dissolved, suspended or emulsified within the base. Ointments are used topically for several purposes, e.g. as protectants, antiseptics, emollients, antipruritic, keratolytics and astringents. Ointment bases are nearly always anhydrous and usually contain one or more medicaments in suspension or solution or dispersion. Ointment bases could also be hydrocarbon (oligeanous), absorption, water removable and water soluble type. On the idea of their level of action, they're classified as: epidermatic, endodermatic and diadermatic. An antiseptic ointment is aimed to destroy or inhibit the expansion of bacteria[7].

Antimicrobial Natural Products

Natural products are chemical compounds or substance produced by a living organism or found in nature that has pharmacological or biological activity. Living organisms produce manifold primary and secondary metabolites. Primary metabolites have essential function in the organism whereas secondary metabolites may have important functions for their producers or they could simply be waste products. But, it's possible that secondary metabolites may have therapeutic uses for people. Cancer, bacterial infections, inflammation, and a wide variety of other human disorders may be treated using these compounds. However it has been discovered that some of these secondary metabolites have antibacterial properties[8].

The majority of living things, from plants like fruits and vegetables to seeds and spices to milk and eggs and even bacteria and fungus, produce secondary metabolites having antimicrobial action. The rising unease about chemical preservatives among consumers has led to a greater focus on natural antimicrobials. Several chemical preservatives nevertheless pose harm to human health despite being permitted for human consumption by regulatory organisations. Thus, the scientific communities have given more attention towards the potential antimicrobial activities of natural products. On the other hand, the increasing antibiotic resistance against chemical preservatives of some pathogens associated with foodborne illness is in increasing rates. Natural antimicrobials seems to be the most promising answer to many of the increasing concerns regarding antibiotic resistance and could yield better results than antimicrobials from combinatorial chemistry and other synthetic procedures. Therefore, novel types of effective and healthy antimicrobial compounds that could protect food against contamination and consumer against infection is highly demanded[9].

Several investigations into natural materials' potential antibacterial effects have been carried out in recent years. There has been a renewed interest in plants, particularly culinary herbs and spices. Nowadays, approximately 30,000 antimicrobial compounds have been extracted from plants, and there are more than 1300 species with established antimicrobial properties. Yet, a great deal of research has been done on antimicrobials derived from microbes and animals. Moreover, natural antimicrobial compounds' potential food uses, in food items and animal feeds, against foodborne infections have been the subject of substantial investigation[10].

Natural antimicrobial products from plants

Secondary metabolites are compounds produced by plants and present in foods, medicines, and essential oils (EOs). Plants' secondary metabolites have been the subject of intense research because of their potential as therapeutic agents or preventative measures against human illness. Antimicrobial activities against pathogenic and spoilage bacteria are only one of the many advantages provided by these secondary metabolites. Plants have long been known to contain natural antimicrobials, but it is only in the past 30 years that this has been validated by science. As a result, there has been a rise in the search for natural antimicrobials that may be added to foods to delay the onset of spoilage. They are superior as food preservatives because they combine antioxidant and antibacterial capabilities in a single molecule[11].

Plants often suppress Gram-positive bacteria much more effectively than Gram-negative bacteria. It's possible that the presence of wide range antibiotic chemicals or maybe just general metabolic poisons explains the effectiveness against both kinds of bacteria. Plants' ability to kill microbes is proportional to the chemical structure of their active components and the amount of those components. Plants include a wide variety of chemical components, such as saponin, flavonoids, thiosulfinates, glucosinolates, phenolics, and organic acids, that have antimicrobial effects. Nevertheless, phenolic chemicals such as terpenes, aliphatic alcohols, aldehydes, ketones, acids, and isoflavonoids are the major components in plants with antibacterial action. For instance, phenolic components have been linked to the antibacterial activity of 46 spice and herb extracts. Against Bacillus cereus, Listeria monocytogenes, Staphylococcus aureus, Escherichia coli, and Salmonella anatum, all of the tested spices showed significant antibacterial activity, as stated by the authors. Anthocyanins, a kind of phenolic molecule, were proposed as a possible explanation for red cabbage's antibacterial activity[12].

Nonphenolic oil compounds, such as those found in oregano, clove, cinnamon, citral, garlic, coriander, rosemary, parsley, lemongrass, muscadine seeds, and sage, are effective against both Gram-positive and Gram-negative groups, but phenolic compounds of EOs, such as those found in lemon, olive oil (oleuropein), tea-tree oil (terpenoids), orange, and bergamot, have broader antimicrobial effects. Certain essential oils, including garlic oil and allylisothiocyanate, include nonphenolic components that are more or somewhat efficient against Gram-negative bacteria. Fruits, vegetables, nuts, seeds, stems, flowers, and leaves are all good sources of saponin and flavonoids. The antimicrobial activity of saponins and flavonoids derived from plants like Bersamaengleriana (Melianthaceae) have been proven when extracted from roots, stem bark, leaves, and wood. Antimicrobial activity of thiosulfinates has been shown particularly well against Gram-negative bacteria. Glucosinolates are secondary metabolites that occur in many species of plants include mustards, cabbage, cauliflower, brussel sprouts, broccoli, kohlrabi, kale, horseradish, and radishes. Directly or in synergy with other chemicals, glucosinolate hydrolysis products have been shown to exhibit potent antibacterial action against Gram-positive bacteria, Gram-negative bacteria, and fungi. Herbs and spices (like rosemary, sage, basil, oregano, thyme, marjoram, cardamom, and clove), fruits and vegetables (like guava, xoconostle, pepper, cabbage, garlic, and onion), and seeds and leaves (like grape seeds, caraway, fennel, nutgem, parsley, and olive leaves) all contain antimicrobial compounds[13].

PIPER BETLE

Piper betle L. is a perennial, dioecious and tropical shade loving creeper, belonging to the Piperaceae family. This climber is one of the crucial asexually propagated cash crop including 3,600 species in 13 genera. The two leading genera of this family are; Piper, consisting of 2000 species and Peperomia having 1600 species; they form the fundamental unit of pepper. The term Piperaceae is derived from the Sanskrit word "pippali" which is known to characterize long peppers like *Piper longum*. *Piper betle* is popular in India by various names i.e., Tambula in Sanskrit, Vettilakkoti in Malayalam, Pan in Hindi and Bengali, Villayadela in Kannada, Tamalapaku in Telugu, Vettilai in Tamil, Nagarbel in Gujurati and Videch-pan in Marathi. Apart from India, it is also popular as Burg-e-Tanbol in Persian and Tanbol in Arabic[14].

Taxonomic Classification

The taxonomic classification is as follows -

Kingdom	Plantae
Phylum	Tracheophyta
Class	Magnoliopsida
Order	Piperales
Family	Piperaceae
Sub-family	Piperoideae
Genus	Piper
Species	betle

Available Species

Numerous species of genus *Piper* are commercially prevalent in various agro-climatic regions of several countries. Example, *P.betle*, *P.nigrum*, *P.longum*, *P.aduncum*, and *P.cubeba* are a few customary members of the Piperaceae family; and *P.betle* is one of the most studied and ubiquitously cultivated due to its invaluable bioactive constituents and therapeutic properties of essential oil present in it.

Origin

P. betle is cultivated extensively in India and China due to its well-established roles in timeworn practices along with the plant's immense medicinal properties, establishing it as economically important. *Piper* species flourish well in the lowland tropical rainforests and are also grown in high altitudes like cloud forests. *P. betle* is known to have originated from Malaysia and it is broadly distributed throughout the South and Southwest regions of China. Its cultivation is commonly practiced in the Asian countries like India, Indonesia, Nepal, Sri Lanka, Bangladesh, Myanmar, Pakistan, Vietnam, Thailand, Laos, Kampuchea, mainly for its ethnomedicinal properties.

Distribution in India

In India, *P. betle* is considered as an essential cash crop in various states like Karnataka, Andhra Pradesh, Tamil Nadu and Kerala and is tremendously cultivated in states such as Maharashtra, Madhya Pradesh, Bihar, Assam, Uttar Pradesh, Orissa, West Bengal and Tripura. *P. betle* is widely distributed in areas of Africa, Himalaya, India, western Asia, Southeast Asia, Taiwan, China, Malaysia, Thailand Nepal, Sri Lanka and other Southeast Asian countries. Betel has become one of the most prominent spices in Nepal, India, and China and is also cultivated for recreational purposes like chewing and has many other traditional and aesthetical uses. There are 100 different varieties of betel available all over the world and out of them, 40 are available in India.

Importance

P. betle is an extremely important plant in the world, considering its medicinal importance and the part, it plays in ancestral practices. The plant is really popular in India due to its significant use in every sphere of life like social, cultural and religious activities. In Tamil Nadu, Kerala, Uttar Pradesh, Maharashtra and Madhya Pradesh, it is regarded as a major crop of commercial importance[15].

Economy

This plant is mostly cultivated by small farmers with an estimated area of 53,539 ha. The annual production of betel leaves was about Rs 9,000 million and from the survey, it was found that about 20 million people acquire their livelihood from maintenance, plantation, management, export and import of betel leaves in India. The cultivation economy depends on both in terms of benefit-to-cost ratio and net income. For the last 7 years, an average productivity of 19.41lakh leaves/ha has been recorded. Owing to its immense medicinal property and traditional importance, it stands out in the race for one of the most important commercial crops which is able to attract adequate amount of foreign exchange to the country. Betel leaves, worth about Rs 30–40 million per year, are exported to other countries of the world like Great Britain, Baharin, Canada, Nepal, Pakistan and Saudi Arabia. The annual turnover of betel is estimated to be Rs. 10,000 million. The betel leaves are also exported to UK, USA, Bangladesh, Malaysia, Singapore, Sri Lanka and other Arabian Countries, which, in turn, helps India to earn about 198 lakh rupees per year through foreign exchange. In India, betel cultivation provides an annual production of Rs. 9000 million, when practiced on about 55,000 hectares of land, which claims to support around 40,000 to 5,00,000 poor agricultural families. *P. betle*L. is an economically and medicinally important cash crop, valued for its fresh leaves, in many parts of the country. In the Asiatic region, betel ranks next to coffee and tea in terms of daily consumption. This crop provides Rs 6000-7000 million of national income per year and at the same time leaves worth Rs 30-40 million is exported to other countries[16].

Cultivation

About 100 local cultivars of betel are available in India. Many of them differ from each other in several organoleptic properties. There are many synonyms are available for the same cultivar. The existing chemotypic and genotypic variation in betel landraces necessitate chemical and molecular profiling of available germplasm. On the basis of chemical constituents and essential oil, five groups have been identified and there is no report on phytochemical variation among the available genotypes. Betel cultivation suffers a great deal of problems due to the existence of its synonyms. In some places, the same betel plant is being cultivated with different names and in some regions, different betel plants are cultivated with same names. Thus, the investigation validates that the betel landraces having prefix 'Desi' in their names belongs to the 'Bangla' landrace in West Bengal, 'Desawari' landrace in Madhya Pradesh and 'Kapoori' landrace in Maharashtra. Reports on proper identification or its characterization are still scanty. As a result of which, a lot of confusion is existing among the farmers. Cultivation is performed mainly through the traditional farming system and is controlled by the society. The local farmers specified the betel, according to the region where it is cultivated, taste and shape of the leaves. Although cultivation of betel is extensively distributed, the genetic diversity assessment is restricted to few landraces. On the basis of morphological characteristics, there are reports on hundreds of betel types categorized into six cultivars like Bangla, Desawari, Kapoori, Khasi, Meetha, and Sanchi. Eight cultivars were studied on the basis of their morphoanatomic details of leaf, dissociation and powders. Chemical or molecular fingerprinting in betel has not yet been reported in most of the cultivars. Therefore, it is always difficult to differentiate the cultivars which are invariably named by the local farmers[17].

Modern research

Recently, molecular marker based characterization of genotypes, is becoming a reliable tool for proper selection and authentication of economically important plant species. In betel characterization through molecular marker, the process is only confined to RAPD and ISSR. Molecular profiling of betel by ISSR marker was reported but there is no report of molecular characterization using SSR markers.

Most of the cultivars need to be characterized. As it is a cash crop of India, proper characterization and authentication are of utmost importance to resolve the synonym problems and to select elite genotypes of betel. Genotypes with high essential oil quality and quantity are always in demand for its commercial propagation and improvement programme. Bioactivity based studies in betel is restricted to different landraces, reported by different authors. But it is almost impossible to correlate them due to lack of their molecular and genetic fingerprinting. Bioactivity based screening of betel germplasm is still not reported by any workers. Thus, it is always important to select elite betel germplasm of desirable phytoconstituents with bioactivity for industrial application[18].

Ethnopharmacological uses

The betel leaves, though predominantly used as mouth freshener, is also eminent for curing many communicable and non-contagious diseases such as cough, cold, rheumatism, stomachalgia, bronchial asthma. It is also used for treating other diseases such as pyorrhea, conjunctivitis, cuts, injuries, constipation, boils, leucorrhoea,mastitis, mastoiditis, otorrhoea, swelling of gum and abscesses. A volatile volatile oil, which is contained in betel leaves, has antiseptic, cardiotonic, vital sign lowering and cardiac also as respiratory depressant properties. The substantial antiseptic property of betel oil is due to the presence of a bioactive constituent referred to as chavicol. The essential oil also has anti-protozoan, anti-bacterial, and anti-fungal properties[19].

Modern pharmacotherapeutics

It is known that the aqueous extract of betel leaves, reduces the adherence of early dental plaque bacteria. It is also found that betel has significant anti proliferative activity in prostate cancer models. Betel leaves are rich in the important phytochemicals i.e. hydroxychavicol that contributes to the antiproliferative efficacy of betel leaf extract. The betel leaf, consisting of phenolic compounds, inhibits prostate cancer through ROS drove DNA damage and apoptosis. Some of the important constituents of the leaf oil are α-Pinene, Safrole, Eugenol, Selinene, Hydroxychavicol, Cadinene, Caryophyllene, etc. *P. betle* has become a reliable source of employment and income throughforeign exchange of the country. The size and color of the betel leaf are the most significant elements for the betel producers to categorize products in the market. The betel of different landraces has been bundled into five prominent groups namely Bangla, Meetha, Desawari, Kapoori, and Sanchi, basing on the chemical constituents of their leaf essential oils. The betel is called as 'green gold of India' as the livelihood of about 20 million people depends directly or indirectly on the production, transportation, processing, marketing and handling of betel leaves in India. The betel leaves along with its roots, fruits and flowers are antiseptic, carminative and stimulant, which facilitate its use in the treatment of malaria. The betel leaves can also be used in treating different diseases both externally and internally. The external uses include healing of ulcers, boils, bruises, ulcerations of the nose, eye injury and night blindness, respiratory ailments, headache, throat infection, inflamed joints, and hoarseness of voice. The internal uses include treating stomach disorder, throat irritation, filaria, impaired digestion, bad breath, gastritis. The leaves are widely used in the Indian system of medicine for treatment of conjunctivitis, constipation, headache, hysteria, ringworm, rheumatism, cut and injuries etc while the root is known for its female contraceptive effects. Further, the essential oil contained in the leaves possesses many volatile constituents like eugenol, chavibetol, chavicol and hydroxyl chavicol, responsible for anti fungal, anti oxidant and anticancer properties. Inspite of its great economical and medicinal importance, betel is still neglected by the researchers and no proper characterization and authentication is done for selection of elite landraces for commercial utilization[20].

SPECIFIC REPORTS

Misra et al. (2014) studied that antioxidant and anti inflammatory, antihistaminic activities of P. betle affect wide selection diseases. Researchers evaluated the anti-Asthmatic effect of P. betle in guinea pigs. Asthma is hyper responsiveness of the tracheobronchial smooth muscle to a spread of stimuli. Asthma is an inflammatory condition, radical and superoxide could also be liable for asthma. Histamine may cause bronchoconstriction. The effect of asthma are often reduced significantly by P. betle extract, though its action is a smaller amount than that of diphenhydramine. But in humans for asthma, other mediators like leukotriene play a crucial role. Although effect of P. betle Linn. on human asthma isn't known well ,but from the studies, it had been concluded that P. betle L. has the power to scale back asthma in guinea pigs[21]. Hasan et al. (2014) reported that P. betle induces phase I & II genes through the Nrf2/ARE signaling pathway in mouse embryonic fibroblasts derived from wild type and Nrf2 knockout cells. Nuclear factor-erythroid 2 p45 related factor 2 (Nrf2) may be a primary transcription factor, protecting cells from oxidative stress by regulating variety of antioxidants and phase-II detoxifying enzymes. Dietary components like sulforaphane in broccoli and quercetin in onions are shown to be inducers of Nrf2. P. betle grows well in tropical climate and therefore the leaves are utilized in variety of traditional remedies for the treatment of stomach ailments and infections among Asians[22].

Ghosh et al. (2014) conducted studies on Piper species and observed some species exhibiting antimicrobial activity. The studies on antimicrobial activity are done by using extracts of the Piper using n-hexane as solvent was done. it had been found that compound 3-(4'-Methoxyphenyl) propanoylpyrrole of P. lolot showed antibacterial activity. Study reported the petroleum ether extract of leaves of P. gibbilimbum had antibacterial activity against Staphylococcus epidermidis and Bacillus cereus[23].

Nilugal et al. (2014) investigated the wound healing capability of P. betle leaves and stem extract. Wounds are mentioned as an interruption of normal anatomic structure and performance. Wound healing may be a very complex, multifactor sequence of events involving several cellular and biochemical processes. Researchers investigated the improved rate of wound contraction and drastic reduction in healing time in male albino rats, which could flow from to enhanced epithelialization. The results showed wound healing and repair, accelerated by applying ointment formulation containing P. betle leaves and stem extract, which was highlighted by the complete thickness coverage of the wound area by an organized epidermis. The animals treated with ointment formulation containing 10% P. betle leaves and stem showed significant results in comparison with providone iodine and control group. From investigations, it had been concluded that P. betle has the potential ability in wound healing[24]. Mishra et al. (2014) investigated the role of Petiole within the protein metabolism of senescing P. betle L. Leaves. In normal petiole leaves, the extent of chlorophyll and proteins and extent of protein synthesis declined, while the protease activity registered man fold increase with the advancement of senescence. All of those changes were delayed by depetiolation de-midribbing treatments, through without affecting the overall pattern of senescence. Thus, the presence of petiole seems to expedite protein degradation[25].

Venkadeswaran (2014) demonstrated the antihypercholesterolemic and antioxidative potential activity of P. betle. Hypercholesterolemia may be a dominant risk factor for atherosclerosis and cardiovascular diseases. during this study the putative antihypercholesterolemic and anti-oxidative properties of an ethanolic extract of P. betle and of its active constituent, eugenol, were evaluated in experimental hypercholesterolemia induced by one intraperitoneal injection of Triton WR-1339 (300 mg/kg b.w.) in Wistar rats. Hypercholesterolemic rats receiving the P. betle extract (500 mg/kg b.w.) or eugenol (5 mg/kg b.w.) for seven days orally, of these parameters were significantly better than those in saline treated hypercholesterolemic rats. The hypercholesterolemia-ameliorating effect was better defined in eugenol-treated than in P. betle extract-treated rats, being as effective as that of the quality lipid lowering drug, lovastatin (10 mg/kg b.w.). These results suggest that eugenol, a lively constituent of the P. betle extract, possesses anti-hypercholesterolemic and other activities in experimental hypercholesterolemic Wistar rats. Results indicated that blood sugar level in hypercholesterolemic, saline treated (group-II) rats was significantly above that on top of things (group-I) rats. In hypercholesterolemic rats treated with lovastatin (group-III), P. betle extract (group-IV), or eugenol (group-V). Significantly lower mean blood sugar levels were observed in comparison thereto in saline treated hypercholesterolemic rats though the amount were still above that within the control rats. The mean blood sugar level was higher in P. betle extract treated hypercholesterolemic rats than that in lovastatin-treated or eugenol treated hypercholesterolemic rats[26].

Widowati et al. **(2013)** reported anticancer and free radical scavenging potency of *Catharanthusroseus*, *Dendrophthoepentandra*, *P. betle*, and *Curcuma mangga* extracts in breast cancer cell lines. Research was conducted to identify the anticancer and antioxidant activity of *C. roseus* [L.] G. Don, *D. pentandra* L., *P. betle* L., and *C. mangga* Val aqueous extracts in T47D human ductal breast epithelial tumor cell line. The anticancer potency was determined via the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay while the apoptotic activity was determined with Sub-G1 flow cytometric analysis. The antioxidant activity was determined by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity[27].

Arambewela et al. (2011) observed the anti-larvicidal activity of P. betle. The researchers introduced the P. betle volatile oil at different concentrations, i.e. 500ppm, 100ppm, 50ppm, 25ppm, 12.5ppm, and 6.25 ppm concentrations, and motility was recorded between 1 hr to 24 hrs. Mortalities of 43% and 100% were observed for 100 ppm and 500 ppm concentrations, respectively, within 1 hr. Compared to the control, significant mortality was observed even at lower concentrations, 25 ppm and 50 ppm, after 24 hrs. The concentration of oil used was 1%, 0.8%, and 0.5%, respectively, and therefore the death =rate of 100% was observed in 1% betel oil solution within 1 hr. Betel solutions ranging in conce/ntration from 1% to 4% were prepared using 1% Tween 80, sodium lauryl sulfate (0.05 g/100 mL, as a stabilizer) and methyl paraben (0.01 g/100 ml, as a preservative). The 4% and three preparations of the oil of betel were effective in killing 100% of the larvae of C. megacephala within 3 hrs, while betel oil at 2% concentration killed 97% of C. megacephala larvae within 4 hrs. The positive control, mineral turpentine, also killed the larvae within 4 hrs. This shows that betel oil is effective within the treatment of wound myiasis[28].

Singh et al. (2009) investigated the anti-filarial activity of P. betle. The n-hexane and chloroform fractions of P. betle L. trigger different arms of immune responses in BALB/c mice and exhibit ant filarial activity against human lymphatic filarid Brugiamalayi. Modulation of immune functions by using herbal plants and their products has become a fundamental regime of therapeutic approach. it had been reported that the antifilarial and anti-leishmanial efficacy within the leaf extract of Bangla mahoba landrace of P. betle which may be a female plant. The report describes the in-vivo immunomodulatory efficacy of the crude methanolic extract and its n-hexane, chloroform, n-butanol fractions of the feminine plant at various dose levels ranging between 0.3 and 500 mg/kg in BALB/c. Attempts were made to watch ant filarial activity of the active extracts and correlate it with the antigen specific immune responses in another rodent Mastomyscoucha infected with human lymphatic filarial parasite Brugiamalayi[29].

Row et al. (2009) studied the antimicrobial activity, mosquito larvicidal activity, antioxidant property and tyrosinase inhibition of P. betle. The volatile oil and methanolic and aqueous extracts of P. betle L. were assayed for his or her antimicrobial activity, mosquito larvicidal activity, antioxidant property and mushroom tyrosinase inhibition. The methanolic and aqueous extracts showed strong activity against the yeasts: C. albicans, and M. pachydermatous. The crude volatile oil exhibited a broad-spectrum strong antimicrobial activity against all test organisms. The strongest activity was observed against C. albicans, followed by S.aureus and M. pachydermatis. The chemical composition of the volatile oil and its fractions was analyzed by GC/MS analysis. Eugenol (36.2%), chavibetol acetate (16.9%), 4-allylphenyl acetate (9.4%), and 4-allylphenol (7.2%) were the most components, comprising 69.7% of the oil. The fractionation of the volatile oil gave two fractions. Fraction-I was rich in eugenol (71.3%) and fraction-II in eugenol (46.4%), chavibetol acetate (19.4%) and 4-allylphenyl acetate (11.8%). The volatile oil exhibited the mosquito Larvicidal activity with 2 hr and 24 hr LD50 value of 86 ppm and 48 ppm, respectively[30].

Cristina et al. (2009) studied the insecticidal activities of volatile oil from P. betle against storage insect pests. The insecticidal activity of volatile oil extracted from the leaves of P. betle Linn, was evaluated against the Acanthoscelidesobtectus (Callosobruchusmaculatus F.), corn weevil (Sitophiluszeamais Motchulsky) and lesser grain borer (Rhizoperthadominica F.) using aged grain assay. The efficacy of treatments was assessed by determining the acute toxicity on adult insects and therefore the extent of preventing or suppressing the assembly of progenies. The essential oil in 30% dust formulation exhibited toxicity against adult C. maculatus, S. zeamais, and R. dominica at varying application rates, such as 0.2 g/100g, 1.75 g/100g, and 2.0 g/100g, respectively. Survival of adult C. maculatus was prevented until six months by 52%, while the treatment allowed six months protection of corn against S. zeamais and R. dominica. Although eggs were visible within the treated mung, the treatment prevented them to develop further. The study disclosed that the biologically active component of P. betle leaf oil may possess ovicidal properties that inhibited the event of eggs of C. maculatus into larvae, thus prevented the emergence of the adult stage. Meanwhile, the absence of eggs of both S. zeamais and R. dominica was prominent in treating corn. The treatments were ready to inhibit entirely the emergence of progenies. No living progenies were observed in treated samples until six months while progenies were abundant in two control samples, check and untreated. the info revealed that P. betle leaf oil may be a fecundity-reducing agent to adult S. zeamais and R. dominica. Likewise, the oil's ovicidal effect can't be discounted. it had been suggested that the volatile oil from P. betle leaves may be a promising grain protectant[31].

Kanjwani et al. (2008) studied the efficiency of methanolic extract of P. betle for its novel candidature in immunosuppressive activity. The animal studies were administered to guage the effect of methanolic extract of P. betle on T-cell and B-cell mediated immune reaction. in vivo studies in mice showed suppression of cell-mediated immune reaction and antibody-mediated immune reaction during a dose-dependent manner. The methanolic extract of P. betle at various concentrations produces suppression of mitogenicity induced by Phytohaemagglutinin. Interferon-C is an anti-inflammatory cytokine secreted by lymphocytes in response to external stimuli within the presence of immunosuppressive substance the extent of IFN-c is reduced. Obtained results showed that the crude methanolic extract decreased antibody titer. The methanolic extract of P. betle at different concentrations on delayed sort of hypersensitivity was measured from T-cell mediated immunity. DTH is characterized by an outsized influx of nonspecific inflammatory cells, mainly macrophages. it's developed when antigen activates sensitized TH cells. The methanolic extract of P. betle at 500 mg⁄kg dose produced immunosuppression that was almost like that produced by the well-known immunosuppressant cyclophosphamide (2 mg⁄kg). The research concluded that P. betle a possible candidate for immunomodulatory drug[32].

Sharma et al. (2007) studied the antifertility efficacy of P. betle Linn. (Petiole) in female albino rats. Normal cyclic female albino rats (Rattusnorvegicus) of Wister strain weighing between 150-200 g were treated with P. betle (Petiole) ethanolic (50%) extract (100 mg/day/rat) for 30 days. The results revealed that P. betle treatment caused a discount in sex organ weights, circulating levels of estrogen, fertility, number of litters, serum glucose concentration, enzyme activity of acid phosphates, SGOT and SGPT as compared to regulate values. The concentration of cholesterol and vitamin C increased following P. betle treatment, revealing non-utilization of cholesterol by the system and mobilization of vitamin C during Phyto-drug treatment to beat from induced stress condition. The estrus cycle was irregular and prolonged within the treated group of rats indicative of an estrus condition, which resulted in infertility. The hematological parameters remained within normal range. Withdrawal of Phyto-drug for 30 days restored complete/partially decreased sex organ weights, circulating levels of estrogen, fertility, number of litters, the concentration of glucose and enzyme activity of acid phosphates SGOT and SGPT to regulate values. The cholesterol and vitamin C concentration was also restored to regulate level. The info suggest that the P. betle ethanolic extract exerted anti-fertility and anti-estrogenic effects in female rats. The consequences brought by P. betle extract are non-toxic and transient. The alcoholic extract of the leaf-stalk showed significant anti-fertility effects in both male and feminine rats[33].

Nalina et al. (2007) investigated the antibacterial effect of P. betle. The antimicrobial influence of crude aqueous extract of P. betle L. on Streptococcus mutans was investigated. The main target of the antimicrobial effects includes the ultra-structure and acid producing properties of S. mutans. From the micrographs of the transmission electron, it had been found that the crude extract of P. betle L. leaves causes plasmacyte Membrane damage and coagulation of the nucleoid. The extract was found to significantly reduce acid producing properties of the bacteria. Qualitative analysis of the extract showed that hydroxychavicol, carboxylic acids (stearic and palmitic) and hydroxyl fatty acid esters (stearic, palmitic, and myristic) because the main components. From the results obtained, it had been concluded that the crude extract of P. betle L. leaves may exert anti-cariogenic activities that are associated with decrease in acid production and changes to the ultrastructure of S. mutans. Recent studies in Sri Lanka infer that P. betle inhibit the expansion of microorganism namely Escherichia coli, Streptococcus, Pyogenes, and Staphylococcus aureus at lower activity[34].

Maisuthisakul et al. (2007) studied antioxidant activities of P. betle L., extracts with different solvents and extraction times. Total phenolic content was evaluated consistent with the Folin-Ciocalteu procedure. The polarity of the plant extract from various solvents was assessed by determining the oil-water partition coefficient by high-performance liquid chromatography (HPLC). The extract showed the very best antioxidant activities, total phenolic content and yield. P. betle leaf phenolics were found to possess less polarity than other phenolic antioxidants thanks to their high value of oil-water partition coefficient. The results indicated that the extraction solvent and time are important for the preparation of the betle leaf extract to be used as a natural antioxidant[35].

Bhattacharya et al. (2007) studied the Anti-ulcerative property of the P. betle against indomethacin-induced stomach ulceration and its mechanism of action. They also evaluated the protective activity of allylpyrocatechol (APC), the main antioxidant constituent of P. betle, against the indomethacin-induced stomach ulceration in threat model and correlated the info obtained with its anti-oxidative and mucus protecting properties. The models used were male Sprague-Dawley rats. The study revealed that the treatment with APC (2 mg/kg b.w. per day) and misoprostol (1.43 µg/kg b.w. per day) for 7 days could effectively heal the stomach ulceration as revealed from the ulcer index and histopathological studies [36].

Wirotesangthong et al. (2007) studied the inhibitory effects of P. betle on production of allergic mediators by bone marrow derived mast cells and lung epithelial cells. the consequences of P. betleethanolic extract on the assembly of histamine and granulocyte macrophage colony-stimulating factor (GMCSF) by murine bone marrow mast cells (BMMCs) and on the secretion of exotoxin and IL-8 by the human lung somatic cell line, BEAS-2B, were investigated in vitro. The extracts significantly decreased histamine and GM-CSF produced by an IgE-mediated hypersensitivity, and inhibited exotoxin and IL-8 secretion during a TNF-α and IL-4-induced allergy. The results suggest that P. betle may offer a replacement therapeutic approach for the control of allergic diseases through inhibition of production of allergic mediators[37].

Bhattacharya et al. (2006) investigated the inhibitory property of P. betle extract against photosensitization-induced damages to lipids and proteins. The protective activity of P. betle ethanolic extract against the photosensitization-induced damage to lipids and proteins of rat liver mitochondria was studied and it had been found that P. betle ethanolic extract could effectively prevent lipid per oxidation, as assessed by measuring thiobarbituric acid reactive substances, lipid hydro peroxide and conjugated diene. Additionally, it prevented photo-induced oxidation of proteins during a concentration dependent manner. Furthermore, its preventive capacity against iron-mediated lipid per oxidation was also confirmed. The protective activity of P. betle ethanolic extract might be attributed to its radical and singlet oxygen scavenging properties. The activity of the P. betel extract was primarily thanks to its phenolic constituents, which were identified as chavibetol and 4-allylpyrocatechol[38].

Shun-Chieh et al. (2006) first examined the effect of P. betle extract on the activity of Glutathione S-transferase (GST) iso-forms, and located that P. betle inhibited total GST and therefore the a category of GST (GSTA), but not the p class of GST (GSTP), and therefore the l class of GST (GSTM), activity in Hep G2 cells. RTPCR results verified a discount within the expression of GSTA1. Researchers examined whether P. betle extract could increase the sensitivity of Hep G2 cells to anti-cancer drugs. These data showed that the cytotoxicity of cisplatin was significantly enhanced by the presence of P. betle extract, amid a discount within the expression of multidrug resistance protein-2 (MRP2). These effects of P. betle extract were attributed to its major constitute eugenol. Although eugenol decreased MRP2 level more effectively than P. betle extract, it exhibited less sensitizing effect. it's also observed that P. betle extract was ready to increase the sensitivity of HepG2 cells to cisplatin via a minimum of two mechanisms, reducing the expression of MRP2 and inhibiting the activity of total GST and therefore the expression of GSTA. Further, they evaluated the antihepatotoxic effect of P. betle extract on the carbon tet (CCl4) induced liver injury during a rat model. Fibrosis and hepatic damage, as revealed by histology and therefore the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were induced in rats by an administration of CCl4 (8%, 1 ml/kg body weight) thrice every week for 4 weeks. P. betle extract significantly inhibited the elevated AST and ALT activities caused by CCl4 intoxication. The histological examination showed the P. betle extract protected liver from the damage induced by CCl4 by decreasing a smooth muscle actin (a-sma) expression, inducing active matrix metalloproteinase-2 (MMP2) expression, though Ras/Erk pathway, and inhibiting TIMP2 level that consequently attenuated the fibrosis of the liver. The info of this study support a preventive potential of P. betle against liver fibrosis[39].

Trakranrungsie et al. (2006) studied the antidermatophyticactivity of P. betle cream. Crude ethanolic extracts of P. betle leaves (Piperaceae), Alpinia galangal rhizomes (Zingiberaceae), and shallot bulbs (Liliaceae) were previously tested against selected dermatophytes (Microspore canis, Microsporumgypseum, and Trichophytonmentagrophyte). The results suggested a promising antifungal property of P. betle extracts than its counterparts. The researcher formulated 10% P. betle cream for antidermatophytic activity, subjected to physical and microbial limit tests, and evaluated for its effect against dermatophytesin vitro. The freshly prepared P. betle cream (pH~5.0) was dark green with a pungent odor of P. betle leaves. After repeated freeze-thawing, the cream was darkening and markedly thickening. Its pH also increased significantly no bacterial or fungal contamination was detected from the P. betle cream samples[40].

Arambewela et al. (2005) reported that P. betle has antinociceptive activity. About 200 mg/kg and 300 mg/kg doses of P. betle extract markedly reduced the licking time in early and late phases of the formalin test during a bell-shaped dose-response curve. Within the formalin test, the pain within the early phase is caused thanks to the direct stimulation of the nerve fibers by formalin, while the pain within the late phase is thanks to the inflammatory mediators, like histamine, prostaglandin, serotonin and bradykinin. It's reported that NSAIDs reduce both phases of the formalin test. The betel extracts too induced interruptions in both phases of this test, suggesting possible impairments of sensory transmission and release of inflammatory mediators. the very best antinociceptive activity was evident with 200 mg/kg dose of both HWE and CEE. because the antinociceptive activity of CEE was above that of HWE, CEE was wont to investigate its antinociceptive mechanism[41].

Arambewela et al. (2004) evaluated the gastroprotective activity of HWE and CEE of P. betle leaves in rats. to work out the gastroprotective activity two components; hot water extract (HWE) and cold ethanolic extract (CEE) with three different concentrations (200mg/kg, 300mg/kg, and 500 mg/kg) were fed to rats to induce ulcer. Oral administration of HWE and CEE gave information about an activity which depends on dose-age and significant protection against gastric damage caused by absolute ethanol. The HWE significantly increased the mucus content (by 49%) adhering to the wall of the gastric mucosa. Mucus layer is taken into account to be important within the mucosal defense against endogenous aggressors, e.g., acids, and also as an agent in facilitating its repair. it's generally believed that enhanced acid secretion is that the most vital factor for the induction of gastric lesions. during this study, the very best dose of HWE didn't cause significant inhibition in acidity (both total and free) or pH of gastric fluid. From the investigation, it had been concluded that the gastro protective effect of P. betle was not mediated via inhibition of acid secretion within the gastric mucosa but by increasing its mucus content[42].

Kaleem et al. (2004) suggested that P. betle can also be used effectively within the treatment of diabetes. The anti-diabetic properties of some plants like Bitter gourd (Momordicacharantia), Neem (Azadirachtaindica), Tulsi (Ocimumsanctum), and Garlic (Allium sativum) are documented in India. In Piperaceae family P.sarmentosum, P.longum, P.nigrum, and P. betle are identified as potential antidiabetic agents. Oral administration of the water extract from the entire plant of P. sarmentosumRoxb. (Chaplu) at doses of 0.125 and 0.25 g/kg significantly lowered the plasma glucose levels in healthy rats. In contrast, the repeated oral administration of the water extract at a dose of 0.125 g/kg for 7 days produced a hypoglycemic effect within the diabetic rats. The aqueous extract of P. nigrum seeds were administered orally to alloxan induced diabetic rats once each day for 4 weeks. These treatments cause significant lowering of blood glucose level and reduction in serum lipids. the amount of antioxidant enzymes, catalase and peroxidase decreased in alloxan induced diabetic rats, however these levels returned to normal in insulin and P. nigrum treated rats. These results suggest that oxidative stress plays a key role in diabetes, and treatment with P. nigrum are useful in controlling not only the glucose and lipid levels but these components can also be helpful in strengthening the antioxidant potential. Recent investigations on P. betle grown in Sri Lanka show that both HWE and CEE of P. betle leaves have marked hypoglycemic activity (tested in fasted normoglycemic rats). In glucose tolerance test, HWE, CEE and tolbutamide lowered the external glucose level during a similar manner. Further, HWE significantly reduced the blood sugar level of rats with STZ induced diabetes treated with a dose (50 mg/kg) which is understood to irreversibly damage the insulin-secreting β-cells of the pancreas. the power of lowering the blood sugar levels of rats with STZ-induced diabetes also suggests that P. betle extracts have insulin omimetic activity. The increased glycogenesis may result from enhanced glucose uptake from the liver and striated muscle by sensitization of insulin receptors and/or inducing the activity of enzymes involved in glycogen synthesis and concluded that P. betle has better antidiabetic activity[43].

Ramji et al. (2002) studied the anti-halitosis activity of P. betle L. leaves which are traditionally utilized in India and China within the prevention of oral malodor was examined by bioassay-guided fractionation to yield allylpyrocatechol (APC) because the major active principle which showed promising activity against obligate oral anaerobes liable for halitosis. The biological studies with APC indicated that the potential to scale back methyl mercaptan and sulfide was mainly thanks to the anti-microbial activity as established using dynamic in vitro models[44].

Kumarasingha et al. (2002)estimated the efficiency of volatile oil from P. betle against the larvae of Chrysomyabezzianain vitro conditions with 4% betel oil, all the first instar larvae were killed within 2 hrs, and therefore the 2nd instar larvae were killed within 4 hrs. The positive control showed no mortality until 4 hrs, but all larvae were weak - for first half-hour. Betel oil at 3% killed all the first instar larvae within 150 minutes; and 74% of the 2nd instar larvae, within 4 hrs. These results indicated that betel oil extracted from the P. species with nativity of Sri Lanka proved to be an efficient larvicide[45].

Chen et al. (1995) investigated the P. betle florescence extracts and located that it contained eugenol (6.2%) and safrole (78.9%). Intravenous injections of water extracts of P. betle in rats induced hypotensive and bradycardia effects thanks to the presence of eugenol and safrole. Moreover, the consequences of intravenous injections of P. betle extracts were reversed or inhibited by the pretreatment with atropine (1 mg/kg, i.p.) and capsaicin (100 mg/kg, s.c.). Eugenol and safrole induced an equivalent pattern on vital sign and pulse changes as P. betle extracts in rats after various treatments. This report suggests that acute administration of betle inflorescence extracts by different routes may activate C-fiber evoked parasympathetic and sympathetic cardiovascular reflexes in rats[46].

CONCLUSION

Asian nations employ the *Piper betle* L., a member of the Piperaceae family, as a traditional herbal medicinal plant for a variety of health advantages. The demand for its goods, including herbal medications, treatments, and natural herbal formulations, has grown recently. The therapeutic properties of betel leaves and their compounds have long been used to cure a variety of illnesses, including indigestion, foul breath, wounds, inflammations, and inflammatory conditions are comprehensively mentioned. Until recently, a wide variety of bioactive substances from betel leaf extracts and essential oils (EO), such as polyphenols and terpenes, have been found. The bioactive phenolic chemicals in betel leaves have been linked to the majority of the plant's health advantages. The material in this review successfully covered *Piper betle*'s pharmacognostic properties, bioactive ingredients, and biological activities.

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CONFLICT OF INTEREST

The authors declare no Conflict of Interest regarding the publication of the article.

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