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Review Article

A Comprehensive Review on the Traditional and Pharmacological Benefits of Heart Leaf (*Piper betle* Linn)

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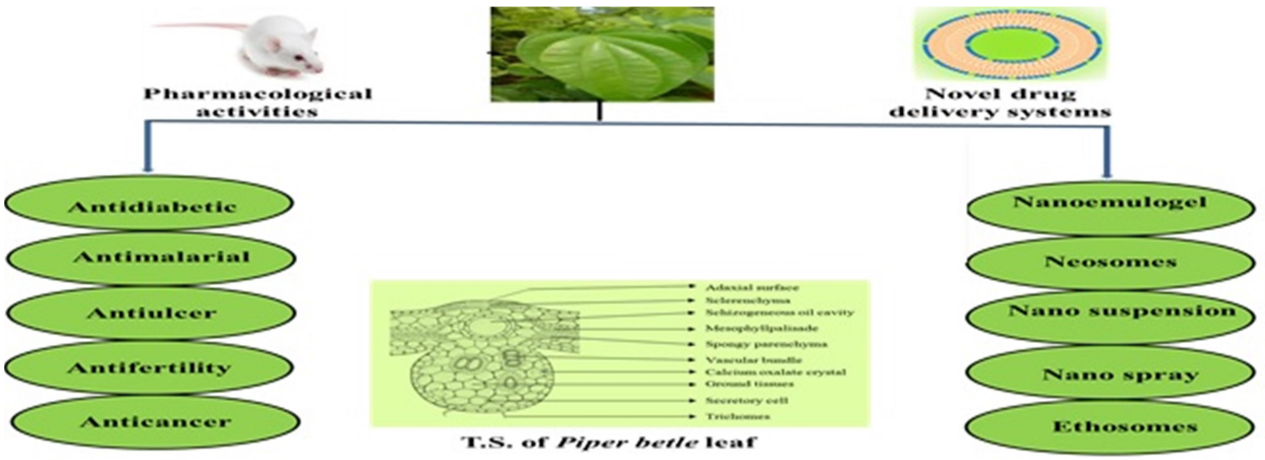
ABSTRACT

Traditional remedies have been valued greatly in the global healthcare system since ancient times. *Piper betle* is a well reported evergreen and perennial plant, used in several traditional medicines to treat a variety of illnesses. A number of pharmacological uses such as anti-inflammatory, antifungal, antifilarial, antiulcerogenic, antiplatelet, antidiabetic, immunomodulatory, antileishmanial, antioxidant, antiamoebic, and antibacterial properties have been reported for this plant. Many chemical compounds have been isolated and reported from different parts of this plants, such as eugenol, germacrene-D, safrole, chavicol, allyl pyrocatechol, ß-pinene, caryophyllene, hydroxychavicol, quercetin, α-pinene, myrcene, chavicol, α- terpineol, camphene, etc. This review article focuses on numerous studies related to plant geographical findings, cultivation, morphological features, phytochemistry, therapeutic properties, pharmacological uses and innovative drug delivery systems of *P. betle* which demonstrate its extraordinary pharmacological potential.

Graphical abstract



INTRODUCTION

The use of natural remedies has become more and more famed day by day in the traditional system of medicine. Numerous plants and plant-based products have been reported for their medicinal value. The distinctive chemical constituents present in herbal medicines show different pharmacological actions and have been used to cure several diseases [1]. The isolation, identification and detection of active phytoconstituesnts present in the plant extract are quite difficult. This further complicates the research related to its biological assay, nutraceuticals, agrochemicals, and traditional medical research. The unknown nature of the plant and the presence of secondary metabolites in abundance are two major challenges which arise during the study of natural products. Such primary and secondary metabolites are difficult to isolate possibly due to their minute quantity in extracts. In plants, the presence of major bioactive secondary metabolites has a great biological significance. The problem may further be augmented due to the instability of many metabolites during extraction and isolation. In recent years World Health Organization study data revealed that 80% of individuals in developing countries are dependent on traditional herbal medicines for their health care requirements [2]. In Southeast Asia, *Piper betle* (also known as the betel vine) is considered as an important medicinal plant [3]. This plant is available in many varieties with a broad range of color, size, taste, and odour of its leaves. The most famous Indian variety of *P. betle* leaves are known as Banarasi. Other famous varieties are Bagerhati Kauri, Ghanagete, Calcutta, Venmony, Mysore, Salem, and Magahi [4]. The genus Piper (family-Piperaceae) is found in tropical and subtropical regions in all over the world.

P. betle is a perennial, evergreen, climber plant blessed with heart shaped leaves. East Africa, India, Philippines, Indonesia, Thailand, Malaysia and Sri Lanka are well reported regions for the cultivation of *P. betle* [5]. In the spirit caves of Northwest Thailand, the residue of this plants were discovered by some Anthropologists [6]. Similar findings have been discovered in the teeth of an Indonesian skeleton around 3000 BC found in Timor, and in the human teeth around 2600 BC found in Palawan, Philippines. In Sri Lanka these findings were mentioned in the Pali version of the oldest historical book named as “Mahawamsa” [7].

P. betle plant is extensively grown in hotter and more humid regions of the nation, including India. It climbs by several short adventitious rootless climbs. It is found worldwide but is called by different names [4, 8]. The proverbial name of *Piper betle* is summarized in Table 1.

GEOGRAPHICAL FINDINGS

P. betle is native to central and eastern Malaysia and was first used in tropical Asian and Malaysian agriculture around 2500 years ago. Later on, it came to the West Indies and Madagascar and East African agriculture.

During the Tang era (A.D. 618-907), Southeast Asia was described as a betel-using region in written Chinese records. When the first European settlers came in South India and South China in the fifteenth century, betel chewing was common there. The plant is widely used in India, Indonesia, and other Indo-Chinese nations (Malaysia, Kampuchea, Vietnam, Thailand, Myanmar, and Singapore) due to its well-known ethnomedical characteristics [9]. The betel plant is extensively distributed throughout all of India, except Rajasthan and Gujarat because of warm, dehydrated weather and Jammu and Kashmir, Haryana, Punjab, and Himachal Pradesh because of extreme cold [3, 10].

Table 1: Proverbial name of *P. betle.*

Language	Proverbial name
Sanskrit	Mukhbhushan, Nagini, Nagavallika, Nagavallari, Saptashira, Tambool, Varnalata
Malaysia	Sirih, Sirih cina, Sirih carang, Sirih hudang, Sirih melayu, Sirih kerakap
English	Betel, Betel pepper, Betel-vine
Tamil	Vetrilai
Telugu	Tamalpaku, Nagballi
Hindi	Pan

MORPHOLOGY

Stems

Stems are dichotomous, rooted, articulate, slightly flattened, swelling, stout with pinkish-stripe nodes, dilated and slightly woody with the presence of 2.5–4 cm long internodes at nodes that vary from 3 mm in diameter.

Leaves

The leaves are ovate to ovate-oblong shaped, simple, spiral, estipulate, heart-shaped, yellowish to dark green with glossy upper surfaces with pleasant odors. Petioles (5 mm long) are pubescent and channeled. The blade is bright green below and measures 10 x 6cm and 9.5 x 5cm. The secondary nerves are organized in three pairs, along with the cordite base and acuminate apex of the blade. The axillary spike that is 5.5 cm long known as the inflorescence [11]. The size of the leaves differs due to the changed cultivar from 7-15cm in length and 5-14cm in width [12].

Fruits

Fruits are drupaceous, orange, and 3mm in diameter [13,14].

Table 2: Active phytoconstituents of *P. betle* with respect to their different parts.

Plant part	Active principle	Reference
Leaves	Chavibetol, Quercetin, Terpineol, β-Pinene, Luteolin, Camphene, Caryophyllene, Diosgenin lactone, Farnesene, Eugenol, Allyl catechol, Bisabolene, Ledol, Methyl ether, Eucalyptol, Stearaldehyde, Eugenyl acetate, Allyl diacetoxy benzene, Allyl pyrocatechol diacetate, 4-Allyl phenol, A-Myrcene, D-Limonene, Camphor, Bergamotene, Allyl anisole, 3-Allyl-6-Methoxyphenol, β-Isosafrole, Thymol, Muurolene, Cadinol, Isoledene, Tocopherol, β-Sitosteryl palmitate, Dotriacontanoic acid, Stearic acid, 2,3-Bis (hydroxy) propyl ester, Myristic acid, Limonine Octadecanoic acid, 2-Monopalmitin, 2,3 Bis (hydroxyl) propyl ester, Germacrene-D, Benzene acetic acid, Hexadecanoic acid, β-Ocimene, Terpinolene, Allo ocimene, Cymene isoeugenyl acetate.	[24- 39]
Flower	Eugenol, Safrole, Hydroxychavicol, β–Sitosterol, Myrcene, Isoeugenol, Cepharadione –A, Methyl eugenol, Flavones.	[23, 34,36, 38, 39]
Stem	Cepharadione, Dotria, Contane, Triacontane, Piperine, Piperlonguminine.	[6,30]
Rizomes	Pyrocatechol, Linalool, Monoacetate, Terpinen-4-ol, Thujene, Camphene, Sabinene, 1,4 Cineole, (Z)-β-Ocimene, (E)- β-Ocimene, Cis Sabinene hydrate, Fenchone, Terpinolene, 2- Noanone, Cis-Limonene oxide, m-Cymen-8-ol, Cis-Piperitol, n-Decanal, Thymol, 2-Undecanone, Isoascaridole, 5-Indanol, α-cubebene, α -copaene (E)-ß- Damascenone, Vanillin , α -Selinene, Cuparene, Germacrene A, n-Eicosane α -pinene, β- caryophyllene, Myrcene.	[34,40-43]

PHYTOCONSTITUENTS

Numerous chemical constituents have been isolated from *P. betle*. Bajpai et al. reported that the presence of phenol and terpenes in leaves are responsible for strong pungent aromatic flavor [15]. Apart from these, phytochemical results revealed that this plant also contains water (85-90%), amino acids, carbohydrates (0.5-6.1%), proteins (3%), fat (1%), essential oil (0.2%), minerals (3.3%), fibre (2.3%), tannin (0.1-1.3%), alkaloid (arakene), and steroidal compounds in leaf extract [10]. Studies also confirmed the presence of different vitamins like vitamin-A, vitamin-C, nicotinic acid, thiamine and riboflavin in 1.9-2.9%, 0.005-0.01%, 0.63-0.89%, 0.010-0.070% and 0.019-0.030% respectively [16]. Furthermore, numerous minerals including calcium (0.2-0.5%), potassium (1.1- 4.6%), iron (0.005-0.007), phosphorus (0.05-0.6%) and iodine (3.4µg/100grams) are also present. The terpenoids ally pyrocatechol, carvacrol, camphene, cadinene, chavibetol,

chavicol, 1,8-cineole, caryophyllene, eugenol, limonene, pinene and safrole, are also found in betel leaf. The antifungal properties were reported due to presence of eugenol. Fresh leaves are rich in essential oil, diastase enzyme and sugar as compared to old leaves [17-20]. . The level of bitter compound (thiocyanate) and total phenolic content are gender specific. The male part contains more amounts of thiocyanate and total phenols as compared female part. The more phenolic content reflects better leaf quality [21]. Betel leaves also contain sugars, starch, diastases and an essential oil. Essential oil mainly composed of eugenol, safrole, terpinen-4-ol, allyl pyrocatechol monoacetate, eugenyl acetate, etc. [22, 23].

Numerous researchers have found different phytoconstituents in individual parts of *P. betle*. The amount of these phytoconstituents also varies and depends on their site of presence as listed in (Table 2).

FOLKLORIC OR TRADITIONAL USES

In the ancient Vedic literature and in modern research literature, the use of *P. betle* either alone or in combination with other plants has been well reported for its therapeutic properties (table 3) [44].

Table 3: Reported traditional uses of *P. betle* in diseases.

Plant part	Disease	Method of application	References
Leaves	Pulmonary infection, cough	Soaked leaves in mustard oil and applied warm to the chest	[44]
	Nervous pain, nervous exhaustion and debility	The juice of betel leaves with honey serve as a tonic	[21]
	Boils, arthritis, inflammation	A soft leaf gel coated with a layer of castor oil spread over the inflammation	[44,45]
	Wounds	The juice of the leaves applied on the wounds	[46]
	Diuretic	Betel leaf juice with milk or honey helps in easing urination	[20]
	Promote lactation	The leaves smeared with oil promote secretion of milk after application to the breast.	[47]
Fruit	Sore throat, irritating cough	The crushed fruits or berry mixed with honey	[48]

PHARMACOLOGICAL PROPERTIES

Antibacterial Activity

The antibacterial activity of *P. betle* is well researched and reported too. The *in vitro* antibacterial activity of *P. betle* extracts was investigated against the soft rot disease-causing bacteria, *Erwinia Caratovora* sub sp. *Caratovora* (ECC). The water, ethanol, and hexane extracts of *P. betle* were evaluated for their antibacterial activity. The highest antibacterial activity was observed with ethanol extract, followed by hexane and water extracts with minimum inhibitory concentration (MIC) of 1.562, 6.25, and 12.50 mg/mL, respectively. A bactericidal mode of action were observed as ECC growth was destroyed within 6 to 8 hours after treatment [49].

The ethanolic leaf extract of *P. betle* showed antibacterial activity against antibiotic resistant *Salmonella spp.* For the study 12 isolates of the *Salmonella spp*. were collected from 24 pig fecal samples. *S. typhimurium* was used as reference strain. The isolates were checked for the antibiotic susceptibility by using disc diffusion method against ampicillin, penicillin, tetracycline and doxycycline. The results revealed that the isolates were resistant to ampicillin (91.67%), penicillin (91.67%), doxycycline (81.81%) and tetracycline (81.81%). *P. betle* extracts exhibited antibacterial activity against *S. typhimurium* with the inhibition zone ranged from 15.11 ± 0.34 to 20.30 ± 0.50 mm in as disc

diffusion assays. The bactericidal activity of extract showed MIC and MBC values ranging from 0.5-1.0 mg/mL [50].

Antimutagenic Activity

Epidemiological studies revealed that chewing betel quid (containing betel nut, betel leaf), with or without tobacco are responsible for oropharyngeal cancer. To investigate the antimutagenic activity of betal leaf, phenolic compounds (eugenol and hydroxychavicol) were isolated from ethanolic extract *P. betle* leaves using C~ phase bonded Hiflosil silica gel. The mutagenic effect of both isolates was tested on various strains of *Salmonella typhimurium*. A dose-dependent suppression of dimethylbenzanthracene-induced mutagenesis in *S. typhimurium* strain TA98 with metabolic activation was observed. Hydroxychavicol at 481Lg/plate caused 73% inhibition, as compared to eugenol which showed same degree of inhibition at 222/Lg /plate. Hydroxychavicol was found to be a more potent antimutagen than eugenol. Hence it was claimed that the presence of hydroxychavicol and eugenol in betal leaf will reduce the carcinogenic effect of tobacco and other organic materials when consumed with it [51].

Antidepressant Activity

Depression is the most recurrent increasingly neuropsychiatric disorder that affects approximately one-eighth of the global population at some stages during their life. About 4.4 % of the global population is living with depression as reported in WHO report [52]

Meti et al. screened the antidepressant activity of ethanolic extract of *P. betle* leaves in force swimming test and tail suspension test, using imipramine as a positive control. In both models, ethanol extract (100, 200 mg/kg) reduced more immobility time ($p \leq 0.05$) as compared to positive control. Antidepressant activity of *P. betle* leaves extract might be due to the presence of alkaloid arakene which has similar activity to cocaine [53].

Anti-inflammatory Activity

P. betle extract showed anti-inflammatory activities in various previously reported studies [54]. Recently Seo et al. investigated the anti-inflammatory activity of methanolic extract of leaves and stem of *P. betle*. Both extracts have showed remarkable inhibition of proinflammatory biomarkers level (tumor necrosis factor-α, interleukin-1β, and interleukin-6) by inhibition of the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways in LPS-treated RAW 264.7 macrophages. In the nucleus both the extract suppressed the LPS-induced translocation of NF-κB p65 present in the cytoplasm. Additionally level of nuclear factor erythroid 2-related factor 2 (Nrf2) protein and transcription levels of Nrf2 target genes was found to be increased in a dose-dependent manner. Authors concluded that this activity may be due to the presence of hydroxychavicol, a major active constituent present in the plant extract [55]

In another study, methanolic extract of *P. betle* leaves extract has been evaluated for antiinflammatory activity. Methanolic extract of *P. betle* leaves (40 mg/kg b.w. i.p) exhibited significant ($p<0.05$) anti-inflammatory activity (66.66%) as compared to indomethacin (10 mg/kg body weight p. o.) (72.72%) [56].

Antifertility Activity

A variety of contraceptives are present in the market for both male and female use. About 90% women use contraceptives worldwide, but male contraceptives like condoms, vasectomy, and withdrawal are also prevalent. Contraceptive choices are available but with a lot of side effects. Researchers reported contraceptive properties of *P. betle* and *Calendula officinalis*. A comparative study of the antifertility activity of ethanolic extract of *P. betle* leaves and *Calendula officinalis* flowers were performed by Singh et al. 50 normozoospermic samples of human sperm were used to perform the study. The activity of sperm samples was tested by the SMAI test. Results showed that the mitochondrial activity was found to be decreased in the samples when treated with both extracts. These results support the contraceptive concept of *P. betle* and *Calendula officinalis* agents [57].

Shah et al. investigated the antifertility potential of *P. betle* leaves extract on female wistar rats at the dose of 500 mg/kg/day for 30 days. Additionally estrogenic, anti-estrogenic, abortifacient, anti-implantation activities and reproductive outcome were evaluated. Alcoholic extract exhibited 51% and aqueous extract showed 37.2% antifertility activity as compared to standard drug ethinyl estradiol. Anti-

implantation activity of alcohol and aqueous extract was found to be 38.45% and 13.62 % respectively. Abortifacient effect was found to be highest in alcoholic extract of the plant (28.96%) as compared to aqueous extract (12.75%). The estrogenic or anti-estrogenic activity was responsible for the decrement in implantation caused by the extracts. However, more potent estrogenic and less potent anti-estrogenic was observed with alcohol extract as compared to standard. These results showed the potential, reversible female antifertility effect of alcoholic extract of *P. betle* [58].

Antifungal Activity

Hydroxychavicol is a phenylpropanoid compound isolated from *P. betle* investigated for its antifungal activity against 124 strains of selected fungi like *Candida* species and *Aspergillus* species. Amphotericin B was used as reference drug. Study results demonstrated that hydroxychavicol showed significant fungicidal effects against all the fungal species (MICs and MFCs were 15.62 and 62.5 µg/ml respectively) [59].

Another study has shown that essential oil present in *P. betle* leaves possess strong antifungal activity against *C. stellatoidia, C. albicans, C. glabrata, C. krusei, C. tropicalis, C. pseudotropicalis and C. parapsilosis* with MIC values of 0.039-0.078 % v/v. Study concluded that betel oil exhibited inhibitory effect on the growth of *Candida species* [60].

Antimalarial Activity

Abdulelah et al. studied the antimalarial activity of methanolic extract of *P. betle* leaves in doess ranging from 50–400 mg/kg against *Plasmodium berghei* (NK65). The leaf extract demonstrated significant ($P<0.05$) schizonticidal activity. Chemo-suppression was found to be 70.88% (400 mg/kg) and 19.57% (50 mg/kg) as compared to standard viz., pyrimethamine which showed 73.04% (1.2 mg/kg) [61].

Anthelmintic Activity

The helminthes infection caused by parasitic worm like Tapeworms (Cestodes), Roundworms (Nematodes), or Flukes (Trematodes). Numerous scientists have been reported various plants for their anthelmintic activity.

Sudrik et al. evaluated the anthelmintic activity of crude extract of *P. betle* leaves in experimental adult earthworm's *Eisenia fetida*. *Eisenia fetida* were collected from moist soils of the botanical garden. Albendazole was used as standard drug. The anthelmintic activity was evaluated by measuring time required to cause the death of *Eisenia fetida*. Aqueous extract was used in different concentrations of 25, 50, 75 and 100 mg/ml. The anthelmintic activity of aqueous extract at different concentrations (50, 75 and 100mg/ml) showed remarkable activity against *Eisenia fetida* as compared to albendazole. These results confirmed the anthelmintic activity of leaves of *Piper betle* against *Eisenia fetida*. [62].

Furthermore, Adate et al. confirmed the anthelmintic activity of stem extract of *P. betle* against *Pheritima posthuma* (Indian adult earthworms). Observations were made for the time taken to paralysis (P) and death (D). Ethanolic extract showed significant activity [P (min) = 1.15, D = 2.15] as compared to Albendazole [P (min) = 2.34, D (min) = 5.68]. The study confirmed the potent anthelmintic activity of the *P. betle* [63].

Gastrointestinal Motility Effects

Gastroprotective activity of *P. betle* extract was evaluated in ethanol induced gastric ulcer model in male albino rats. Misoprostol (133 µg/kg/bw) was used as standard drug. On administration of graded doses of extracts, viz. hot aqueous extract and cold ethanolic extract (200-500 mg/kg/bw) in experimental animals, a significant ($P \leq 0.05$) inhibition of the length and the number of gastric lesions induced by absolute ethanol in a dose dependent manner was observed. Extract treated rats at 500 mg/kg/bw showed a better protected mucosa and reduction in gastric lesions as compare to standard drug Misoprostol. Study results proved that *P. betle* provide better gastroprotection in gastric ulcer [64].

Study from Dhakad et al., ethanolic extract of *Piper betel* was reported to accelerate the intestinal transit in normal mice. [65]

Antihistaminic Activity

Histamine is a biogenic amine which plays a role in the regulation of gastric secretion. Many researchers investigated the effective role of *P. betle* on histaminic related diseases.

Hajare et al. reported antihistaminic activity of ethanolic extract and essential oil of *P. betle* leaves on Guinea pigs against histamine-induced bronchoconstriction. The preconvulsive time (PCT) was reported timely during exposure to onset of convulsions. Study revealed that

ethanolic extract and essential oil of *P. betle* (100,200mg/kg) significantly protected against the bronchospasm induced by histamine release in Guinea pigs as compared to standard drug Chlorpheniramine maleate (2mg/kg) [66].

Radio Protective Activity

In lieu of synthetic radioprotectants, which are reportedly harmful, the radioprotective qualities of an ethanolic extract of *P. betle* leaves have recently been investigated as a low-cost preventive medication. The ethanolic extract of *P. betle* leaves was found to exhibit strong immunomodulatory and superior radical scavenging properties, which may be explained by the presence of bioactive phenols like allylpyrocatechol and chavibetol. It implies that the herb possesses strong natural radioprotective properties [27].

Platelet Inhibition Activity

Zeng, et al. reported that piperbetol, methylpiperbetol, piperol A, and piperol B, isolated from *Piper betle*, selectively inhibited the washed rabbit platelet aggregation induced by platelet activating factor (PAF) in a concentration-dependent manner suggesting them to be effective PAF receptor antagonists in vitro [67].

Patent Summary

Some selected patented applications of *P. betle* are listed in table 4.

Table 4: Patents filed and awarded for various activities of *P. betle*.

Patent filed for activity	Place of filing	Filing country/year	Grant date/patent no
Antileishmanial	USA	USA/2001, 2002; World/2000	USA/2003/6610332 WO/20002/045731
Anticancer	India (CSIR/ IICB, Kolkata); USA	World/2000; USA/2001; Japan/2003; India/2003	GB/2004
Immunomodulatory	India (CSIR/IICB, Kolkata); USA	World/2000; USA/2002, 2005; India/2003	WO/2002/049655 USA/2003/6531166
Anti-5 lipoxygenase	India (CSIR/IICB, Kolkata); USA	USA/2001; World/2002; Europe/2004; India/2004	USA/2004/6773728 Europe/2005
Anticancer	USA	USA/2004; USA/2002, 2003	USA/2007/7306817 USA/2005/6852344 USA/2005/6967034
Antiwart	USA (Deerfield, IL)	USA/2001	USA/2001/6312735
Dye	India (CSIR/NBRI, Lucknow)	USA/2004	USA/2007/7186279
Bronchial disorders	India (CSIR/IICB, Kolkata)	USA/2001	USA/2004/6773728
Anti-inflammatory	India (CSIR/CIMAP, Lucknow)	USA/2001	USA/2003/6531115

Novel Drug Delivery Based Formulations Containing *P. betle*

Numerous studies confirmed that therapeutic efficacy, solubility and stability of *P. betle* can be enhanced by using novel drug delivery based techniques. Numerous techniques and vesicular systems were developed and reported by several researchers to enhance therapeutic efficacy and minimize the side effects of bioactive compounds. Nanoemulogel,

nanocapsules, lipid vesicles like ethosomes, transferosomes, liposomes, phytosomes, nano-emulsions, polymer micelles, polymeric nanoparticles microspheres, injectable hydrogels, dendrimers, and other therapeutic formulations have been developed using bioactive compounds and plant extract of *P. betle*.

Nanoemulogel

P. betle essential oil containing nanoemulogel was prepared by using soybean oil, tween 80, glycerol, water and Carbopol 940. The formed Nanoemulgel was characterized for particle size analysis by dynamic light scattering (DLS). Tyndall effect, spreadability test and pH test were used for characterization. The droplet size was in the range of 28 to 161 nm with a neutral pH. The obtained results suggested that *P. betle* essential oil containing nanoemulogel showed a very high potential to be used as an effective carrier for the topical drug delivery of active ingredients [68].

Gold Nanoparticles

The effectiveness of *P. betle* containing gold nanoparticles in cancer was evaluated by Punuri et al. The nanoparticles (AuNPs) were synthesized via green synthesis by using extract of *P. betle*. Different biophysical techniques were used to characterize the synthesized AuNPs. TEM results confirm the size and shape of nanoparticles ranging from 10 to 35 nm. HeLa (human cervical cancer) and MCF-7 (human breast cancer) cells were used to evaluate the cytotoxicity effect of synthesized AuNPs. This study outcome revealed that the synthesized AuNPs may provide a new prospect application in drug delivery and molecular imaging [69].

Neosomes

Jufri et al. designed, formulated and evaluated the antibacterial activity of niosomal gels containing betel leaf essential oil in the treatment of acne. Neosomes were prepared by using volatile oil, surfactant (Span 60) and Cholesterol. Formulation was optimized for their particle size and shape. Prepared neosomes were incorporated into the gel containing carbomer 940 as gelling agent. Niosome gel was evaluated for its organoleptic properties, pH and viscosity. *In vitro* anti-acne activity of nano-vesicles containing betel leaf (*P. betle*) essential oils was tested against *Propionibacterium acnes*. Clindamycin gel was used as standard drug. The results suggested that formed nanogel could be a good alternative for the treatment of acne [70].

CONCLUSION

Traditional medicines are often deeply rooted in the cultural heritage of communities. They represent centuries-old knowledge passed down from generation to generation, reflecting the historical practices, beliefs, and values of a society. These medicines have contributed valuable knowledge to modern medical practices. Many pharmaceutical drugs are derived from natural compounds found in plants and other traditional remedies. Traditional medicines offer a diverse range of treatment options, including herbal remedies. *P. betle is* an indigenous plant with several medicinal properties, attributed by producing secondary metabolites such as phenol, terpenes, essential oil and so on. In this review, up-to-date information on folklore or traditional uses, phytoconstituents, novel formulations, filed patents, pharmacological works done on different parts of *P. betle* which have been performed in recent years has been duly compiled. This helps to study the unexplored area of this potent herb.

CONFLICT OF INTEREST

None

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None

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