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Review of Traditional Use, Phytochemical and Pharmacological Activity of *Piper betle* L.

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ABSTRACT

Currently, traditional treatment in the form of medicinal plants or herbs is widely used by the community. The rapeutic using plants that exist in nature a part from having no sid effects can also be used for a long time. Betel leaf extract has been used as a mouth wash when the mouth is swollen, cleanses bad breath, stops bleeding, and treats other diseases such as vaginal discharge, coughing, hoarseness, and skin wounds. Betel (*Piper betle*) is known to have pharmacological effects, in cluding antibacterial, antimicrobial, analgesic, anti-inflammatory, antioxidant, antiproliferative, and antidiabetic. The phytochemicals of the betel plant contain saponins, flavonoids, polyphenols, and triterpenoid essential oils, essential oils (consisting of chavicol, chavibetol, carvacrol, eugenol, estragol), sesquiterpenes, sugar, and starch.

Keywords: Betel; *Piper betle* L; traditional use; phytochemicals; pharmacological activity

INTRODUCTION

Indonesian people have known various types of traditional medicinal plants that have been known from generation to generation. A kind of conventional medicine known is the betel plant (*Piper betle*) from the Piperaceae family. Betelis a native Indonesian plant that grows vinesorleans on other treet runks. Betelisused as a medicinal plant that plays a role in life and various Malay family ceremonies. In Indonesia, betelis a typical flora of the Riau archipel ago province. The peopleofthe Riau Islands highly up hold the culture of the beteleating ceremony, especially during the welcoming ceremony for guests and using betel as a medicine for various types of diseases. However, betelplants are often found through out Indonesia, usedoronly as an or namental plant. [1]

The betel plant (*Piper betle*) can reach tens of meters in length. The shape of the flat betel leaf resembles a heart, and the stalk is rather long. The leaf surface is green and slippery, while the tree trunk is slightly brownish-green with a rough and wrinkled skin surface. Betel fruit is a buni fruit that is round in shape and is grayish-green. Roots tap, round and yellowish-brown. [2]

The betel plant has compound flowers with gender 1, a house of 1 or 2. The bulb stands alone at the end and facing the leaves. grain length about 5 - 15 cm and width 2 - 5 cm. The male ear is about 1.5 - 3 cm long, and there are two short stamens, while the female ear is about 2.5 - 6 cm long, where there are three to five white and yellowish green pistils. [3]

Figure 1. BetelPlant[1]

The classificationofbetel (*Piper betle* L.) is as follows: [4]

Kingdom	: Plantae
Division	: Spermatophyta
Sub-division	: Angiosperms
Class	: Magnoliopsida
Sub-class	: Magnolilidae
Order	: Piperales
Familia	: Piperaceae
Genus	: Piper
Species	: *Piper betle* L.

Betel is scattered throughout Indonesia, often found in yards. The preferred growing place is at an altitude of 200-1000 masl, which has a rainfall of 2250 - 4750 mm per year. This plant grows in slightly humid forest areas with moist soil conditions, areas that are shaded and protected from the wind. [5] Betel leaf has a distinctive aromatic smell, is spicy and warm. Betel leaf extract is used as a mouth wash when the mouth is swollen, cleanses bad breath, stops bleeding, and other diseases such as vaginal discharge, coughing, hoar seness, and skin wounds. [6]

Secondary metabolitec ompounds produced by the betel plant are saponins, flavonoids, polyphenols, and triterpenoi dessential oils, essential oils (consisting of chavicol, chavibetol, carvacrol, eugenol, estragol), sesquiterpenes, sugar, and starch. [7] The essential oil content in betel leaf has also proven to be an effective antiseptic. [5]

DATA COLLECTION

In compiling this review article, the technique used is to use literature review by looking for sources or literature in the form of primary data or official book forms and national and international journals in the last 20 years (2000-2020) as well as in making this review, traditional use, and pharmacology. The primary references used in this review article were searched through trusted website ssuch as Science Direct, Research Gate, Google Scholar, NCBI, and other published and relied on journals.

TRADITIONAL USE

Betel (*Piper betle*) is a plant that contains secondary metabolites which are useful as a base for traditional medicine. This betel plant is native to central and eastern Malesia and was planted around 2,500 years ago in the Malesia regionand tropical Asia to Madagascar and East Africa. This type of betel also grows and spreads in South India and South China, which was brought by Europeans in the 15thcentury. [7]

Piper betle leaves have been used traditionally in India, China, and Thailand for the prevention of bad breath due to their antibacterial activity, as a mouth freshener and chewing, for their wound healing properties, to enhance digestion and pancreatic lipase stimulant activity, for the prevention of cataracts and pulmonary diseases and, to prevent secretions or to bleed as well as aromatic stimulants and anti-flatulence agents. [24]

In Ayurveda, the betel leaf extract is often used as an adjuvant and can be mixed with different drugs for better effects besides being used as a single drug. Betel leaf has been used as an aromatic, beneficial for the sound, laxative, appetizer. Besides that, the aphrodisiac effect of chewing betel has been shown in ancient texts. Betel is also believed to give strength to the liver and regulate blood flow. Its anti-inflammatory and antimicrobial utility is emphasized in several places. In Ayurveda, it acts as a Vata and Kapha suppressant. Betel leaf also helps expel mucus from the respiratory tract because of the potential heat generated from the leaves. According to the Greek system, it has a pleasant taste and smellsto increase taste and appetite, tonic to the brain, heart, and liver, reduce taste, clear the throat and cleanse the blood. [26]

The study was conducted to determine the types of plants used by the community in Masbangun Village, Kayong Utara Regency, West Kalimantan Province, mostly traditional medicine toover come health problems related to femininity, how

to process and use it. The field study was conducted from January - February 2019. All data obtained were analyzed with use value (UVi) and electability level (Fidelity level, FL). The number of medicinal plants pecies known to the public is 16 species. A total of 320 respondents who were interviewed using a questionnaire with the criteria of residents who are permanently domiciled, and are 17 years old or have grown up. The types of plants with the highest use value (UVi) were banana, ginger, turmeric, andbetel. Medicinal plants that have the highest Fidelity level (FL) value are banglai, gotu kola leaves, ginger (pre/postpartum, banana heart (breast feeding), majakani (vaginal discharge), singkil leaves (body odor), bean sprouts (female fertility) and coconut oil (black hair). Betel leaf is widely used by the community in Masbangun Villagere lated to femininity issues. Betelleaf is believed for postpartum treatment, vaginal discharge, menstrualpain, body odor, and fertility. Betel leaf is a multifunctional plant and contains phenolic compounds that are cytotoxic and canfunction as antibacterials. [28]

Piper betle leaves are also used to stop nose bleeds by taking two fresh *Piper betle* leaf sheets, washed, rolled, and then inserted into the nostril. [1] Besides, *Piper betle* is also used as a medicine, especially for fever, wounds, eye infections. [25]

PHYTOCHEMICAL REVIEW

Extraction of betel leaf with differents olvents, namely ether (40-60 ^{o}C), chloroform, ethanol, and water extract obtained phytosterol results in all extracts except water extract. Alkaloids were not found in petroleum ether extracts, while carbohydrates, water, tannins, and phenols were found in ethanol and water extracts. Flavonoids were found in ethanol extract and essential oil only in the water extract. It can be concluded that *Piper betle* leaf extract contains phytosterols, alkaloids, carbohydrates, water, tannins, phenols, flavonoids, and essential oils. The essential oils from the leaves contain carvacrol, eugenol, chavicol, allylkatekol, cineol, estragol, caryophyllene, cardinene, p-cymenedaneugenolmethylether. [8]

Identification of essential oils from fresh *Piper betle* var. Bangla desi and *Piper betle* var. Deswari leaves were isolated using conventional Clevenger type water distillation for 3 hours. The essential oils were obtained 0.12% and 0.15% (v/w), respectively. The oil is dried over anhydrous sodium sulfate and stored in a sterile tube in the refrigerator at 4°C. The essential oils were analyzed using Perkin-Elmer GC 8500, equipped with a flame ionization detector, using BP-1 (polydimethylsiloxane, 50 mx 0.25 mm). The results of the analysis of essential oils by GC and GC-MS identified twenty-five and thirty-five components, respectively. Eugenol (50.29%), α selinene (11.39%), β selinene (10.14%), germacrene D (2.82%), α farnesene (2.48%), hydroxyl chavicol (1.20 %), methyl eugenol (1.17%) was the main component identified, accounting for 79.4% of the total oil from the leaves of the *Piper betle* bangladesi variety. Like wise, the main components identified in *Piperbetle* leaf oil of deswari variety were eugenol (28.44%), safrole (27.48%), α selinene (7.32%), α farnesene (4.70%), β selinene (1.72%), methyl eugenol (1.46%), germacerene D (0.91%), eugenyl acetate (1.72%), isosafrol (1.62%) and caryophyllene (1.14%). [9]

Ethylacetate extract from betel leaf (*Piper betle*) was fractionated using column chromatography. The fraction collected is then concentrated using a rotary evaporator. The estimation of total flavonoids was determined using the colorimetric method of aluminum chloride, the absorbance was measured at 420 nm using a UV-Visible Spectrophotometer. The isolated component is further purified by recrystallization. The compounds were identified and confirmed by HPTLC, 1 H-NMR and IR, and the spectrum of the compounds. The compounds were characterized based on spectroscopic analysis and compared with data in the literature. Spectral analysis of the

isolated fraction revealed the presence of Hydroxy Chavicol, Chavibetol, and Eugenol as compounds in the leaf extracts of different betel leaf extracts. [27]

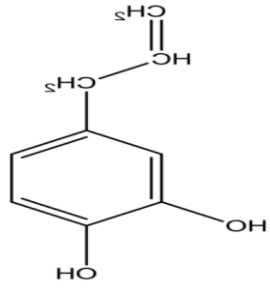

Figure 2. HydroxyChavicol [27]

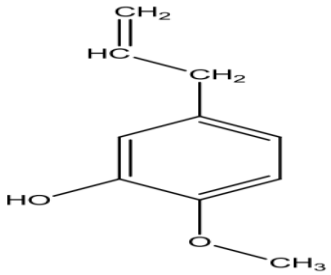

Figure 3. Chavibetol [27]

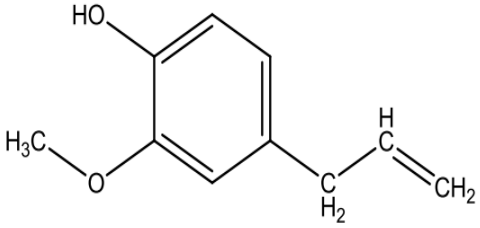

Figure 4.Eugenol [27]

Phytochemical analysis of betel leaf was also carried out using water, ethanol, methanol, butanolic, and acetone solvents to evaluate the presence of secondary metabolites such as steroids, saponins, flavonoids, phytosterols, phenolic compounds, tannins, and other compounds. The results obtained were betel extractcontaining steroids, diterpenes, and tannins in all extracts. Alkaloids and phenols are contained only in water extracts and butanol. Coumarin and saponins were contained in acetone and water extracts, emodin in butanol extracts, and flavonoids in all extracts except methanol extract. [10]

In other studies, it was also found that the ethanol extract of betel leaf (*Piper betle*) contains alkaloids, tannins, and phenolics, while the water extract of betel leaf contains saponins and glycosides. [14]

PHARMACOLOGICAL ACTIVITIES

ANTIBACTERIAL

Measurement of antibacterial activity using the disc diffusion method, first dried betel leaves (*Piper betle*), and then pounded using a blender, after which the betel leaves were extracted with water and then heated for 15 minutes at 90 ^{o}C. The bacteria used were bacteria (*S.aureus, S. epidermidis*, and *E. coli*) and, as a positive control, used ampicillin-sulbactam. From the results obtained, betel leaf (*Piper betle*) is proven to show inhibition of zone diameter against Gram-positive bacteria (*S.aureus, S. epidermidis*) and gram-negative bacteria (*E. coli*). Betel leaf contains alkaloids, phenols, flavonoids, tannins, saponins, glycosides, terpenoids, steroids, and essential oils. The essential oil contains 5- (2-propenyl) - 1,3-benzodioxole (25.67%), eugenol (18.27%), and 2-methoxy-4- (2-propenyl) acetate-phenol (8.00%). The antibacterial activity comes from essential oils, namely oxygenated terpenoids, eg alcohol and phenolic terpenes are the most active, while some hydrocarbons are usually inactive. [11]

The results of other studies also showed an antibacterial effect on betel leaf (*Piper betle*), which was tested on gram-positive bacteria (*Bacillussubtilis*, *Staphylococcusaureus*, and *Micrococcusluteus*) and gram-negative (*Escherichia coli* and *Pseudomonas Aeruginosa*). The extraction of *Piper betle* leaves with ethanol and water solvents showed that both extracts had anti bacterial activity. The significant antibacterial effect may be due to the presence of many potent compounds such as alkaloids, tannins, phenolic substances, and glycosides. [14] Anti bacterial effects were also found, especially in betel leaf extract (*Piper betle*) with ethanol, ethylacetate, and methanol as

solvents. [15]

Methanol extract of betel leaf (*Piper betle*) was macerated and refluxed and then tested for antibacterial activity using the disc diffusion method similar to the previous research method. The test bacteria used was *Staphylococcus aureus* ATCC 25923. The test solutions were made in 6 (six) different concentrations, namely 0, 5, 10, 15, 20, 25%. Observations were made for three days by calculating the diameter of the inhibition area (mm). For macerated methanol extract, the highest inhibition zone is shown at a concentration of 25% at 1.66 mm, and the lowest zone at a concentration of 5% betel leaf extract is 1.07 mm. In contrast, at a concentration of 0%, it does not show an inhibition zone. Refluxed methanol extract had the highest inhibition zone shown at a concentration of 20% at 1.64 mm and the smallest inhibition zone at a concentration of 5% betel leaf extract which was 1.12 mm, whereas at a concentration of 0% it did not show an inhibition zone. [21]

ANTIMICROBIAL

The antimicrobial activity test of betel leaf ethanol extract used the discdiffusion method. Previously, phytochemical tests were carried out on betel leaf powder (*Piper betle*), and it was found to contain carbohyd rates, proteins, polyphenol compounds, flavonoids, alkaloids, and total antioxidants. The ethanol extract showed antioxidant activity using the DPPH method. The antioxidants in medicinal plants can provide antimicrobial properties; it is eviden tthat these extracts confirm significant antimicrobial activity against all tested bacterial strains (*Pseudomonas aeruginosa, Klebsiella pneumonia, Proteus vulgaris* and *Staphylococcus aureus*). [12]

Other experiments also prove four different extracts (water, methanol, ethyl acetate, and petroleum ether) of *Piper betle* leaf, which were tested against four different pathogenic bacteria, namely *Streptococcus pyogenes, Staphylococcus aureus, Proteus vulgaris,* and *Escherichia coli* showed a clear zone of inhibition against all bacteria. This is due to the sterol activity, which is obtained in large quantities in the betel extract. Also, betel extract contains fatty acids, palmitic acid, stearic acid, and hydroxy ester fatty acids, which show potent antimicrobial activity against various pathogenic microorganisms. [13]

Antimicrobial activity of fresh *Piper betle* Linn leaf extract also demons tratedinhibition against both gram-positiveand gram-negative bacterials trains by the discdiffusion method. The result srevealed that all extract sexhibite deffective in hibitory action against*S. aureus*. The ether extract was shown to be more effective than standard penicillin. The aqueous extract was also found to be significantly effective against *Bacillus* and *P. Aureginosa* compared tost and ardpenicillin. [17]

ANALGESIC AND ANTI-INFLAMMATORY

The betel leaf hydroalcoholic extract (HEPBL) was extracted using Soxhlet equipment, and phytochemical analysis was performed. Wistar rats weighing 150-220 grams (age 8 to 12 weeks) and Swiss albino mice weighing 22-25 g of both sexes were experimental animals. The methods used were tail-flick and acetic acid induction methods to study analgesic activity, while carrageenan-induced paw edema and cotton pellet granuloma models were used for anti-inflammatory action. HEPBL showed significant analgesic activity at doses of 100 mg/kg and 200 mg/kg, and showed significant anti-inflammatory activity at doses of 50 mg/kg, 100 mg/kg and 200 mg/kg. The sub-therapeutic dose of HEPBL at 50 mg/kg also strengthens the sub-therapeutic effect of the standard analgesic dose. The analgesic and anti-inflammatory activity of *P.betle* can be attributed to the presence of phytochemical compounds, namely flavonoids, tannins, phenols and glycosides. [16]

ANTIOXIDANTS

The ethanol extract of betel leaf is antioxidant with a mean IC_{50} (µg/ml) for DPPH ascorbic acid radical was found to be 3.128. The mean IC_{50} (µg/ml) of the ethanol extract was found to be 9,362. The ethanolic extract of *Piper betle* L. leaves showed a moderate effect on DPPH radical. [18]

The ethanol extract of betel leaf (*Piper betle*) with various concentrations (5%, 10%, and 15%) has been shown to have an antioxidant effect through experiments with experimental animals used in rabbits. Rabbits were shaved, then affixed with hot metal to the rabbit's back, until the dermis and the tissue that was bound under it, causing blisters on the skin. The treatment was carried out for seven days, basting the treatment evenly once every day. Then carried out macroscopic observations of the development of wound healing on the rabbit's back. Bioplacenton was used as a positive control. Betel leaf ethanol extract at concentrations of 5%, 10%, and 15% can heal burns on the back skin of rabbits (*Oryctolagus cuniculus*). The healing process is faster because the betel leaf contains bioactive molecules such as saponins, tannins, essential oils, flavonoids, and phenols. [19]

ANTIPROLIFERATION

Ethylacetate extract of*Piper betle* leaves showed the highest in hibitory effecton MCF-7 human breast cancer cellproliferation (IC_{50} = 65 µg/ml) compared to *Piper betle* leaf extrac twith water, methanol, andhexane. MCF-7 cells were grown and maintained in RPMI 1640 culture media with the addition of some supplements. The test parameters used included cellviability (MTT method), enzymeantioxidant activity test, Catalasetest (CAT), super oxided is mutase test (SOD), and glutathione peroxidase test (GPx). [20]

ANTIDIABETIC

Exvivo studies prove that Crude betel leaf (*Piper betle*) flower extract is efficient in reducing glucose synthesis. The sample extract was known to have good antioxidant properties with ethanol extract having a high DPPH radical scavenging activity of 92.0 ± 0.68%, while the methanol extract was found to contain gallic acid equivalent 0.39 ± 0.05 mg/ml. Antioxidants are effective in reducing glucosere leased by cortisol-induced chicken hepatocytes. Treatment with 15% methanol extract of fresh betel leaf was seen to increase in the first hour and then decrease to a maximum of 60 minutes when compared to glucose released by cortisol-induced chicken hepatocytes withdry 5% ethanol extract of *Piper betle* leaf powder. Gluconeogenes is was seen to decrease over time with hepatocy tetreatment with 15% methanol extract of fresh *Piper betle* flowers and 5% ethanol extract of dry powdered betel leaf. The methanol extract showed a more significant reduction in gluconeogenesis when compared to the ethanol extract. The MTT test proved that the sample extract was not found to betoxicat volumes of 10, 20, 30, 40, and 50 µl after incubating hepatocytes for 24 hours. [22]

In vivo studies were carried out by analyzing the metabolites of bete lleaf (*Piper betle*) in water and ethanol extracts with GC-MS. Fourteen metabolites were found in *Piper betle* leaves, five of which were first discovered. Alanine and β-sitosterol are the primary amino acids and sterols. Stearic and palmitic acids are the primary fatty acids. Meanwhile, the evaluation of the ability to inhibit α-glucosidase was determined spectrophotometrically with the Ascent Multiskan plate reader (Thermo Electron Corporation), based on the reaction with PNP-] G. The absorbance was measured at 400 nm, and three independent tests were performed in triplicate then the results were compared with acarbose (positive control), tested under the same conditions. The ethanol and water extracts of *P. betle* leaves showed a strong capacity to inhibit α-glucosidase in a concentration-dependent manner, with IC_{50} values of 0.069 and 0.257 mg/mL, respectively. [23]

HEPATOPROTECTIVE

The hepatoprotector is a compound that functions to protect the liver. Methotrexate (MTX) and folate are folate antagonists that are currently used as first-line therapy for autoimmune diseases such as rheumatoid arthritis and psoriasis. Still, their use is limited because they can cause hepatotoxicity or liver poisoning. The ethanol extract of betel leaf (*Piper betle*) can reduce hepatoxicity in methotrexate (MTX) inducedrats. Miceinduced with extra betel leaf ethanol intraperitoneally with a concentration of 50 or 100 mg kg-1 bw showed hepato protective activity in mice given a single dose of MTX of 20 mg kg -1, bw, intraperitoneally and had more hepato protective properties. Higher compared to folicacid at a concentration of 1 mg kg -1 bb, ip. [29]

CONCLUSION

Betel (*Piper betle*) is a type of plant from the Piperaceae family which has traditionally been widely used as a mouth freshener, wound healing, for the prevention of cataracts, bleeding, and stimulants. In Ayurveda, the betel leaf extract is often used as an adjuvant, aromatic, beneficial for sound, laxative, appetizer, aphrodisiac effect, and helps increase taste and appetite, stop nose bleeds, fever, sores, and eye infections. Chemical content in betel includes saponins, flavonoids, polyphenols, and triterpenoid essential oils, essential oils (consisting of chavicol, chavibetol, carvacrol, eugenol, estragol), sesquiterpenes, sugar, and starch. Based on studies, *Piper betle* has bioactivity as antibacterial, antimicrobial, analgesic, anti-inflammatory, antioxidant, antidiabetic, antiproliferative, and hepatoprotective.

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