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Review Article

A Review: Traditional Use, Phytochemical and Pharmacological Review of Red Betel Leaves (*Piper Crocatum* Ruiz & Pav)

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A B S T R A C T

Red betel leaf (*Piper crocatum* Ruiz & Pav) is a plant that grows in tropical areas and was previously known as an ornamental plant, but was later used as a medicinal plant. The use of red betel leaf (*Piper crocatum* Ruiz & Pav) is traditionally beneficial in curing diseases such as thrush and toothache. Meanwhile, red betel leaf decoction, which is antiseptic, can act as a mouthwash, prevent bad breath and eliminate body odor. From chromatography, it is known that red betel leaves contain flavonoids, polyphenolic compounds, tannins, and essential oils. In the use of red betel leaves, it is widely used to get rid of body odor, vaginal discharge, ulcer, fatigue, muscle aches, and to smoothen the skin, as well as for itchy, red eye cleansers, and canker sore. Red betel leaves decoction is also believed to be able to eliminate bad breath in the mouth if used as a mouthwash.

Keywords: Red betel leaf (*Piper crocatum* Ruiz & Pav); Traditional Use; Phytochemicals; pharmacological activity.

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INTRODUCTION

Betel plants (*Piper*, tribe: *Piperaceae*) are widely used by the community as ornamental plants, vegetables, spices, medicinal herbs, or as equipment in traditional ceremonies. In the world there are around 700 species of *piper*[1], 1000 types.[2,3], there are between 1400-2000 types of *pipers* from various countries. On the island of Java, there are about 23 species of *piper*[4]. *Piper* grows at an altitude of 0 - 2500 m, and only a few species grow at an altitude above 3000 m[5]. In Indonesia, betel plant is a popular plant for medicine, including: pepper (*Piper* nigrum L.) as an antimicrobial, antihypertensive, anti-inflammatory, anti-inflammatory, hepatoprotective and antioxidant[6], betel (*Piper* betle L.) as an antidiabetic, platelet inhibition, immunomodulator, antioxidant, and anticancer[7], Javanese chili (*Piper* longum L.) as an analgesic, antioxidant, anti-inflammatory, immunomodulatory, anti-diabetic, and anti-plasma[8], and cubeb (*Piper* cubeba Lf) as an antioxidant[9].

Recently a type of *piper* has been introduced which is used by the community not only as an ornamental plant, but also as the Nusantara medicinal herb, namely red betel (*Piper crocatum* Ruiz & Pav). Red betel is native to Peru[10], then spread to several regions in the world, including Indonesia. Red betel is a shrub, with stems, branches and joints, with the distance between nodes of 5-10 cm and a root will grow in each node. Leaves are stemmed, elliptical, acuminates, with tapered tops, flat edges, glossy or hairless. 9-12 cm long and 4-5 cm wide. Leaf veins are half the bottom, leaf veins 4-5 x 2, Petioles, 10 mm long, 90-110 mm long spikes, 5 mm thick[11]. The upper leaves are dark green, with the area around the leaf bones silvery, and the bottom is purple. Leaves are slimy, with bitter taste and with less specific odor.

In traditional medicine, red betel is widely used for the treatment of hypertension, inflammation of the liver, inflammation of the prostate, inflammation of the eyes, vaginal discharge, ulcers, breast cancer, joint pain, lowering and controlling blood sugar levels, cosmetics, heart disease

drugs, bone tuberculosis, acute vaginal discharge, breast tumors, antiseptics to eliminate microorganisms from the skin or wounds, for example those caused by *Candida albicans*. As a mouthwash can help prepare dental plaque and gingivitis, cough medicine expectorant.

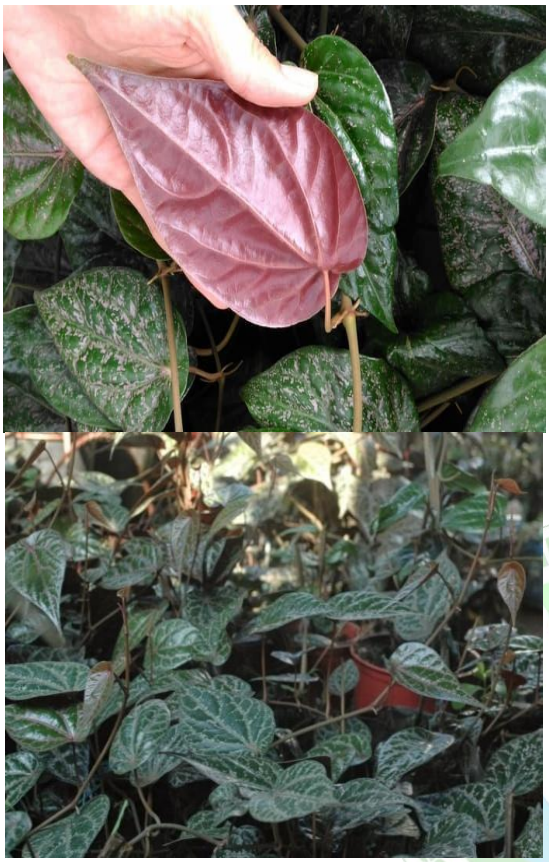

Figure 1. Red Betel Leaf (*Piper crocatum* Ruiz & Pav) [12].

Classification of Red Betel Leaf (*Piper crocatum* Ruiz & Pav) [13].

Kingdom	: Plantae
Subkingdom	: Ttracheobionta
Super Division	: Spermatophyte
Division	: Magnoliophyte
Class	: Magnoliopsida
Sub Class	: Magnolidae
Order	: Piperales
Family	: Piperaceae
Genus	: Piper
Species	: *Piper crocatum* Ruiz & Pav

METHODS

In compiling this review article, the technique used was literature study by searching for sources or literature in the form of primary data or official book, as well as national and international journals in the last 20 years (2000-2020). In the making of this review article, the search for data was done via online media with keywords as follows: (*Piper Crocatum* Ruiz & Pav), phytochemicals, traditional use, and pharmacology. The main references used in this review article were searched through trusted websites such as, ScienceDirect, ResearchGate, Google Scholar, and other published and trusted journals.

A. Traditional Use

Betel is widely used as an important medicinal plant in the traditional medicine system of Southeast Asian countries for the treatment of various diseases such as bad breath, ulcers and abscesses, conjunctivitis (red eye disease), constipation, headaches, itching, vaginal discharge, swelling from gums, rheumatism[14]. Betel leaf also has anti-cancer, anti-amoebic, anti-amoebic, antigiardial, anti-inflammatory, mosquito larvicidal, antimicrobial, immunomodulatory, antiulcerogenic, radioprotective, antileishmanial, and antifungal activities[15]. The leaves are often heated and applied to the chest to relieve coughs and asthma[16]. The leaves are used to relieve sore throats[17]. The essential oil of betel leaf is used as a mouthwash or inhalation in diphtheria and catarrh inhalation[18].

B. Phytochemical Review

The extraction of betel leaf can be done with different solvents, namely ether (40-60^{0C}), chloroform, ethanol, and water extract resulted in phytosterols in all extracts except water extracts. 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 water extract. It can be concluded that the red betel leaf extract contains alkaloids, carbohydrates, water, tannins, phenols, flavonoids, and essential oils. The essential oils from the leaves contain carvacrol, eugenol, chavicol, allylkatekol, cineol, estragole, caryophyllene, cardinene, pcymenedaneugenol methyl ether[19]. The identification of essential oils was isolated using conventional Clevenger type water distillation for 3 hours. The essential oil was obtained 0.12% and 0.15% (v / w), respectively. The oil was 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 (polydimethyl siloxane, 50 mx 0.25 mm). The results of the essential oil analysis 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 leaf of Bangladeshi *Piper* betel variety. The main components identified in *Piper* betel leaf oil were eugenol (28.44%), safrole (27.48%), α selinene (7.32%), α farnesene (4.70%), selinene β (1, 72%), methyl eugenol (1.46%), germacrene D (0.91%), eugenyl acetate (1.72%), isosafrol (1.62%) and caryophyllene (1.14%)[20]. Ethyl acetate extract from betel leaf (*Piper* betel) was fractionated using column chromatography. The fraction collected was then concentrated using a rotary evaporator. Estimation of total flavonoids was determined by colorimetric aluminum chloride method; absorbance was measured at 420 nm

using UV-Visible Spectrophotometer. The isolated component was further purified by recrystallization.

The compounds were identified and confirmed by HPTLC, 1 H-NMR and IR, and spectra of the compounds. The compounds were characterized based on spectroscopic analysis and compared with data in the literature. Spectral analysis of the isolated fraction files revealed the presence of Hydroxy Chavicol, Chavibetol, and Eugenol. 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 extract containing steroids, diterpenes, and tannins in all extracts. Alkaloids and phenols were only found in water and butanol extracts, coumarin and saponins were found in acetone and water extracts, emodin in butanol extracts, and flavonoids in all extracts except methanol extract[21].

In other studies, it was also found that the ethanol extract of betel leaf (*Piper* betel) contained alkaloids, tannins, and phenolics, while the water extract of betel leaf contained saponins and glycosides[22].

RESULTS AND DISCUSSION

Pharmacological Activities

A. Anti-inflammatory

By using the carrageenan induction method in rats' feet, the experiment was using three doses of dry methanol extract of red betel leaf, 25, 50 and 100 mg / kgBW respectively and a comparison of 1% acetosal suspension[23]. The results of the experiment showed that the extract with a dose of 50 mg / kgBW had the largest anti-inflammatory activity (based on swelling reduction power) (85.60%), greater than the dose of 25 mg / kgBW (72.3%); dose of 100 mg / kg BW (81.02%) and 1% acetosal suspension (77.58%). There was a significant difference in anti-inflammatory activity between the extract at a dose of 25 and 50 mg / kgBW with 1% acetosal, but there was no significant difference between the extract at the dose of 100 mg / kgBW and acetosal 1%. Several types of *pipers* also exhibit anti-inflammatory activity[24] on the ethanol leaves extract of *Piper* sarmentosum, P. argyrophyllum, P. longum, P. betel and P. chaba. The active anti-inflammatory components that have been reported from *piper* extracts include: dillapiole and dihydrodillapiole (essential oil component) from P. aduncum[25], piperovatine and piperlonguminine (amide compounds) from P. ovatum Vahl[26], [27].

B. Anti-Microbial and Anti-fungal

The ethanol extract of red betel leaf has been shown to have anti-bacterial effects against Staphylococcus aureus ATCC 25923 and Escherichia coli ATCC 35218, respectively at a Minimal Inhibitory Concentration (MIC) and 25% Minimal Killing Concentration (KBM) for S. aureus and 6% for E. coli[28]. 12.5% red betel leaf extract can improve the histopathological image of the skin incision wounds of white rats infected with S. aureus. This conclusion was obtained based on data on the number of neutrophils, macrophages, fibroblasts, angiogenesis and collagen density[29]. The ethanol extract of betel red leaves at a concentration of 40% v / v had the most effective inhibition against the growth of the fungus Candida albicans ATCC 10231 compared to other concentrations, with the highest inhibition width (13.3 mm). The ethanol extract of red betel leaves at a concentration of 40% v / v showed higher inhibition than the 10%, 20%, 80% and 100% v / v extracts[30]. Aqueous extract (infusion) of red betel leaf with a concentration of [1,875 to 30% was unable to inhibit the growth of C. albicans[31]. 100% red betel leaf extract has good effectiveness in inhibiting the growth of the fungus Pityrosporum ovale in dandruff sufferers, with an anti-fungal power comparable to Zinc Pyrithion 1%[32]. The essential oil of P. aduncum leaves and fruit (highest component: linalool) showed antifungal activity against C. sphaerospermum. The essential oil of P. tuberculatum fruit (the highest component of monoterpene compounds: ß-pinene, α-pinene and sesquiterpene compounds: ß-caryophyllene) showed anti-fungal activity against C. cladospoiroides, while the stem essential oil (the highest component was ß-caryophyllene, α-pinene and ß-pinene) inhibits the fungus C. sphaerospermum. All essential oils showed a MIC of 10 µg / ml [33]. Methanol extract and fraction of hexane, dichloromethane and ethyl acetate extract of methanol leaves of *Piper* solmsianum DC.C.var. solmsianum was able to inhibit the growth of 12 types of pathogenic dermatophyte fungi, with a MIC between 20-60 µg / ml. But, all of them were unable to inhibit the growth of hyaline hypho-mycetes and are only slightly active against zigomycetes and yeast.

The isolates from these plants, namely neolignans: eupomatenoid-5 and conocarpan, as well as flavonoid compounds, orientin were able to inhibit 12 types of dermatophytes (MIC between 1-9 µg / ml) with a potency equivalent to ketoconazole. Conocarpan was also able to inhibit yeast growth. The conclusions drawn were: the active anti-fungal compounds of P. solmsianum were neolignans: eupomatenoid-5 and conocarpan, and flavonoid orientin compounds [34]. Hydroxychavicol (HC) isolated from the chloroform fraction of P. betel L. leaf aqueous extract showed antifungal properties against various yeasts (MIC: 1562 - 500 µg / ml), various types of Aspergillus (MIC: 125-500 µg / ml), various Dermatophytes (MIC: 7,81-62,5µg / ml) while the Minimum Fungicide Concentration (KFM) was about the same or two times greater than MIC. HC showed an extended post antifungal effect from 6.25 to 8.70 hours at a concentration of 4 times the MIC against Candida species, and suppressed the emergence of mutants from the tested fungi at concentrations of 2 to 8 times the MIC. HC also inhibits biofilm formation caused by C. albicans and reduces its preformed biofilms. Due to the increased use of propidium iodide by C. albicans cells when treated with HC, it is suspected that the anti-fungal action of hc against C. albicans was to disrupt the membrane of C. albicans[35]. Red betel leaf essential oil showed weak anti-fungal power against mutants Streptococcus (MIC> 0.6%), but had the power to inhibit the formation of biofilms and high biodegradability of biofilms, each with IC_{50} = 0.012%, and EC_{50} = 0.017%[36].

C. Antihyperglycemic

Fresh red betel leaf decoction with a dose of 3.22 and 20 g / kgBW per day for 10 days was able to reduce blood glucose levels (measured using an electronic glucometer) of Sprague Dawley rats with alloxan diabetes (dose 150 mg / kgBW, ip), amounting to 23.61 and 37.41%. This reduction is the same as giving Daonil (dose 3.22 mg / kgBW per day for 10 days). In giving decoction with the above dose, the rat body weight decreased by 17.05 and 5.43%, respectively. The results of the study concluded that fresh red betel leaf decoction is antihyperglycemic and especially at a dose of 3.22 mg / kgBW was able to reduce the weight of diabetic alloxan rats[11].

D. Antiproliferation

That the leaf methanol extract (*Piper crocatum* Ruiz & Pav) was able to inhibit the growth of human breast cancer cells (T47D) in vitro, through the mechanism of inhibition of phosphorylation p44 / p42. No apoptotic cells were observed. T47D cells were grown and maintained in DMEM medium, with the addition of some supplements. The test parameters used included cell viability (MTT method), cell and nucleus morphology (DAPI method), and determination of the sub-G1 section after adding the extract (Flow cytometric analysis). In addition, the detection of changes in p44 and p42 nitrogen levels, which were activated by the protein tyrosine kinase enzyme (Immunoblotting Method). Signaling p44 and p42 were studied because these signaling pathways have been linked to cell growth and represent important targets for cancer therapy[37].

E. Antioxidants

Using the DPPH (1,1-diphenyl-2-picrylhydrazyl) method, the n-hexane, ethyl acetate and ethanol extracts of red betel leaves are antioxidants, each with an IC50 value of 94.63; 127.74 and 134.29 ppm, while the comparison of vitamin C showed an IC50 value of 3.61 ppm [38]. In addition, the fraction containing alkaloids had an IC50 value of 50.91 ppm, while the red betel leaf neolignane isolates were not active as antioxidants. The methanol extract of P. nigrum and P. cubeba fruit showed antioxidant effects by the DPPH method, with IC50 of 144.1 and 11.3 ppm, respectively, while vitamin C showed an IC_{50} of 8.9 ppm[39].

F. Tyrosinase inhibitor

Tyrosinase is an enzyme that can synthesize tyrosine. This enzyme can oxidize phenols to melanin. Melanin is a pigment that plays an important role in preventing skin cancer by protecting body surface cells from ultraviolet radiation. As a result of the formation of melanin, the skin turns dark. Based on this, enzyme inhibition can be used as a substance or compound capable of inhibiting melanin formation, thus, it is used as a skin lightener. The volatile oil from P. betel was able to inhibit tyrosinase activity, while the essential oil from P. crocatum did not. It is estimated that the essential oil components that can inhibit tyrosinase activity are phenylpropanoids (chavicol and eugenol) which are found in P. betel essential oil, but not in P. crocatum Rui & Pav essential oil[8].

CONCLUSION

Red betel (*Piper crocatum* Ruiz & Pav.) is a type of piper that is spread in several regions in the world, including Indonesia. This plant has been widely used by Indonesian people for various kinds of alternative medicine. Chemical content of red betel leaves include: flavonoid compounds: quercetin and aurone group compounds; essential oils with monoterpene components: α-thujene, α-pinene, sabinene, ß-myrcene, α-terpinene, ß-phellandrene, γ-terpinene, α-terpineol, terpinolene, copaene, sesquiterpenes: caryophyllene, α-caryophyllene and germacrene D ; neo-lignans: 1-allyl-3,5-dimethoxy7-methyl-oxo-6- (3,4,5-trimethoxyphenyl) bicyclo [3,2,1] oct-2-en-8-yl acetate; alkaloid class compounds, tannins-polyphenols, steroids-terpenoids and saponins. Research on several pharmacological activities showed that the red betel leaf has anti-inflammatory, antimicrobial and anti-fungal, antihyperglycemic and anti-proliferative properties.

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