Malaysian Journal of Applied Sciences 2018, **Vol 3(1)**: 1-8

eISSN 0127-9246 (Online)

Malaysian Journal of Applied Sciences

REVIEW ARTICLE

Chemical Composition and The Potential Biological Activities of Piper Betel – A Review

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Received: 16/04/2017, Accepted: 28/01/2018

Abstract

Piper betel is a member of the family Piperaceae, commonly known as Sirih (Malaysia and Indonesia), Paan (India and Bangladesh), Betel (English) and Phlu (Thailand). It is widely found and grown in India, Sri Lanka, Malaysia, Indonesia, Philippines, other Southeast Asian and East African countries. Piper betel is widely used throughout the world even in modern days due to its known medicinal properties. Betel plant contains various biologically active compounds, which are responsible for its numerous pharmacological actions. The therapeutic profile reveals Piper betel to have a high potential for treating many diseases and conditions such as chronic renal disease, atherosclerosis, and diabetes mellitus. Further studies of betel plant are recommended to focus on the variety of metabolic activities in human, thus, improving its usage medically that will be beneficial to humanity.

Keywords: Piper Betel, Antimicrobial activity, Antifungal activity, Antioxidant activity.

Introduction

Piper betel is a member of the family Piperaceae, commonly known as Sirih (Malaysia and Indonesia), Paan (India and Bangladesh), Betel (English) and Phlu (Thailand) (Mahfuzul Hoque et al., 2011). Over 700 species of *Piper betel* discovered in both of the hemispheres of the world. It is widely found and grown in India, Sri Lanka, Malaysia, Indonesia, Philippines, other Southeast Asian and East African countries. It was claimed to be originated from Malaysia but taken into cultivation in over more than 2500 years (Sripradha, 2014). *Piper betel* is widely used throughout the world even in modern days due to its known medicinal properties. It is also used in every sphere of human life including social, cultural and religious aspect (Guha, 2006). The taxonomic position of *Piper betel* is shown in Table 1.

Table 1. The taxonomic position of *Piper betel* (Pradhan, 2013).

Kingdom	**Plantae**
Order	Piperales
Family	Piperaceae
Genus	Piper
Species	Betel
Binomial name	*Piper betel*

Botanical description

Betel plant is an evergreen vine that extensively used as home remedy for various diseases. The whole plant of *Piper betel* is utilized; leaves, root, stem, stalks, and fruits. The plant required support to grow upward and may attain up to 10-15 meters with profuse branching (Kumar et al., 2010). The betel leaf is a heart shaped with different sizes from 7-20 cm in length and 5-15 cm in width. The leaves vary from yellowish green to dark green with a glossy upper surface (Mubeen et al., 2014). The stem is stout with a pinkish-yellow stripe. The flowers are tiny with no sepal and petal, have 2-6 stigmas that covered with short beautiful fur. *Piper betel* has a distinct characteristic and pleasantly aromatic odor (Periyanayagam et al., 2012). Interestingly, the leaves taste from sweet to pungent due to the presence of essential oils (Lakshmi et al., 2010, Vasuki et al., 2011).

Traditional uses

The intense spicy aromatic flavored betel leaves are traditionally used by the folks for being masticate in their natural raw condition, along with other ingredients such as sliced areca nut, slaked lime, coriander, aniseed, clove, cardamom, sweetener, coconut scrapings, ashes of diamond, pearl, jelly, peppermint, flavoring agent, fruit pulp, gold and silver (CSIR, 1969). The betel leaves are usually used in conventional medicine as carminative, aphrodisiac, stimulant, analgesic and cooling properties, antiseptic, wound healing, anti-parasitic, antifungal, and antibacterial agent (Ratnasooriya et al., 1990, Caburian and Osi, 2010). The leaf is also useful for the treatment of various diseases; bad breath, boils and abscesses, ulcers, conjunctivitis, constipation, headache, hysteria, itches, mastitis, mastoiditis, leucorrhoea, catarrh, diphtheria, ringworm, swelling of gum, rheumatism, abrasion, cuts and injuries (Chopra et al., 1956, Jayaweera, 1982).

According to the Unani system, the sharp taste and pleasant smell of the leaves help to improve appetite. It acts as a tonic to the brain, heart, and liver (Bajpai et al., 2010). *Piper betel* also helps to promote healthy teeth and skin (Santhanam et al., 1990). The leaf is chewed to relieve constipation in children, used as a poultice for cuts and ulcerated noses, heated and applied to the chest to reduce a cough and asthma by expelling out the mucus (Kirtikar et al., 2005). The leaf is rolled up and covered with oil as a suppository and purgative in newborns (Tewari et al., 1970, Velazco, 1980). Chewing the betel leaf is believed to help to increase the stamina and improving the voice (Usmanghani et al., 1997). The foliage also is known to has a diuretic property. A previous study conducted by Arambewela et al., (2004) found that betel leaf juice with milk or honey helps to ease urination. Other parts of the plant such as the fruits of *Piper betel* are used to treat a cough and indigestion in children (Tawan et al., 2002) while its root is used as a long-lasting female oral contraceptive (Agarwal et al., 2012).

Chemical constituents

Betel vines are one of the highly investigated plants. Phytochemical studies showed that *Piper betel* contains a wide variety of biologically active compounds whose concentration depends on the variety of the plant, season and climate. The fresh betel leaves were found to have

water (85-90%), protein (3-3.5%), fat (0.4-1%), carbohydrates (0.5-6.1%), fibers (2.3%), essential oil (0.08-0.2%) and Tannin (0.1-1.3%) (Lakshmi et al., 2005). A previous investigation by Guha (2006) revealed that the leaves packed with vitamins and minerals such as calcium, phosphorus, potassium, iron, iodine, carotene, nicotinic acid, thiamine, riboflavin, vitamin C and a significant amount of amino acids. In addition, a phytochemical analysis performed by Sugumaran et al., (2011) showed that the betel leaves contained saponin, phenol, alkaloids, amino acids, tannins, flavonoid, steroid and other compounds.

The previous study conducted by Sugumaran et al., (2011), identified sixty-five chemical constituents from betel leaves essential oil, extracted using hydro-distillation method. The predominant chemical constituents are 5-(2-propenyl)- 1,3 benzodioxole (25.67%) followed by eugenol (18.27%) and 2-methoxy-4-(2-propenyl) acetate-phenol (8.0%). Previous efforts by Rimando et al., (1986) and Ghosh & Bhattacharya (2005) discovered fourteen chemical constituents from the essential oil and ether-soluble fraction from the leaves. Major chemical constituents recognized are chavibetol (53.1%) and chavibetol acetate (15.5%). Other constituents were allypyrocatechol diacetate (0.71%), camphene (0.48%), chavibetol methyl ester (methyl eugenol 0.48%), eugenol (0.32%), a-pinene (0.21%), ß-pinene (0.21%), a-limonene (0.14%), safrole (0.11%), 1,8-cineole (0.04%) and allypyrocatechol monoacetate.

Hexane fraction of *Piper betel* (leaf stalk) yields four aliphatic compounds in pure forms; Pentadecyl 6-hydroxytridecanoate, Pentatriacontanol, Methyl hexacos-7-enoate and 6, 9-heptacosa diene. These compounds were isolated and purified by repeated silica gel, reverse phase silica gel, column chromatography and thin layer chromatography (Dwivedi and Mehta, 2011). A gas chromatography-mass spectrometry (GCMS) analysis performed by Deshpande & Kadam (2013) identified the presence of 4 chromanol (27.81%) as a primary compound in *Piper betel* aqueous extract while phenol two methoxy 4 – (-2 propenyl) acetate (61.15%) as a primary compound in ethanol extract. Eugenol (20.37%) and four chromanol (27.81%) were present in both extracts. However, Squalene (21.78%) and Tocopherol (12.62%) were found only in the aqueous extract.

Allylpyrocatechol is known as the significant antioxidant chemical constituent of *Piper betel* and can protect indomethacin-induced gastric ulceration due to its antioxidative and mucin preserving properties (Bhattacharya et al., 2007). Hydroxychavicol and eugenol have been regarded as the significant compounds belonging to the propenylphenol group. Eugenol is the principal constituent of betel leaf that shown to possess antifungal and anti-inflammatory effects (Akhtar and Naveed, 2012). Chavibetol is another organic chemical compound, the primary parts of betel essential oil that contribute to its spicy odor (Tripathi et al., 2011).

Biological activity

Various research that involved *Piper betel* has given a lot of information about the medicinal potential of the plant (Table 2).

Table 2. The reported biological activity of *Piper betel*.

Extracts	Biological activity	Reference
Aqueous	Antibacterial	(Shameen et al., 2013)
	Antioxidant	(Subashkumar et al., 2013)
	Anticancer	(Nur Sazwi et al., 2013)
	Anti-acetylcholinesterase	(Das and De, 2011)
	Antifungal	(Himrazatul-Aznita et al., 2011) (Nordin et al., 2014)
	Anti-diabetic	(Arambewela et al., 2005)
	Neuroprotective	(Norfaizatul et al., 2011)
Ethanol	Apopotosis-inducing	(Widowati et al., 2013)
	Antihistaminic	(Hajare et al., 2011)

	Antibacterial	(M. Mahfuzul et al., 2011) (Datta et al. 2011)
	Anticancer	(Roy and Vijayalaxmi, 2013)
	Anti-diabetic	(Arambewela et al., 2005)
	Anti-fertility	(Sharma et al., 2007)
	Anti-hypercholesterolemic	(Karuppasamy et al., 2014)
	Antioxidant	(Datta et al. 2011)
	Immunomodulatory	(Biswajit et al., 2013)
	Wound healing	(Nilugal et al., 2014)
	Anti-inflammatory	(Sudipto et al., 2007)
Methanol	Antibacterial	(Agarwal et al., 2012)
	Anticancer	(Sriwiriyajan et al., 2014)
	Hypolipidemic	(Thirunavukkarasu et al., 2014)
Essential oil	Antibacterial	(Sugumaran et al., 2011)
	Antihistaminic	(Hajare et al., 2011)
	Anti-larvicidal	(Wardhana et al., 2007)
Ethyl acetate	Anticancer	(Chakraborty et al, 2012)
Dichloromethane	Anticancer	(Sriwiriyajan et al., 2014)

Antimicrobial activity

Mahfuzul Hoque et al., (2011) revealed that the betel leaves ethanol extract showed an excellent potential to inhibit the growth of foodborne pathogens such as *Escherichia coli* ATCC 25922, *Vibrio cholera* ATCC 6395 and *Staphylococcus aureus* ATCC 25923. It was discovered that the antibacterial activity was highest at neutral pH and moderate temperature (37–50°C). The aqueous extract was discovered to be efficient against *Bacillus* and *Pseudomonas aeruginosa* as compared to standard penicillin (Patra et al., 2016). Also, the crude ethanol extract of *Piper betel* showed potent antimicrobial activity against clinical isolate bacterial strains of *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Proteus vulgaris* and *Staphylococcus aureus* (Datta et al. 2011).

A study conducted by Nalina and Rahim (2007) showed that the nucleoid material of *Staphylococcus mutants* coagulated into thick electron dense filaments which subsequently a destroyed cell membrane and inner cell wall. The adverse outcome caused by the betel crude extract could be due to the fatty acids and hydroxyl fatty acid ester components. The hydrophobic parts of the compound enable them to separate the lipids of the bacterial cell membrane, thereby disturbing the structures and rendering them to be more permeable. When the membrane is more permeable, other existing components in the extract will enter the bacterium and coagulate the nucleoid while maintaining the cell to be intact. The effect is more significant with a higher concentration of the extract.

The betel plant also possesses an anti-bacterial activity against urinary tract pathogenic bacteria such as *Enterococcus faecalis*, *Citrobacter koseri*, *Citrobacter fruendi* and *Klebsiella pneumoniae*. The bioactive molecule thought to be responsible for anti-bacterial activity is hydroxychavicol; highly known with a potential to destroy the permeability barrier of microbial membrane structures. A study conducted by Chakraborty & Shah (2011) revealed that *Piper betel* gives a better antimicrobial action when compared with streptomycin as a positive control.

Antifungal activity

Piper betel has an antifungal activity against *Candida albicans* (Rath and Mohapatra, 2015). The methanolic and aqueous extracts of *Piper betel* leaves showed potent activity against the yeasts of *Candida albicans* and *Malassezia pachydermatis* (Saini, 2016). The chloroform extract of *Piper betel* shows higher efficiency compared to the methanol fraction against dermatophytes (*Trichophyton*, *Microsporum*, and *Epidermophyton*) because of the presence of non-polar chemical constituents in the portion (Sharma, 2009).

Antifungal activities of hydroxychavicol from *Piper betel* extract demonstrated fungicidal effects against all the fungal species tested including *Candida* species, *Aspergillus* species, and dermatophytes including *Trichophyton rubrum*. According to Wan Hinrazatul et al., (2013), the fungi *Candida albicans*, *Candida parapsilosis* and *Candida tropicalis* showed a low level of adhesins production when treated with betel crude aqueous extract. These adhesins are crucial as it allows the fungi to colonize various substrates and bind to host tissues.

A crude essential oil was observed to exhibit a broad-spectrum of antimicrobial activity against tested organisms especially *Candida albicans*, followed by *Staphylococcus aureus* and *Malassezia pachydermatis* (Sharma, 2009). The investigation has identified Phenols (carvacrol), and Phenilpropan (eugenol and chavicol) from *Piper betel* are shown to exhibit antifungal activity as it increases the permeability of fungal membranes (Sharma, 2009).

In addition, study performed by Mohamed et al., (1996) using two varieties of *Piper betel* ethanolic extracts showed potent activity against all the pathogens tested *(Colletotrichum capsici, Fusarium pallidoroseum, Botryodiplodia theobromae, Alternaria alternata, Penicillium citrinum, Phomopsis caricae-papayae* and *Aspergillus niger* with inhibition diameters significantly *(P* < 0.01) bigger than 2.5 mg/mL prochloraz or 10 mg/mL clotrimazole.

Antioxidant activity

The 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay study by Lei et al., (2003), showed that *Piper betel* ethanol extracts of Bangla variety, possess the highest antioxidant when compared to three varieties (Bangla, sweet, and Mysore). Column chromatography of the Bangla variety extract led to the isolation of chavibetol, allylpyrocatechol, and their respective glucosides. High-performance thin layer chromatography (HPTLC) analysis of the extracts also revealed similar chemical profiles in all three *Piper betel* varieties, although the concentrations of chavibetol and allylpyrocatechol were significantly less in the sweet and Mysore betel.

Also, Sundang et al. (2012) discovered that *Piper betel*, extracted with methanol has higher antioxidant activity than vitamin E, butylated hydroxytoluene, and catechin but lower than quercetin. The antioxidant activity was further investigated in an aqueous inflorescence, and it was found to scavenge the H_2O_2, superoxide radical, and hydroxyl radical (Dorman et al.,1999). DPPH radical scavenging activity of betel leaves methanolic extract (IC50 16.33±0.16 µg/mL) was similar to the standard ascorbic acid (IC50 12.10±0.02 µg/mL) (Badrul Alam et al. 2013). Moreover, it was discovered that the extract has a proton donating ability and could serve as a free radical inhibitor or scavenger.

Betel extract has the proton reducing the ability, and it is associated with the presence of reductones that exert antioxidant activity by breaking the free radical chain by donating a hydrogen atom (Tanaka et al., 1988). Polyphenolic compounds such as flavonoids, tannins and phenolic acids, which are commonly found in plants, have also reported having multiple biological effects, including antioxidant activity (Khanam et al., 2004). The phenolic compounds show their ability as an antioxidant by inducing the cellular antioxidant system and increases the concentration of cellular glutathione by 50%. Betel leaves are believed to have a significant antioxidant effect due to rich in phenol, polyphenol, and tannin (Kahkonen et al., 1999).

Conclusion

Betel plant contains various biologically active compounds, which are responsible for its numerous pharmacological actions. Recently, a study showed that there is a possible effect of the bioactive components of *Piper betel* leaves extract as anti Quorum sensing properties in reducing the virulent ability of the bacteria such as *Pseudomonas aeruginosa*. Therefore, further identification of bioactive compound in *Piper betel* leaves extract is essential as it might possess other beneficial effects. The medicinal profile of *Piper betel* also showed to have a high potential for treating many diseases and conditions. Further studies of betel plant are also recommended to focus on the variety of metabolic activities in human, thus, improving its usage medically that will be beneficial to humanity.

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How to cite this paper:
Umar, R. A., Sanusi, N.A., Zahari M.N., Rohin, M.A.K., & Ismail, S. (2018). Chemical Composition and The Potential Biological Activities of Piper Betel – A Review *Malaysian Journal of Applied Sciences, 3*(1), 1-8.