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Research Article

Chemistry behind the Betel Leaves and Betel Quid: Their Health Benefits and Adverse Health Effect-a Review

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Abstract

Piper betle leaves have been used in Indian and Chinese folk medicine for centuries and is well known for its extensive use in Ayurvedic medicine. Recently, it has been used as a chemo-preventive agent because of its anti-oxidant activity. Several biologically active compounds from P. betle have potential for use as medicines, neutraceuticals and industrial compounds. Consumption of betel leaf is usually in the form of betel quid which consists of areca nut, lime and some spices with or without tobacco. Long term consumption of betel quid with tobacco is known to cause adverse health effects, mainly carcinomas. In addition to oral cancer it is also known to induce chromosomal aberrations and tumours in the pharynx and oesophagus. However, consumption of betel leaf alone does not induce cancer and has invaluable health benefits due to its tremendous medicinal properties. Phenol-rich leaves of P. betle show high antioxidant activities and because of its anti-oxidant properties, it has been used as a chemo-preventive agent. Its oil is used as an industrial raw material for manufacturing of medicines, perfumes, mouth fresheners, tonics, food additives etc. The leaves are nutritive and contain anti-carcinogens showing promise for manufacturing of a blood cancer drug. It is also playing a vital role in various ceremonies and auspicious occasions as an indicator of goodness. Since the traditional use of P. betle involves chewing, it offers possibilities of use in drug delivery through buccal mucosa bypassing the gastric route.

Keywords: Betel leaves; Betel quid; Chemical composition; Medicinal properties; Health benefits and Adverse health effect

Introduction

Medicinal plants are of proven value as potential therapeutics with the increase of resistant pathogens to commonly used antibiotics and the emergence of new infectious diseases. Human dependence on plants as source of medicine dates back to prehistoric times. Even now, more than three-fourths of the world's population relies mainly on plants and plant extracts for healthcare. Piper betle L. is one of the important plants in the Asiatic region which ranks second to coffee and tea in terms of daily consumption. Piper betle L., is an evergreen perennial creeper belonging to family Piperaceae and is known to possess numerous medicinal properties. Piper betle is a plant with known ethno-medicinal properties and its use in India, Indonesia and other countries of the Indo-China region like Malaysia, Vietnam, Laos, Kampuchea, Thailand, Myanmar, Singapore, and Bangladesh is well known. It is a mild stimulant and has a lot of medicinal properties. Betel leaves have been used in Indian and Chinese folk medicine for centuries and is also well known for its extensive use in Ayurvedic medicine. Use of betel leaves are known for its curative properties such as: to reduce/prevent body

odour and bad breath, throat and lung problems, cough prevention and healing, to prevent itching caused by fungus and internal/external bacteria [1]. The leaf extract, fractions and purified compounds are found to exhibit several biological activities including oral hygiene, anti-diabetic, cardiovascular, anti-inflammatory, anti-ulcer, anti-cancer, hepato-protective, and anti-infective etc [2,3]. Many patents were also awarded for some of the biological activities like anti-inflammatory, [4] anti-cancer [5] and immunomodulatory [6] associated with leaf extracts and purified compounds. The betel leaves are also credited with wound healing, digestive, and pancreatic lipase stimulant activities in the traditional medicine [7]. The active compounds isolated from leaf and other parts are hydroxychavicol, hydroxylchavicol acetate, allylpyrocatechol, chavibetol, piperbetol, methylpiperbetol, piperol A and piperol B. Phenol-rich leaves of P. betle show high antioxidant activities. The Essential oil isolated from the leaves is supposed to be useful in treating respiratory catarrhs and as an anti-septic [8]. Its leaves, with strong pungent and aromatic flavour, are widely consumed as mouth freshener. On the other hand, consumption of betel quid with tobacco poses serious health hazard. Long term consumption of betel quid with tobacco is known to cause adverse health effects, mainly carcinomas. In addition to oral cancer it is also known to induce chromosomal aberrations and tumours in the pharynx and oesophagus. Betel leaf is the most valuable home remedy for common illness. Since the traditional use of P. betle involves chewing, it offers possibilities of use in drug delivery through buccal mucosa bypassing the gastric route. This review presents a systematic overview on chemical compositions, health benefits of betel leaf and the health effect of betel quid.

Cultivation of Betel Leaf

Betel leaf is widely grown in the tropical humid climate of South East Asia and thus, cultivated in most of South and Southeast Asia. In India, it is widely cultivated in Tamil Nadu, Madhya Pradesh, West Bengal, Orissa, Maharashtra and Uttar Pradesh. Leaves 10-20 cm long, broadly ovate, slightly cordate and often unequal at the base, shortly acuminate, glabrous, glaucous on both sides, bright green and yellowish, petiole stout 2.0-2.5 cm long. Male spikes cylindrical dense. Female spikes 2.5-5.0 cm long, pendulous. Fruits rarely produced, often sunk in the fleshy spike, forming nodule-like structures [9]. For the proper growth of betel requires high land and especially fertile soil; waterlogged, saline and alkaline soils are not suitable for its cultivation. Proper shade and irrigation are essential for the successful cultivation of this crop. In Bangladesh, farmers called Barui prepare a garden called a Barouj in which betel is grown. The Barouj is fenced with bamboo sticks and coconut leaves. The soil is flowed into furrows of 10 to 15 meters length, 75 centimetres in width and 75 centimetres depth. The creeper cuttings are planted after proper dressing in the months of May and June at the beginning of the monsoon season. The leaves of the plant become ready for plucking after one year of growth and the production of the Barouj lasts for several years from the date of planting. Betel needs constantly moist soil, but there should not be excessive moisture. In 3 to 6 months the vines reach 150 to 180 centimetres in height and they will branch. The harvested leaves are used both for domestic consumption and for export to other parts of Asia, the Middle East, Europe, and the United States. Betel is an important part of the economy in rural India as well as Bangladesh.

Consumption of Betel Leaf

Betel leaf is mostly consumed in Asia and elsewhere in the world by some Asian emigrants, as betel quid or paan, with or without tobacco. It has an addictive psycho-stimulating and euphoria-inducing formulation with adverse health effects. The deep green heart shaped leaves of betel vine are popularly known as Paan in India. An extensive research monograph by the World Health Organization in 2004 reports that betel leaf is consumed in South East Asian community worldwide, predominantly as a betel quid or paan. The betel quid contains betel leaf, areca nut and slaked lime, and may contain tobacoo. Other substances are often added to the betel quid, in particular spices, such as cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners according to local preferences. The betel quid is thus a mixture of substances and betel leaf is not consumed alone. For a predominant majority, the paan usually contains the betel leaf with two basic ingredients, either tobacco, or areca nut or both, in row or any processed form. There is archaeological evidence that the betel leaves have been chewed along with the areca nut since very ancient times. In most countries the mixture of both has a ceremonial and highly symbolic value. In India, Burma, Nepal, Sri Lanka and other part of South Asia and Southeast Asia, the leaves are chewed together in a wrapped package along with the areca nut which, by association, is often inaccurately called the 'betel nut' and mineral slaked lime (calcium hydroxide). The lime acts to keep the active ingredient in its freebase or alkaline form, thus enabling it to enter the bloodstream via sublingual absorption. The areca nut contains the alkaloid arecoline, which promotes salivation, and is itself a stimulant. In India, the betel and areca play an important role in Indian culture, especially among Hindus. Many traditional ceremonies governing the lives of Hindus use betel and areca. Moreover, offering betel morsel (pan-supari) to guests in Indian subcontinent is a common courtesy. The betel and areca also play an important role in Vietnamese culture. The betel leaves and areca nuts are used ceremonially in traditional Indian and Vietnamese weddings. The lime must be purchased and processed from corals, especially the fast-growing stag horn corals of genus Acropora. Chewing betel quid to give fragrance to mouth.

Composition

The specific spicy burning taste of betel leaf is derived from the presence of volatile oil consisting of phenols and terpenes etc. The taste and aroma depends on the presence and proportion of the various components in the oil which are vary markedly among the cultivars and makes them differ in aroma and taste. An analysis of the betel leaf shows that it consist of moisture (85.4%), protein

(3.1%), fat (0.8%), minerals (2.3%) including Iron and Aluminium, Fiber (2.3%), and Carbohydrates (6.1%) per 100 grams.3 Its minerals and vitamin contents are Calcium, Riboflavin, Carotene, Niacin, Thiamine, Vitamin B and C. Its calorific value is 44. Recent studies have shown that betel leaves contain tannins, sugar and diastases and an essential oil. The essential oil is a light-yellow liquid of aromatic odor and sharp burning in taste. It contains a phenol called chavicol which has powerful antiseptic properties. The alkaloid arakene has properties resembling cocaine in some respects. The active ingredients of betel oil, which is obtained from the leaves, are primarily a class of allylbenzene. Though particular emphasis has been placed on chavibetol (betel phenol, 3-hydroxy-4-methoxy-allylbenzene), it also contains chavicol (p-allyl phenol), estragole (p-allyl anisole, 4-methoxy allylbenzene), eugenol (allylguaiacol, 4-hydroxy-3-methoxy allylbenzene, 2-methoxy-4-allylphenol), methyl eugenol (eugenol methyl ether, 3,4-dimethoxy allylbenzene) and hydroxycatechol (2,4-dihydroxy allylbenzene) [2,10]. Several terpenes and terpenoids are present in the betel oil as well. There are two monoterpenes such as p-cymene and terpinene, and two monoterpenoids, eucalyptol and carvacrol. Additionally, there are two sesquiterpenes, cadinene and caryophyllene. They also contain significant amounts of all essential amino acids except lycine, histidine and arginine. Large concentrations of asparagines are present while glycine and proline occur in good amount. Essential oil of leaf gives it the aromatic flavour. Importantly, β-sitosterol is present in the root [11] (Figure 1).

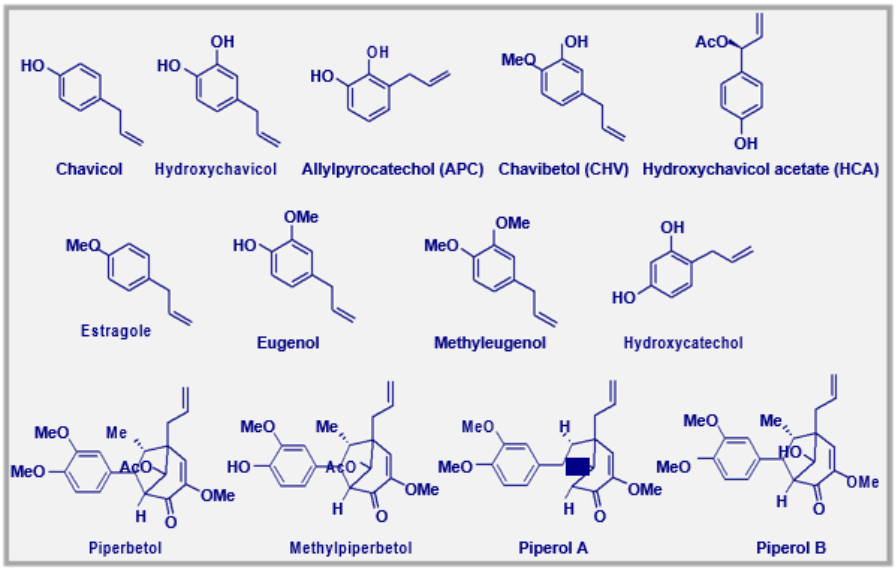

Figure 1: Structure of some biologically active found in betel leaf extract.

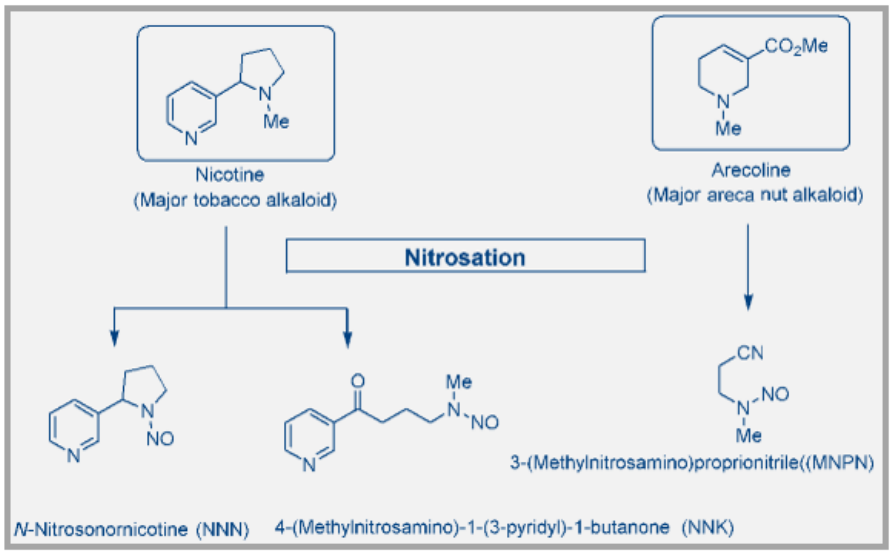

Figure 2: Carcinogenic nitrosamines that could be derived from major ingredients of panmasala (areca nut) and gutkha (areca nut and tobacco). NNN: N′-nitrosonornicotine; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; MNPN: 3-(methylnitrosamino)proprionitrile.

Leukoplakia

It is a white patch on the mucosa that cannot be characterized clinically or pathologically as any other disease. It is mostly associated with the use of Tobacco which may be consumed in smoked or smokeless forms; as well as mixed with areca nut in Gutkha or other such preparations. It is a precancer lesion and may progress to cancer, especially if the irritant substance is not withdrawn.

Erythroplakia

It is a Red Patch on the mucosa that cannot be identified clinically or pathologically as caused by inflammation or any other disease process. It is a precancer lesion with a high risk of progressing to cancer.

Diagram 1

Antimicrobial Activity: Nair and Chanda (2008), have studied the aqueous and methanol extract of the leaves of Terminalia catappa L., Manilkara zapota L. and Piper betel L., for antibacterial activity against 10 Gram positive and 12 Gram negative bacteria [13]. In this study, Piperacillin and gentamicin were used as standards for antibacterial assay, while fluconazole was used as standard for antifungal assay. The three plants showed different degree of activity against the microorganisms investigated and observed that the most active antimicrobial plant was Piper betel among this three trees. The methanolic extract was considerably more effective than aqueous extract in inhibiting the investigated microbial strains.

Antihistaminic activity: Hajare et al., (2011), were evaluated Piper betel Linn. leaves for its antihistaminic activity [14]. In the study, the pharmacological evaluation of ethanolic extract and essential oil extract of leaves of P. betel Linn. has been done for their antihistaminic activity on guinea pig. Chloropheniramine maleate was used as a standard drug. In isolated guinea pig tracheal chain preparation, there was a right side shift of dose response curve (DRC) of histamine. Moreover, extracts of P. betel disturbed histamine aerosol induce bronchoconstriction in whole guinea pig, where essential oil was more effective comparatively to ethanolic extract. Thus, they concluded that ethanolic extract and essential oil of P. betel Linn possess antihistaminic activity.

Anti-inflammatory effects: The betel leaf is used as a common household remedy for inflammation in the oral cavity [8]. Dohi et al., (1989), has shown that the ethanolic extract of betel leaf has been reported to possess anti-inflammatory activities at non-toxic concentrations in the complete Freund's adjuvant-induced model of arthritis in rats.15 It was observed that Eugenol, one of the principal constituent of betel leaf has also been shown to possess anti-inflammatory effects in various animal models of studies with various inflamogens.

Antioxidant effects: Bhide et al., (1991) [12] and Azuine et al., (1991) [16] described that the betel leaf constituent's eugenol, hydroxychavicol and alpha-tocopherol were also shown to enhance the levels of GSH in mouse skin and liver. Together all these observations clearly indicated that the betel leaf extracts and some of its constituents increased the cellular antioxidants and mediate the chemopreventive effects. The combination of betel leaf extract with turmeric was also observed to be effective between two dietary agents [16b].16b Anticancer and free radical scavenging potency of Catharanthus roseus, Dendrophthoe pentandra, Piper betle and Curcuma mangga extracts in breast cancer cell lines was investigated by Widowati et al., 2013 [12b]. Lei et al., (2003) have shown that the aqueous extract of the inflorescence of Piper betel extract was effective in scavenging H2O2, superoxide radical and hydroxyl radical. The extract also prevented the hydroxyl. Radical-induced DNA strand breaks in the PUC18 plasmid [17]. Rathee et al., (2006) have shown that the ethanol extracts of Bangla, sweet, and Mysore varieties of betel leaf were effective in scavenging DPPH radicals in vitro, with best effects being observed with the Bangla variety. Recently, Manigauha et al., (2009) observed that the methanolic extracts of the betel leaves possess reducing power, DPPH radical, superoxide anion scavenging and deoxyribose degradation activities [18]. Studies have also shown that the hydroalcoholic extract of the betel leaf possess nitrogen oxide scavenging effect in vitro [19].

Antimutagenic effects: Multiple studies have shown that the betel leaf is devoid of mutagenic activities in both prokaryotic and eukaryotic assaysystem [20] and also to possess antimutagenic (Shirname et al., 1983) [21] and anticlastogenic effects (Bhattacharya et al., 2005) [22]. In vitro studies with cultured cells have shown that betel leaves did not cause any morphological transformation

of the hamster embryo cells or induce sister chromatid exchanges in both virally transformed cells and PHA-stimulated human lymphocytes [16]. Additionally, the ethanolic extract of betel leaf is also reported to possess γ-ray induced clastogenesis in plasmids [22].

Anti-haemolytic activity: Anti-haemolytic activity was studied by Chakraborty et al., (2011), using erythrocytes model piper betel leaf extracts and the extent of lipid peroxidation of the same was also determined [23]. The erythrocyte membranes are susceptible to peroxidation because they are rich in polyunsaturated fatty acids. They contain haemoglobin, which may catalyze the oxidation as they are continuously exposed to high concentration of oxygen. The oxidation of erythrocytes serves as good models for the oxidative damage of biological membranes. It has been found that certain chemicals, having ability to generate radicals attack the erythrocyte membrane, inducing the chain oxidations of lipids and proteins and eventually causing membrane damage leading to haemolysis. When red blood cells were treated with betel leaf extract along with H2O2 marked reduction in haemolysis was found [24,25].

Antiulcer Activity: Vyawahare et al., (2010), evaluated the antiulcer activity of hydroalcoholic extract of Piper betel (HEPB) leaves, in rats employing the HCl-ethanol, acute stress and pylorusligation models to induce the experimental gastric ulcers. Pre-treatment with Piper betel extract provided significant ulcer protective effect in all the experimental models along with significant increase in gastric pH and decrease in gastric fluid volume. The hydroalcoholic extract of Piper betel leaves possesses antiulcer activity which can be attributed to its putative mechanism of action [26].

Antibacterial activity: The four varieties of Piper betel; namely Desawari, Desi, Bangladeshi and Jaleswar, cultivated in India. Agarwal et al., (2012) evaluated that the cold aqueous, methanolic, ethanolic, and ethyl acetate extracts of dried leaves of all the four varieties of Piper betel at a finalconcentration of 500 mg/ml were tested against pathogenic microorganisms such as Pseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli using agar well diffusion method [27]. Nalina et al., 2007 reported the crude aqueous extract of Piper betle L. and its antibacterial effect towards Streptococcus mutans. The focus of antimicrobial effects includes the ultra-structure and acid producing properties of Streptococcus mutans.

Antifungal activity: Ali et al., (2010) have shown that the Hydroxychavicol, isolated from the chloroform extraction of the aqueous leaf extract of Piper betel L., (Piperaceae) was investigated for its antifungal activity against 124 strains of selected fungi [28a]. Hydroxychavicol exhibited inhibitory effect on fungal species of clinical significance, with the MICs ranging from 15.62 to 500 µg/ml for yeasts, 125 to 500 µg/ml for Aspergillus species, and 7.81 to 62.5 µg/ml for dermatophytes whereas the MFCs were found to be similar or two fold greater than the MICs. There was concentration-dependent killing of Candida albicans and Candida glabrata up to 8 × MIC. Hydroxychavicol also exhibited an extended post antifungal effect of 6.25 to 8.70 h at 4 × MIC for Candida species and suppressed the emergence of mutants of the fungal species tested at 2 × to 8 × MIC concentration. Their conclusion was that antifungal activity exhibited by this compound can be used as an antifungal agent particularly for treating topical infections, as well as gargle mouthwash against oral Candida infections [28]. In vitro screening of antifungal activity of plants in Malaysia were studied by Nazmul et al., 2011 and Nazmul et al., 2013. The results concluded that Piper betle produced the best result in antifungal susceptibility testing and showed to possess antifungal property against 4 out of 5 strains of fungus [28b,c].

Anti-diabetic activities: Arambewela et al., (2005) investigated the antidiabetic activity of Piper betel leaves, tested in normoglycaemic and strepozotocin (STZ)-induced diabetic rats using oral administration of hot water extract (HWE) and cold ethanolic extract (CEE) [29]. In normoglycaemic rats, both HWE and CEE significantly lowered the blood glucose level in a dose-dependent manner. In glucose tolerance test, both extracts markedly reduced the external glucose load. The antidiabetic activity of HWE is comparable to that of CEE. Both extracts were found to be non-toxic and well tolerated after following chronic oral administration (no overt signs of toxicity, hepatotoxicity or renotoxicity). However, the weight of the spleen had increased in treated groups possibly indicating lympho-proliferative activity [29].

Palpebral skin antiseptic: The antiseptic effectiveness was measured by Amalia et al., (2009), counting the microbial colonies before and after administration of the antiseptic solutions.30 This study demonstrates that the mean colony counts after application of 20% Piper betel leaf infusion showed a significant reduction of 27-100% compared with those before administration (p=0.001). Mean colony counts after 10% povidone-iodine administration showed a significant reduction of 88-100% compared with the mean counts before the solution was applied (p=0.000). The 20% Piper betel infusion has an antiseptic potential [28-30].

Local anaesthetics action: Krishnakumar et al., (2001), have shown that, extracts of plain betel leaf with betel nut, with and without autoclaving, were tested for surface and infiltration anesthetic activities using rabbits and Guianese pigs [31]. The results were compared with normal saline control and xylocaine drug control. Betel leaf showed dose-dependent infiltration anesthetic activity comparable with xylocaine. As a surface anesthetic, the onset was as quick as xylocaine and the duration was shorter than xylocaine. Betel nut significantly reduced the infiltration activity and abolished the surface anesthetic activity of betel leaf. Autoclaving did not result in any loss of activity. Betel leaf has potent local anesthetic action both by surface and infiltration techniques. This effect is reduced by the addition of betel nut but not lost on autoclaving [31].

Role of betel leaf extract on thyroid function: Panda and Kar (1998) demonstrated that the effects of betel leaf extract (0.10, 0.40, 0.80 and 2.0 g kg−1day−1for 15 days) on the alterations in thyroid hormone concentrations, lipid peroxidation (LPO) and on the activities of superoxide dismutase (SOD) and catalase (CAT) were investigated in male Swiss mice [32]. Administration of betel leaf extract exhibited a dual role, depending on the different doses. While the lowest dose decreased thyroxine (T4) and increased serum triiodothyronine (T3) concentrations, reverse effects were observed at two higher doses. Higher doses also increased LPO with a concomitant decrease in SOD and CAT activities. However, with the lowest dose most of these effects were reversed. Their findings suggested that betel leaf can be both stimulatory and inhibitory to thyroid function, particularly for T3generation and lipid peroxidation in male mice, depending on the amount consumed [32].

Anti-nociceptive Activities: Arambewela et al., (2005), examined the antinociceptive activity of hot water extract (HWE) and cold ethanol extract (GEE) of P. betel leaves using rats and three models of nociception (tail flick, hot plate, and fonnalin tests) [33]. Different concentrations of H WE (125, 200, 300, 500mg/kg) and CEE (125, 200, 300, 500mg/kg) were made and orally administrated to rats, and the reaction times were determined. Their results showed that the extracts have marked antinociceptive activity when evaluated in the hot plate and the formalin tests but not in the tail-flick test. The overall antinociceptive effect of CEE was higher than that of HWE [33].

As contraceptive: Singh et al., (2011), studied the mitochondrial activity of sperm, after treating semen with different concentrations of Piper betel [34]. The mitochondrial activity was also evaluated after subjecting the semen samples for different incubation time periods. Test was done on more than 75% motile normozoospermic semen sample and was found that as the concentration of extracts increases the mitochondrial activity decreases significantly ($p < 0.001$), similar results were observed when constant concentration of extracts with increasing time intervals. The mitochondrial activity decreases significantly ($p < 0.001$) in 5 minutes to 20 minutes incubation time. They concluded that Piper betel has properties to decrease mitochondrial activity in human sperm and ability to work as contraceptive [34].

Other Health Benefits of Betel Leaf

Betel leaf has long been recognised as one of the medicinal plants that has tremendous health benefits. The medicinal properties of betel leaf are well known since time immemorial. Betel leaf is used as a stimulant, an antiseptic and a breath freshener. According to traditional Ayurvedic medicine, chewing betel leaf is a remedy for bad breath.

- **Healing Power and Curative Properties:** Betel leaf has been used from ancient times as an aromatic stimulant and anti-flatulent. It is useful in arresting secretion or bleeding and is an aphrodisiac. Its leaf is used in several common household remedies [35].
- **Scanty or Obstructed Urination:** Betel leaf juice is credited with diuretic properties. Its juice, mixed with dilute milk and sweetened slightly, helps in easing urination.
- **Weakness of Nerves:** Betel leaves are beneficial in the treatment of nervous pains, nervous exhaustion and debility. The juice of a few betel leaves, with a teaspoon of honey, will serve as a good tonic. A teaspoon of this can be taken twice a day.
- **Headaches:** Betel leaf is a popular home remedy for headache. The betel leaf has analgesic and cooling properties. It can be applied with beneficial results over the painful area to relieve intense headache.
- **Respiratory Disorders:** Betel leaves are useful in pulmonary affection in childhood and old age. The leaves, soaked in mustard oil and warmed, may be applied to the chest to relieve cough and difficulty in breathing.
- **Constipation:** In the case of constipation in children, a suppository made of the stalk of betel leaf dipped in castor oil can be introduced in the rectum. This instantly relieves constipation.
- Sore Throat: Betel leaf is an excellent household remedy in the treatment of cough and sore throat. Local application of the leaves is effective in treating sore throat. The crushed fruit or berry should be mixed with honey and taken to relieve irritating cough.
- **Inflammation:** Applied locally, betel leaves are beneficial in the treatment of inflammation such as arthritis and orchitis that is inflammation of the testes.
- **Wounds:** Betel leaves can be used to heal wounds. The juice of a few leaves should be extracted and applied on the wound. Then a betel leaf should be wrapped over and bandaged. The wound will heal up with a single application within 2 days [36].
- **Boils:** The herb is also an effective remedy for boils. A leaf is gently warmed till it gets softened, and is then coated with a layer of castor oil. The oiled leaf is spread over the inflamed part. This leaf has to be replaced, every few hours. After a few applications, the boil will rupture draining all the purulent matter. The application can be made at night and removed in the morning.
- **Lumbago:** A hot poultice of the leaves or their juice mixed with some bland oil such as refined coconut oil can be applied to the loins with beneficial results in lumbago.
- **Problem of Breast Milk Secretion:** The application of leaves smeared with oil is said to promote secretion of milk when applied on the breasts during lactation [37].
- **Aphrodisiac:** Pan-supari, especially the pan, is prescribed by Ayurvedic physicians as an aphrodisiac. Partly owing to its de-

odorant, aphrodisiac, and invigorating properties, pan-supari came to form a part of the ritual with which a wife welcome her husband.

Health Effects of Betel Quid

The betel leaf is predominantly consumed in the world as betel quid or paan, which is a mixture of substances. The paan almost always contains a betel leaf with basic ingredients, either areca nut or tobacco or both, with lime (Calcium hydroxide or calcium carbonate) [38]. Both tobacco and areca nut are considered as carcinogenic. Betel quid is strongly carcinogenic [39]. Cancer of the mouth and lips has been found to be more frequent in areas where the betel chewing habit is widely prevalent. Other ill-effects of pan-chewing like dyspepsia, pyorrhea, cancer of the tongue and cheeks have also been observed amongst excessive chewers. It is said that the percentage of oral cancer among all cancers diagnosed in hospitals in Asia has always been much higher than that usually found in western countries, where the habit of chewing betel quid, with or without tobacco, is virtually unknown. In many descriptive studies, investigators have obtained histories of chewing betel quid with tobacco from series of patients with oral cancer; and in all these studies the percentage of patients who practice betel leaf chewing was found to be extremely large. Researchers also noted that the cancer generally develops at the place where the betel quid is kept. In an earlier study in 1985 scientists linked malignant tumours to the site of skin or subcutaneous administration of aqueous extracts of betel quid in mice. In human populations, there are reports of elevated frequencies of micronucleated cells in buccal mucosa of people who chew betel quid in Philippenes and India. Scientists also found that the proportion of micronucleated exfoliated cells is related to the site within the oral cavity where the betel quid is kept habitually and to the number of betel quids chewed per day [40]. This proportion, they report, could be reduced by administration of vitamin A or -carotene or a mixture of two. In related studies, scientists have reported that oral leukoplakia shows a strong association with habits of betel-quid chewing in India. Some follow-up studies have shown malignant transformation of a proportion of leukoplakia. Oral sub-mucous fibrosis and lichen planus, which are generally accepted to be precancerous conditions, appear to be related to the habit of chewing betel quid, that is paan (WHO, 2008). In a study conducted in Papua New Guinea, it was found that the most common malignant tumour was oral squamous cell cancer which is associated with betel chewing.41 They reported that the oral cancer is concentrated at the corner of the mouth and check, and corresponds precisely with chewing site of betel leaf with lime in 77% of 169 cases. Powdered slaked lime applied to the chewed areca nut placed inside a betel leaf causes the mean pH to rise to 10, at which reactive oxygen species are generated from betel quid ingredients in vitro. They claim that Reactive oxygen species, together with sustained lime-induced cell proliferation which is a possible mechanism of carcinogenesis. Betel chewing increases the risk of cardiovascular disease and mortality [41,42]. In this study, they investigated the association between betel nut chewing and general obesity (BMI 25 kg/m^2) and central obesity. Using multiple linear regression analysis, they claim betel consumption was statistically significantly associated with obesity. The reason for these links between obesity and betel leaf chewing, the scientists admit is unclear. In another study, they reported the extent of cancer risks of betel quid chewing is beyond oral cancer. In addition to oral cancer, significant increases were seen among chewers for cancer of the oesophagus, liver, pancreas, larynx, lung, and all cancer [43,44]. Chewing and smoking, as combined by most betel chewers, interacted synergistically and was responsible for half of all cancer deaths in this group. They also said that chewing betel quid and smoking shortened the life span by nearly 6 years. A Lancet Oncology publication claims that betel leaf quid or paan masala may cause tumours in different parts of the body and not just the oral cavity as previously thought. A study conducted in Sri Lanka by found that there was a high prevalence of oral potentially malignant disorders in rural Sri Lanka populations [45]. After screening for various causes he reported that betel quid chewing is the major risk factor, with or without tobacco. In October 2009, 30 scientists from 10 countries met at the International Agency for Research on Cancer (IARC), a World Health Organization sponsored group, to reassess the carcinogenicity of various agents including betel leaf quid with areca nut, and mechanisms of the carcinogenesis. They concluded that there is sufficient evidence that betel quid without tobacco leads to tumour in oral cavity and oesophagus, and that betel quid with added tobacco is a carcinogen to the oral cavity, pharynx and oesophagus [46]. The high rate of oral cancer in South Asia is thought to be due to the chewing of betel preparations; the inclusion of tobacco may worsen the risk, but there is also evidence that the areca nut, alone or as part of betel quid, may cause cancer even without tobacco [47,48]. Scientific studies that evaluate the health effects of betel leaves by itself are limited, in contrast to the extensive medical studies on betel quid or paan.

Mechanism of Carcinogenic Property Betel Nut

Betel nut contains pyridine alkaloids, like arecoline, arecaidine, guvacine, guvacoline and arecolidine. They have stronger chemical reactivity than those of the nicotine alkaloids. Slaked lime contains strong alkali-calcium hydroxide which can release free alkaloids bases from their esters and also results in the hydrolysis of arecoline to arecolidine. Thus, incorporating slaked lime into the chew appear to potentiate action of alkaloids. The carcinogenic alkaloids in betel nut are made even more dangerous by the inclusion of tobacco and lime in gutkha. Nitrosamine was reported to be an important carcinogen. It can be formed from the action of betel arecoline, nitrite and thiocyanate in vivo. Saliva of betel chewers offer a favourable condition for nitrosamine formation in view of the presence of high levels of nitrites and thiocyanates. NNK and NNN appear to have the greatest mutagenic potential and have been shown to cause DNA adducts associated with tumors in rodents and are classified as probable human carcinogens.

Conclusion

This review suggests that the leaves of Piper betle L. contains number of phyto-constituents and as a source for various therapeutic purposes. It may be concluded that though consumption of betel quid with tobacco poses serious health hazard, the leaves alone when consumed have innumerable health benefits. Due to the higher phenol content in the leaf, the plant possesses high antioxidant activity and other pharmacological activities. Hope better understanding of the biological effects and chemical constituents of betel leaf will be appeared in future publications.

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