Review Article

Piper betel - not only a mouth freshener but also a medicinally wonder herb: A review

ABSTRACT

Piper betle L. or betel vine, an economically and medicinally important cash crop, belongs to the family Piperaceae, is often known as the green gold. The most likely place of origin of betle vine is Malaysia but it is also cultivated in India, Sri lanka, Bangladesh, Myanmar and Nepal. It is cultivated in the coastal regions of Odisha in the districts of Balasore, Jagatsinghpur, Puri, Khordha, and Ganjam. Betel vine has immense nutraceutical, medicinal and economic importance with significant opportunity in employment generation and upliftment of socioeconomic conditions of rural peoples in India and also in other Asian countries. But there are other various important aspects of this plants which have not been given proper attention. Paan is consumed by over 1 million people throughout the Odisha, but people are mostly unaware of its high nutritional quality. *Piper betel* is mostly used to chew with sliced areca nut, slaked lime, coriander, aniseed, clove, cardamom, sweetener, coconut scrapings etc. Besides the traditional use, the medicinal properties of *Piper betel* has the potential to cure many diseases and reduce the oral cancer which actually happens due to sliced areca nut, slaked lime not because of betel leaves. Betel leaves are rich in minerals, vitamins, antioxidants, phytochemicals and many nutrients like protein, fats, fibre, calcium and iron etc. Many research studies on *Piper betle* have reported that it contains important chemical constituents such as chavibetol, chavibetol acetate, caryophyllene, allylpyrocatechol diacetate, campene, chavibetol methyl ether, eugenol, a-Pinene, f-Pinene, u-Limonene, saprobe, 1-8-cineol, allylpyrocatechol monoacetate etc. Betel leaf is considered superior to pharmaceuticals and is one of the best remedies in nature. Furthermore, the leaves retain eugenol-rich essential oil (EO) (1-3%), which is the hotspot for medication, stimulants, antiseptics, tonics, and other ayurvedic compositions. Currently, demand for its products such as herbal drugs, medicines, and natural herbal formulations has increased. *Piper betel* also helps in curing various diseases like diabetes, hypertension, halitosis, boils and abscesses, obesity, wound healing, voice problems, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, ringworm, swelling of gum, rheumatism, abrasion, cuts and injuries etc. The present review comprehensively summarizes the botanical description, geographical distribution, economic value and cultivation, ethnobotanical uses of *P. betle*. The findings suggest that *P. betle* represents an orally active and safe natural agent that exhibits great therapeutic potential for managing various human medical conditions. However, further research is needed to elucidate its underlying molecular mechanisms of action, clinical aspects, structure-activity relationships, bioavailability and synergistic interactions with other drugs.

Key Words: *Piper betel*, Nutrients, Phytochemical, Antioxidants, nutraceutical.

1.INTRODUCTION

The betel leaf commonly known as 'Paan' (family-Piperaceae) is an evergreen and perennial creeper. It is an important herb and has known medicinal and recreational properties. It also has many traditional benefits. It is cultivated in Southeast Asia. Though, the place of origin of betel is Malaysia, today it has been cultivated in Srilanka, India, Bangladesh and many other parts of the world (Rai et al., 2011). *Piper betel* is a plant with known ethno- medicinal properties. Its use was known for centuries to many people for its unprecedented medicinal properties. Significance of betel leaves has been explained in relationship to every sphere of human life including social, culture, religious and is very much relevant even in modern days (Guha, 2006). From ancient time betel are chewed along with areca nut, slaked lime, cardamom and clove in many Asian countries (Walter and Sofia., 2007). Various properties of betel leaf include antioxidant, antifungal, antiulcergenic, antidiabetic, immunomodulatory, anti-inflammatory, antifilarial, antimicrobial, antifertility, antihyperglycemic,

antidermatophytic and radioprotective properties (Nagori et al., 2011). Betel leaf has been described from ancient time as an aromatic stimulo-carminative, astringent and aphrodisiac. Scientific research on the leaf of this plant reveals that it possesses many beneficial bioactivities and its extract from betel leaves has a great potential to be used in developing commercial products. The best conditions for commercial betel vine cultivation are those of tropical rain forests, which provide cool shade, considerable humidity and an adequate supply of soil moisture like Indonesia, Malaysia, Philippines, Thailand, Cambodia, Vietnam and India (Rawat et al., 1989). The betel leaves contain vitamins and significant amount of all essential amino acid except lysine, histidine and arginine which occurs in traces.

Piper betel L. is widely used as a mouth freshener after meal. Indian system of medicine and health has adopted the use of betel leaves in various ways. In Indian folkloric medicine, betel leaf is popular as an antiseptic and is commonly applied on wounds and lesions for its healing effects. Essential oil extracted from betel leaf may be used as an industrial raw material for manufacturing medicines, perfumes, mouth fresheners, tonics, food additives etc. (Guha, 2006).

In this review, the various therapeutic effects including antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, cardioprotective, radioprotective, anticancer, antidiabetic and analgesic properties of different bioactive components of betel leaf are highlighted.

2.PLANT PROFILE

The scientific classification of *Piper betel* Linn.

Kingdom- Plantae

Division- Magnoliphyta

Class- Magnolipsida

Family- Piperaceae

Genus -*Piper*

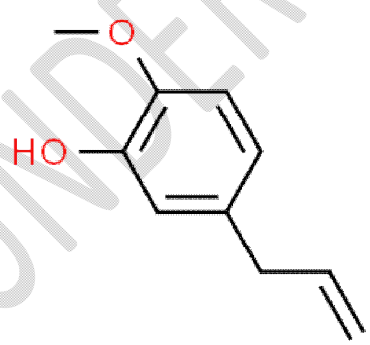
Species- *Piper betel*

Fig. 1: *Piper betle* leaf

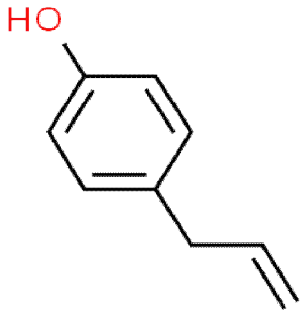
Fig. 2: *Piper betle* plant in the betel vine yard (locally known as *"Pana Baraja"*)

3.CONTENTS OF BETEL LEAF

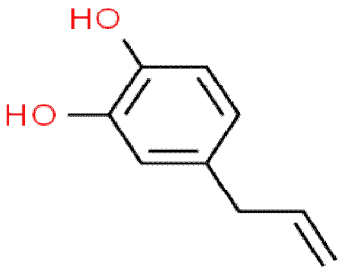
Piper betel contains a wide variety of biologically active compounds whose concentration depends on the variety of the plant, season and climate. The aroma of betel leaf is due to the presence of essential oils, consisting of phenols and terpenes. The various phytochemicals found in the betel plants are chavibetol, chavicol, hydroxychavicol, estragole, eugenol, methyl eugenol, hydroxycatechol, caryophyllene, eugenol methyl ether, cadinene, γ-lactone, allyl catechol, p-cymene, cepharadione A, dotriacontanoic acid, tritriacontane, p-cymene, terpinene, eucalyptol, carvacrol, sesquiterpenes, cadinene, caryophyllene, dotriacontanoic acid, hentriacontane, pentatriacontane, stearic acid, n-triacontanol, triotnacontane, piperlonguminine, allylpyrocatechol diacetate, isoeugenol, 1, 8-cineol, α-pinene, β-pinene, sitosterol, β-sitosteryl palmitate, γ-sitosterol, stigmasterol, ursolic acid, ursolic acid 3β-acetate (Rao et al., 1985) .



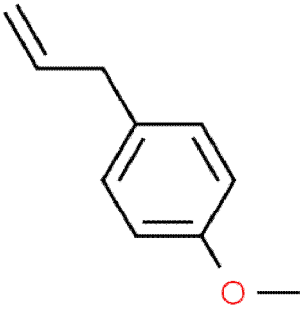
Chavibetol



Chavicol

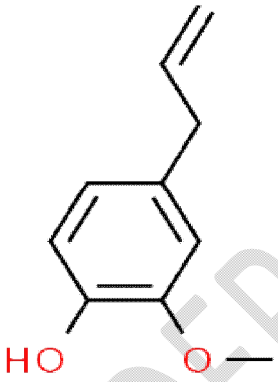


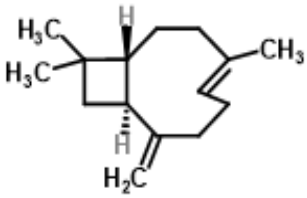
Hydroxychavicol



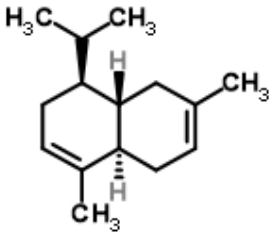
Estragole

Eugenol

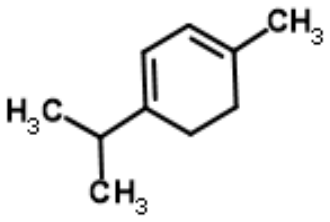




Caryophyllene



Cadinene



Terpinene

Fig.3*:* Structure of some of the constituents of the plant

4.TRADITIONAL ETHNOBOTANICAL USES OF *Piper betel*

The medicinal properties of pan were recognized long back during 600 A D when Ayurvedic system of medicine came into practice (Balasubramanyam, 1994). Betel leaf, also known as one of the grandmother's remedies, is prescribed as traditional medicine, by experienced, older members of the family. Betel leaves help to heal the following illnesses. Such as: -

4.1 Respiratory disorders: Betel leaves are useful in pulmonary infection in childhood and old age. The leaves, soaked in mustard oil and warmed, are applied to the chest to relieve cough and difficulty in breathing. (Madan et al.,2014).

4.2 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 is mixed with honey and taken to relieve irritating cough (Rathee et al., 2006).

4.3 Weakness of nerves: Betel leaves play a vital role in the treatment of nervous pains, nervous exhaustion and debility. The juice of a few betel leaves, with a teaspoon of honey, serve as a good tonic. A teaspoon of this can be taken twice a day for good results (Chopra et al.,1982).

4.4 Inflammation: When applied locally, betel leaves are beneficial in the treatment of inflammation such as arthritis and orchitis that is inflammation of the testes (Azuine et al.,1991).

4.5 Headache: 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 (Guha, 2000).

4.6 Boils: Betel leaf is also an effective remedy for boils. Here the 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 boilwill rupture draining all the purulent matter. The application should be made preferably at night and removed in the morning (Dohi et al., 1989).

4.7 Wounds: Wounds are referred to as disruption of normal anatomic structure and function (Patra et al., 2016). Wound healing is a very complex, multifactor sequence of events involving several cellular and biochemical processes (Patra et al., 2016). Betel leaves can be used to heal wounds (Nilugal et al., 2014). The juice of 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.

4.8 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 (Chopra et al.,1982).

4.9 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 (Guha, 2006).

4.10 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 (Rathee et al.,2006).

4.11 Filariasis: The paste of *Piper betel* leaves along with salt and hot water (not very hot) can be used for treating filariasis.

4.12 Obesity: It also helps in curing obesity when one *Piper betel* leaf is mixed with *Piper nigrum* and used for two months.

4.13 Piles: The leaves of this plant have proved to be extremely useful remedy for piles. First, the leaves are warmed. When they get soft, they are coated with castor oil layer. Now this oily leaf when applied to the inflammatory area, it yields better results. (Arambewla et al., 2005, Guha, 2006).

The betel leaves are nutritive and hold considerable quantity of vitamins and minerals and therefore, six leaves with a small bit of slaked lime are said to be equivalent about 300 ml of cow milk mainly for the vitamin and mineral nutrition.

5. MODERN MEDICINAL USES

5.1 Antibacterial activity

Piper betel Linn. leaf extract helps increase salivation in oral cavity. It thus increases peroxidases, antibodies and lysozyme in saliva which act against bacterial growth in mouth (Madhumita et al., 2020). Its leaf extracts have certain important phenolic constituents and essential oils which have anti-bacterial properties against many bacteria in oral cavity. Moreover, it has proven effects against bacteria *Vibrio cholera*. Further, its leaf extract also kills and inhibits outrageous bacteria which cause typhoid and tuberculosis etc., (Dwivedi and Tripathi., 2014). Research based study indicates that *Piper betel* is effective against following bacterial strains: *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Streptococcus pyogenes*, *Streptococcus mutans*, *Enterococcus feacalis*, *Fusobacterium nucleatum*, and *Prevotella intermedia* (Bangash et al., 2012).

5.2 Prevention of halitosis

Halitosis is defined as oral malodour or bad breath. It is caused by gingival cervical fluid, microbial degradation of proteins, amino acids, and peptides in saliva, and sometimes food retained on teeth because of no proper brushing. The leaves of *Piper betel* have been used traditionally for halitosis since long time. It has been proven by research-based study that it helps in prevention of bad breath and acts as breath freshener. For this purpose, its leaves are chewed either solely or along with other spices such as: clove, cardamom, cinnamon and areca nut (Ramji et al., 2002).

5.3 Antidiabetic activity

Studies show that the ethanolic and aqueous extracts of *Piper betel* leaves have marked antidiabetic activity. When its leaf extracts were used in streptozotocin-induced diabetic rats, it yielded better results by significantly lowering the blood glucose levels. This hypoglycaemic effect of betel leaves extracts was dose dependent and remained till four hours. Its extracts have also showed marked antihyperglycemic activity in glucose tolerance test (Madan et al., 2014).

5.4 Gastro protective activity

Piper betel Linn. has been used for curing gastric ulcers since long time. Gastroprotective action Pathogenesis of gastroduodenal ulcer is multifactorial, depending on the balance between exposure to offensive factors that cause damage to the mucosal lining and gastro protective mechanism that limit the injury (Zakaria et al., 2014). Damaging factors can be exogenous e.g., non-steroidal anti-

inflammatory (NSAIDs) and *Helicobacter pylori* infection which increases ROS formation, while endogenous factors include condition that leads to gastric hyper secretion (Zakaria et al., 2014). Gastro protective mechanism includes factors that contribute to the ability of ulcer to heal and produce protective mucous which has buffering capacity (Kumar et al., 2010). Antioxidant action also contributes to the protective role by scavenging oxygen radicals (Kumar et al., 2010). In experimental animals, NSAIDs are commonly used to induce gastric ulcer. In NSAIDs induced gastric ulcer, tissue damage can be measured through increase in the level of lipid peroxidation, extensive protein oxidation and reduction of the DNA tissue concentration (Bhattacharya et al., 2006). Healing capacity can be assessed by histological examination by measuring size and number of the ulcer formation, by using Alcian blue binding protein which measures mucous production and antioxidant levels (Bhattacharya et al., 2006). A study comparing between the ethanolic extracts of *P. betle*, *Emblica officinalis*, *Terminalia bellerica*, and *Terminalia chebula*, showed *P. betle* to possess the highest healing capacity in indomethacin gastroduodenal induced ulcers (Bhattacharya et al., 2006). Another study done in albino rats, showed healing effect following ten days of treatment with *P. betle* leaves extract. The histological examination showed the number of ulcers to be reduced proportionate to duration of the treatment while comparing with the untreated group (Majumdar et al., 2003). Lipid peroxidation, protein oxidation and DNA damage were reduced following *P. betle* treatment (Bhattacharya et al., 2006). Antioxidant enzymes such as SOD and catalase activities were increased following *P. betle* extract treatment. Similar findings were reported when allylpyrocatechol was given in indomethacin induced stomach ulcers (Banerjee et al., 2008). Hence, allylpyrocatechol is the most likely active component of *P. betle* which is responsible for its gastroprotective action.

5.5 Antiallergic activity

Piper betel ethanolic extracts show considerable antiallergic activity. Study shows that it affects the production of granulocyte macrophage-colony-stimulating factor (GM-CSF) and histamine. These are produced by murine bone marrow mast cells (BMMCs). Betel extracts have considerably decreased the production of GM-CSF and histamine by an IgE-mediated hypersensitive reaction. Therefore, it can be substantiated that betel offers great control of allergic diseases. It stops the production of allergic mediators (Wirotesangthong et al., 2008).

5.6 Antihypercholestrolemic effects

Piper betel has exceptional Antihypercholestrolemic effects. Hypercholesterolemia or hyperlipidaemia can be defined as increase cholesterol or lipid level in blood. It is a major risk factor in causing cardiovascular (CVS) disorders. It causes atherosclerosis; which ultimately leads to scores of CVS disorders. When hypercholesterolemic rats who possessed higher blood level of glucose, triglycerides, low density lipoproteins (LDL), and total cholesterol; were treated with betel extract up to 500 mg/kg orally for up to seven days, results were affirmative as cholesterol and other related parameters got better than before. Thus, the results showed the *Piper betel* extract's anticholesterolemic effects (Venkadeswaran et al., 2014).

5.7 Anti-inflammatory activity

Inflammation is the response of supporting and vascular elements of tissue to any sort of injury. Cardinal signs of inflammation include redness, swelling, heat, pain and loss of functions (Kumar et al., 2010). Inflammation serves as a protective mechanism against various harmful stimuli. However, excessive reaction leads to development of various inflammatory disorders (Serhan et al., 2010). Inflammation was induced in experimental animals by administration of noxious agents such as acetic acid and carrageenan to their paws and ears and the development of edema was measured (Romay et al., 1998). The rats which received *P. betle* extract showed significant reduction in the volume of the edema produced following administration of noxious agents (Alam et al., 2013). Prostaglandin E2 (PGE2) and nitric oxide (NO) are known to be potentiators of acute inflammation (Morimoto et al., 2014). In Freund's adjuvant induced model of arthritis in rats, extracellular NO production was observed to be decreased in murine peritoneal macrophage incubated with *P. betle* (Ganguly et al., 2007). In synovial infiltrate of patients with rheumatoid arthritis, it was observed, allylpyrocatechol reduced production of NO in infiltrate macrophages (Kundu et al., 2011). In lipopolysaccaride (LPS)-

induced production of NO and PGE2 in a murine macrophage cell line, allylpyrocatechol was shown to inhibit the production of both NO and PGE2 in a dose dependent manner (Sarkar et al., 2008). Allylpyrocatechol also reduced the inflammatory response of macrophages via inhibition of mRNA expression of iNOS, COX-2 and IL-12 p40 through down regulation of the nuclear factor-kappaB (NF-κB) pathway, indicating that allylpyrocatechol may have therapeutic potential in reducing inflammation. Allylpyrocatechol also significantly scavenged superoxide and hydroxyl radicals in infiltrated neutrophils (Kundu et al., 2011). *Piper betel* has significant anti-inflammatory activities too.

5.8 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.

5.9. Antifungal activity

Piper betel has an antifungal activity against *Candida albicans* (Sharma et al., 2009). The methanolic and aqueous extracts of *Piper betel* leaves showed potent activity against the yeasts of *Candida albicans* and *Malassezia pachydermatis* (Shalini et al., 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 et al., 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 et al., 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 et al., 2009).

5.10. Antioxidant action

Reactive oxygen species (ROS) are oxygen derived free radicals such as superoxide anions, hydroxyls radicals, alkoxyl and peroxyl (Circu and AW, 2010). At physiological level, it involves in intracellular signalling and regulations of cell functions, as redox messengers. Excessive production of ROS increases the activity of lipid peroxidation resulting in cellular damage and cell death. Antioxidant components, including the enzymes system, such as catalase and superoxide dismutase (SOD), and non-enzymatic system, including glutathione (GSH) may play a major role in reducing excessive ROS formation. Compared to human and animals, plants possess better antioxidant production mechanism thereby justifying their role for therapeutic purposes (Kumar et al., 2010). In vitro study of *P. betle* leaves, showed an increment in scavenging activities of 1,1- diphenyl-2-picrylhydrazyl (DPPH), superoxide and hydroxyl radicals with inhibition of lipid peroxidation (Rathee et al., 2006). In photosensitization-induced damage to lipids and proteins of rat liver mitochondria, *P. betel* ethanolic extract prove to be beneficial in preventing lipid peroxidation which was shown by the reduction in the level of Thiobarbituric acid reactive substances (TBARS), lipid hydroperoxide (LOOH) and conjugated diene (Bhattacharaya et al., 2006). The activity of SOD enzymes was increased in rats exposed to gamma radiation following 2 weeks administration of *P. betle* extract (Choudhury and Kale., 2002). Allylpyrocatechol, a phenolic compound of *P. betle* is reported to possess antioxidant properties by the reduction of phorbol-myristate-acetate-induced generation of ROS and superoxide anions, in murine peritoneal macrophages (Sarkar et al., 2013). Allylpyrocatechol also increased catalase and GSH of murine macrophages. Another phenolic compound of *P. betle*, hydroxychavicol also showed antioxidant activity by reducing lipid peroxidation as indicated by reduction of malondialdehyde (MDA) level (Sazwi et al., 2013) reactive substances (TBARS), lipid hydroperoxide (LOOH) and conjugated diene (Bhattacharaya et al., 2006). The activity of SOD enzymes was increased in rats exposed to gamma radiation following 2 weeks administration of *P. betle* extract (Choudhury and Kale., 2002). Allylpyrocatechol, a phenolic compound of *P. betle* is reported to possess antioxidant properties by the reduction of phorbol-myristate-acetate-induced generation of ROS and superoxide anions, in murine peritoneal macrophages. Allylpyrocatechol also increased catalase and GSH of murine macrophages. Another phenolic compound of *P. betle*, hydroxychavicol also showed antioxidant activity by reducing lipid peroxidation as indicated by reduction of malondialdehyde (MDA) level.

5.11 Hepatoprotective action

There are several models which have been used to induce hepatotoxicity, including cadmium, ethanol and carbon tetrachloride in experimental animals (Prabhu et al., 2012). Hepatotoxicity caused by these xenobiotics activates Kupffer cells to release ROS (Jaeschke et al., 2003). The liver also expresses many cytochrome P450 isoforms, including CYP2E1 which further generates ROS (Cullen, 2005). Xenobiotics cause uncoupling of oxidative phosphorylation in the mitochondria, which leads to increase in lipid peroxidation, DNA damage and altered calcium homeostasis. Treatment with *P. betle* extract significantly reduced lipid peroxidation products including TBARS, LOOH, protein carbonyl contents and conjugated diene (Prabhu et al., 2012). *P. betle* extract was reported to increase the antioxidant level of catalase, SOD, GSH. Allylpyrocatechol was postulated to be involved in hepatoprotective action.

5.12 Cardioprotective action

Cardial infarction occurs as a result of prolonged ischemic, from imbalance between increased oxygen demand and reduced blood supply (Smilowitz et al., 2015). ROS production during ischemia further damages the heart. Hence, the increment of antioxidant level may slow down progression of further infarction (Hertog et al., 1992). In rats with iso-proterenol (ISP)-induced myocardial infarction, pre-treatment with *P. betle* improved hemodynamic and ventricular function parameters (Smilowitz et al., 2015). It restored SOD, CAT, GSH, and GPx, level, reduced lipid peroxidation of the heart hence, reduced the leakage of CK-MB isoenzyme and LDH into the blood. Platelet hyperactivity which contributes to intravascular thrombosis is an important factor in the pathogenesis of cardiovascular diseases. Piperbetol, ethylpiperbetol, piperol A and piperol B isolated from *P. betle* leaves, showed

selective activity in inhibiting platelet aggregation induced by platelet activating factor (PAF) (Pisar et al., 2007).

5.13 Radioprotective action

Radiotherapy is the mainstay of cancer treatment, which aims to destroy cancer cells. However, damaging effect to normal tissue is unpreventable (Verma et al., 2004). Exposure to ionizing radiation increases mitochondria dependent ROS production, which increases lipid peroxidation (Verma et al., 2004). Treatment with *P. betle* decreases lipid peroxidation as indicated by the reduction in the level of TBARS, lipid hydroperoxide and conjugated diene (Bhattacharaya et al., 2006), Protective effect of *P. betle* is contributed by its phenolic constituents such as chavibetol and allylpyrocatechol, which were reported to possess radical scavenging activities.

5.14 As an anticancer agent

Contrary to general belief that betel leaves cause cancer of oral cavity, studies have amply proven the fact that *Piper betel* leaves have no such cancerous effects; rather, they possess anticarcinogenic and antimutagenic effects. It prevents oral carcinogenesis. As per standard data, globally, oral cancer has been ranked amongst one of the ten common cancers. Betel leaves have important phytochemicals which possess anticancer effects. Its leaf extracts help reduce tumour burden and is utilized to increase latency period of tumour. By combining its extracts with turmeric, it yielded positive results against cancer. It also helps prevent skin cancer. 75% of skin carcinoma is originated by basal cells and 15% accounts for squamous cells carcinoma. Studies show that by topical application of betel leaf extracts β-carotene and α-tocopherol, tumour formation can be reduced effectively. Moreover, betel leaf has also preventive effects in mammary cancers. Breast cancer is the second most common cancer in the world. It is the leading cause of cancer related death in women. Betel leaf extracts administration through mouth decreased tumour incidence and also tumour burden (Rai et al., 2011).

ROS is known to be cytotoxic and it has been implicated in the process of carcinogenesis. Excessive production of ROS plays an important role in the initiation and progression of cancer through DNA damage caused by lipid peroxidation (Waris and Ahsan, 2006). On the contrary, recent research that ROS may also have a beneficial role as a chemotherapeutic agent by inducing apoptosis. Interestingly, these dual effects showed that ROS can act both as carcinogenic and chemotherapeutic agent. While comparing with other Piperaceae family members, *P. betle* was shown to possess higher anticancer and antioxidant activities (Widowati et al., 2010). In vitro study using breast cancer cell line MCF-7 showed, *P. betle* ethyl acetate extract at 65µg/ml, had cytotoxic activity, which may be due to the increment of antioxidant activity thereby reducing ROS formation (Abrahim et al., 2012). Hydroxychavicol at 150mg/Kg body weight showed inhibition of growth and proliferation in human prostate cancer, PC-3 cells (Gundala et al., 2014). Hydroxychavicol derived from methanol extract showed apoptosis of CML cells via mitochondrial ROS-dependent endothelial nitric oxide synthase-mediated pathway (Chakraborty et al., 2012). Another study which used KB carcinoma cells, showed that low doses of hydroxychavicol possess antioxidant activity while at higher concentration, it induced apoptosis, inhibited growth and cell cycle progression (Chang et al., 2002).

5.15 Analgesic action

Based on mechanism of action, the analgesics can be divided into centrally acting drugs which involve the central nervous system and peripheral acting drugs which involve anti-inflammatory reaction (Olesen et al., 2012). In animal studies, hot plate was commonly used to assess centrally acting analgesic (Alam et al., 2013). While acetic acid-induced writhing test was commonly used to assess peripherally acting substance through inhibition of the pain mediator's production such as prostaglandin and bradykinin. Formalin test is a biphasic pain model having two peaks of pain response, where narcotic analgesic affect both phases equally while anti-inflammatory analgesic affect only the second phase (Shibata et al., 1989). Following administration of *P. betle* extract at 100

and 200 mg/kg body weight, it was shown that there was significant latency to pain response in hot plate test up to five hours, compared to the control group (Alam et al., 2013). Treatment with *P. betle* extract also significantly reduced number of writhing movement in acetic acid-induced writhing test. In formalin test, significant analgesic reaction was reported in both early and late phase following administration of *P. betle* extract. These pain models suggest that *P. betle* possesses both central and peripheral acting analgesic effects. *P. betle* contains high level of alkaloid. Hence, opiod receptors were proposed to be involved for its central analgesic effect. Concomitant administration of naloxone, an opiod antagonist, reduced analgesic effect produced by *P. betle* (Arambewala et al., 2005). Thus, to conclude the central action is contributed by the opiod receptors while the peripheral action is contributed by its anti-inflammatory action.

6. CONCLUSION AND FUTURE PROSPECTS

Betel plant contains various biologically active compounds, which are responsible for its numerous pharmacological actions. Further research may be performed to study the detailed mechanism of action of betel leaves in various metabolic activities in human, which will be beneficial to mankind. Identification of constituents in different landraces using modern gas chromatographic techniques could be useful for future elite landraces selection and their improvement programmes. At the same time efforts should be made on characterization of most of the available landraces which could be useful for resolving synonym problem and their proper authentication. In consideration of the proven therapeutic value of *P. betle,* proper characterization could be useful for long term research for drug development. Efforts are to be intensified towards obtaining promising landraces with high eugenol and chavibetol content. In addition to its bioactivity studies, attention may also to be addressed towards proper authentication of a particular landrace and their conservation for continuous supply. As plant secondary metabolites are always affected by soil and environmental factors it is also imperative to study the effect of abiotic factors on production and quality of betel vine. Further standardization of factors for quality and quantity of betel vine essential oil and extracts could be the future line of research before clinical trial and large commercial cultivation. Biotechnological intervention has opened up new horizon for genetic improvement, proper authentication and identification of elite chemotypes of this medicinally and economically important cash crop. Hence, further detail studies on leaf extract should be necessary for improving its uses for various medicine productions. Therefore, in the near future the standardization and stabilization studies on the leaf extract can be carried out which can help in improving its usage for varied medicinal purposes.

REFERENCES

Abrahim, N., N, Kanthimathi., M, S, Abdul, Aziz, A. (2012). *Piper betle* shows antioxidant activities, inhibits MCF-7 cell proliferation and increases activities of catalase and superoxide dismutase. ***BMC. Comp. Alt. Med***; 12(1):220.

Alam, B., Akter, F., Parvin, N. (2013). Antioxidant, analgesic and anti-inflammatory activities of the methanolic extract of *Piper betle* leaves. ***Avic. J. Phyto***.; 3(2):112.

Arambewala, LSR., Arawwawala, LDAM., Ratansooriya, WD. (2005). Antinocepative activities of aqueous and ethanol extract of *Piper betle* leaves in rats. ***J. ethnopharm***.; 102(2): 239- 245.

Azuine, M. A., Amonkar, A. J., Bhide, S. V. (1991). Chemopreventive efficacy of betel leaf extract and its constituents on 7, 12-dimethylbenz(a) anthracene induced carcinogenesis and their effect on drug detoxification system in mouse skin. ***Ind. J. Exp. Biol.***, **29**,346–351.

Balasubrahmanyam, V, Johri, J.K., Rawat, A.K.S., Tripathi R.D., and Chaurasia R.S. (1994) *Betel* vine (*Piper betle L.*). ***Nat. Bot. Res. Inst***., 24.

Banerjee, D., Bhattacharya, S., Bandyopadhyay, S.K., Chattopadhyay, S. (2008). Biochemical mechanism of healing activity of the natural phenolic, allylpyrocatechol against indomethacin induced gastric ulceration in mice. ***Digest. Dis. Sci***.; 53(11):2868-2877.

Bhattacharya. S, Mula. S, Gamre. S, Kamat. J.P, Bandyopadhyay. S.K, Chattopadhyay. S. (2006). Inhibitory property of Piper betle extract against photosensitization-induced damages to lipids and protein. ***Food Chem***, 1474-1480.

Chakraborty. Devjani, Shah. Barkha. (2011). Antimicrobial, antioxidative and anti-haemolytic activity of Piper betel leaf extracts. ***Int. J. Pharm. Pharm. Sci.*** 3,192-199

Chakraborty, J, B., Mahato, S.K., Joshi, K. (2012). Hydroxychavicol, a *Piper betle* leaf component, induces apoptosis of CML cells through mitochondrial reactive oxygen species dependent JNK and endothelial nitric oxide synthase activation and overrides imatinib resistance. ***Canc. Sci***.; 103(1):88- 99.

Chang, M, C., Uang, B.J., Wu, H, L (2002). Inducing the cell cycle arrest and apoptosis of oral KB carcinoma cells by hydroxychavicol: roles of glutathione and reactive oxygen species. ***Br. J. Pharmacol***; 135(3):619-630.

Choudhary, D., Kale, R.K. (2002). Antioxidant and non-toxic properties of *Piper betle* leaf extract: in vitro and in vivo studies. ***Phytotherapy. Res***; 16(5):461-466.

Chopra, R. N., Chopra, I. C., Handa, K. L., and Kapur, L. D. (1982). Chopra's indigenousdrugs of India. ***Cal. Acad. Pub***., **2**, (325–327).

Circu, M.L., Aw, T.Y. (2010). Reactive oxygen species, cellular redox systems, and apoptosis. ***Free. Rad. Biol. Med***; 48(6):749-762.

Cullen, J.M. (2005). Mechanistic classification of liver injury. ***Toxicol. Pathol***.; 33(1)6- 9.

Datta. Arani, Ghoshdastidar. Shreya, Singh. Mukesh. (2011). Antimicrobial Property of Piper betel Leaf against Clinical Isolates of Bacteria. ***Int. J. Pharm. Sci***. Res.2(3), 104-109.

Dohi, T, Terada, H, Anamura, S, Okamoto, H, and Tsujimoto, A. (1989). The anti-inflammatory effects of phenolic dental medicaments as determined by mouse ear edema assay**.** ***Jap. J. Pharm***., 49: 535-539.

E.S. Chauhan, J. Aishwarya, A. Singh, A. Tiwari. (2016). A review: Nutraceuticals properties of Piper betel (Paan***). Am. J. Phytomed. Clin. Ther***, 4: 28-41.

F.A. Bangash, A.N. Hashmi, A. Mahboob, M. Zahid, B. Hamid, S.A. Muhammad, Z.U. Shah, H. Afzaal. (2012). In-vitro antibacterial activity of Piper betel leaf extracts**. *J. App. Pharm.***, 3 :639- 646.

Ganguly. S, Mula. S, Chattopadhyay. S. (2007). An ethanol extract of *Piper betle* Linn. mediates its anti-inflammatory activity via downregulation of nitric oxide. ***J. Pharma. Pharmaco.***; 59(5):711-718.

Guha, P. (2000). Commercial exploitation of oil from betel leaves. IIT, Kharagpur, India: Agricultural and Food Engineering Department. (56-57).

Guha, P. (2006). Betel leaf: The neglected Green Gold of India. ***J. Hum. Ecol***.; 19(2): 87-93.

Gundala, S.R, Yang. C, Mukkavilli. R. (2014). Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis. ***Toxico. App. Pharmacol***.; 280(1):86-96.

Hertog, M.G, Feskens, E.J, Kromhout, D. (1992). Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. ***The. Lancet***; 342(8878):1007-1011.

Jaeschke, H., Gores. G.J., Cederbaum. A.I. (2003). Mechanisms of hepatotoxicity. ***Toxico. Sci***.; 65(2):166-176.

K. Venkadeswaran, A.R. Muralidharan, T. Annadurai, V.V. Ruban, M. Sundararajan, R. Anandhi, P.A. Thomas, P. Geraldine. (2014). Antihypercholestrolemic and antioxidative potential of an extract of the plant, Piper betle, and its active constituent, eugenol, in triton WR-1339-induced hypercholesterolemia in experimental rats. ***Evid. Comple. Alt. Med***.

Kundu. S, Bala. A, Ghosh. P. (2011). Attenuation of oxidative stress by allylpyrocatechol synovial cellular infiltrate of patients with rheumatoid arthritis. ***Free. Rad. Res***; 45(5):518-526.

Kumar. N, Misra. P, Dube. A, Bhattacharya. S, Dikshit. M, Ranade. S. (2010). Piper betle Linn. A maligned pan-Asiatic plant with an array of pharmacological activities and prospects for drug discovery. ***Curr. Sci***.; 99(7):922-932.

L.D.A.M. Arawwawala, L.S.R. Arambewela, W.D. Ratnasooriya. (2014). Gastroprotective effect of Piper betle Linn. leaves grown in Sri Lanka. ***J. Ayurve. Integ. Med***., 5 :38.

Madan, A, Balan, N, Barma, R.D, (2014). Reducing postharvest losses of betel (*Piper betle* L.) leaves by various preservation techniques. ***J. Agri***, 1(4):251-256.

Majumdar. B, Chaudhuri. S.G.R, Ray. A. (2003). Effect of ethanol extract of piper betle linn. leaf on healing of NSAID-induced experimental ulcer-A novel role of free radical scavenging action. ***Ind. J. Exp. Biol***; 41(4):311-315.

Md.Pisar, Mazura. Hashim, Nuziah. Ali, R.M. (2007). Evaluation of Piper betle on platelet activating factor (PAF) receptor binding activities. ***Malays. J. Sci***. 26.

M. Mahfuzul, H., Shemona, R., M. Asaduzzaman. S., Bari. M. L., Inatsu. Y., Kawamoto. S. (2011). Antibacterial Activity of Ethanol Extract of Betel Leaf (*Piper betle* L.) Against Some Food Borne Pathogens. ***Bang. J. Microbiol***, 28(2), 58-63.

M. Madhumita, P. Guha, A. Nag, Bio-actives of betel leaf (*Piper betle* L.): (2020). A comprehensive review on extraction, isolation, characterization, and biological activity. ***Phyto. Res***., 34 :2609-2627.

Morimoto. K, Shirata. N, Taketomi. Y. (2014). Prostaglandin E2–EP3 signalling induces inflammatory swelling by mast cell activation. ***J. Immuno***.; 192(3):1130-1137.

M.P. Rai, K.R. Thilakchand, P.L. Palatty, P. Rao, S. Rao, H.P. Bhat, M.S. Baliga. (2011). Piper betel Linn (betel vine), the maligned Southeast Asian medicinal plant possesses cancer preventive effects: Time to reconsider the wronged opinion. ***Asian. Pac. J. Cancer. Prev***, 12: 2149-2156.

M. Wirotesangthong, N. Inagaki, H. Tanaka, W. Thanakijcharoenpath, H. Nagai. (2008). Inhibitory effects of Piper betle on production of allergic mediators by bone marrow-derived mast cells and lung epithelial cells. ***Int. immune***., 8: 453-457.

Nagori. K, Singh. M.K, Alexander. A, Kumar. T, Dewangan. D, Badwaik. H. (2011). *Piper betle* L.: A review on its ethnobotany, phytochemistry, pharmacological profile and profiling by new hyphenated technique DART-MS (Direct Analysis in Real Time Mass Spectrometry). ***J. Pharm. Res***.; 4(9): 2991-2997.

Nalina. T, Rahim. Z. H. A. (2007). The crude aqueous extract of Piper betle L. & its antibacterial effects towards Streptococcus mutans. ***Am. J. Biotechnol. Biochem***, 3(1), 10-15.

Nilugal, K.C., Perumal, K, Ugander, R.E., Chittor, A.I., (2014). Evaluation of wound healing activity of *Piper betle* leaves and stem extract in experimental wistar rats. ***Americ J Pharm Tech Res***.; 4(3).

N. Ramji, R. Iyer, S. Chandrasekaran. (2002). Phenolic antibacterial from Piper betle in the prevention of halitosis. ***J. Ethnopharm***., 83: 149-152.

Olesen. A.E, Andresen. T, Stahl. C. (2012). Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. ***Pharmaco. Rev.;*** 64(3) :722-779.

Patra, B, Das, M.T. and Dey, S.K. (2016). A review on Piper betle L. ***J. Med. Pl. Stud.,*** 4(6), 185-192.

Prabhu. S.M, Muthumani. M, Shagirtha. K. (2012). Protective effect of Piper betle leaf extract against cadmium-induced oxidative stress and hepatic dysfunction in rats. Saud. J. Biol. Sci.; 19:229-239.

Rao, A, R, Sinha. A, Selvan. R.S. (1985). Inhibitory action of *Piper betle* on the initiation of 7.12-dimethylbenz[a] anthracene-induced mammary carcinogenesis in rats. ***Can. Lett***;26: 207-214.

Rathee. J.S, Patro. B.S, Mula. S. (2006). Antioxidant activity of Piper betel leaf extract and its constituents. ***J. Agri. Food. Chem***.; 54(24):9046-54.

Rawat, A. K. S., Tripathi, R. D., Khan, A. J., Balasubrahmanyam, V. R. (1989). Essential oil components as markers for identification of Piper betle L. cultivars. ***Biochem. System. Ecol.,*** *17*(1), 35-38.

Romay. C, Ledón. N, González. R. (1998). Further studies on anti-inflammatory activity of phycocyanin in some animal models of inflammation. ***Inflam. Res***.; 47(8):334-338.

Sarkar. D, Saha. P, Gamre. S. (2008). Anti-inflammatory effect of allylpyrocatechol in LPS-induced macrophages is mediated by suppression of iNOS and COX-2 via the NF-κB pathway. ***Int. immune***.; 8(9):1264-1271.

Sarkar. D, Kundu. S, De. S, Hariharan. C, Saha. P, Manna. A, Chatterjee. M. (2013). The antioxidant activity of allylpyrocatechol is mediated via decreased generation of free radicals along with escalation of antioxidant mechanisms. ***Phyto. Res***; 27(3): 324-329.

Sazwi, N.N, Nalina. T. Rahim. Z.H.A. (2013). Antioxidant and cytoprotective activities of Piper betle, Areca catechu, Uncaria gambir and betel quid with and without calcium hydroxide***. BMC. Comp. Alt. Med;*** 13(1):351.

Serhan. C.N, Ward. P.A, Gilroy. D.W. (2010). Fundamental of inflammation. New York: ***Camb. Univ. Press***; 1-39.

Goyat, Shalini. Grewal, Anita. Singh, Devendra. Katiyar, R. Tewari, Shri. Nainwal, Rakesh Bindu, K. (2016). Evaluation of Genetic Diversity of Piper betle cultivars using ISSR markers***. Int. J. Adv. Res***. 4. 571-579.

Sharma. S, Khan. I.A, Ali. I. (2009). Evaluation of the antimicrobial, antioxidant, and anti-inflammatory activities of hydroxychavicol for its potential use as an oral care agent. ***Antimicrob. Agen. Chemother***. 53(1):216–222.

Shibata. M, Ohkubo. T, Takahashi. H. (1989) Modified formalin test: characteristic biphasic pain response.; 38(3) 347-352.

Smilowitz. N.R, Naoulou. B, Sedlis. S.P. (2015). Diagnosis and Management of Type II Myocardial Infarction: Increased Demand for a Limited Supply of Evidence. ***Curr. Athero. Rep.;*** 17(2):1-7.

V. R. Balasubrahmanyam, A. K. S. Rawat. (1990). Betel vine (*Piper betel*, Piperaceae) ***Eco. Bot..***44: 540-543.

V. Dwivedi, S. Tripathi. (2014). Review study on potential activity of *Piper betle.* ***J. Pharmacogn. Phytochem***, 3: 93-98.

Verma. A, Kumar. N, Ranade. S (2004). Genetic diversity amongst landraces of a dioecious vegetatively propagated plant, betel vine (*Piper betle* L.). ***J. Biosc***. 29:319–328.

Walter. T.M, Sofia. H.N. (2007). Effect of consumption of thamboolam (conventional betel chewing) ***trad. Sid. med.***

Waris. G, Ahsan. H. (2006). Reactive oxygen species: role in the development of cancer and various chronic conditions. ***J. Carcino***; 5(1)14.

Widowati. W, Wijaya. L, Wargasetia. T.L. (2010). Antioxidant, anticancer, and apoptosis-inducing effects of Piper extracts in HeLa cells. ***J. Exp. Integ. Med***; 3(3):225-30.

Zakaria. Z.A, Balan. T, Suppaiah. V. (2014). Mechanism (s) of action involved in the gastroprotective activity of Muntingia calabura. ***J. Ethnopharmaco.***; 151(3):11