Review Article

Piper betel - not just a mouth freshener but also a miraculous herb for healing: A review article

ABSTRACT

Piper betle L., often known as betel vine, is a member of the Piperaceae family and is a significant cash crop for both economic and therapeutic purposes. The betle vine is most likely from Malaysia, while it is also grown in India, Sri Lanka, Bangladesh, Myanmar, and Nepal. It is grown in the districts of Balasore, Jagatsinghpur, Puri, Khordha, and Ganjam along Odisha's coast.With tremendous potential for creating jobs and improving the socioeconomic situations of rural people in India and other Asian nations, betel vine has enormous economic, medical, and nutraceutical value. However, there are still a number of significant elements of these plants that have not received enough consideration.Over a million people in Odisha use paan, yet most are not aware of its superior nutritional value. The most common chewing combinations for *Piper betel* include sliced areca nut, slaked lime, coriander, aniseed, clove, cardamom, sweetener, and coconut scrapings.Along with its traditional uses, Piper betel's therapeutic characteristics have the power to treat a variety of illnesses and lessen mouth cancer, which is actually brought on by sliced areca nuts and slaked lime rather than betel leaves. Betel leaves are a great source of vitamins, minerals, phytochemicals, antioxidants, protein, lipids, fibre, calcium, iron, and many other nutrients.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 one of nature's best medicines and is thought to be superior to medications. Additionally, the leaves retain an essential oil (EO) with a high eugenol content (1-3%), which is a popular ingredient in medicines, stimulants, antiseptics, tonics, and other ayurvedic formulations. The demand for its goods, such as herbal medications, treatments, and natural herbal formulations, has grown recently. Additionally, *Piper betel* aids in the treatment of a wide range of illnesses, including rheumatism, diabetes, hypertension, halitosis, boils and abscesses, obesity, voice issues, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, ringworm, gum swelling, and many others. The botanical description, geographic distribution, economic worth, cultivation, and ethnobotanical use of *P. betle* are all succinctly summarised in the current paper. According to the research, *P. betle* is a naturally occurring, safe, and orally active drug with significant therapeutic potential for treating a range of human medical disorders. To better understand its underlying molecular mechanisms of action, clinical features, structure-activity connections, bioavailability, and synergistic interactions with other medications, more research is still required.

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

1.INTRODUCTION

The perennial, evergreen creeper known as "Paan" is the betel leaf, which belongs to the Piperaceae family. It is a significant herb with documented therapeutic and recreational benefits. It also offers lots of conventional advantages. In Southeast Asia, it is grown. Although betel originated in Malaysia, it is now grown in Sri Lanka, India, Bangladesh, and a number of other countries (Rai et al., 2011).*Piper betel*is recognised for its traditional uses in medicine. Due to its extraordinary medical qualities, many people have been aware of its use for ages. Betel leaf significance has been discussed in regard to every aspect of human life, including social, cultural, and religious spheres, and it is still highly important today (Guha, 2006).In several Asian countries, betel has traditionally been chewed with areca nut, slaked lime, cardamom, and clove (Walter and Sofia, 2007). According to Nagori et al. (2011), betel leaf has a number of beneficial qualities, such as radioprotection, immunomodulation,

anti-inflammatory, anti-filarial, antibacterial, antifertility, and anti-hyperglycemia.Betel leaf has been referred to as an aromatic stimulo-carminative, astringent, and aphrodisiac since ancient times. An extract from betel leaves has a significant deal of potential to be employed in the creation of commercial products, according to scientific studies on this plant's leaf. The best tropical rain forests, including those in Indonesia, Malaysia, the Philippines, Thailand, Cambodia, Vietnam, and India, provide cool shade, significant humidity, and a sufficient supply of soil moisture for betel vine production.

After meals, *Piper betel* L. is frequently used for refreshment. Betel leaves are used in a variety of ways in the Indian medical and health systems. Betel leaf is frequently used as an antibacterial and topically applied to wounds and lesions in Indian folk medicine to promote healing. Betel leaf essential oil can be utilised as a raw material in the production of pharmaceuticals, fragrances, mouthwashes, tonics, and food additives, among other products (Guha, 2006).

In this review, many therapeutic effects of the various bioactive components of betel leaf are discussed. These effects include antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, cardioprotective, radioprotective, anticancer, antidiabetic, and analgesic characteristics.

2.PLANT PROFILE

The scientific classification of *Piper betel* Linn.

Kingdom- Plantae

Division- Magnoliphyta

Class- Magnolipsida

Family- Piperaceae

Genus -*Piper*

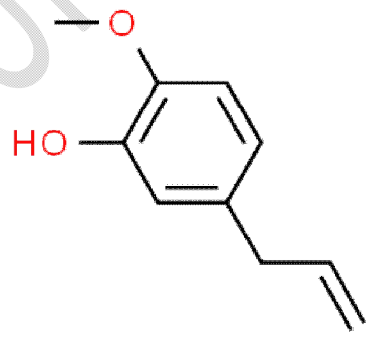
Species-*Piper betel*

Fig. 1: *Piper betle* leaf

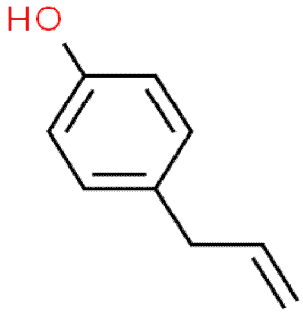
Fig. 2: *Piper betle* plant in the betel vine yard (locally known as *"Pana Baraja"*)

3.CONTENTS OF BETEL LEAF

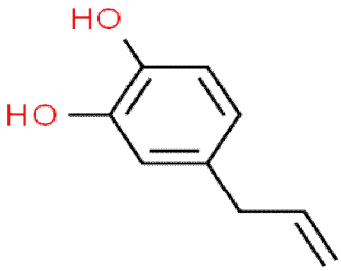
Terpene, Phenol, P-cymene, carvacrol, chavicol andits derivatives, allyl catechol,eugenol, estragol,oxalic acid, malic acid, amino acids etc. are found to be present in the betel leaves. The particular strong aromatic flavour of betel leaves is mostly caused by phenol and terpene compounds (Bajpai et al., 2010). The phenol content differs from plants to plants on the basis of their sexes. The total phenol content of the male plants is three times higher than that of the female plants. Even the quality of the leaf is affected by the phenol concentration. The glossier the leaf, the higher the phenol concentration (Bissa et al., 2007, Pradhan et al., 2013). Betel leaves also contain good amounts of vitamins, including nicotinic acid, ascorbic acid, and carotene. Aside from lysine, histidine, and arginine, betel leaves contain significant amounts of all other essential amino acids. Its aromatic flavour comes from the essential oil. The essential oil has a strong, scorching taste and an aromatic light-yellow liquid appearance. It contains chavicol, a phenol with powerful antiseptic properties. Theroot contains β-sitosterol(Joshi, 2009). The mid-region of the midrib of the vine possesses the highest of tannin. The highest amount of tannin is found in the mid region of the midrib of the vine.Betel leaves are very nutritious and rich in essential oil (EO), proteins, enzymes, vitamins and minerals (Nayaka et al., 2021).



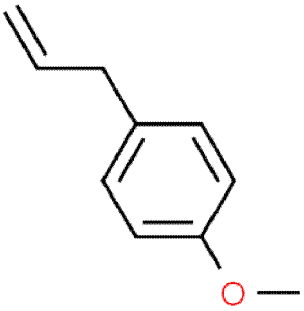
Chavibetol



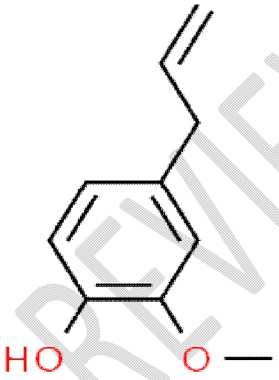
Chavicol

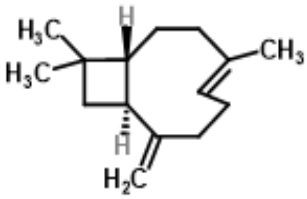


Hydroxychavicol

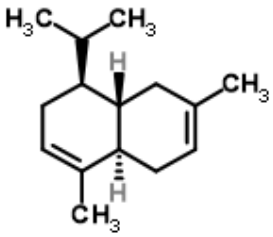


EstragoleEugenol

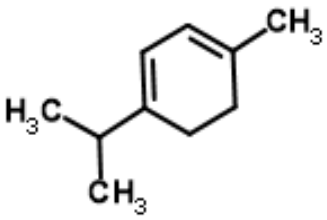




Caryophyllene



Cadinene



Terpinene

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

4.TRADITIONAL ETHNOBOTANICALUSES OF*Piper betel*

The therapeutic powers of pan were recognized during 600 A D when the Ayurveda medical system came into practice. One of the grandmother's remedies is betel leaf, which is prescribed as traditional medicine by experienced, older family members. The following illnesses can be healed using betel leaves. Such as: -

4.1 Respiratory disorders: Betel leaves are beneficial in treating pulmonary diseases in childhood and oldage. The leaves, soaked in mustard oil and warmed, can be applied to the chest to relievecoughand breathing difficulties(Madanet al.,2014).

4.2 Sore throat: Cough and sore throat can both be effectively treated at home with betel leaf. The leaves can be applied locally to soothe sore throats. The crushed fruit orberryshould bemixed with honeyandtakento treatirritatingcough(Ratheeet al.,2006).

4.3 Weakness of nerves: Betel leaves are essential in the treatment of nervous pains, nervousexhaustion and debility. A teaspoon of honey and the juice of a few betel leaves make a potent tonic. This can be taken twice daily with a teaspoon for best benefits**.**

4.4 Inflammation: Applying betel leaves locally can help treat inflammatory conditions like arthritis and testicular inflammation (orchitis**).**

4.5 Headache: A popular home remedy for headache is betel leaf. The betel leaf has cooling and analgesic qualities.To treat a severe headache, it can be applied over the painful area with positive results(Guha,2000).

4.6 Boils: Boils can be effectively treated with betel leaf as well.A leaf is gently warmed until it becomes soft and is then coated with a layer of castor oil. Over the inflamed area, the oiled leaf is applied. Inevery couple of hours, this leaf needs to be replaced. After a few applications, the boil will rupture draining all the pus-filled material.The applicationcan be made at nightandremovedin themorning.

4.7 Wounds: Disruption of normal anatomical structure and function is referred to as a wound(Patraetal.,2016). The process of healing a wound is an extremely complicated one that involves several cellular and biochemical processes (Patra et al., 2016). Wounds can be treated with betel leaves (Nilugal et al., 2014). The juice of a few leaves should be extracted andapplied on the wound.Then the area should be bandaged and wrapped in a betel leaf. The woundwillheal up with asingleapplication withintwodays.

4.8 Problem of breast milk secretion: The application of betel leaves smeared with oil is said tohelp insecretion ofmilk whenapplied onthe breastsduringlactation.

4.9 Scanty or obstructed urination: Juice made from betel leaves is said to have diuretic qualities. Its juice, when combined with diluted milk and slightly sweetened, helps in easingurination(Guha,2006).

4.10 Constipation: A suppository made of the stalk of betelleaf dipped in castor oil can be inserted into the rectum, in case of constipation in children. This immediately relieves constipation. (Ratheeetal.,2006).

4.11 Filariasis: Filariasis can be treated with a paste made from *Piper betel* leaves, salt, and warm (but not very hot) water.

4.12 Obesity: When one *Piper betel* leaf is combined with *Piper nigrum* and used for two months, it also aids in the treatment of obesity.

4.13 Piles: This plant's leaves have proven to be a very effective treatment for piles. The leaves are first warmed. They are covered with a layer of castor oil after they become pliable. Now, this oily leaf produces superior outcomes when applied to the inflammatory area(Arambewla et al., 2005, Guha, 2006).

5. MODERNMEDICINALUSES

5.1Antibacterial activity

Leaf extract from *Piper betel* Linn. promotes salivation in the mouth. As a result, salivary peroxidases, antibodies, and lysozyme levels rise, acting to inhibit oral bacterial development (Madhumita et al., 2020). Certain significant phenolic components and essential oils found in its leaf extracts have antibacterial activity against numerous microorganisms in the oral cavity. Additionally, it is effective against the *Vibrio cholera* bacteria. Additionally, its leaf extract slows and kills harmful bacteria that cause typhoid, tuberculosis, and other diseases (Dwivedi and Tripathi, 2014).Research based studies indicate that *Piper betel* is effective against the following bacterial strains: *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Salmonella enteritidis,Streptococcus pyogenes*, *Streptococcus mutans*, *Enterococcus feacalis*, *Fusobacteriumnucleatum*, and *Prevotella intermedia* (Bangash et al., 2012).

5.2 Prevention of halitosis

Oral malodour or poor breath is what is referred to as halitosis. It is brought on by salivary protein, amino acid, and peptide breakdown, gingival cervical fluid, and occasionally food that has been left on the teeth due to improper brushing. Halitosis has long been treated traditionally with *Piper betel* leaves. It has been demonstrated through research-based study that it aids in breath freshening and the prevention of foul breath. Its leaves are chewed for this purpose either on their own or in combination with other spices like clove, cardamom, cinnamon, and areca nut. (Ramji et al., 2002).

5.3 Antidiabetic activity

Nowadays, diabetes disorder is becoming more prevalent in human beings.It is a heterogeneous and metabolic disorder of carbohydrate, lipid and protein metabolismcharacterized by high blood glucose levels due to the absolute lack of insulin. Due tothis deficiency, body cells do not respond properly to insulin. Thus, several anti-diabeticdrugs,asamedicine,areusedtocontroltheincreasedbloodglucoselevelinthebody. According to some researchers, the oral administration of betel leaf suspension at 75and 150 mg/kg of body weight for 30 consecutive days to streptozotocin-induced diabetic rats causedasignificantreductioninbloodglucoseandglycosylatedhemoglobinlevel.Administering betel leaf to diabetic animals is also reported and, in this report, it was foundthat glucose 6-phosphatase and fructose-1, 6-bisphosphatase levels drop in the liver withan increase in hexokinase levels (Madan et al., 2014). Arambewela et al., (2005) examinedtheantidiabeticpropertyof*Piper betle*leaves.

5.4 Gastro protective activity

Since a long time ago, *Piper betel* Linn. has been utilised to treat stomach ulcers. gastrointestinal protection. The balance between exposure to aggravating stimuli that harm the mucosal lining and gastro protective mechanisms that prevent further injury determines the complex pathogenesis of gastroduodenal ulcers (Zakaria et al., 2014). Exogenous variables that enhance the production of ROS include NSAIDs and Helicobacter pylori infections, while endogenous factors include conditions that cause excessive stomach output (Zakaria et al., 2014). According to Kumar et al. (2010), the gastroprotective mechanism contains elements that affect an ulcer's potential to heal and the production of protective mucus with a buffering effect. By scavenging oxygen radicals, antioxidant activity also plays a protective role (Kumar et al., 2010). NSAIDs are frequently used to create stomach ulcers in lab animals. The extent of protein oxidation, the amount of lipid peroxidation, and the drop in DNA tissue concentration are all indicators of tissue damage in NSAID-induced stomach ulcers (Bhattacharya et al., 2006). Histological examination can be used to quantify the size and

quantity of ulcer formations, as well as mucus production and antioxidant levels using Alcian blue binding protein (Bhattacharya et al., 2006). When ethanolic extracts of *P. betle, Emblica officinalis, Terminalia bellerica, and Terminalia chebula* were compared, *P. betle* was found to have the highest potential for healing ulcers caused by indomethacin gastroduodenal injection (Bhattacharya et al. 2006). Following ten days of therapy with *P. betle* leaf extract, another trial conducted on albino rats demonstrated healing effects. When compared to the untreated group, the histological analysis revealed that the number of ulcers had decreased according to the length of the treatment (Majumdar et al., 2003). Following *P. betle* therapy, lipid peroxidation, protein oxidation, and DNA damage were decreased (Bhattacharya et al., 2006). Following treatment with *P. betle* extract, the activity of antioxidant enzymes including SOD and catalase increased. When indomethacin-induced stomach ulcers were treated with allylpyrocatechol, similar results were obtained (Banerjee et al., 2008). As a result, allylpyrocatechol is the *P. betle* compound that most likely exerts the gastroprotective effect.

5.5 Antiallergic activity

Ethanolic extracts from *Piper betel* exhibit strong anti-allergic properties. According to research, it has an impact on histamine and granulocyte macrophage-colony-stimulating factor (GM-CSF) production. These are created by murine BMMCs, or bone marrow mast cells. The generation of GM-CSF and histamine has been significantly reduced by betel extracts through an IgE-mediated hypersensitivity response. So, it is proven that betel offers excellent control of allergic illnesses. According to Wirotesangthong et al. (2008), it prevents the synthesis of allergy mediators.

5.6 Antihypercholestrolemic effects

On hypercholesterolemia, *Piper betel* has exceptional results. Hypercholesterolemia or hyperlipidaemia are terms used to describe elevated amounts of lipids or cholesterol in the blood. The probability of having cardiovascular (CVS) illnesses is greatly increased. The outcome is atherosclerosis, which is followed by numerous CVS issues. Betel extract was administered orally to hypercholesterolemic rats for up to seven days, and the results revealed improvement in cholesterol and other associated parameters. These rats' blood glucose, triglyceride, low density lipoprotein (LDL), and total cholesterol levels were greater. The results therefore showed that the Piper betel extract has anticholesterolemic effects (Venkadeswaran et al., 2014).

5.7 Anti-inflammatory activity

Inflammation is considered as a part of the complicated biologicalresponse of vascular tissues to potentially harmful stimuli like pathogens, damaged cells, etc. Anti-inflammatory is the activity that aids in the treatment of inflammation or swelling. Betel leafhas a significant role in the anti-inflammatory action which has been used as a household treatment for the oral cavity inflammation. Eugenol, the main component ofbetel leaf, also has anti-inflammatory properties in several animal models of research withvariousinflammogens.

5.8 Antimicrobial activity

Antimicrobial activity is the process of killing or inhibitingthe pathogenic microbes. Antimicrobial may be antibacterial, antifungal or antiviral. Betel leaf contains chavibetol, chavibetol acetate, chavicol, allylpyrocatechol, and allylpyrocatechol diacetate etc. Presence of these bioactive components is the primary cause for its antimicrobial effectiveness.A recent study by Roy and Guha (2018) reported the antimicrobial effectiveness, where nano emulsion made with betel leaf essential oil showed in-vitro inhibition of many foodborne pathogens, including *Escherichia coli, Bacillus cereus, Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebsiella pneumonia.* The EO, extracted from betel leaves, holds strong antimicrobial properties that lessen theadhesionofbacteria that cause earlydentalplaque(Punurietal.,2012).Eugenol,a significantcomponent extracted from *Piper betle* has strong antifungal activity against *Aspergillus flavus.* The extracts of the betel vine parts (stalks and stems) and the EO extracted from the leaves

also shown potent anti-fungal action and found to be effective at 450µg/ml concentration (Bandyopadhyay et al.,2006).Additionally, the aqueous and methanolic*Piperbetle*L.leafextractwereselectedtoanalysetheantibacterialactivityagainstsome selected microorganisms (Antimicrobial activity using10 gram positive, 12-gram negativebacteria and one fungalstrain, *Candida tropicalis*) and the methanolic extract wasfound tobe more effective at inhibiting the microbial strains(Nair& Chanda, 2008).Trakranrungsieetal. (2008) investigated the antimicrobial efficacy of crude ethanolic extracts of betel leavesagainst several zoonotic dermatophytes, including *Microsporum canis, Microsporum gypseum*and*Trichophyton mentagrophyte* and the yeast-like *Candida albicans*. The findings of that anti-microbialactivityexaminationrevealedthatbetelleavesextractshownmorepotentantifungalactivities, withanantioxidantactivitywith anaverageIC50valuesthatrangedfrom 110.44 to 119.00 lg/ml. Using the disk diffusion method, Row and Ho (2009) investigated the antimicrobial activity *of P. betle's* EO and solvent extract (methanolicandaqueousextracts)againsttheselectedyeastsincluding C. *chromatography-mass* and *M. pachydermatis*. Together with EO, the methanolic and aqueous extracts exhibited strong activity against the yeasts.

Four varieties of pan (Desawari, Desi, Bangladeshi and Jaleswar) were studied andreported by Agarwal et al.,2012. The findings described that the cold aqueous, methanolic,ethanolic and ethyl acetate extracts of dried leaves of all four varieties of *Piper betle* atconcentrationof500mg/mlweretestedagainstpathogenicmicroorganismslike*Pseudomonasaeruginosa,StaphylococcusaureusandEscherichiacoli*using the agarwelldiffusion method and discussed the antimicrobial screening on leaves of *Piper betl*e. Because of the high concentration of sterols, the results showed that all the extracts exhibited a clear zone of inhibition against all the bacteria. Moreover, the crude ethanol extract of *Piper betel*showedstrongantimicrobialactivityagainst*Pseudomonasaeruginosa,Klebsiellapneumonia,Proteusvulgaris*and*Staphylococcusaureus*(Dattaetal.,2011).(Khanand Kumar 2011) assessed the antibacterial efficacy of *Piper betle* leaf extracts (ethanolic andmethanolic) against pathogenic bacteria including *Escherichia coli*, *Pseudomonas aeruginosa*and *Staphylococcus aureus.* The methanolic extract was found to be more efficient thanethanolicextractagainstthepathogens studied. Also,threegram-positivebacteria(*Bacillus subtilis, Staphylococcus aureus, and Micrococcus luteus)*, and two gram-negativebacteria (*Escherichia coli and Pseudomonas aeruginosa)* were carefully chosen for the antibacterialactivity of aqueous and ethanol betel leaf extracts. Ethanol extract exhibited more significantandeffectiveantibacterialactionthanaqueousonesduetothepresenceofalkaloids,tannins,phenolicsubstances,andglycosides,etc.(Kavetietal.,2011).Also,theantibacterialeffectsofvariousdriedbetelleaves(Desawari,Desi,Bangladeshi,andJaleswar)extractswereassessedagainstpathogenicbacteria such as *Pseudomonasaeruginosa,Staphylococcusaureus,andEscherichiacoli*using theagarwelldiffusion method. The dried leaf extracts were obtained by cold aqueous, methanol (80%),ethanol (70%), and ethyl acetate (80%) solvent extraction technique. The findings discovered thatBangladeshi and Jaleswar varieties of betel leaf extract were an effective and good source ofherbal medicines with strong antibacterial activity (Agarwal et al., 2012). Ali et al., (2010) have demonstratedthat the Hydroxychavicol, extracted from the chloroform extraction of the aqueous leafextract of *Piper betle* L., was examined for its antifungal activity against 124 strains ofselectedfungi.

5.9. Antifungal activity

According to Sharma et al. (2009), *Piper betel* exhibits an antifungal action against *Candida albicans.* According to Shalini et al. (2016), the methanolic and aqueous extracts of *Piper betel* leaves were

highly effective against the yeasts *Candida albicans* and *Malassezia pachydermatis*. Because it contains non-polar chemical components, the *Piper betel* chloroform extract is more effective than the methanol fraction against dermatophytes (Trichophyton, Microsporum, and Epidermophyton) (Sharma et al., 2009). The antifungal properties of the *Piper betel* extract's hydroxychavicol showed fungicidal effects against all of the tested fungal species, including *Trichophyton rubrum*, *Candida* species, and *Aspergillus* species. The fungi *Candida albicans*, *Candida parapsilosis*, and *Candida tropicalis* displayed a reduced amount of adhesin synthesis when treated with betel crude aqueous extract, according to Wan Hinrazatul et al. (2013). These adhesins are essential because they enable the fungi to attach to host tissues and colonise a variety of substrates. According to Sharma et al. (2009), a crude essential oil was found to have a wide range of antibacterial activity against the tested pathogens, most notably *Candida albicans*, *Staphylococcus aureus*, and *Malassezia pachydermatis*. As it improves the permeability of fungal membranes, phenols (carvacrol) and phenilpropan (eugenol and chavicol) from *Piper betel* are demonstrated to display antifungal action (Sharma et al., 2009).

5.10. Antioxidant action

Antioxidants are molecules that protect our body from free radicals. Freeradicals are the compounds that harm our body if their levels become too high. Theyare connected to numerous diseases, including diabetes, heart disease and cancer. Free radicalreactions happening in the body are associated with neurological diseases and pulmonarydiseases also. These free radicals have a major role in the aging process. The antioxidant activity is another significant property of betel leaf.A large number of researchers have reported on it. It has been demonstratedthattheaqueousextractoftheinflorescenceof*Piperbetle*extractwaseffectiveinscavenging H_2O_2, superoxide radical and hydroxyl radical (Lei et al., 2003). It has also beendemonstratedthattheethanolextractsof the Bangla,sweet,andMysorevarietiesofbetelleafwere effective in scavenging DPPH radicals in vitro, with best effects being detected with theBangla variety (Rathee et al., 2006). Moreover, studies have revealed that the hydroalcoholic extractof the betel leaf has an in vitro nitrogen oxide scavenging activity (Jagetia et al., 2004).Moreover, it can help fight oxidative stress and eradicates free radicals by which it canprevent cancer (Rai et al., 2011). Ascorbic acid, as a powerful antioxidant, is very advantageous inlessening the levels of free radicals in the body and thus preventing cancer. Shah et al. (2016) also describedthatbetel leafextracts showedfreeradical scavengingactivity.

5.11 Hepatoprotective action

Cadmium, ethanol, and carbon tetrachloride are just a few of the models that have been used to cause hepatotoxicity in test animals (Prabhu et al., 2012). These xenobiotics' hepatotoxicity stimulates Kupffer cells, which then generate ROS (Jaeschke et al., 2003). Numerous cytochrome P450 isoforms, including CYP2E1, which contributes to the production of ROS, are also expressed in the liver (Cullen, 2005). The mitochondria's oxidative phosphorylation is decoupled by xenobiotics, which increases lipid peroxidation, damages DNA, and changes calcium homeostasis. Treatment with P. betle extract considerably decreased the levels of conjugated diene, TBARS, LOOH, protein carbonyl contents, and other lipid peroxidation products (Prabhu et al., 2012). It has been noted that P. betle extract raises catalase, SOD, and GSH levels of antioxidants. It was hypothesised that allylpyrocatechol played a role in hepatoprotective activity.

5.12 Cardioprotective action

The imbalance between increased oxygen demand and decreased blood supply, which results in prolonged ischemia, leads to Cardial infarction (Smilowitz et al., 2015). The formation of ROS during ischemia worsens the heart's damage. As a result, increasing the antioxidant content may prevent additional infarction from developing. Pre-treatment with P. betle improved hemodynamic and ventricular function measures in rats with iso-proterenol (ISP)-induced myocardial infarction (Smilowitz et al., 2015). It improved the levels of SOD, CAT, GSH, and GPx, decreased the heart's lipid peroxidation, and as a result, less CK-MB isoenzyme and LDH leaked into the blood. Cardiovascular disorders are mostly caused by platelet hyperactivity, which results in intravascular thrombosis. Piperbetol, ethylpiperbetol, piperol A, and piperol B, which were extracted from the leaves of P. betle, demonstrated specific action in suppressing platelet aggregation brought on by platelet activating factor (PAF).

5.13 Radioprotective action

The cornerstone of cancer treatment, which tries to eradicate cancer cells, is radiotherapy. However, it is impossible to avoid the detrimental effect on normal tissue (Verma et al., 2004). Ionising radiation exposure boosts the generation of mitochondria-dependent ROS, which boosts lipid peroxidation (Verma et al., 2004). According to Bhattacharaya et al. (2006), treatment with *P. betle* reduces lipid peroxidation as shown by the levels of TBARS, lipid hydroperoxide, and conjugated diene. P. betel's phenolic constituents, such as chavibetol and allylpyrocatechol, which have been reported to have radical-scavenging properties, contribute to this protective effect.

5.14 As an anticancer agent

Betelvinehasreportedcancerpreventiveeffects(Kudvaetal.,2018;Shuklaetal.,2018;Malkanietal.,2021;ChowdhuryandMarkus,2022).Anabundant sourceofcalcium,vitaminC,niacin,thiamine,carotene,andriboflavin,(Yinetal.,2009),betelleavesareundoubtedlyrelatedwithnutritivebenefits.Otherbetelphytochemicalsincludeallylpyrocatechol(APC;2-hydroxychavicol),4-hydroxycatechol,b-caryophyllene,methyleugenol,carotenes,starch,diastases,andanessentialoilcontainghydroxychavicol (Singlaetal.,2009).Hydroxychavicol,aphenoliccomponentquantitativelypresentatabout26%inbetelleaves,hasantiproliferativeactiononprostatecancer(Paranjpeetal.,2013).Hydroxychavicolhasalsobeendemonstratedtoobstructcell-cycle progression ofprostatecancerandoralKBcarcinomacells(Paranjpeetal.,2013). Someother research indicatesthathydroxychavicol,alsoknownasAPChasantiulcerogenic property and hasbeenshowntotreat indomethacin-inducedstomachulcerationleadingtogastriccancer(Bhattacharyaet al.,2005).Chlorogenicacid(ChA), anotheractivecomponent extracted frombetel leaves,hasbeentestifiedtoeradicatecancerouscellswithoutharmingnormalcells,unlikemostconventional chemotherapeutics(Guhaetal.,2006).Mouthcanceris one of thetenmostcommoncancers,with90%ofcasesoccurringinSoutheastAsia,where cigarette andsmokingbehaviorsarecommon(Jiangetal.,2019).Oneoftheearliestexperiments discoveredthattopicaltreatmentwithleafextractsinhibitedpinene-inducedmouthcancerinhamsters (TopraniandPatel,2013).Itwasalsofoundthatcombiningleafextractsandturmericintothedietarysupplementswasvery helpful.Theleafextractshave bothanti-proliferativeandpreventativechemicalpropertiesandcanthereforebeappliedtotreatseveralconditions includinghuman lungcancer (Banerjeeand Shah, 2014).

5.15 Analgesic action

According to their mode of action, analgesics can be classified as peripherally acting medications that affect the anti-inflammatory response or centrally acting medications that affect the central nervous system (Olesen et al., 2012). Hot plates were frequently utilised in animal research to evaluate centrally acting analgesics (Alam et al., 2013). While the generation of pain mediators such as prostaglandin and bradykinin are inhibited during the acetic acid-induced writhing test, which is frequently used to evaluate substances with peripheral action. According to Shibata et al. (1989), the formalin test is a biphasic pain model with two peaks of pain response. Narcotic analgesics influence both phases equally while anti-inflammatory analgesics primarily effect the second phase.It was discovered that there was a considerable latency to pain response in the hot plate test after *P. betle* extract administration at 100 and 200 mg/kg body weight, compared to the control group (Alam et al., 2013). In the acetic acid-induced writhing test, treatment with *P. betle* extract also markedly decreased the number of writhing movements. Following administration of *P. betle* extract in the formalin test, a strong analgesic effect was noted in both the early and late phases. According to these pain models, *P. betle* has analgesic properties that work both centrally and peripherally. *P. betle* has a high alkaloid content. As a result, it was suggested that opiod receptors were implicated in its central analgesic impact.Naloxone, an opiod antagonist, was administered concurrently with P. betle and diminished its analgesic efficacy (Arambewala et al., 2005). As a result, it can be said that the opiate receptors contribute to the central activity, while its anti-inflammatory effect contributes to the peripheral action.

6.CONCLUSION AND FUTURE PROSPECTS

The betel plant's diverse pharmacological effects are caused by a variety of physiologically active chemicals. It may be possible to do additional research to elucidate the precise mechanisms through which betel leaves affect various human metabolic processes. The selection of future elite landraces and their improvement plans may benefit from the identification of constituents in various landraces using contemporary gas chromatographic techniques. The majority of the landraces that are now available should be characterised in order to solve the synonym problem and properly authenticate them. Proper characterization could be helpful for long-term study for drug development in light of the P. betle's demonstrated therapeutic efficacy. To get potential landraces with high eugenol and chavibetol content, efforts must be stepped up. In addition to its bioactivity research, consideration may also be given to correct landrace authentication and their preservation for ongoing supply. Studying the impact of abiotic factors on the production and quality of betel vine is essential since soil and environmental factors always affect plant secondary metabolites. Prior to clinical trials and extensive commercial production, additional standardisation of parameters for quality and quantity of betel vine essential oil and extracts may be the focus of future research. The use of biotechnology has created new opportunities for genetic advancement, accurate authentication, and identification of elite chemotypes of this economically and medicinally significant cash crop.Therefore, more in-depth research on leaf extract should be required to enhance its applications in the creation of diverse medicines. As a result, investigations on the standardisation and stabilisation of the leaf extract can be conducted soon, which will serve to improve its application for a variety of medical applications.

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