

An overview of Betel vine (*Piper betle* L.): Nutritional, pharmacological and economical promising natural reservoir

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Abstract: With its magnificent green heart-shaped leaf, the betel vine (*Piper betle* L.) is also known as Paan in India. It is a member of the Piperaceae family. It is cultivated in the coastal regions of Odisha (Balasore, Jagatsinghpur, Puri, Khordha, and Ganjam). Paan is consumed by over 1 million people throughout the state, but they are unaware of its high nutritional quality. It is considered superior to pharmaceuticals and is one of the best remedies in nature. It has anti-microbial, anti-apoptotic, anti-cancer, antioxidant, and anti-inflammatory attributes. Furthermore, the leaves retain eugenol-rich essential oil (EO) (1-3%), which is the hotspot for medication, stimulants, antiseptics, tonics, and other ayurvedic compositions. This oil can also be used as an industrial raw material to make medications, fragrances, tonics, mouth fresheners, food additives, and other products. It contains anticarcinogens, which show potential for the development of medicines against cancer treatment. Betel plant farming is an agricultural activity that provides a source of income for remote farmers. Sometimes economic crises occurred due to the development of diseases such as foot rot, leaf spot, powdery mildew, and collar rot. Most farmers got seasonal revenue, whereas betel vine cultivation provided year-round income from a tiny plot of land.

1. Introduction

The betel vine (*Piper betle* L.) belongs to the Piperaceae family, which also contains pepper and kava. Paan leaves are produced in the Philippines, Malaysia, India, Sri Lanka, Taiwan, Thailand, and other Southeast Asian countries as a post-meal mouth freshener. It is primarily consumed in South Asia and by certain Asian emigrants worldwide as betel quid or paan, in combination with areca nut or tobacco (Saraswat *et*

al., 2020; Shah *et al.*, 2021). A sheaf of betel leaves is typically presented in Odisha as a token of respect and auspicious beginnings in traditional culture. It belongs to the genus *Piper* of the Division Magnoliophyta, Class Magnolipsida, Order Piperales, and Family Piperaceae. It is a unisexual perennial evergreen climber with shiny cardio leaves and white catkins that bloom in the spring. Betel vine is categorized into odorous and non-pungent kinds depending on the form, length, and flavour of the leaf. The plant's leaves are basic and have an acuminate crown. Mostly, the leaves are smooth and shining. The leaves differ in color from light green to dark green. The leaves are long-stalked with 2-3 pairs of secondary veins (Swapna *et al.*, 2012). The betel plant's limbs usually bulge at the nodes and are completely smooth. Female spikes are cylindrical, whereas male spikes are pendulous. Female spikes measure 2.5-5.0 cm in length. In the humid environment of East India, female plants often generate blooms or fruit (Sengupta and Banik, 2013; Rahman *et al.*, 2020).

Throughout thousands of years, nature has provided a reservoir of medical substances, and current medications are derived from ecological resources. The betel leaves contain a variety of bioactive compounds and are employed in ancient medical methods. Such leaves are high in minerals, vitamins, enzymes, proteins, and essential oil (EO), and they are very nutritious (Nayaka *et al.*, 2021; Paswan *et al.*, 2021). They also include certain useful therapeutic components for the therapy of disorders of the brain, liver, and cardiac (Pradhan *et al.*, 2013; Ullah *et al.*, 2020). Polyphenols, alkaloids, steroids, saponins, and tannins were also found. In the Indian subcontinent, medicinal plants are a resource of economical worth (Sen and Chakraborty, 2017; Madhumita *et al.*, 2020). Medicinal plants are the primary source of medicine for the bulk of the rural community in emerging nations, and consequently play a key role in their health systems (Patra *et al.*, 2014; WHO, 2019). Upto 80% of people in developing countries still use local medicinal herbs for their basic health care needs (Sen and Chakraborty, 2017; WHO, 2019). Furthermore, diastase and catalase activities are detected in the leaflets (Abrahim *et al.*, 2012; Shah *et al.*, 2021). It assists in curing and treating many conditions, including halitosis, boiling and absceding, conjunctivitis, headache, constipation, hysteria, itching, mastitis, leucorrhoea, otorrhoea, mastoiditis, gum swelling, ringworm, rheuma-

tism, abrasions, injuries, cuts, etc (Shukla *et al.*, 2018). Because of their antibacterial and antioxidant properties, these oils have a promising future in the novel food packaging industry (El Asbahani *et al.*, 2015; Guha and Nandi, 2019; Nguyen *et al.*, 2021), as well as being a prospective and appealing flavouring component for the food and beverage sectors.

This plant is grown as a cash crop in the Balasore, Jagatsinghpur, Puri, Khordha, and Ganjam areas of coastal Odisha (Jena, 2021). In Assamese/Urdu/Hindi/Odia/Bengali, the betel leaf is recognised as Paan, whereas in Sanskrit it is considered as Taambuul and Nagavalli. The finest betel leaf is the "Magadhi" type cultivated near Patna in Bihar, India. The popular type of betel leaf in Kerala is called "Venmony Vettilla" and comes from Venmony near Chengannur (Guha and Nandi, 2019). In Odisha, four distinct forms of betel leaf are grown. The Bhograi block in the Balasore district is known throughout the country for its betel vine farming (Patra and Pradhan, 2018). Cultivars with the prefix Desi in their names, on the other hand, always relate to the cultivars Desavari in Madhya Pradesh, Kapoori in Maharashtra, Bangla in West Bengal (Guha and Nandi, 2019), Bali and Chandrakana in Bhogarai (Fig. 1 A1-A2, B1-B2). The varieties are Nova Cuttak, GodiBangala (Fig. 1 C1-C2), Sanchi (Fig. 1 D1-D2), and Birkoli. Only one type, GodiBangala, is grown by the locals in the research region Bhainchigodi (Patra and Pradhan, 2018). Odisha is one of the states that produce the most betel vine. In the context of such scientific research, this review article tries to summarise all the possible information on betel leaf with its propagation, socio-economics, and bioactive compounds, justifying wider possibilities for its use as a natural source for people in Coastal Odisha.

2. Habitat and Ecology

Betel vine is primarily grown in Odisha's coastal districts such as Balasore, Jagatsinghpur, Puri, Khordha, and Ganjam (Jena, 2021). All the respective district locations are as follows. 20.27°N and 86.17°E, 19.48°N and 85.48°E, 20.18°N and 85.62°E, 19.38°N and 85.05°E (Fig. 2). North-Western highlands, the inner alluvial plain, and the coastal belt are the three geographical regions that can be found in all five districts. Those regions are flooded with brackish water from estuarine rivers, making them unsuited for agriculture in a regular manner. Those lands are current-

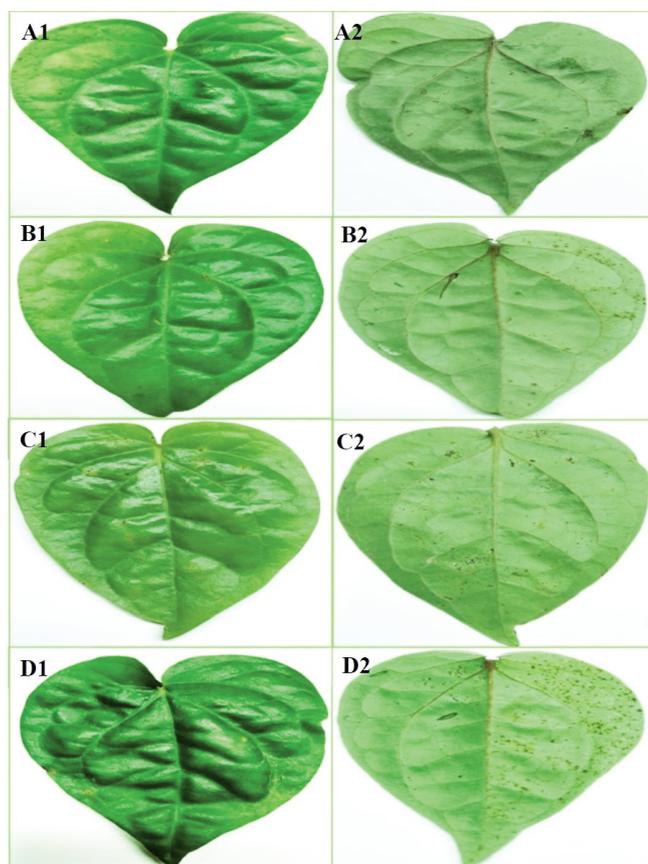


Fig. 1 - Major varieties of *Piper betle* (A1) ventral and (A2) dorsal side of 'Bali', (B1) ventral and (B2) dorsal side of 'Chandrakana', (C1) ventral and (C2) dorsal side of 'Godi Bangala', (D1) ventral and (D2) dorsal side of 'Sanchi' cultivated in coastal region of the Odisha.

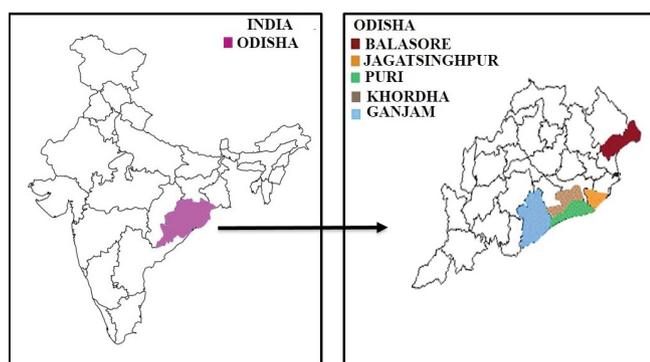


Fig. 2 - Map showing the study sites of coastal Odisha (Balasore, Jagatsinghpur, Puri, Khordha and Ganjam district).

ly used for betel and coconut agriculture (Ahuja and Ahuja, 2011). Recently, prawn culture and salt production units have sprouted in this region. Paddy, fish, and betel vine farming are important parts of the local economy in these districts. The soil in the central zone is mostly sandy loam and clay loam,

making it perfect for producing rice and betel vines (Kaleeswari and Sridhar 2013). Coastal Odisha has an oceanic climate and experiences rainfall from the south-west monsoon (Gouda *et al.*, 2017). The coast-line area has a pleasant temperature. The summers in such districts are hot, having excessive humidity during the monsoon season, a dry winter, and little diurnal temperature fluctuation over the year (Krishnan *et al.*, 2020). The district's average annual precipitation is 1591 mm, which is over 9% greater than Odisha's average. Tropical cyclones, which bring a lot of rain to the area, are responsible. Due to the district's proximity to the Bay of Bengal, cyclones are common. Cyclones, which begin in the Bay of Bengal over the Andaman and Nicobar Islands and proceed towards India's east coast, are a common occurrence in the district (Sahoo and Bhaskaran, 2016). The South-West monsoon brings more than 70.9% of the annual precipitation from June to September. The three distinct seasons observed in the area are summer (March-June), rainy (July-October), and winter (November-February) (IMD, 2020).

3. Cultivation and propagation in coastal Odisha

This plant's cultivation needs consistent soil wetness, adequate humidity, and moderate heat, which are not usually present in the ecological environment (Filipovic, 2020). Variations in these environmental variables were found to be harmful to the plant. As a result, it is grown in an artificially manufactured hut-like structure that keeps the plant's growth parameters within a reasonable range, simulating natural ecological conditions (Raza *et al.*, 2019). The building is known as a 'Baraja,' and is made up of various plant materials like (*Bambusa vulgaris* Sch. ex Wendl.) and Bamboo stems (*Bambusa bambos* L. Voss.), jute (*Corchorus capsularis* L.), paddy straw (*Oryza sativa* L.) (Fig. 3 A-B), Khadi or Chae stick, and coconut leaves (*Cocos nucifera* L.) make up the Baraja architecture (*Arunda donox* L.) (Haider *et al.*, 2013). The structure's proportions are limited to 2 to 3m in height, 10 to 20 m in length, and 5 to 15 m in breadth. The plant is grown through vegetative proliferation from cuttings of 3 to 5-year-old vines. Plantlets with one or two nodes and connected leaves are commonly used as propagating specimens. The planting season varies depending on the area to area. It takes roughly a month for roots to develop and grow after planting. Plants are supported when

they have 5-7 leaves. After one year of plating, harvesting begins by plucking the leaves. The harvests are known locally as Maghei paan, Jhanji paan, Vejua paan, Nua paan, and Jagannath paan. Nua paan is harvested during the months of February and April. Cultivators remove dry or damaged leaves during this plucking period. Jhanji paan is harvested between May and mid-July. This is the season with the highest yield. Cultivators are removing some broken Khadi or Chae sticks this season. During the months of August and September, Jagannath paan is collected. Farmers strategically gather the leaves from the lowest section of the branches during this plucking. During the months of October and November, Vejua paan is collected. Cultivators pick the tops of branches in this plucking technique. Maghei paan harvesting begins in December and continues until February (Patra and Pradhan, 2018). All total leaves are plucked in this collection. Farmers sprinkle water on leaves and use cotton sheets or paddy straw to keep them fresh. A "Pono" is made up of eighty paan leaves. After that, the leaves are distributed in local markets or transferred to other towns (Haider *et al.*, 2013).



Fig. 3 - Cultivation and propagation of *Piper betle* inside the Baraja at Bhograi area of Balasore district, Odisha (A-B).

4. Nutritional composition of betel leaf

Ayurveda, or traditional Indian medicine, has long been a part of Indian culture and 'Herbal Materia Medica. The ancient Sanskrit books 'Charaka and Sushruta Samhita' (600-400 B.C.) document betel leaf chewing, establishing its identity as an old use. "Charaka and Sushruta Samhita," "Astanga

Hridayam," "Bhabaprakasha," "Harivamsa," "Varahapurana," and "Panchatantra and Jataka Stories" are among the Sanskrit writings that allude to it as "tamabool" (Kumar, 1999). In Asian countries, this plant is a frequent element in the creation of various indigenous medicines. In comparison to related Indian traditional plants such as "tulsi" (*Ocimum sanctum*), for example, this plant has received very little research aside from strong ethnomedicinal promises (Cohen, 2014; Kurepa and Smalle, 2021). Nayaka *et al.* (2021) revealed that the betel leaves contain many ingredients such as water (80-90%), EO (0.05-0.2%), fat (0.5-1.0%), protein (3-4.5%), riboflavin (4.5-15.5 µg/100 g), fibre (2-2.5%), minerals (2.5-3.5%), chlorophyll (0.05-0.25%), tannin (0.1-1.3%), vitamin C (0.005-0.01%), carbohydrate (0.5-6.5%), vitamin A (2-3 mg/100 g), nicotinic acid (0.65-0.9 mg/100 g), potassium (1.5-4.5%), thiamine (10-80 µg/100 g), iron (0.005-0.01%), phosphorus (0.05-0.06%), nitrogen (2.0-7.0%), calcium (0.2-0.5%), iodine (3-3.5 µg/100 g) respectively (Madhumita *et al.*, 2019). Fresh betel leaves contain minerals 2.3-3.3%, protein 3-3.5%, fat 0.4-1.0%, moisture 85-90%, carbohydrate 0.5-6.10%, fibre 2.3%, calcium 0.2-0.5%, phosphorus 0.05-0.6%, iron 0.0050-0.07%, vitamin C 0.005-0.01%, and energy 44Kcal per 100 g (Mazumder *et al.*, 2016; Vernekar and Vijayalaxmi, 2019). After dehydration, the betel leaf samples became a concentrated source of nutrients, according to the results of the nutritional analysis. The findings support those of (Subhash and Neeha, 2014), who found that after sun drying and cabinet drying, the leaves preserved high levels of protein, fibre, and calcium. The moisture material of dehydrated betel leaves flour was 9.45%, fat 1.10%, protein 3.30%, ash 6.87%, carbohydrate 63.92%, fiber 10.15%, vitamin C, calcium, and iron were 1.11%, 2.57%, and 1.53% (Chauhan and Aishwarya, 2016; Akshata *et al.*, 2018).

5. Phyto-chemicals found in betel leaf

The phytochemicals screening was analyzed on the ethyl alcohol extract of betel vine using standard protocol for identification of the constituents. The leaf extracts have various pharmacological activities which are prepared by using different solvents such as aqueous, ethanol, powder, and hot water (Kumari and Rao, 2015) (Table 1 and Table 2). By this analysis, it was concluded that it consists of Tannins, Anthraquinones, Flavanoids, Alkaloids, Terpenoids,

Table 1 - Components of *Piper betle*

Sl No.	Components of <i>Piper betle</i>	Percentage of components (%)	References
1	1.8-cineol	0.04	Rajamani <i>et al.</i> , 2016
2	α -pinene	0.21	Pradhan <i>et al.</i> , 2013
3	Allypyrocatechol diacetate	0.71-6.2	Mazumder <i>et al.</i> , 2016; Sakinah <i>et al.</i> , 2020
4	Allypyrocatechol monocetate	0.23	Junairiah <i>et al.</i> , 2018
5	Campene	0.48	Junairiaha <i>et al.</i> , 2020
6	Caryophyllene	3.71	Pradhan <i>et al.</i> , 2013; Junairiaha <i>et al.</i> , 20
7	Chavicol	0.4	Pradhan <i>et al.</i> , 2013; Sakinah <i>et al.</i> , 2020
8	Chavibetol	53.1-80.5	Junairiaha <i>et al.</i> , 2020; Azahar <i>et al.</i> , 2020
9	Chavibetol acetate	11.7-15.5	Pradhan <i>et al.</i> , 2013
10	Chavibetol methyl ether	0.48	Mazumder <i>et al.</i> , 2016; Junairiaha <i>et al.</i> , 2018
11	(E)-caryophyllene	0.4	Pradhan <i>et al.</i> , 2013; Sakinah <i>et al.</i> , 2020
12	Eugenol	0.32-0.4	Junairiaha <i>et al.</i> , 2020
13	β -pinene	0.21	Pradhan <i>et al.</i> , 2013; Junairiah <i>et al.</i> , 2018
14	Methyl eugenol	0.4	Rajamani <i>et al.</i> 2016; Junairiaha <i>et al.</i> , 2020
15	Methyl salicylate	0.05	Pradhan <i>et al.</i> , 2013
16	Saprobe	0.11	Shameem <i>et al.</i> , 2013
17	U-limonene	0.14	Akther <i>et al.</i> , 2014

Saponins, Caediac glycosides, Glycosides, Reducing sugars (Rajamani *et al.*, 2016). The compounds reported in betel plants include Bisabolene, Cavacrol, Isoeugenyl acetate, Eugenol methyl ether, 2-Mono palmitin, Allypyrocatechol, Eugenol, Piperitol, Chavibetol, Chavibetol acetate, Myrcene, Quercetin, Hydro-xychavicol, Stearic acid, Allyl catecol, Germacrene-A, α -terpineol, Luteolin, Caffeic acid, Limonene, Piperlonguminine, α -cadinol, β -sitosterol, 4-allyl phenyl acetate, D- limonene, m-Cymen-8-ol, 2-noanone, Ocimene, N-decanal, 2-undecanone, Allo ocimene, Sabinene, 3-allyl-6-methoxyphenol, Humlene, Cymene, Terpinolene, β -pinene, α -Myrcene, Allyldiacetoxy benzene, Vanillin, Thymol, Cispiperitol, Terpinolene, Propcatechuic acid, Eucalyptol, Gallic acid, Iso eugenyl acetate, (E)- β Damascenone, Linalool, Camphene, 4 cineole, α -pinene, Germacrene-D, Piperol-B, Piperol-A, Estragol, Arecoline, Isoeugenol, Isoascaridole, Chavicol, Ellagic acid, Safrole, Eugenyl acetate, 4-allyl phenol, 5- Indanol, 4-allyl resorcinol, α -bergamotene, (E)- β -ocimene, Ferulic acid, Carryophyllene, Anethole, α -farnesene, Cephadradione-A, Piperine, 4E-decadienamamide, 4-Allyl anisole, Cuparene, β -iso safrole, α muurolene, Cadinene, α -copaene, α -cubebene, Benzene acetic acid, α -selinene, Methylpiperbetol (Pradhan *et al.*, 2013; Mazumder *et al.*, 2016; Junairiah *et al.*, 2018; Junairiaha *et al.*, 2020; Sakinah and Misfadhila, 2020; Azahar *et al.*, 2020) (Fig. 4, Table 1).

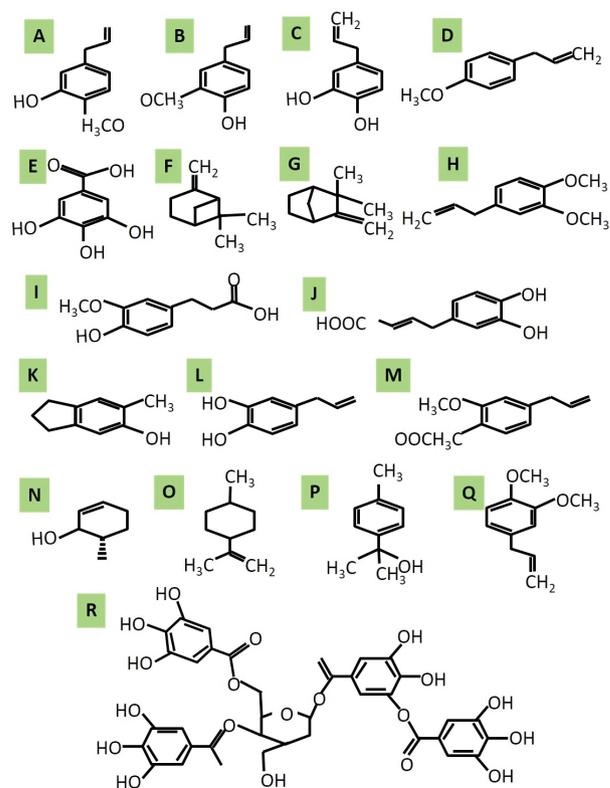


Fig. 4 - Structure of major bioactive constituents of *Piper betle* a) Chavibetol, b) Eugenol, c) Hydroxychavicol, d) Estragol, e) Gallic acid, f) β -pinene, g) Camphene, h) Allyl diacetoxy benzene, i) Ferulic acid, j) Caffeic acid, k) 5-Indanol, l) Allopyrocatechol, m) Chavibetol acetate, n) Piperitol, o) D-limonene, p) α -terpineol, q) Eugenol methyl ether, r) Quercetin (Flavonoids).

6. Pharmacological activities

Paan is healthy and significant because of its medical, religious and ceremonial history (Rai *et al.*, 2011). Asthma is also prevented, vocalisation is improved, and gums are strengthened. Indigestion, constipation, congestion, cough, and asthma are treated (Peddapalli *et al.*, 2020). The anti-alzheimer bioactive compounds were found in various varieties of betel vine (De *et al.*, 2021). The following biochemical roles of phytochemicals from leaves are depicted in figure 5.

Possible source of wound healing agents

Betel vine component at 0.025 ml/l concentrations boosted fibroblast reproduction and encouraged umbilical cord-mesenchymal stem cells (UCMSCs) proliferation at 0.03 ml/l, increasing *in vitro* model wound healing in accordance with empirical evidence. The homogenate reduces the presence in

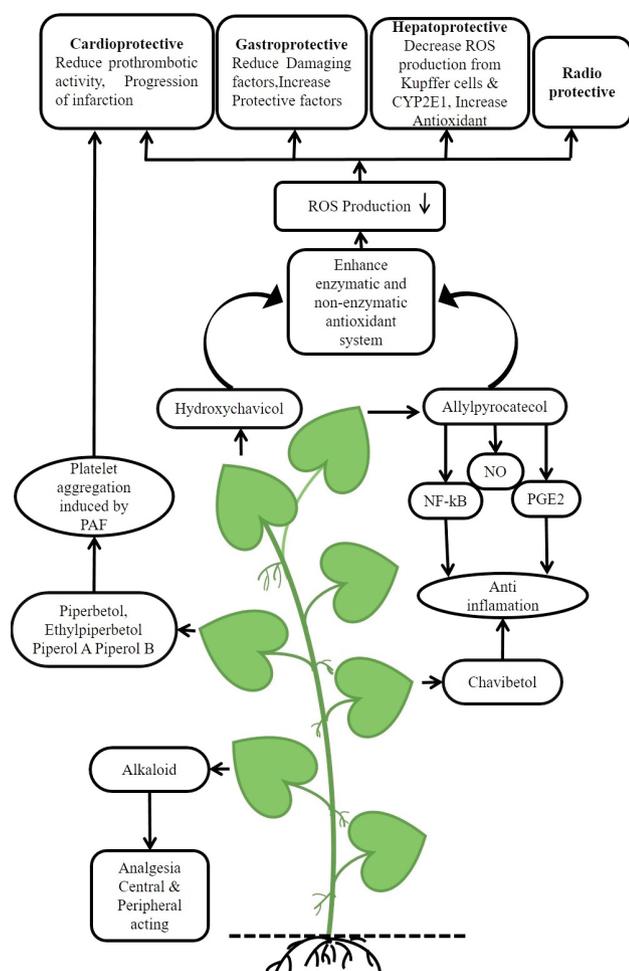


Fig. 5 - Various biochemical activities of phytochemicals extracted from *Piper betle*.

cells of oxidative stress factors such as VCAM, CD248, and IL-33, so that recovery of umbilical cord cells can be accelerated (Thi *et al.*, 2021). Researchers discovered that natural lysates of leaves containing phenolic compounds can reduce the activity of inflammatory factors and oxidative stress, which could be useful in regenerative medicine.

Insecticidal activity

The crucial oil extracted from the sheets of betel vine was examined on the corn weevil (*Callosobruchus maculatus* F.) and the beetle (*Sitophilus zeamais* M.) and has been suggested as a potential crop protective agent (Nair and Kavrekar, 2017). Piperaceae EO has been extensively researched for its larvicidal role in mosquito larvae control (Huong *et al.*, 2019; Alves *et al.*, 2021). *Piper permucronatum*, *Piper arboreum*, *Piper gaudichaudianum*, *Piper marginatum*, *Piper longum*, *Piper humaytanum*, and *Piper aduncum* EO have the ability to regulate *Aedes aegypti*, *Anopheles gambiae*, and *Culex quinquefasciatus* (Santana *et al.*, 2015; Takeara *et al.*, 2017; Silva *et al.*, 2019; Durofil *et al.*, 2021). *Piper aduncum* was found to be larvicidal, killing *Aedes aegypti* mosquito larvae at concentrations of 500 and 1000 ppm (Oliveira *et al.*, 2013; Martianasari and Hamid, 2019). Within a few days of being exposed to similar amounts of *Piper marginatum* EO, 100% of *Aedes aegypti* larvae died (Santana *et al.*, 2015; Marques and Kaplan, 2015). The EO of betel vine has regulated the population as well as various stages of mosquito (*Aedes aegypti*) and acts as an alternative bioinsecticide (Martianasari and Hamid, 2019).

Antimicrobial activity

The antibacterial properties of the EO obtained from the leaves are impressive (Prasetya *et al.*, 2021). They prevent bacteria from adhering to initial tooth plaque (Punuri *et al.*, 2012). The antifungal activities of magahi variant betel leaf EO were investigated by (Madhumita *et al.*, 2019; Madhumita *et al.*, 2020). Towards *Aspergillus flavus*, the minimum level of EO inhibition (MIC) from leaves was found to be 0.8 ml/l Chavicol, allylpyrocatechol diacetate, chavibetol acetate, propenylphenols, hydroxychavicol, and chavibetol are some of the aromatic compounds discovered in the chloroform extracts (Aliahmat *et al.*, 2012). Antibacterial properties against *Proteus vulgaris*, *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pyogenes*

were investigated (Chakraborty and Shah, 2011; Patra et al., 2014; Nayaka et al., 2021) (Table 2). The drug was used as a solution against chosen pathogens such as *Streptococcus pyogenes*. Additionally, antifreeze action was evaluated on pathogenic microorganisms, such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (Lubis and Marlisa, 2020; Nayaka et al., 2021; Nguyen et al., 2021) for several species of dried betel leaves (Desawari, Desi, Bangladesh, and Jaleswar). Cold aqueous, methanol (80%), ethanol (70%), and ethyl acetate (80%) solvent removal techniques were achieved for the dried leaf extract. It has been shown that the variety of Bangladeshi and Jaleswar betel leaf extracts are a potent and efficient source of antibacterial herbal medicines (Agarwal et al., 2012; Valle et al., 2021). The ethanol compound from betel leaves appeared to be quite active at preventing the

proliferation of harmful pathogens such as *Staphylococcus aureus*, *Vibrio cholerae*, and *E. coli* (Hoque et al., 2011; Valle et al., 2021). The combination of betel and red betel exhibited reduced action against *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus epidermidis* (Hartini et al., 2018). The model influence of betel leaf EO of 'Meetha' was explored by (Basak, 2018) on the *Aspergillus flavus* germination period and the population spore of *Penicillium*.

Antigiardial assay

Giardiasis is regarded by humans worldwide as the most frequent protozoan diarrheal illness. Researchers have sought out novel, herbal medicines that might replace commercial pharmaceuticals with unpleasant potential side effects in the treatment of giardia (Nazer et al., 2019). The betel vine extracts

Table 2 - Different therapeutic activities of *Piper betle* extract

Sl No.	<i>Piper betle</i> extract	Function	Result	References
1	Aqueous extract	Antimicrobial activity in different microorganism by disc diffusion method. Antihemolytic and Antioxidative activity in <i>Staphylococcus aureus</i> , <i>Streptococcus pyogenes</i> , <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i>).	The bacteria were effectively inhibited by aqueous extracts. The high content and combined action of flavonoids and polyphenols were linked to the antioxidative and antihemolytic properties.	Rai et al., 2011; Shameem et al., 2013
2	Spray dried powder extract	Antidiabetic activity in diabetes mellitus patients.	Piper betle, as a nutraceutical, has been identified as a possible therapy for type 2 diabetic patients.	Chakraborty and Shah, 2011
3	Aqueous and ethanol extract	Antibacterial Activity in gram positive bacteria such as <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> and <i>Micrococcus luteus</i> and also gram negative bacteria like <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i> by Agar diffusion method.	According to the findings, both aqueous and alcoholic extracts are potent against bacteria types that are major causes of illnesses.	Arawwawala et al., 2011
4	The hot water extract	Gastroprotective activity.	Due to its antioxidant and mucin-protecting characteristics, the study found that it can protect against indomethacin-induced stomach ulcers.	Kaveti et al., 2011
5	The methanolic extract	Anti-inflammatory and analgesic efficacy in Swiss albino mice and Wistar rats in a carrageenan-induced hind paw edoema model, as well as hot plate, writhing, and formalin tests.	The dosage considerably increased the pain threshold in the hot plate technique, significantly decreased the writhing generated by acetic acid, and dramatically inhibited carrageenan-induced paw edoema.	Pradhan et al., 2013
6	The <i>Piper betle</i> plant extract	Antifertility activity in female rats.	According to the findings, betel extract had antifertility and antiestrogen effects in female rats.	Akther et al., 2014

containing methanol, tetrahydrofuran, and water have the potential of anti-diarrheal activities (Peckova *et al.*, 2017). It has been examined for its physiological and pharmaceutical properties, but its significance for *Giardia intestinalis* has yet to be proven. Various solvents for extract preparations have been utilized in investigations of these effects. They discovered a significant reduction in cyst shedding in the group of gerbils administered with the aqueous solution that matched the most relevant settings. The anti-adhesive effects on vasodilatory activities (Runnie *et al.*, 2004), antioxidant effects, early settlers (Aara *et al.*, 2020), and antihepatotoxicity have already been demonstrated with aqueous excerpts of *Piper betel*.

Antidiabetic activity

More troublingly, the increase in the incidence of diabetes has an impact not only on advanced countries but also on emerging nations that have less money to deal with another serious illness burden again. Present diabetes therapies can have side effects, so the move now to herbal remedies is more effective, cheaper, less risky, and less side-effective. The present information reveals that the juice of the betel vine has assurance for antidiabetes. Betel vine leaves have been examined in induced diabetes rats (CEE), normoglycaemic, and streptozotocin (STZ) with anti-diabetic action assessed by oral hot water and ethanol extract (HWE) (Khatun *et al.*, 2016; Arawwawala *et al.*, 2011). Blood glucose levels were dose-dependent in both HWE and CEE in normoglycaemic rats. During the glucose tolerance process, both extracts considerably lower the external glucose load. HWE has an antidiabetic action comparable to CEE. Both extracts have not been harmful and tolerated since prolonged oral administration (No open evidence of renototoxicity, and hepatotoxicity). Moreover, the weight of the spleen was increased in treated groups, indicating lymph regenerative effects (Khatun *et al.*, 2016). Betel leaf extraction is a useful anti-diabetic feature that enables blood sugar levels to be regulated. This investigation discovered betel vine extracts lowering the blood glucose level by the activation of insulin/biomimetic action and have a possible therapy for type-2 diabetic patients (Arawwawala *et al.*, 2011) (Table 2). Increased transaminase activity (SGPT and SGOT) has been found in several investigations in liver and serum diabetic rats (Ramachandran *et al.*, 2012).

Gastroprotective activity

Extraction of betel vine was also found to be mediated gastro defensive activity, resulting in (i) an increase in the production of mucus and/or bicarbonate, (ii) a decrease in the amount of stomach acid secreted, or (iii) a decrease in gastric acidity (Arawwawala *et al.*, 2014; Ahmed *et al.*, 2021). The leaf extracts have marked gastroprotective properties which are shown by the strong ($P \leq 0.05$) inhibition of gastric lesions caused by absolute ethanol (in terms of duration and number) (Arawwawala *et al.*, 2014). CEE gastric activity was comparable with HAE activity. The existence of alkaloids, flavonoids, steroids, saponins, and tannins has been seen by a phytochemical sampling of betel vine (Syahidah *et al.*, 2017; Altemimi *et al.*, 2017). Polyphenols, especially tannins, are antioxidant phytochemicals and can protect against indomethacin-induced stomach ulcers (Neyres *et al.*, 2012; Zakaria *et al.*, 2015; Sharifi-Rad *et al.*, 2018; Ahmed *et al.*, 2021) (Table 2). The antiulcerogenic properties of these compounds were also shown by their protein-prone and blood pressure effects. Powerful gastroprotective behaviors were demonstrated (Berenguer *et al.*, 2006). Thus, the gastroprotective effect can also be influenced by secondary metabolites, such as alkaloids, saponins, tannin, flavonoids, and other phenolic compounds (Barbosa *et al.*, 2019).

Anti-asthmatic effect

Betel vine's antioxidant, anti-inflammatory, and antihistamine activity have been linked to a wide range of diseases (Alam *et al.*, 2013; Aara *et al.*, 2020; Ahmed *et al.*, 2021; Clemen-Pascual *et al.*, 2022). The anti-asthmatic activity of betel vine in guinea pigs has been tested (Misra *et al.*, 2014). Asthma is the tracheobronchial smooth muscle's hyper reactance to a multitude of stimuli (Chapman and Irvin, 2015). Bronchitis is a chronic inflammatory disease. Bronchial asthma may be caused by free radicals and superoxide (Phaniendra *et al.*, 2015; Boukhenouna *et al.*, 2018). Histamine has the potential to produce bronchoconstriction (Yamauchi and Ogasawara, 2019). The extract can substantially minimize the impact of bronchial asthma, but it has fewer effects than di-phenylhydramine. But other mediators such as leukotriene play a vital part in asthma in humans. Betel vine has been reported to have the ability to reduce bronchial asthma in guinea pigs, despite its weak influence on human asthma (Darvhekar *et al.*, 2011; Misra *et al.*, 2014; Rekha *et al.*, 2014; Ahmad *et*

al., 2021).

Role of betel leaf extract in thyroid disease

Ethylacetate *Piper betle* L. (EPBL) extract administration reverted the T4-induced rise in serum thyroid hormones, heli marker enzymes, MDA, and LOOH, but improved antioxidant enzyme activity and decreased the content of glutathione. Lighter results from liver histology show that the EPBL administration has enhanced twisted hepatic tissue architecture in hyperthyroid species. Analysis of the mass-spectroscopy of high-resolution liquid chromatography showed the presence of four primary glycosides, including quercetine, rutin, kaempferol, and luteoline. The antithyroidism of EPBL was seen to be caused by hyperthyroidism induced by T4. EPBL's antithyroid and antioxidant properties may be attributable to the existence of extracted flavonoid glycosides in hyperthyroid animals which may have blocked the secretion of the thyroid hormone and translation of T4 into T3 by 5'DI inhibitors (Panda et al., 2018).

Anticancer activity

Anti-cancer agents with antioxidant activities may provide their beneficial effects by balancing ROS, such that cancer cells do not proliferate when apoptosis is not allowed to occur (Abraham et al., 2012). Chronic inflammation is the root cause of many human diseases, including cancer and tumors, according to experimental and clinical research (Kangralkar and Kulkarni, 2013). The betel leaf was used for irritation in the mouth cavity as a typical folk medication. Mouth cancer is among the ten most common cancers, with 90% of cases occurring in Southeast Asia, where cigarette and smoking behaviors are common (Jiang et al., 2019). One of the earliest studies (Toprani and Patel, 2013) discovered that topical treatment with leaf extracts inhibited - pinene-induced oral cancer in hamsters. It was also discovered that combining leaf extracts and turmeric into the dietary supplements was beneficial. *Curcuma manga*, *Dendrophthoe pentandra*, *Piper betle* L., and *Catharanthus roseus* extracts in breast cancer cell lines were explored as anti-cancer and radical free scavenging power (Widowati et al., 2013; Rekha et al., 2014). Betel vine has reported cancer preventative effects (Kudva et al., 2018; Shukla et al., 2018; Malkani et al., 2021; Chowdhury and Markus, 2022). Supplementing leaf extract with potable water significantly reduced the concentration of benzo (a)

pyrene-induced neoplasia of the forestomach. The leaf extracts contain anti-proliferative and preventative chemical potential and can thus be utilized to treat several conditions, including human lung cancer (Banerjee and Shah, 2014).

Cardioprotective action

Acute myocardial infarction is caused by an imbalance between raised oxygen demand and decreased blood supply caused by prolonged ischemia (Smilowitz et al., 2015). During ischemia, the heart is further damaged by the formation of ROS. As a result, increasing antioxidant levels may help to prevent future infarction (Munzel et al., 2017; Zhou et al., 2018). Pre-treatment with betel vine enhanced hemodynamic and ventricular function parameters in rats with isoproterenol (ISP)-induced myocardial infarction. It restored SOD, CAT, GSH, and GPx levels, decreased lipid peroxidation of the heart, and therefore lowered CK-MB isoenzyme and LDH leakage into the blood (Arya et al., 2010). Platelet hyperactivity, which leads to intravascular thrombosis, is a key component in the development of cardiovascular disorders (Kaur et al., 2018; Alkarithi et al., 2021).

Anti-malaria activity

As compared to the well-known insect deterrent citronella oil, EO provided greater resistance against mosquito bites from *Anopheles stephensi* and *Culex fatigans* (Johirul et al., 2016). The oil provided greater than 4h of resistance from *Anopheles stephensi* and *Culex fatigans* when sprinkled at a rate of 20l/cm², whereas citronella oil provided only 2.2 and 2.6h of protection, correspondingly. As a result, the power of paan to resist mosquitos has been established (Pal and Chandrashekar, 2010; Ibrahim et al., 2017; Cang et al., 2020).

Antioxidant activity

Many researchers have investigated the antioxidant activity of extracts using a variety of solvents and extraction times (Alam et al., 2012; Aliahmat et al., 2012). The properties of the leaf extracts from various solvents were determined using high-performance liquid chromatography to calculate the oil-water partition coefficient (HPLC). Due to their high oil-water partition coefficient, leaf phenolics have been shown to be less polar than other phenolic antioxidants. The investigation showed that the solvent extraction and the period for preparing betel leaf extract (petroleum ether, methanol, water,

and ethyl acetate) for use as a natural antioxidant are crucial acts against four different harmful bacteria, such as *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Proteus vulgaris*, have been investigated by Chakraborty and Shah (2011), Lubis and Marlisa (2020) Nayaka *et al.* (2021), and Nguyen *et al.* (2021). Others were isolated from these extracts, with few recognized and unknown metabolites. Various analytical methods such as NMR, Mass Spectroscopy, and IR Spectroscopy have been used for structural investigation. TBARS and DPPH methods conducted anti-oxidative investigations. Abdullah *et al.* (2015) found antioxidant betel vine extract activity and its components. 1-1-diphenyl-2-picrylhydrazyl (DPPH) demonstrated that the Bangla variety of betel vine is the best antioxidant that can be combined with total phenol contents and lower the strength of these respective extracts in a test for ethanol extracts of three varieties (Bangla, Sweet, and Mysore) of *Piper betle* L. (Swapnil *et al.*, 2014; Sarma *et al.*, 2018). Bangla extract column chromatography resulted in chavibetol (CHV), allylpyrocatechol (APC) separation, and corresponding glucosides. Similar chemical characteristics of three *Piper betles* were identified after HPLC analysis (Abdullah *et al.*, 2015).

7. Marketing and socio-economic status

Around 15 to 20 million Indians regularly eat betel leaves, and there are an estimated 2 billion betel leaf consumers worldwide, proving the crop's enormous economic potential (Jeng *et al.*, 2002). As for national employment generation, an estimated 15million people in India depend on betel leaf production, processing, handling, transportation, and selling as a source of income (Jana, 1995). It has been reported that these varieties of betel leaf, such as Nova Cuttak, Godi Bangala, Sanchi, and Birkoli, are grown in coastal Odisha. Barajas' construction, annual maintenance, leasing costs, and input costs like labor and fertilizers are included in the cost of betel leaf production, which are essential for their crop propagation. Throughout the observation phase, each seasonal and annual money expenditure in a Barajas in coastal Odisha was examined. Patra and Pradhan (2018) reported that US\$ 474.20 and \$ 596.70 were invested for watering and irrigation for one year. However, it is too costly for a cultivator. As a result,

some cultivators are unable to hire labor and must rely on their own manpower to irrigate their crops. As a result, they are no longer charged for watering labor, and their annual financial investment is merely \$ 122.50. As a result, excluding irrigation and watering costs, the cultivator paid \$ 21.00, \$ 21.08, \$ 51.37, and \$ 7.90 for each harvesting in a year. Cultivators have spent a lot of money on their traditional agriculture in the hopes of getting a high return on their investment from the local market. However, the area is well-known for its betel vine agriculture, and the market price is quite low. As a result, growers sell their crops through a middleman. Thus, Cultivators can earn money from two different sources. Paan's annual income from the local market is \$ 131.72, with a middleman fee of \$ 172.92, and income from the local market per harvesting is \$ 16.47, \$ 24.70, \$ 32.93, \$ 32.93, and \$ 24.70. Annual market prices varied depending on the purity of the paan. The local market rate was higher in the winter season, at \$ 32.93, in the rainy season, at \$ 24.70, and in the summer season, at \$ 16.47, i.e. cheaper in all seasons. People worked 360 days a year in a paan Baraja, plus 26 days of minor work within the Baraja. Laborers take five vacations each year, all of which are self-initiated. Its economic operations are now restricted to the local and national levels (Patra and Pradhan, 2018). In tropical nations, cash crops such as cocoa, cola nuts, coffee, citrus fruits, and other high-income-generating crops were more highly valued than the production of betel vine. Several unidentified infections and insects harm betel vine cultivation, resulting in significant losses for growers (Vishwakarma and Purohit, 2020). Another issue is seedling transportation. It happens when seedlings are damaged. Transportation, too many middlemen, a lack of grading, price fluctuations, and a lack of financial resources were all issues in marketing. The intensity of pests and illnesses, lack of water, soil quality, and the frequency of rains and winds were all agro-biological issues that limited productivity (Bar *et al.*, 2020). The primary reasons for the low betel leaf output are conventionally handled operations, uneducated laborer, and inferior planting materials.

8. Diseases

"Foot rot," "leaf spot," "powdery mildew" and "collar rot" are major diseases that affect betel vines

(Vijayakumar and Arumugam, 2014).

Foot Rot

Phytophthora spp. causes the most common fungal illness. The plantation suffers from foot rot (Haider et al., 2013; Meszka and Michalecka, 2016). *Phytophthora* species was discovered in 1927, which was eventually recognised as *P. nicotianae* var. *parasitica* (Meng et al., 2014). Foot rot induced by *P. parasitica* and *Phythium vexans* de Bery (*Phythium piperinum* Dastur) was documented by (Haider et al., 2013). The lamina of the leaves begins to drop gradually, while the petiole remains upright. This sickness is known in the area as 'Khada Kala', 'Khada Pacha', or 'Madua'. Local growers are spraying Blitox and Tegrone drugs to avoid the sickness from spreading (Haider et al., 2013). *Sclerotium rolfsii* causes foot and root rot which is the most devastating disease that decreases the production of betel leaf (Rahman et al., 2021).

Leaf spot

Patra and Pradhan (2018) reported a leaf spot disease induced by *Fusarium semitectum*. Berk. et Rav. Singh and Shanker (1971) described infections induced by *Cladosporium pipericola*, *Drechslera rosstrata*, *Corynespora cassicola*, and *Cercospora piperisbetle* in Madhya Pradesh and Uttar Pradesh, India (Maiti and Sen, 1979). The sickness is called "Champa Fulia" or "Champa Tipa" in the area. The leaves' tips are tiny and curling. Farmers must cut sick leaves as soon as they are spotted, or the virus may migrate to the main stem of betel vines in a few days. It was also carried by ants and insects from one vine to another. This disease is more prevalent during the wet season. Farmers apply Diethen-M 45 and urea water to these diseases to eradicate them (Maiti and Sen, 1979).

Powdery mildew

In India, the disorder was discovered in Mysore by Narasimhan in 1933. *Oidium piperis* Uppal is the major cause of powdery mildew disease (Park et al., 2012). This ailment is referred to as 'Jhalma' in the local community. On the bottom of the leaves, the infection appears as white to light brown powdery patches. At this phase, little white and black particles can be seen in the upper and lower regions of the leaves. This is a very communicable disease. There is no way to prevent or treat this illness. Farmers use a combination of dried fruit dust and Neem tree (*Azadirachta indica* A. Juss.) leaf juice mixed with water to dust betel vine leaves (Patra and Pradhan,

2018).

Collar rot

Sclerotium rolfsii Sacc., is a soil-borne fungus, infecting the collar and root parts of various crops, its growth, development, and pathogenicity were dependent on environmental factors like temperature, relative humidity, and rainfall (Garibaldi et al., 2013). It is confirmed that *S. rolfsii* caused collar rot disease in betel vine which is reported to Garain et al. (2021) and cause 17-100% crop loss in West Bengal.

One hundred twenty million kg of EO is produced globally from approximately 300 crops, which are worth about \$4 billion, including 4% production from India (Shukla, 2015). The EO extracted from coastal areas of Odisha and obtained from different varieties such as Chandrakala (0.42%), Godi Bangla (0.37%), Balia (0.35%), Desibangla (0.32%), Maghai (0.30%), Dandabalunga (0.20%), Nahua (0.15%), and Karpada (0.15%) (Das et al., 2016). The leaves have indispensable oils which are known for their anti-allergic, anti-cancer, insecticidal, antibacterial, and antioxidant properties (Seow et al., 2014), making them healthy food preservatives with significant customer interest. The application of an alternative food preservative to prevent microbial spoiling is necessitated by the growing customer desire for natural products (Mandal et al., 2014; Roy and Guha, 2021). Besides being possible natural food preservatives, these oils could also have a future in novel food packets due to their antibacterial and antioxidant properties (El Asbahani et al., 2015; Roy and Guha, 2021), as well as being a viable and appealing flavoring component for the food and beverage sectors. The EO ingredients added in ice cream, chocolate, suji halwa, cupcake, lozenge, rosogolla, etc. (Guha and Nandi, 2019). Basak (2018) reported that the EO of betel vine (var. *Tamluk Mitha*) has many potentials as a natural preservative in the food sector due to its safety and antimicrobial effectivity without affecting the sensory qualities of the food products. As a result, around Rs 30-40 million worth of leaves are sold to nations like Italy, Great Britain, Bahrain, Hong Kong, Pakistan, Canada, Kuwait, Saudi Arabia, Nepal, and many other European countries each year (Pandey et al., 2018). Clearly, this shows the crop's ability to generate foreign money, which should be enhanced in the national interest. Export policy decisions may be modified to increase betel leaf exports, in addition to an adequate study on export systems and intelligence. Rural

and urban populations are increasingly using the plant for culinary and ethnomedicinal purposes, which has led to an increase in demand. Cultivation and preservation of betel vine in rural areas should receive renewed attention in order to prevent the extinction of these species and to provide economic benefits to rural populations.

9. Future studies

The leaves are frequently used as remedies because they contain important bioactive components. Due to their inexpensive cost and ease of usage, they are widely utilized in India and abroad. To cure alcoholism, bronchitis, asthma, leprosy, and dyspepsia, it can be taken as a dietary additive or taken separately (Peddapalli *et al.*, 2020). Because betel leaves decompose quickly, they cannot be preserved for long periods of time. As a result, extra leaves are dumped aside or sold as cow feed in the marketplace. In this scenario, improved research approaches should be used to extend the shelf life of leaves. Usually, several diseases and insects attack the betel vine throughout production, causing significant losses to the growers. Microbes, parasites, and other contaminants can readily contaminate the leaves during preservation and transit. As a result, garbage utilization in the manufacturing industry is one of the most significant and difficult occupations on the globe. There are only a limited number of studies on the use of leaf isolates and EO. Because there is a dearth of study in this field, we should concentrate on its possible technologies in a variety of procedures such as food applications, pharmaceutical industries, cosmetic industries, and so on. Betel leaf post-harvest damages can be reduced by using superior storage techniques. The functioning of each unit (manufacturing, processing, packaging, handling, transportation, and marketing) of betel leaves affects the majority of individuals directly or indirectly.

Based on the foregoing, the federal and state governments should collaborate more effectively to fund diverse initiatives. A Research and Development Board should also be established by the government. This could help keep the price of betel leaves stable. This also aids in the expansion of cultivation and export-oriented operations, the development of conservation methods, and the reduction of waste and by outflow, among other things. If farmers, scientists, technicians, and researchers work together to

resolve the limits, the economy and job prospects will grow.

10. Conclusions

This review article looked at the cultivation, nutritional components, pharmaceuticals compounds, pharmacological activities, antimicrobial compounds, diseases, and economy. Betel vine has ample of various metabolites such as phenolic tannins, anthraquinones, flavanoids, alkaloids, terpenoids, saponins, caediac possess more number of pharmacological activities and responsible for health benefits. As a result, there is a rising demand for using betel leaf extract and EO in a variety of industrial uses, including food supplements, cosmetics, and pharmaceuticals. Therefore, farmers of coastal Odisha have completely depended on the economy of betel vine cultivation and marketing at the national and international level. Sometimes, the betel vine is plagued by many diseases during cultivation, which generates a huge loss for farmers. The betel vine production was devastated due to being infected with several fungal pathogens resulting in foot rot, leaf spot, powdery mildew, and collar rot. In addition, this study discusses the recently accepted extraction technologies and characterization, both of which are critical for the growth of the product's economic worth. Bioactive chemicals from betel vine should be isolated, extracted using common and advanced technologies, and characterized for further bioactive properties, such as antibacterial activity, antioxidant activity, antidiabetic activity, anticancer activity, and so on. Such potential of betel vine made itself a green medicine in nature. It concludes that the betel vine keeps promising as a natural reservoir with regard to its nutritional, pharmacological and economical aspects for the rapidly growing human population.

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