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Golden Heart of the Nature: *Piper betle* L.

D. Pradhan[1*], Dr. K. A. Suri[2], Dr. D. K. Pradhan[3] and P. Biswasroy [4]

1. Ixoreal biomed. Pvt. Ltd., APIIC, Green Industrial Park, Jadcherla, Mahaboobnagar, Hyderabad, Andhra Pradesh. 509302. India. [E-mail: hi_honey.com@rediffmail.com, Tel: +91-9000203912]
2. Director grade Scientist-G, Natural Product Chemistry Department, Indian Institute of Integrative Medicine (IIIM), Jammu, India.
3. Community Health Centre, Gumagarh, Phulbani, Odisha, India.
4. Ixoreal biomed. Pvt. Ltd., APIIC, Green Industrial Park, Jadcherla, Mahaboobnagar, Hyderabad, Andhra Pradesh. 509302. India.

The heart shaped betel leaves are found in ancient Sanskrit texts, including Charaka, Sushruta Samhita and Astanga Hradayam. *Piper betle* L. have been used in chinese, Indian folk medicine for centuries. In this review, different research works related to Ayurvedic consequence, geographical distribution and cultivation, morphoanatomy, phytochemistry, biological activities, along with tradomedicinal uses which signify the tremendous potential of "*Piper betle* L." to come out as *Green medicine*. The objective of it is to revels the potential effect of this plant in the development of therapeutically active herbal drugs against different microbial infections especially for oral cavity, which also gives the opportunity to pharmaceutical companies interested in formulation and production of natural product based drugs targeted towards specific aliments

Keyword: *Piper betle* L., Morpho-anatomy, Antimicrobial Activity.

1. Introduction

Piper betel is blessed as evergreen and perennial plant, that has God created and have given the shape of his own heart. Anthropologists have found traces of betel in the spirit caves in Northwest Thailand dating back as to 5500-7000BC, which is even before systematic and organised agriculture came to be practiced. There have been similar findings in Timor in Indonesia going back to 3000 BC and in the blacked teeth of a human skeleton in Palawan in a Philippines going back to 2600 BC. It had found a place in the most ancient Sri Lanka Historical Book "Mahawamsa" written in *palli*. Even today some hardened betel chewers in Thailand, Myanmar and Indonesia with black teeth as result of long years of chewing[1]. There is archaeological evidence that the betel leaves have been chewed along with the Arica nut since very ancient times it is not known when these two different stimulants substances were first put together. It may difficult to clearly ascertain the period when the tradition of paan chewing was started. However, its mention in the Vatsyayana's Kamsutra and Kalidas's Raghuvamsa in itself reflects the antiquity of this practice. Social status of pan can also be appreciated from the fact that it was considered to be a great honour to receive *paan bida* [A pair of leaves with Churna (Lime), kattha (catechu) and supari (areca nut)] from kings and nobles. Such was the status of pan in ancient India. During this period (Circa 600AD)

words like Tambuladhikara, Tambuladyaka, Tambuladayini and Tambulika etc. used in different texts. Some of the common usages are mention in Kadamberi[2]. Paan has been referred to in Sakta-tantra as one of the means of achieving siddhi. It was believed that without betel chewing and offering pan to Guru no siddhi can be gained. Tambool has also been referred to as facilitating the sadhak in chewing dharma, yasha aisvarya, Srivairagya and mukti. Tambool find frequent mention in writings from the fifth century onwards especially, Reetikaaleen Hindi poetry[3, 4, 5].

2. Ayurvedic Significance:

Piper betel is a Vedic plant and its Vedic name is Saptasira[6] and in sankrit it known as Tambool, Nagvelleri, Nagani[7] were used as remedy against various diseases. In most of these texts were various medicinal properties has been highlighted. Reference to Tambool occurs right from Vatsyayana's Kamasutra & Panchatantra down to Kalhan's Rajatarngni (which may perhaps be the last of the recognise old Sanskrit writing of historical significance). Tambool has been referred to, thus roughly across a period of about 2000 year.

In Ayurveda medicine system, the properties of betel leaf describe as given below[8]:

Guna (Quality)	:Laghu, Ruksha, Tikshan
Rasa (Taste)	:Tikta
Vipak (Metabolism)	: Katu
Virya (Potency)	: Ushan
Prabhav (Impact)	: Hridya

In Ayurveda betel leaf extract is frequently used as an adjuvant & mixed with different medicines possibly for better effects beside its independent use as medicine. In Susrta Samhita (Ch 28-46, 279-280) tambool leaves have been described as aromatic, sharp, hot, acrid and beneficial for voice, laxative, appetizer, beside this they pacify vata and aggravate pitta. Similar characteristics have been described in Bhabaprakash (Sloka180-183)[2].

ताम्बूलवल्ली तम्बूली भागिनी नागवल्लरी I ताम्बूलं विशदं रूच्यं तीक्ष्णोष्णं तुवरं सरमू II११II
वश्यं तिक्तं कटु क्षारं रक्तपितकरं लघु I बल्यं श्लेष्मास्यदौर्गन्ध्यमलवातश्रमापहमू II१२II
(भा. प्र. गुडूच्यादिवर्ग ११-१२)

In addition to these, the aphrodisiac effect of betel chewing has been indicated in ancient texts. Pan also believed to provide strength to heart and regulate blood. Its utility as anti-inflammatory and anti-microbial is emphasized at several place. In ayurveda it acts as vata and kapha suppressant. It also helps in expelling out the mucus from the respiratory tract because of its hot potency[7]. According to Yunani system the leaf has a sharp taste and good smell improves taste and appetite, tonic to brain, heart and liver, lessens the thirst, clear the throat and purify the blood[9].

3. Plant Profile:

I. Botanical name and taxonomic classification[10,11]:

- Kingdom: Plantae
- Division: Magnoliphyta
- Class: Magnolipsida
- Order: Piperales
- Family: Piperaceae
- Genus: Piper
- Species: *betle*
- Binomial name*: Piper betle* L.

II. Vernacular name[7, 12, 13]:

- Sanskrit: Nagavallari, Nagini, Nagavallika,Tambool, Saptashira, Mukhbhushan, Varnalata
- Malaysia: Sirih, Sirih melayu, Sirih cina, Sirih hudang, Sirih carang, Sirih kerakap
- English: Betel, Betel pepper, Betel-vine
- Tamil: Vetrilai
- Telugu: Nagballi, Tamalpaku
- Hindi: Pan

- Gujurati: Nagarbael
- Marathi: Nagbael
- Bengali: Pan
- Arabic: Tambol, Tambool
- Semang: Serasa, Cabe
- Jakun: Kerekap, Kenayek
- Sakai: Jerak
- Javanese: Sirih, Suruh, Bodeh
- Thai: Pelu

III. Geographical distribution:

Piper betel is native to central and eastern Malaysia and was taken into cultivation more than 2500 years ago throughout Malaysia and tropical Asia. It reached Madagascar and East Africa much later and was also introduced into the West Indies. Written Chinese sources from the period of the Tang dynasty (A.D. 618-907) described Southeast Asia as a region of betel users. Betel chewing was widespread in South India and South China when the first Europeans arrived in the 15th century. With known ethno medicinal properties, this plant is widely use in India, Indonesia and other countries of the Indo-China region (Malaysia, Vietnam, Laos, Kampuchea, Thailand, Myanmar, Singapore)[2,12] as shown in Fig no. 01.

Fig.no.1. Region within the dotted lines shows major areas of *Piper betel* consumption.

Where, AFR: Africa, MAD: Madagascar, PAK: Pakistan, IND: India, NEP: Nepal, SRI: Sri Lanka, THI: Thailand, CAM: Cambodia, MAL: Malaysia, PNG: Papua New Guinea, BOR: Borneo, SIN: Singapore, LOA: Laos, VIT: Vietnam

Fig.no.1. Region within the dotted lines shows major areas of piper betel consumption. Barring the areas where the climatic conditions (high or low temperature accompanied by very low humidity) do not support its cultivation. Betel vine is widely distributed in all over the state of India except northern regions (Jammu and Kashmir, Haryana, Punjab, Himachal Pradesh), due to sever winter and northern west (Rajasthan, Gujarat) due to hot dry summer[14,15] as shown in Fig No. 02.

IV. Habitat & Ecology

Betel vine thrives under humid forest conditions with high relative humidity. It prefers deep, well-drained, friable loamy and clayey soils, rich in organic matter with a pH of about 7-7.5. It flourishes in areas with 2250-4750 mm annual rainfall and is cultivated at altitudes up to 900m[12].

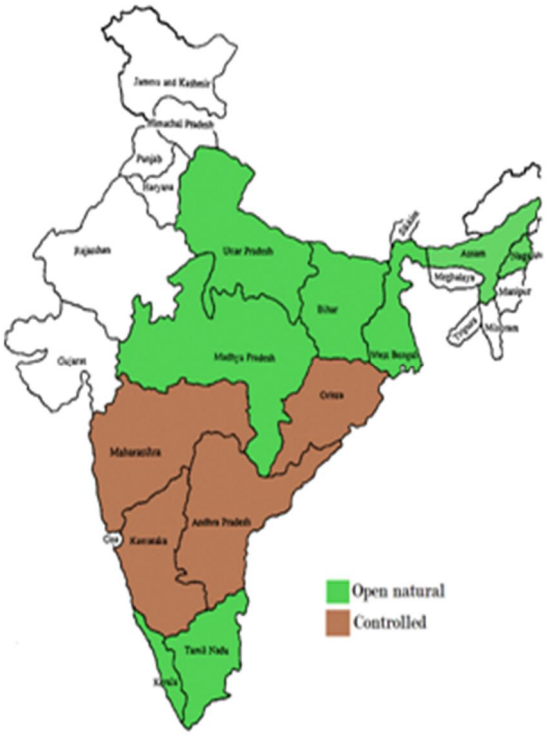


Fig no.2 Major Betel vine growing areas in India.

V. Cultivation and propagation

Cultivation

It is cultivated in soil, which is black, friable, clay loam resembling tank earth, contains large portion of organic matter, but the best pans are grown in Bengal on light loam sightless reddish in colour. The plant grown from sea level to1000mt, rainfall of more than 179cm is necessary. It thrives best under tropical forest condition with shade considerable humidity & plenty of soil moisture. Broadly there are two cropping system under natural conditions and controlled conditions. The open system of cultivation under natural conditions is practiced in regions where conditions of high humidity and moderate sunshine prevail throughout the year. The type is basically a climber which required supporting tree like areca nut (*Areca catechu*) and coconut (*Cocos nucifera*) and generally attain 10-15 meters height with profuse branching at the top and lot of foliage. Another type of cropping is partially controlled cultivation which is common in regions where high humidity and low sunshine conditions do not prevail round the year and the plants are to be protected from excessive sunlight dry air. Vines are trained on live support of plants such as *Sesbania grandiflora*, *Sesbania sesban, Erythrina indica* and *Moringa oleifera* which also provide shade and contribute to the increase in humidity. The close planting of vines also helps in moisture retention and creation of microclimate conducive to growth. Unlike the practice in north-east where the vines are allowed to attain height of the supporting tree, it is just 1-2 metre only. This change in plant habitat is achieved by suppressing the linear growth and promoting profuse branching. The plant type in partially controlled cultivation is modified to suit the prevailing conditions. Such weather conditions with adequate sunshine (photo synthetically active radiations 1200-1800µ mole $m^{-2}S^{-1}$) are hardly conducive to good growth. With the advancement in greenhouse/ glasshouse construction technology, now it is quite easy to shift plants from their natural habitat and grow them under controlled conditions by regulating precisely the humidity incident of light and temperature. Cultivation under controlled conditions is practiced in subtropical regions where relative humidity is often low and temperature remaining high (max. temp. above 40°C) in summer and low (min. temp. below 10°C) in winters. The cultivation of betel vine under controlled conditions is also a case of creating indigenous system of "environmental chamber" with the materials available in nature. The covered structure is known as bareja. The bareja structure is made up of locally available materials such as wooden poles, bamboos stalk and a variety of grasses as thatching material. Barejas are generally rectangular in shape and normal workable size often 50×30mt. When a bareja is erected on slopes, west to east gradient is preferred. It is mandatory to keep the east and west side shorter than north and south sides. This shape carries sound logic in terms of humidity and temperature control. Westerly winds are not only dry but also high or low temperature depending on the season. In order to minimise the wind impact, thatching on the west side is thickest so that the wind velocity entering the

bareja is reduced. Thatching on the north side of the bareja is thicker than on the eastern side. The side facing south is kept thinnest, possibly to allow some light from that direction. The top of the bareja is covered by leaves of locally available grasses in order to reduce the light incident on the plant and soil surface. Height of the mandap varies from 2-3 meters or little more depending on the season and growth of the vine. Thus this practice of cultivation in the bareja may be older than 600-400 BC. If the proper irrigation and sunlight controlling cannot be maintained it gets some negative impact in the size, shape, colour, and taste of its leaves. Some of the impacts are given below:

1) Too much light, but adequate soil moisture: leaf becomes darker green, harder, rough taste.
2) Too less light, but adequate soil moisture: leaf becomes light green, thinner leaf, short lasting as chewed, taste becomes lighter, smaller leaf sizes.
3) Adequate light, but less soil moisture: hard leaf, smaller size, rough taste, early falling leafs, turn leafs yellow, weak plant stem, less number of leafs per plant, broken-uneven edges.
4) Adequate light, but too much soil moisture: rotten roots, dying plants, slowdown in leaf maturity, weaker taste, leaf uneven surfaces[2,6].

Propagation

Propagation is easy by root division or cuttings, preferably taken in spring or summer. Betel leaf requires a rich soil and prefers a semi-shade position. Regular feeding and watering will keep it growing very lush.

VI Morpho-Anatomy.

a. Macroscopic characters:

- Colour: Yellowish green to dark green in colour with glossy upper surface.
- Odour: Characteristic and Pleasant.
- Taste: The betel leaves are aromatic with varied taste, ranging from sweet to pungent due to the presence of essential oils.
- Shape and Size: The betel leaf is a heart shaped with different size. The size of the leaf varies with different cultivar from 7-15cm in length and 5-14cm in width. Betel leaves are simple alternate stipulate petiolate with 0.75 to 3.8cm, ovate oblong broadly ovate cordate or obliquely elliptic entire glabrous coriaceous 10 to 18 cm long and 5 to 10 cm broad acuminate oblique and rounded base[16,17,18].

b. Microscopic characters:

Transverse section of leaf through midrib shows four layered upper and two layered lower epidermis. The cuticle is thick on the upper epidermis and thin on the lower epidermis. The cells of the outer epidermal layers on both sides of the leaf are small, that possess tannins and oils. The sub epidermal cells on the abaxial side are enlarged and they store water. Crystal and oil reserves are found in the sub epidermal cells on both sides. The palisade layer are well distinguished they are double layered short wide compact cells and mesophyll cells are 3-4 layered and small lobed. Thick walled irregular secretory cells are seen with dense contents of probable an essential oil as shown in fig no. 3 and 4.

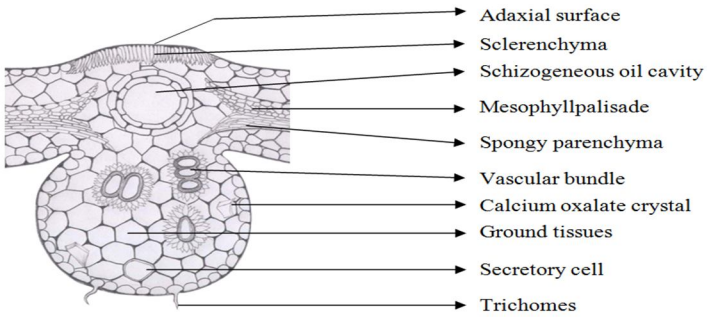


Fig no. 3 Transverse section of Betel leaf with midrib

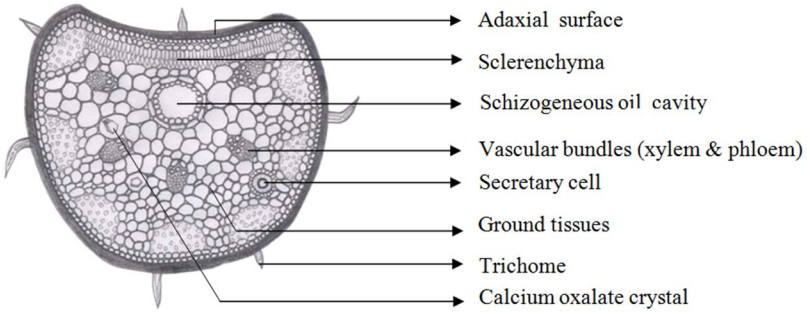
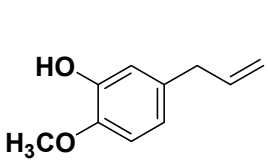


Fig no. 4 Transverse section of petiole of Betel leaf

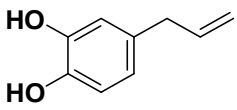
The leaves are hypostomatic, tetra-cytic stomatal complexes are common which is the characteristic feature of the Piperaceae. The trichomes are glandular which have unicellular apical cell and a short pedicel. The pedicle has thicker wall, surrounded by 5 or 6 epidermal cell arranged in a rosette disc like manner. The apical cell of trichome is slightly pointed or clavate shaped. The vascular bundles located at the centre of midrib portion single ovate collateral cells with destea of xylem elements and a thick phloem was observed. The stems are dichotomous, articulate, swollen and rooted at nodes 3mm in diameter, woody and with 2.5 to 4cm long internodes. Stem stout with pinkish-stripe along node dilated and rooting. The inflorescence is an axillaries spike which is 5.5 cm long. The fruits are drupaceous, orange, and 3mm in diameter[8,16,17,18].

VII. Phyto-constituents:

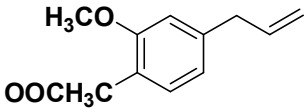
The leaf contains Water (85-90%), Proteins (3-3.5%), Carbohydrates (0.5-6.1%), Minerals (2.3-3.3%), Fat (0.4-1%), Fibre (2.3%), Essential oil (0.08-0.2%), Tannin (0.1-1.3%), Alkaloid (arakene). It also contains different vitamins like Vitamin-C (0.005-0.01%), Nicotinic acid (0.63-0.89mg/100gms), Vitamin-A (1.9-2.9mg/100gms), Thiamine (10-70µg/100gms), Riboflavin (1.9-30µg/100gms) beside this it contains minerals such as Calcium (0.2-0.5%), Iron (0.005-0.007), Iodine (3.4µg/100gms), Phosphorus (0.05-0.6%), Potassium (1.1-4.6%)[14]. Leaves contain bitter compounds that are about (0.7-2.6%). The specific strong pungent aromatic flavour in leaves is due to phenol and terpene like bodies[19]. The total phenol contain is vary on the gender. The male plant contains three fold higher total phenols content and two fold higher thiocyanate content as compare to female plant. The quality of the leaf depends upon the phenolic content, i.e., more the phenolic content betters the leaf quality[20]. Recently many researches works shows the betel leaves contains starch, diastases, sugars and an essential oil composing of safrole, allyl pyrocatechol monoacetate, eugenol, terpinen-4-ol, eugenyl acetate, etc. as the major components[21,22]. Phytochemical investigation on leaves revealed the presence of Alkaloids, Carbohydrate, Amino acids, Tannins and Steroidal components[23]. The middle part of the main vine contains largest quantity of Tannin. The terpenoids include 1, 8-cineole, cadinene, camphene, caryophyllene, limonene, pinene, Chavicol, ally pyrocatechol, carvacrol, safrole, eugenol and chavibetol are the major phenols found in betel leaf. Eugenol was identified as the antifungal principle in the oil. The fresh new leaves contain much more amount of essential oil diastase enzyme and sugar as compare to old leaves. Chavicol is four times potent as antiseptic agent as compare to carbolic acid. Some of the phyto-constituents of the plant are given below[15,24-31].



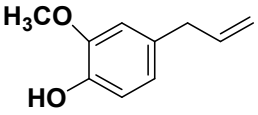
Chavibetol



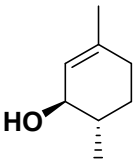
Allypyrocatechol



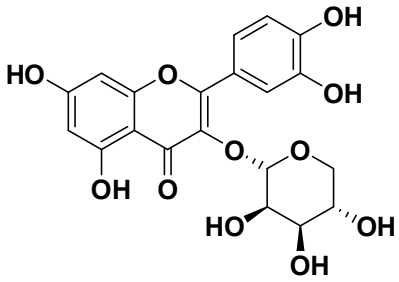
Chavibetol acetate



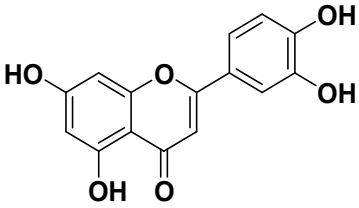
Eugenol



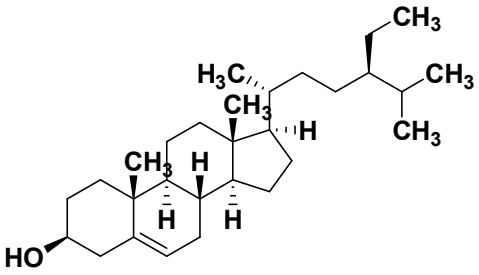
Piperitol



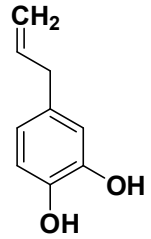
Quercetin



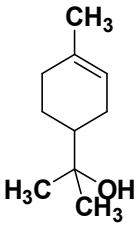
Luteolin



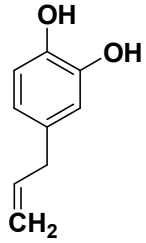
β- sitosterol



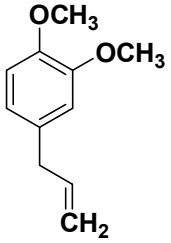
Hydroxychavicol



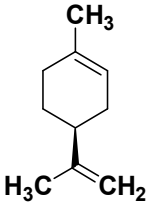
α-terpineol



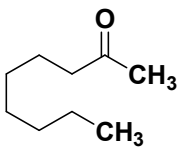
Allyl catecol

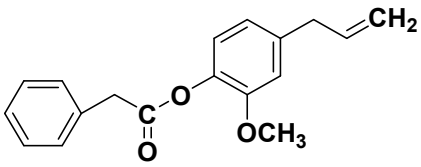


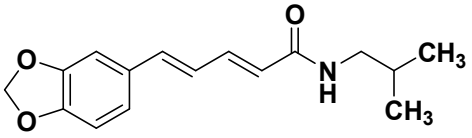
Eugenol methyl ether



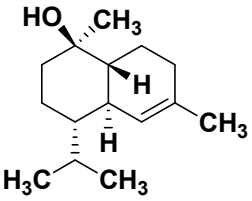
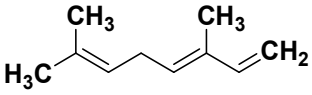
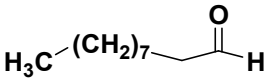
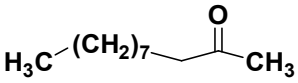
D- limonene



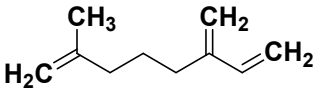
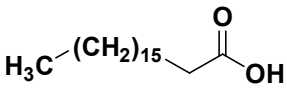
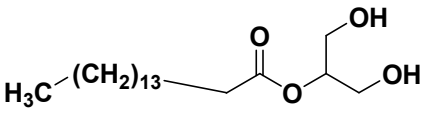




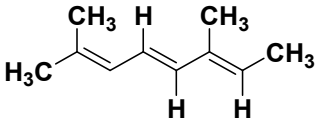
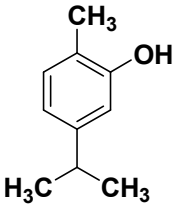
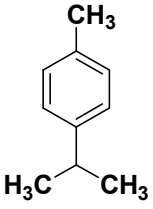
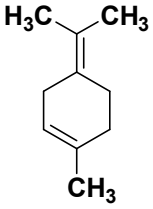
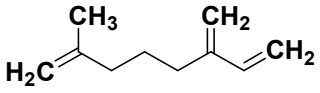
2-noanone 4-allyl phenyl acetate (db) Piperlonguminine

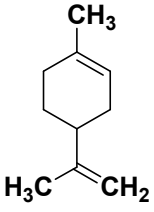
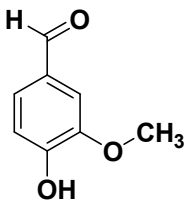
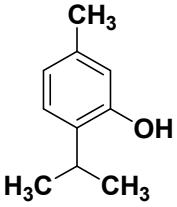
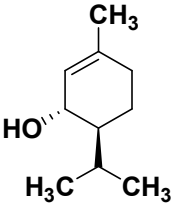
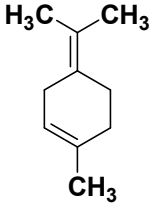
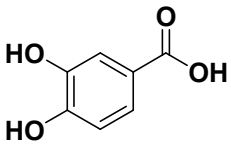
α-cadinol Ocimene N-decanal 2-undecanone

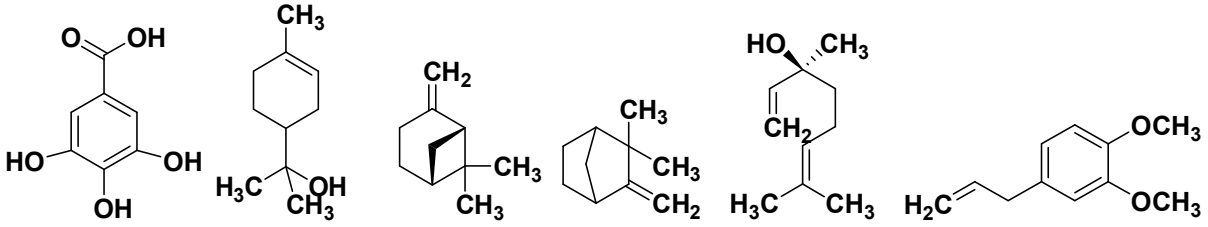
Myrcene Stearic acid 2- Mono palmitin

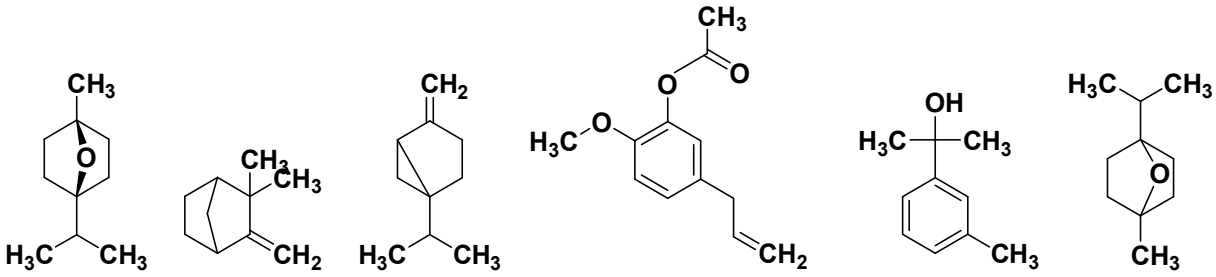
Allo ocimene Cavacrol Cymene Terpinolene α-Myrcene

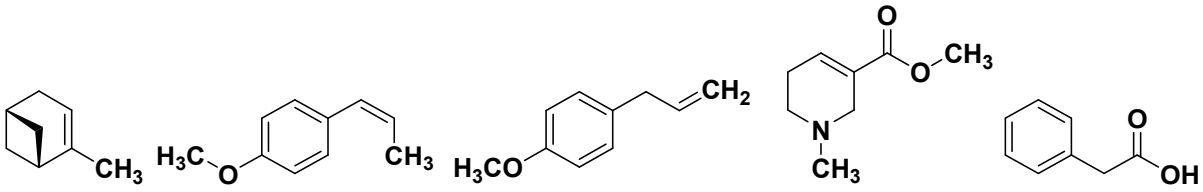
Limonine Vanillin Thymol Cis-piperitol Terpinolene Procatechuic acid



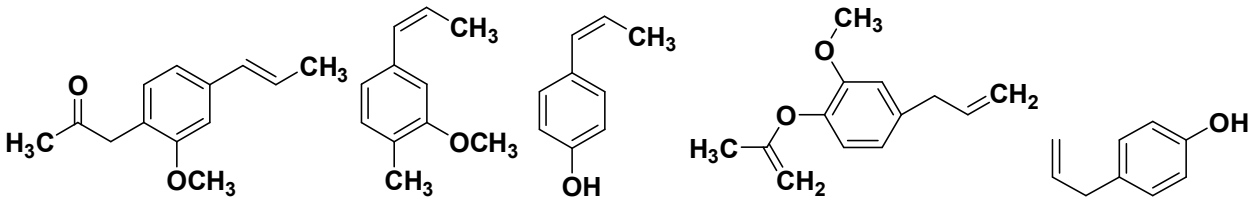
Gallic acid α-terpineol β-pinene Camphene Linalool Allyl diacetoxy benzene



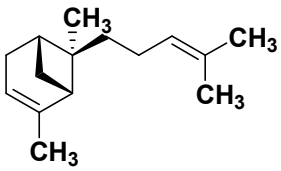
Eucalyptol Camphene Sabinene 3-allyl-6-methoxyphenolb m-Cymen-8-ol 1, 4 cineole



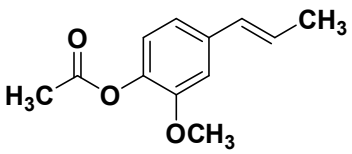
α-pinene Anethole Estragol Arecoline Benzene acetic acid



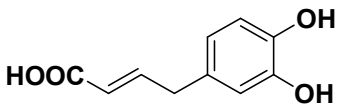
Iso eugenyl acetate Isoeugenol Chavicol Eugenyl acetate 4-allyl phenol



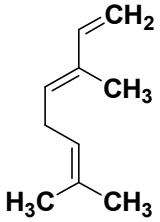
α-bergamotene



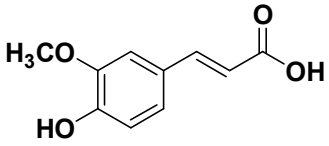
Isoeugenyl acetate



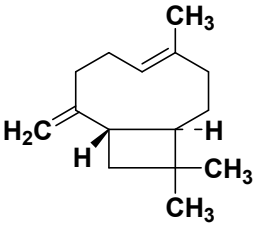
Caffeic acid



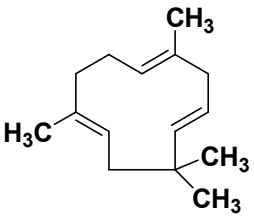
(E)-ß-ocimene



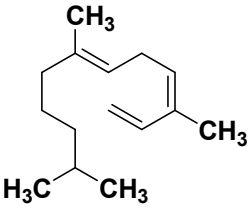
Ferulic acid



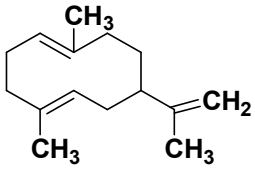
Carryophyllene



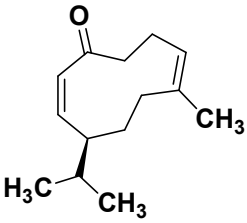
Humlene



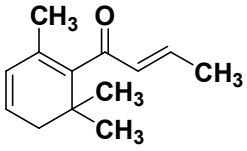
α-farnesene



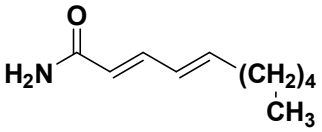
Germacrene-A



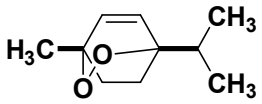
Germacrene-D



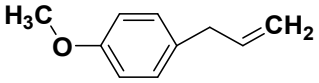
(E)-ß- Damascenone



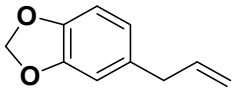
4E-decadienamide



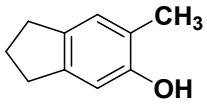
Isoascaridole



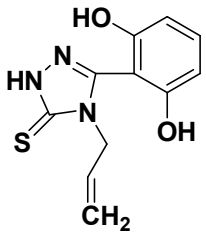
4-Allyl anisole



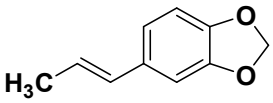
Safrole



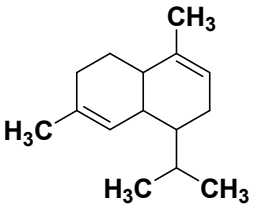
5-Indanol



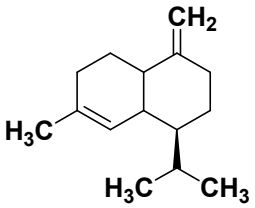
4-allyl resorcinol



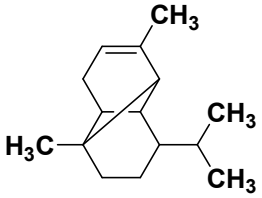
ß-iso safrole



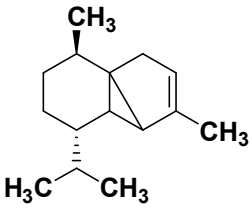
α-muurolene



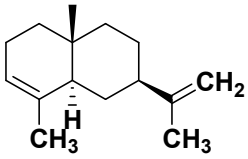
Cadinene



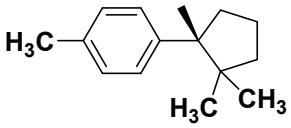
α- copaene



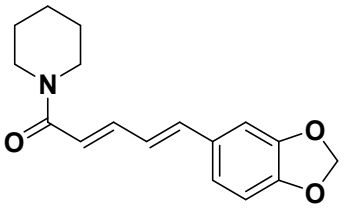
α-cubebene



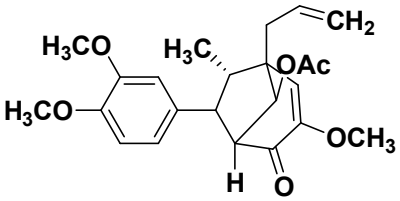
α-selinene



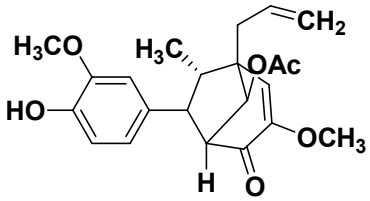
Cuparene



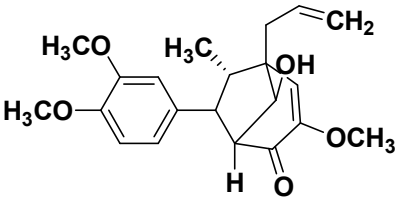
Piperine



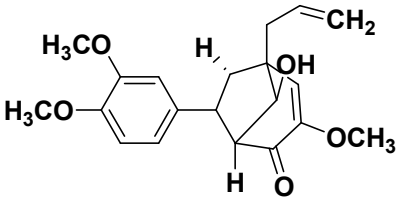
Piperbetol



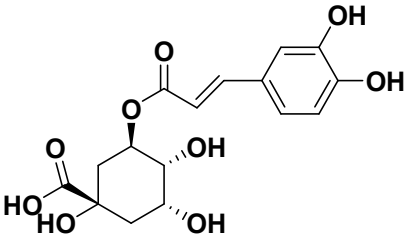
Methylpiperbetol



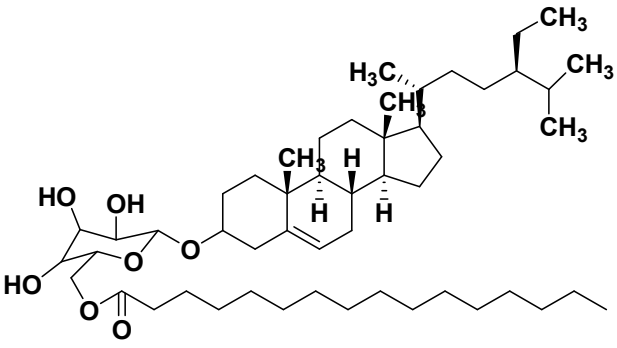
Piperol-B



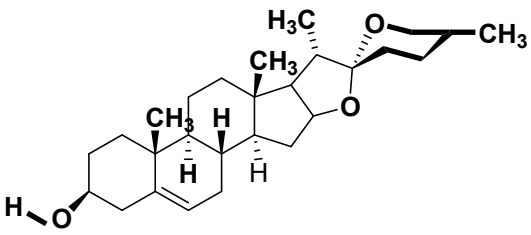
Piperol-A



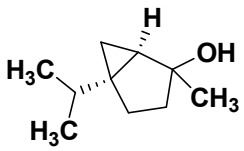
Chlorogenic acid



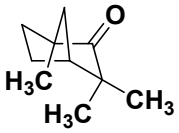
ß-sitosteryl palmitate



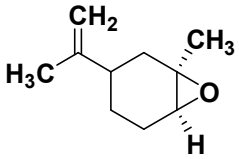
Diosgenin



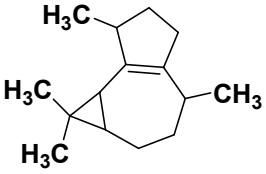
Cis Sabinene hydrate



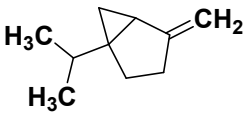
Fenchone



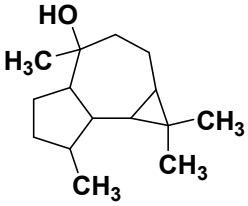
Cis-Limonene oxide



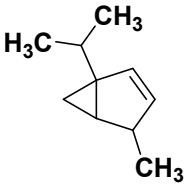
Isoledene



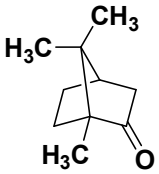
Sabinene



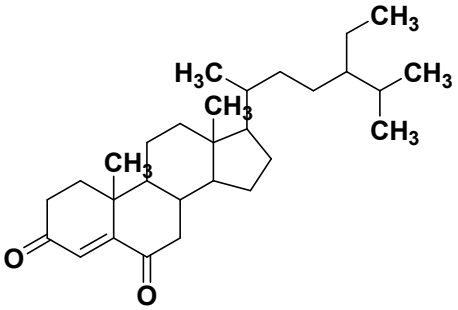
Ledol



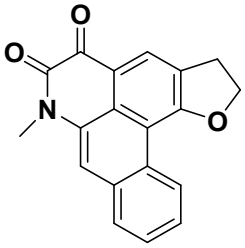
Thujene



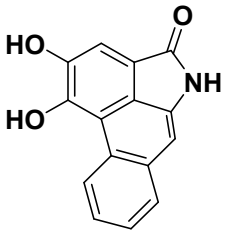
Camphor



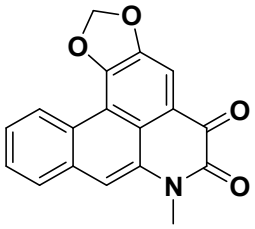
Stigmast-4-en-3,6-dione



Cepharadione A



Aristololactame (A-II)



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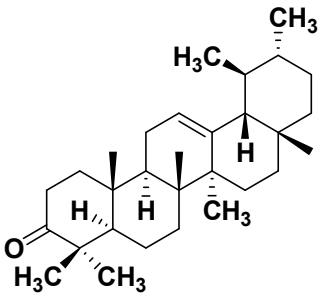
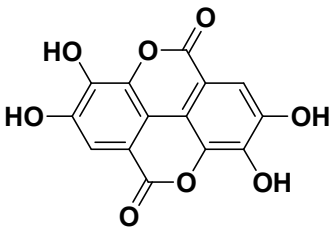
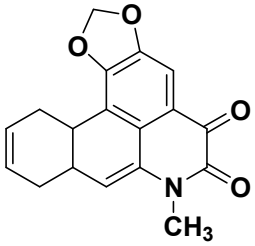


Ursonic acid



Ellagic acid



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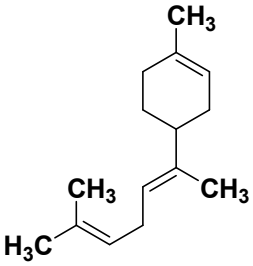

α-Bisabolene

VIII. Therapeutic ethics:

A. Traditional Use

Betel leaf has been described from ancient times as an aromatic, stimulo-carminative[32] (katu), astringent and aphrodisiac (kamagnisandipanam)[33,34]. The leaves are credited with wound healing property[12,35]. The Indian traditional system of medicine has identified the leaves with digestive and pancreatic lipase stimulant activities[36-41]. Betel leaf is traditionally known to be useful for the treatment of various diseases like bad breath, boils and abscesses, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, swelling of gum, rheumatism, cuts and injuries[42]. Fresh juice of betel leaves is used in many ayurvedic preparations[43]. Leaves considered being useful in treating bronchitis and dyspnea[37]. The leaves were chewed by singers to improve their voice[44]. The fruit of Piper betel employed with honey as a remedy for cough[45]. The fresh betel leaves possess antimicrobial, ringworm, antifungal, antiseptic and antihelminthic effects[46]. Leaves are used in eye drops for eye injury/infection as a baby lotion for the new born, for coughs, asthma, constipation and to arrest milk secretion[47]. Essential oil from leaves of this plant has been used for the treatment of respiratory catarrhs and antiseptic[45,48]. Leaf extract is reported to inhibit male reproductive competence[49-51]. The leaves possess antifertility on male rats[51] and anti-motility effects on washed human spermatozoa[49]. In folk medicine root is used as long lasting female oral contraceptive[42, 52]. The users believe that chewing the *'paan'* improves their efficiency and stamina[44]. Piper betel showed hypotensive, cardio tonic, smooth and skeletal muscles relaxant actions[53-55].

B. Biological Activities

i. Antimicrobial activity

The leaf has a significant antimicrobial activity against broad spectrum of micro-organisms[56]. The betel shows the antimicrobial activity against *Streptococcus pyrogen, Staphylococcus aureus, Proteus vulgaris, E.coli, Pseudomonas aeruginosa* etc., beside this the leaf extract also poses the bactericidal activity against the urinary tract pathogenic bacteria such as *Enterococococcus faecalis, C.koseri, C.fruendi, Klebsiella pnemoniae* etc[57,58]. The bioactive molecule thought to be responsible for anti-bacterial activity is sterol, which has been obtained in large quantities in betel leaf extracts. The mode of action may be due to surface interaction of sterol molecule present in the extracts with the bacterial cell wall and membrane leading to alteration in the primary structure of cell wall, ultimately lead to pore formation and degradation of the bacterial components. It is reported that sterol act through the disruption of the permeability barrier of microbial membrane structures[58]. Gram-positive bacteria were more susceptible to the inhibitory effects of the plant extract because of single layer and lack the natural sieve effect against large molecules, whereas gram negative bacteria are multi layered and complex cell wall structure[57,59]. The leaf has also poses the antifungal activity against many fungal infections[60]. One of them is dermatophytosis. Dermatophytosis is a disease of the keratinized parts of the body (skin, hair, and nail) caused by a three genera (*Trichophyton, Microsporum,* and *Epidermophyton*) of highly specialized fungi called the Dermatophytes[61]. The chloroform extract of piper betel shows the much more efficiency than the methanol fraction against dermatophytes because of presence of non-polar components in the fraction[62].

ii. Gastroprotective activity

The hot water extract significantly increased the mucus content adhering to the wall of the gastric mucosa. Mucus layer is considered to be important in mucosal defences against endogenous aggressors, e.g., acids, and also as an agent in facilitate the repair process. It is generally believed that enhanced acid secretion is the most important factor for the induction of gastric lesions. The higher dose of hot water extract does not cause significant inhibition in acidity or pH of gastric fluid. Therefore, gastro-protective effect of piper betel was not mediated

via inhibition of acid secretion in the gastric mucosa but by increasing its mucus content. The gastroprotective activities of the higher dose of hot water extract significantly greater than Misoprostol[63]. The extensive research has been proven that anti-oxidants might be effective mechanism not only in protecting against gastric mucosal injury, but also inhibiting progression of gastric ulceration. Ulceration progression is caused by free radical-induced chain process. Consequently, its arrest by radical scavengers helps in the faster healing[64,65]. Allylpyrocatacol has shown a powerful anti-oxidant potential in various in-vitro models. Treatment with Allylpyrocatacol significantly accelerated the ulcer-healing process, which increases the mucus production usually assist the healing process by protecting the ulcer crater against irritant stomach secretion (HCl and Pepsin) thereby enhancing the rate of local healing process[66].

iii. *Antioxidant activity*

Oxidative damage is an important effect of ionizing radiation on biological membranes. It is a chain reaction[67]. Free radicals generated from the radiolytic decomposition of water can attack fatty acid chains of membrane lipid. A free radical that has sufficient energy to abstract an allylic hydrogen from the methylene carbon of polyunsaturated fatty acids can initiate the peroxidative process. Here the presence polyphenols compounds like chatecol, allylpyrocatecol etc. in betel leaf extract inhibited the radiation induced lipid peroxidation process effectively. This could be attributed to its ability to scavenge free radicals involved in initiation and propagation steps[68]. The extracts reduced most of the Fe^{3+} ions and possess strong reductive ability[69]. The extract also showed strong hydroxyl radical and superoxide anion radical scavenging property when compared with different standards such as ascorbic acid and BHT[70-73].

iv. *Antidiabetic activity*

The aqueous extract of betel leaves possess marked hypoglycaemic activity when tested in fasted normoglycaemic rat[27]. In glucose tolerance test, both extracts markedly reduced the external glucose load. The leaf suspension, significant reduces the blood glucose level, glycosylated haemoglobin and decreased activities of liver glucose-6-phosphatase and fructose-1, 6- bisphosphatase, whereas liver hexokinase increased in Streptozocin (STZ) diabetic rats compared with untreated diabetic rats. The ability of lowering blood glucose level of Streptozocin (STZ) induced diabetic rat gives a suggestion that the extract have the insulinomimetic activity[74,75].

v. *Radio protective activity*

The ethanolic extract of betel leaf shows the radioprotective activity and it has been studied using rat liver mitochondria and pBR 322 plasmid DNA as two model in vitro systems. The extract effectively prevented γ-ray induced lipid peroxidation as assessed by measuring thiobarbituric acid reactive substrates, lipid hydroperoxide and conjugated diene. Likewise, it prevented radiation-induced DNA strand breaks in a concentration dependent manner. The radioprotective activity of betel leaf could be attributed to its hydroxyl and superoxide radicals scavenging property along with its lymphoproliferative activity. The radical scavenging capacity of betel leaf was primarily due to its constituent phenolics, which were isolated and identified as chavibetol and allyl pyrocatechol[76,77].

vi. *Effect on the cardiovascular system / Platelet Inhibition activity*

The heart shape of betel leaf makes it a suitable candidate for heart-related curative properties/medicine[15]. Leaf is considered to provide strength to the heart (cardio tonic) and regulates irregular heart beat and blood pressure[78]. Cardiovascular response of acquires great significance by the fact that it is consumed globally, making it a feasible substitute for *Digitalis purpurea*[79]. The effect chewing can be observed within minutes[80], which includes cardio-acceleration, sweating and salivation. It induces catecholamine secretion from the adrenal cortex contributing to increase in stamina, heart

rate, blood pressure, blood glucose levels and sympathetic neural activity. The effect of on vasorelaxation has been studied on isolated perfuse mesenteric artery rings, wherein it was observed that the vasorelaxant effect of PB was mainly endothelium-dependent and nitric oxide (NO)-mediated, as the effect was prevented by pretreatment with N(omega)- nitro-L-arginine (NOLA), a nitric oxide synthase (NOS) inhibitor, or by removal of endothelium[81]. Platelet hyperactivity is important in the pathogenesis of cardiovascular diseases due to intravascular thrombosis. Piperbetol, ethylpiperbetol, piperol A and piperol B isolated from leaves, selectively inhibited platelet aggregation induced by platelet activating factor (PAF) in a concentration-dependent manner[82].

vii. Antifertility activity

As the structural and functional integrity of reproductive organ depend on circulating level of estrogen, any small change in estrogen level may lead to altered structural and functional activity of reproductive organs[83]. The plant extract may brought about its effect through pituitary-gonadal axis, which resulted in diminished gonadolrophine release, in turn reduced reproductive organ weights and estrogen level affecting ovarian cyst. Serum biochemistry revealed that glucose level was declined but cholesterol and Vitamin C concentrations were elevated beyond control value; indicate non-utilization of cholesterol by the system, hence decrease in estrogen level. The data suggests that betel extract brought about antifertility and antiestrogonic effects in female rats and these effects were reversible on cessation of treatment[84,85].

viii. Immunomodulatory activity

Many of the disorders today are based on the imbalances of immunological processes. This necessitates the search for newer and safer immunomodulators. The methanolic extract has lymphocyte proliferation, interferon-C receptors and the production of nitric oxide were measured in vitro. Further, the extract at different dose levels was studied in vivo for the humoral and cellular immune responses on mice immunized with sheep red blood cells. The result showed that it significantly suppressed haemaglutinin stimulated peripheral blood lymphocyte proliferation in a dose-dependent manner. The decrease in antibody titre and increased suppression of inflammation suggests possible immunosuppressive effect of extract on cellular and humoral response in mice[86]. From literature it conclude that betel leaf a novel candidate for immunosuppressive activity. The same could be further evaluated for its anticancer activity or as a potential candidate in the treatment of autoimmune disorders such as rheumatoid arthritis, systemic lupus erythomatous or emphysema[68].

ix. Cholinomimetic effect

Betel leaf rise in body temperature due to cholinergic responses. Aqueous and ethyl acetate extracts were evaluated for their cholinergic responses using isolated guinea-pig ileum[15]. It was observed that the spasmogenic activity was more in water than ethyl acetate extract. In isolated rabbit jejunum K+-induced contraction was inhibited by both extract, suggesting blockade in calcium channel. Thus, leaves contain cholinomimetic and possible calcium channel antagonist constituents which may provide the basis for several activities shown by this plant[87].

x. Hepato-protective activity

The antihepatotoxic effect of betel leaf extract was evaluated on ethanol and carbon tetrachloride (CCl4) induced liver injury in a rat model[88]. Fibrosis and hepatic damage, as revealed by histology and the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were induced in rats by CCl_4. The extract significantly inhibited the elevated activities of AST and ALT and also attenuated total glutathione S-transferase (GST), which led to a rise in antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT)[15]. The histological examination showed that the betel leaf extract protected liver from the

damage induced by CCl_4 by decreasing alpha-smooth muscle actin (alpha-sma) expression, inducing active matrix metalloproteinase-2 (MMP2) expression through the Ras/Erk pathway, and inhibiting TIMP2 level that consequently attenuated the fibrosis of liver. These findings support a chemo preventive potential of betel leaf against liver fibrosis[89].

xi. As an Oral care agent

Dental caries is a chronic endogenous infection caused by the normal oral commensally flora. The carious lesion is the result of demineralization of enamel and later of dentine by acids produced by plaque microorganisms as they metabolize dietary carbohydrates[90,91,92]. The bacteria primarily responsible for dental decay in man are *Streptococcus mutans*. *Streptococci* belong to four main species groups: *mutan, salivarius, anginosus and mitis.* In addition to *Streptococcis mutans, Lactobacillus acidophilus* bacteria probably also pay a minor role in acid production in the plaque[93]. The stickiness of the plaque is caused by dextran, which is produced by the fermentation of dietary sucrose by *Streptococcus mutans*. The plaque bacteria, particularly *Streptococcus mutans*, act on dietary fructose to produce lactic acid, which causes enamel decalcification (at below or above 5.5pH)[94]. The plaque and dietary carbohydrates are in the initiation of enamel caries. Certain cariogenic and highly acidogenic strains of streptococci, especially *S. mutans* have the ability to metabolize dietary sucrose and synthesize glucan by cell-surface and extracellular glucosyl transferase. This enzyme is considered to be of special importance in the establishment of *S. mutans* in the dental plaque[95, 96, 97]. The aqueous extract inhibit the different acid-producing oral pathogens which changes in the ultra-structure of the enamel and its properties like *Streptococci, Lactobacilli, Staphylococci, Corynebacteria, Porphyromonas gingivalis* and *Treponema denticola*. So it is best natural substance and its rating as second most popular daily consummation item in Asia, which contribute the best oral hygiene to oral cavity[98].

xii. Neuropharmacological profile

Hydroalcoholic extract of betel leaves exhibited improvement in the discrimination index, potentiating the haloperidol induced catalepsy, reduction in basal as well as amphetamine induced increased locomotors activity and delay in sodium nitrite induced respiratory arrest. These results from review suggest possible facilitation of cholinergic transmission and inhibition of dopaminergic as well as nor adrenergic transmission by the extract[96,99].

4. Conclusion

The medicinal importance of the herb as discussed above evidently prove that betel leaf is one of the most promising commercial botanical with earlier reported to possess a lot of therapeutic values. The leaf has the great potency to act as natural antioxidant. The anti-oxidant property is correlated with different biological activities like hepatoprotective, antidiabetic, antiarthritis, anti-stroke and anticancer properties, since free radicals are involved in all these diseases. The leaf poses the broad spectrum antimicrobial activity against various bacterial strains including *Bacillus cereus, Enterococcus faecalis, Listeria monocytogenes, Micrococcus luteus, Staphylococcus aureus, Aeromonas hydrophila, Escherichia coli, Pseudomonas aeruginosa, Salmonella Enteritidis, Streptococcus mutans, Streptococcus pyogenes, Enterococcus faecium, Actinomycetes viscosus, Streptococcus sanguis, Fusobacterium nucleatum, Prevotella intermedia* beside this, the leaves also poses the antifungal and antiprotozoal activity against pathogen, which causing typhoid, cholera, tuberculosis, etc. The leaf extract shows the gastroprotective activity by enhancing the mucus rather than decrease the acid production. Chewing of betel leaf not only accelerating the salivation but also enhances the gastric juice, pancreatic lipase secretion which aids in digestion process. This may the reason for which traditionally pan was chewed after eating. The aqueous extract possess oral protective action against different acid-producing oral pathogens which changes in the ultra-structure of the enamel and its properties like *Streptococci, Lactobacilli,*

Staphylococci, Corynebacteria, Porphyromonas gingivalis and *Treponema denticola*. Chewing of betel leaf increase salivation which increases the contains of peroxidase, lysozyme and antibodies to combat bacterial growth in the oral cavity. It is the best choice for oral hygiene because while chewing bio-active phytochemicals are released into the oral cavity. The betel leaves are also reported to possess anti-mutagenic and anti-carcinogenic properties particularly against the tobacco carcinogens due to presence of phytoconstituents like hydroxychavicol and chlorogenic acid, the latter compound is also reported to kill the cancerous cell without affecting the normal cells unlike the common anticancer drugs. The chewing of betel leaf results cardio-tonic action by accelerating catecholamine from adrenal cortex contributing to increase the stamina of the cardiac muscles, heart rate, blood pressure and sympathetic neural activity. It has also the platelet inhibition activity leads vasorelaxation effect mediated through endothelium dependent and nitric oxide pathways. Hence, betel leaf is beneficial for different cardiovascular disorders like Congestive heart failure, Coronary artery disease, acute myocardial infarction, atherosclerosis etc. The aqueous leaf suspension has significant reduction in blood glucose level, act same as insulinomimetic. The methanolic extract of the betel leaf decrease the antibody titre and increase the suppression of inflammation suggests possible immunosuppressive effect of extract on cellular and humoral response. Considering the above properties, it comes to conclusion that betel leaf place its position in nature same as our heart in our body and role the same with lots of biological activities and has a tremendous strength to come out as a *future green medicine*, hence *Piper betle.* L. leaf regard as "Golden heart of Nature".

5. Future Perspectives

In recent years, multiple drug resistance has developed due to indiscriminate use of existing antimicrobial drugs in the treatment of infectious diseases. These problems stress a transformed attempt to find the antimicrobial agents effective against the pathogenic microorganisms resistant to current antibiotics. Therefore there is an extensive requirement to establish alternative antibacterial molecules for the treatment of infectious diseases from other sources. From this review it concluded that phenolic antibacterial from betel leaf cause suppression of bacterial activity in the oral cavity and prevents halitosis. Activity-directed purification led to the identification of allylpyrocatechol (APC) possessing antimicrobial activity against oral bacteria, *Staphylococcus aureus*. Crude aqueous extract of Piper betel was found effective against other oral microbes, which causes changes in the ultra-structure and its acid-producing properties like *Streptococci, Lactobacilli, Staphylococci, Corynebacteria, Porphyromonas gingivalis* and *Treponema denticola*. Gram positive bacterial strains were found to be more susceptible. It may be due to that cell wall of gram positive bacteria is less complex and lack natural sieve effect against large molecules due to small pores in their cell envelope. So, essential oil obtained from leaf extract may be commercialized by used as active pharmaceutical ingredient in different oral care product like toothpaste, mouthwash, mouth fresheners to get maximum result against dental pathogens. Due to high phenolic content in the leaf, the plant poses high antioxidant activity. Other pharmacological activities like antiulcer, antidiabetic, immunomodulatory, cardiovascular and anticancer were demonstrated in last two decade. Piper betel also offers a possibility for use in drug delivery though buccal mucosa by passing the gastric route, where drug has to endure gastric acidic pH. This route of administration may be beneficial for those Pharmaceutical drugs which acid labile i.e., degrading in the acidic medium. The betel leaf may enhance the bioavailability of a drug because of its nature as described by "Bhabaprakash", (Virya: Ushan). It supposed to elevate the temperature of plasma fluid which may ultimately fasten the drug absorption, hence the betel leaf may be used as natural bio enhancer. The leaves are very nutritive and contain substantial amount of vitamins and minerals. The leaves also contain the enzymes like diastase and catalase besides a

significant amount of all the essential amino acids except lysine, histidine and arginine, which are found only in traces; hence it has great potency to entry to the nutriceuticals industry as food additives.

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