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Review Article

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A REVIEW ON ANTI-INFLAMMATORY POTENTIAL OF *PIPER BETLE*

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ABSTRACT

The present review was aimed to find out the best natural remedies from medicinal plants like *Piper betle* that offer potential efficacy against inflammation. Several phytoconstituents classes such as flavonoids, triterpenoids, alkaloids, steroids, polyphenols etc. have been documented to possess interesting anti-inflammatory properties. Many of them exhibit potent bioactivities in minute concentrations against well-established biomarkers of inflammation. Natural plant metabolites extracted from medicinal herbs can act by modulating the expression of pro-inflammatory signals thus helps to manage arthritic conditions. Other than inflammation *Piper betle* is also reported to possess other bioactivities like antimicrobial, antibacterial, gastroprotective, wound healing, hepatoprotective, antioxidant, anti-fertility & antimotility activities etc. The review indicated that *Piper betle* is very useful medicinal herb to treat inflammation naturally with better safety and efficacy.

KEYWORDS: Inflammation, Arthritis, Natural remedies, Betel, Phytoconstituents, Medicinal herb.

1. INTRODUCTION

Inflammation is a complex biological response of body's vascular tissues to harmful stimuli such as pathogens (bacteria, viruses and parasites), damaged cells due to tissue injury or irritants. The inflammatory response is body's defence mechanism in organisms to protect them from injury or infection thus plays an important role in the healing process. It is a dynamic and multifactorial process involving many systems in the body.[1] The initiation of inflammatory response includes activation of immune cells or certain bio-molecules that are generally associated with inflammatory condition. Inflammation is characterized by the symptoms like redness, swelling, pain, heat and even the loss of function of associated tissue or organ. Cases of chronic inflammation are associated with several lethal diseases like allergies, arthritis, pneumonia, chronic obstructive pulmonary disease, diabetes and cardiovascular disorders etc.[2] There are several allopathic medications available with anti-inflammatory action in market. Among them the most commonly prescribed class of medications for pain or inflammation is Non-steroidal anti-inflammatory drugs (NSAIDs) that are used worldwide with an estimated usage of >30 million per day which is approximately 5-10% of all the medications available for inflammation and related disorders. The major action of NSAIDs is primarily due to their ability to block certain prostaglandins (PGs) synthesis through the inhibition of cyclooxygenase enzymes (COX-1 and COX-2). Most NSAIDs are well absorbed in the gastrointestinal tract and have high bioavailability. Besides the excellent anti-inflammatory potential and high market value of the NSAIDs, it has severe side effects such as gastrointestinal (GI) ulceration, perforation, obstruction, and bleeding etc.[3,4] In order to irradiate such serious side effects most of the population is moving towards the alternative sources for the treatment of inflammatory disorders. According to World Health Organization (WHO), about 3/4th or 80% of the world population depends on traditional medicines (mainly herbs or natural remedies) for their healthcare because natural products are safe, efficacious, biocompatible and cost-effective approach.[5] *Piper betle* is one such plant from natural source that inherits very good anti-inflammatory activities. The aim of this review is to provide detailed information about *Piper betle* and data of scientifically proven pharmacological studies of this plant against inflammation.

2. HERBAL MEDICINES FROM PLANT ORIGIN: A POTENTIAL APPROACH FOR INFLAMMATION TREATMENT

According to World Health Organization (WHO), most of the world's population depends on traditional herbal medicines for their healthcare as they are rich in therapeutically efficacious phyto-constituents. Ayurveda, Siddha, Unani, Homeopathy and Chinese system of medicines are traditional systems of practicing medicines of herbal origin. Discovery of new potential anti-

inflammatory agents from natural origin is a rational and productive approach towards the cure of inflammation related conditions.[6] Several investigations have shown that plants have been used in Traditional medicinal system for the treatment and management of distinct inflammatory disorders and wound healing activities.[7] In chronic inflammation cases biomolecules such as matrix-degrading enzymes, proinflammatory cytokines, and the components of signaling pathways are the promising therapeutic targets. The phyto-pharmaceuticals of natural origin exhibits great potential against inflammatory disorders through a variety of mechanisms i.e. interaction with important cellular targets including the inflammatory pathways or specifically with certain components of the pathways such as pro-inflammatory mediator production, complement cascade activation and leukocyte migration.[8] In the recent years, the use of indigenous knowledge about plants has gained considerable interest. This renewed interest in medicinal plant research has focused on herbal cures among populations around the world.[9] Most of the dietary supplements rich in polyphenols that act against inflammation by two mechanisms: (i) either by inhibiting or stimulating Cyclooxygenase-2 pathway (ii) Inhibition of arachidonic acid peroxidation.[10]

Medicinal plants have showed a significant potential in treatment of inflammation. Current medicinal therapies contain synthetic drugs that produce serious adverse effects on prolonged use such as gastric intolerance, bone marrow depression and water and salt retention etc. Medicinal plants or natural extracts are believed to be an important source of new lead compounds that are safer and with negligible side effects. A considerably large number of scientifically validated anti-inflammatory studies on *Piper betle* have been reported.[11]

3. *PIPER BETLE*: A POTENTIAL ANTI-INFLAMMATORY HERB

Medicinal plant *Piper betle* belongs to Piperaceae family and is commonly called as "betel vine" or "paan". This popular medicinal herb is mainly found in the South East Asia region and cultivated as commercial crop in some areas of India and Sri Lanka.[12] *Piper betle* is an evergreen dioeciously creeper with cordate shaped leaves.[13] Traditionally the betel plant was used as mouth freshener for the prevention of bad breath because of the antimicrobial properties and the leaves were chewed that produce psychoactive and cholinergic effects.[14] Betel leaves are reported to contain a lot of phytoconstituents that plays a major role in the prevention or management of several disease ailments. The main phyto-constituent classes reported are: volatile oil, glycosides, saponins, flavonoids and tannins despite this the plant also contains other chemical constituents such as minerals, enzymes, sugar, starch, vitamins & essential amino acids. In betel leaf the chief proportion of chemical constituent is essential oil (sesquiterpenes) that consists of chavicol, hydroxychavicol, chavibetol, carvacrol, estragol & eugenol etc. All the phytoconstituents present have been ascribed to possess a variety of therapeutic actions like antioxidant, anticarcinogenic, anti-inflammatory, gastroprotective, hepatoprotective, antimicrobial and antiseptic etc.[15–17]

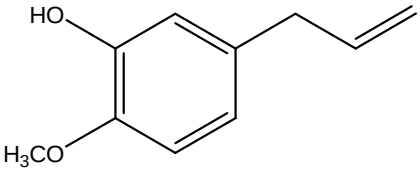
Fig. 1: *Piper betle* plant.

3.1 Active chemical constituents of *Piper betle*

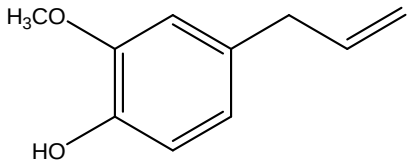
Piper betle leaves were reported to contain various chemical classes such as glycosides, vitamins, minerals, enzymes, tannins, essential amino acids, aromatic and volatile oil etc. Some important phyto-constituents of betel are listed down:

- **Chavibetol:** Chavibetol is a natural chemical compound which belongs to phenylpropanoid class and is the most important component of the leaves of the *Piper betle* plant. Chemically chavicol is an aromatic compound and an isomer of Eugenol.
- **Eugenol:** Eugenol is one of the chief constituent of *Piper betle* leaves. In a number of preclinical studies it showed good anti-inflammatory properties.[18]
- **Hydroxychavicol (HC):** Hydroxychavicol is chemically a phenolic compound and is reported to have anticarcinogenic or antimutagenic activity. It also exhibits anti-inflammatory, antioxidant, antibacterial, anti-platelet and antithrombotic effects without the impairment of hemostatic function. The proposed mechanism behind the anti-inflammatory action of hydroxychavicol is inhibiting the phrase of the pro-inflammatory cytokine TNF-α.[19]
- **Allylpyrocatechol:** Allylpyrocatechol is another important constituent of betel herb which possess great antioxidant effects and is very beneficial constituent for the cure of gastric lesions induced by synthetic NSAIDs such as Indomethacin
- **Quercetin:** Quercetin is a flavonoidal compound and belongs to the subclass category i.e. flavonols. Quercetin exhibits various bioactive properties such as antiviral, antibacterial, anti-carcinogenic and anti-inflammatory properties etc.
- **β-Caryophyllene:** β-Caryophyllene is a chief volatile compound of *Piper betle* leaves and has been shown to possess anti-inflammatory properties. It act as a potent, selective and non-psychoactive full agonist for CB2 receptor and exerts anti-inflammatory properties.[18,20,21]

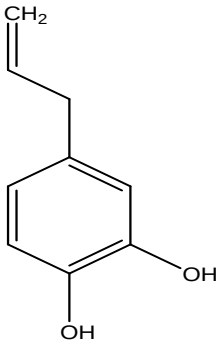
- **Others:** Tannins, Flavonoids, Alkaloids, Terpenoides, Saponins, Anthraquinones, Cardiac-glycosides, Reducing sugars and phlobatanins.[22]



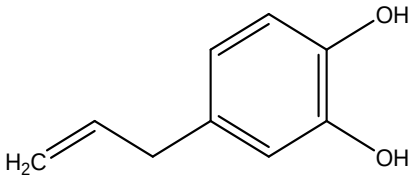
Chavibetol



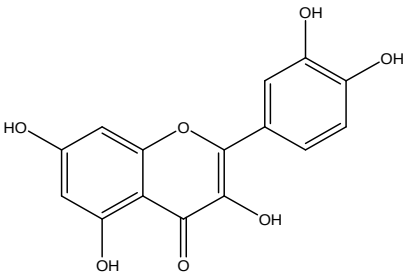
Eugenol



Hydroxychavicol



Allylpyrocatechol



Quercetin

3.2 Therapeutic Profile of *Piper betle*

The *P. betle* plant as a whole reported to possess various therapeutic activities. From being traditionally used as mouth fresher to medical therapies for serious or chronic diseases it has shown great potential with versatile pharmacological activities.[23,24]

P. betle is reported to possess anti-fertility activity in male rats, anti-motility effects on human spermatozoa, gastroprotective and hepatoprotective activities.[25–28] The literature has evidence of various beneficial uses of *Piper betle L.* such as treating bronchitis, difficulty in breathing, cough, inflammation and infections of the respiratory tract etc. The fruits of betel are taken with honey as a remedy for cough. Leaves have been used from centuries for the prevention of body odor, shortness of breath, throat problems and lung treatment. It is also used to prevent and cure coughs and prevents itching caused by fungi or bacteria.[29] The betel leaves extract possesses anti-mutagenic, anti-carcinogenic, antiplaque and antibacterial bioactivities.[30,31]

Piper betle are reported to contain high content of phenolics and this has been attributed to its antioxidant activity. The consumption of antioxidant-rich foods helps to neutralize the free radicals in the body, thus preventing or delaying the oxidative damage of lipids, proteins and nucleic acids. The antioxidants could reduce the risk of cardiovascular diseases and provide protection against cancer or other chronic diseases. The aqueous extract of the inflorescence of *Piper betle* extract is effective in scavenging H_2O_2, superoxide radical and hydroxyl radical.[32] Similarly, high content of flavonoid has been attributed to antioxidant & anti-ulcerogenic activity. The betel extracts has the ability to heal gastric ulcers and peptic ulcers. Earlier gastro protective properties of the leaf extract was also reported on experimentally induced gastric lesions.[33]

Hydroxychavicol (HC) an important chemical constituent of *P. betel* inhibits platelet aggregation. It is a potent COX-1/COX-2 inhibitor, reactive oxygen species (ROS) scavenger and platelet calcium signaling blocker. This phytoconstituent of betel plant used as a therapeutic agent for cardiovascular diseases and anti-inflammatory properties.[34]

The roots of *P. betel* were reported to treat rheumatoid arthritis. It is used in the form of decoction in curing wounds, burns, impetigo, boils, eczema, lymphangitis

and juice is beneficial stomachic. The juice of *P. betel* leaves has been proven effective in healing pharyngitis, abdominal pain and swelling. The leaves are used by the local peoples for skin diseases, halitosis, cuts and injuries, a digestive pancreatic lipase stimulant and for wound healing.[35,36]

The juice of the leaves is dropped into the eye in case of night blindness. The essential oil from the betel leaves is used in the treatment of catarrhal disorders. The aqueous and ethanolic extract of betel leaves have strong antidiabetic activity.[37]

The ethanolic extract of betel possessed radioprotective activity as it can prevent DNA-strand breaks induced by radiation.[38] The roots and fruits are well-known for treatment of malaria.[39] *Piper betle* leaves are used to lighten melasma that may produce leukomelanosis (skin depigmentation).[40] Hydroethanolic extract of *Piper betle* leaves possess great antidepressant and antianxiety activities and the mechanism is based on blocking certain neurotransmitters such as dopamine, serotonin or non-adrenaline etc. in brain.[41]

4. SUMMARY OF SOME REPORTED PHARMACOLOGICAL ANTI-INFLAMMATORY STUDIES ON *PIPER BETLE*

Various experimental anti-inflammatory pharmacological activities has been documented in the literature we have summarized some of them that gives a scientific basis of *Piper betle* herb as potential agent to treat inflammation and its related disorders that are described as below:

4.1 Saeed SA *et al.*, (1993) isolated ursonic acid from *Piper betle* roots and investigated for anti-inflammatory action using Carrageenan induced rat paw edema model. Aspirin was used as standard drug and the drugs were administered orally. The result of study evidence that ursonic acid possesses significant anti-inflammatory activities.[42]

4.2 Khozirah S *et al.*, (2000) isolated active constituents (chavibetol, chavibetol acetate and chavicol) from betel leaves using bioactivity guided fractionation and the extracts were then investigated for *in vivo* as well as *in vitro* anti-inflammatory studies. *In vitro* studies were done using Lipoxygenase inhibition assay whereas *in vivo* studies were carried out using carrageenan induced paw oedema and TPA induced ear oedema. The results of study showed that hexane and dichloromethane extracts were effective against screened models of inflammation.[43]

4.3 Ganguly S *et al.*, (2007) conducted an animal study to explore the anti-inflammatory activity of ethanolic extract of *Piper betle* leaves (100mg/kg) using Freund's adjuvant-induced arthritis model. Dexamethasone (0.1mg/kg) was used as standard drug. The result showed decrease in extracellular production of nitric oxide in murine peritoneal macrophages and it is concluded that the anti-inflammatory activity is due to reduction in generation of reactive nitrogen species.[44]

4.4 Vaghasiya Y *et al.*, (2007) examined *Piper betle* crude leaf powder suspension against acute and chronic inflammation. Diclofenac sodium was used as control. For acute inflammation studies Carrageenan induced paw edema and dextran models were used whereas for chronic inflammation studies cotton pellet induced granuloma model was used. The results of study demonstrated that *Piper betle* possess significant activity against acute and chronic inflammation models.[45]

4.5 Sarkar D *et al.*, (2008) demonstrated the anti-inflammatory potential of Allylpyrocatechol an important constituent of betel leaves using experimental animal model of inflammation. The main objective of this study was to reveal the exact mechanism behind anti-inflammatory activity of allylpyrocatechol so different assays like lipoplysaacharide induced production, effect on TNF-alpha etc. were investigated. The findings of the study indicated allylpyrocatechol inhibits nuclear factor κB pathway activation and suppress iNOS, COX-2 thus act as a potential agent for treatment of inflammatory disorders.[46]

4.6 Sharma S *et al.*, (2008) isolated hydroxychavicol from *Piper betle* leaf extract and examined for the anti-inflammatory activity. The results of study indicated that hydroxychavicol showed anti-inflammatory activity via lipid peroxidation inhibition and suppression of TNF-alpha in human neutrophils.[47]

4.7 Pandey A *et al.*, (2010) examined the anti-arthritic potential of major phenolic compound (hydroxychavicol) from *Piper betle* leaves aqueous extract using adjuvant induced arthritis experimental model. Hydroxychavicol was given as homogenized suspension to test group and prednisolone was used as standard dug for comparison. The results of study showed that hydroxychavicol cause dose dependent significant inhibition of oedema and swelling and the effect produce due to the reduction in pro-inflammatory cytokines level.[48]

4.8 Pink KY *et al.*, (2010) conducted a study to investigate the anti-inflammatory activity of *Piper betel* leaves extracts with solvents of different polarity. Hyaluronoidase, Xanthine oxidase and Lipoxygenase inhibition assays were used to detect the anti-inflammatory potential of betel leaves. All the extracts showed significant inhibition in xanthine oxidase and lipoxygenase level and is believed to be due to the presence of hydroxychavicol and eugenol in high content.[49]

4.9 Alam B *et al.*, (2013) carried out *In vivo* anti-inflammatory studies on methanolic extract of *Piper betle* leaves using Carrageenan induced paw edema

model in wistar rats. Indomethacin (10mg/kg body weight, p.o.) was used as standard drug. Extract of betel leaves was administered to test group (100 and 200mg/kg). The percentage inhibition of inflammation was then calculated. The results showed that *Piper betle* exhibits strong anti-inflammatory activity.[31]

4.10 Lin C-F *et al.*, (2013) isolated a novel hydroxychavicol dimer from the roots of *Piper betle* along with five already known compounds i.e. hydroxychavicol, aristolactam A II, aristolactam B II, piperolactam A and cepharadione A. All the compounds were examined for anti-inflammatory potential using N-Formyl-Methionyl-Leucyl-Phenylalanine assay. FMLP induces reactive oxygen species (ROS) that plays important role during an inflammatory response and the anti-inflammatory potential of chemical compounds isolated from betle roots was calculated on the basis of degree of ability to reduce the ROS. The results of study revealed that among all the isolated compounds only hydroxichavicol and its dimer were found to be moderately active against inflammation.[50]

4.11 Said SM *et al.*, (2013) examined the *in vitro* anti-inflammatory assessment of essential oil from betel herb via inhibition of Interleukin-6 (a pro-inflammatory cytokine). The findings of study suggested that essential oil from betel herb possess significant anti-inflammatory activity.[51]

4.12 De S *et al.*, (2015) conducted an animal study to check the influence of *Piper betle* pre-treatment to minimise the hepatotoxic effect of methotrexate. Rats pre-treated with betel orally were treated with methotrexate intra-peritoneal. Upon assessment it was found that *Piper betle* pre-treatment was effective to mitigate the level of certain parameters which was markedly unbalanced due to hepatotoxic effect of methotrexate. It was concluded from the study that effect may produce due to the beneficial antioxidant and anti-inflammatory activities of betel.[52]

4.13 Paridhi B *et al.*, (2015) conducted an in vitro anti-inflammatory study of essential oil of *Piper betle.* The anti-inflammatory potential was determined using gelatin zymography assay by the measurement of MMP-2 & MMP-9. The study proved that betel leaves exhibits great anti-inflammatory potential.[53]

4.14 Rintu D *et al.*, (2015) evaluated *Piper betle* leaves methanolic extract for anti-inflammatory activity assessment on RAW 264.7 cell lines using lipopolysaccharide (LPS) induced response assay. Dexamethasone was treated as positive control whereas cells treated with LPS was considered as negative control. Cell lines treated with LPS induces the production of TNF-α expression, nitric oxide, iNOS proteins etc. The results of study suggested that betle leaves cause a reduction in the levels of various protein expression agents that was induced upon LPS treatment. Highest anti-inflammatory activity of betle leaves extract was recorded at concentration of 250µg/ml.[54]

4.15 Suganthi R *et al.*, (2016) synthesized titanium nanoparticles from *Piper betle* leaves evaluated for *in vitro* anti-inflammatory activity using protein denaturation bioassay. Diclofenac sodium was used as standard control. The results of study showed that titanium nanoparticles of betel prevent denaturation of protein and thus exhibit anti-inflammatory activity.[55]

4.16 Hegde K *et al.*, (2018) investigated the hydroalcoholic extract of *Piper betle* leaves at two doses 200mg/kg and 400mg/kg using Freund's adjuvant induced arthritis model in male albino wistar rats. Diclofenac sodium (50mg/kg) was used as positive control. Anti-arthritic activity was assessed by the examination of physical parameters (paw volume, paw diameter, body weight etc.), serum parameters (SGOT, SGPT, Rheumatoid factor) and histopathological parameters etc. Upon result analysis it was found that both the doses shows dose dependent anti-arthritic activity.[56]

4.17 Vikrama Chakravarthi P *et al.*, (2018) carried out *in vitro* xanthine oxidase inhibitory assay to explore the antigout ativity of *Piper betel* alcoholic extract. Assay was carried out using UV-Spectrophotometer along with allopurinol as standard. The results of assay stated that betel extract was effective xanthine oxidase enzyme inhibitor at a concentration of 100µg/ml.[57]

4.18 Murugesan S *et al.*, (2020) investigated the anti-arthritic activity of betle leaves crude extact in female wistar rats using Freund's adjuvant-induced arthritis model. Ibuprofen was used as standard drug. Rheumatoid arthritis was induced by injecting 100µl CFA intradermally in right hind paw of animals. All the standard and test doses were administered orally to the experimental animals. The activity was assessed by determination of paw swelling and body weight. In vivo study showed significant activity at a dose of 250 and 500mg/kg.[58]

4.19 Sathi SS *et al.*, (2020) conducted comparative wound healing activity of *Piper betle* leaves and *Ocimum sanctum* leaves using incision wound model in wistar rats. Leaves of betel and tulsi were macerated and 10% ointment of each was prepared. Animals were divided into groups i.e. control, standard, test etc. and treated accordingly. The results of study suggested *Piper betle* is more effective wound healing properties as compared to the *Ocimum sanctum.*[59]

4.20 Chakravarthi Periasamy V *et al.*, (2021) investigated the anti-gout activity of *Piper betle* in gout induced boiler chickens. Allopurinol was used as standard drug. Female chicks were divided into groups i.e. control, standard and test group (eight birds per group was taken). The signs of gout production and

performance of test were examined using serum uric acid and creatinine estimation from blood samples. The results of the study revealed significant decrease in uric acid content which indicates the anti-gout potential of betel herb.[60]

4.21 Nadig PA *et al.*, (2021) performed comparative *in vitro* anti-inflammatory studies on *Piper betel* leaves collected from Western Ghats and Northern region of Karnataka. Ethanolic extract of betel leaves from different regions was used as test sample. Assays used for the assessment of activity were human RBC membrane stabilization method, protease inhibition assay and protein denaturation assay. The results of study showed that betel leaves extract from Western Ghats region showed significant activity against inflammation.[61]

5. CONCLUSION

Inflammation is a major cause of many diseases in human population all over the world. Although numerous synthetic drugs available in the market either steroidal or non-steroidal but their excessive and prolonged use may cause serious or lethal side effects. Hence most of the population is looking forward to the alternate therapies for the management of such diseases. Among all the alternate's available drugs from natural sources is the leading source as they are cost effective, safer, efficacious and biocompatible. Since time immemorial the use of natural products is in practice from ancient time period to this modern era. In this review we choose the herb *Piper betle* which belongs to the natural background and contains several phytoconstituents that inherits a lot of bioactivities like anti-oxidant, antimicrobial, anti-inflammatory, wound healing, antiulcerogenic, gastroprotective, hepatoprotective, anticarcinogenic, radioprotective etc. Among all the above mentioned pharmacological activities betel herb possess potent anti-inflammatory activities hence we summarized the reported scientifically proven bioactivities against inflammation in the review. From the outcomes of this review study we can say that *Piper betle* can serve as a potential lead candidate or prototype for the discovery of novel drugs for the treatment of inflammation and its related disorders.

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