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Therapeutic implications of piper betle: Recent trends and advancement

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Abstract
Plants contain a higher amount of biological compounds that are usually used in distinct types of health issues. Piper betle is one among the various therapeutically active herbal plants and known to possess a diverse range of secondary metabolites. It belongs to the *Piperaceae* or pepper family and commonly used in chewing agents to provoke offensive breath. Heart-shaped betle leaves contain several types of phytochemical compounds with antimutagenic, antiproliferative, antibacterial, and antioxidant properties. The betle plants are usually consumed in south Asian countries. Recent studies showed the remarkable role of such herbal drugs in chemoprevention against several types of cancer. Present review describes the potential of piper to modulate a diverse range of signaling molecules including transcription factors and reactive oxygen species (ROS) to regulate the multiple functions of several cellular processes including proliferation and death pathways.

Keywords: piper betle, bioactivity, chemo-preventive, anti-diabetic, anti-microbial

Introduction

Plants that have therapeutic and pharmacological beneficial effects on human beings are known as medicinal plants [1]. Medicinal plants are generally grown in natural conditions and found to possess a variety of secondary metabolites such as phenolic, flavonoid, terpenoids, alkaloids, saponin, sterols, terpenes, glycosides, tannins, and quinone etc. From thousands of years medicinal plants have been used for the treatment of illnesses, and chronic diseases [2] The demand for medicinal plant-based products and supplements has increased worldwide. Over the past three decades, it has been seen that phytochemicals are economic and cost effective with higher role in the cure disease. In addition, phyto-therapy is found to have either no side effect of a fewer in comparison to modern drugs [3, 4, 5, 6, 7, 8, 9].

Heart-shaped piper betle leaves belong to the family of *Piperaceae*. It is usually found in South Asian countries. It is typically located in hot and moist climate-related conditions. In the Asian region (Malaysia, Indonesia, India, Srilanka) betle leaves are used at social, cultural, and religious Auspicious occasions like marriage, religious festivals, etc [10, 11]. In India, it is cultivated in Bihar, Bengal, Orrisa, South India, and Karnataka [12]. The betle plant is used as a long-lasting and evergreen vine with silky heart-shaped leaves and white ament [12]. Betle leaf has many medicinal uses and has been commended in the old scriptures of Ayurveda for its acrid, antiseptic, aphrodisiac, aromatic, astringent, bitter, carminative hot, and stimulant properties [13]. It has also been used as an edible digestive therapy. It is found to very effective in the treatment of arthritis, orchitis, and gout. There are several types of piper betle leaves that exists in Indian culture such as Banarasi, Calcutta, Magahi, etc.. Among all the variety of leaves Magadhi considered to be very effective and found nearby Patna in Bihar [12]. A preparatory study reported that Piper betle leaves possessed a wide-ranging variability of biologically active compounds. It has several pharmaceutical actions such as anti-Inflammatory, antiplatelet, immuno-moderators, anti-diabetic activity, and gastro-protective. There are very fewer numbers of medicinal plants that have been identified with such a higher efficacy in various diseases.

Chemical constituents

The various chemical composites are found in the betle leaf with promising health associated therapeutic effects.[10] These compounds are piperol-A, piperol-B, methyl piper betlol. Piper betle leaves contain vital oil including safrole, chavibetol, allyl catechol, allyl-pyrocatechol mono-acetate, terpinene-4-oil, eugenyl acetate, eugenol, carvacrol, hydroxyl chavicol, caryophyllene, cineole, and estragole as the major components (Fig. 1). Other components which are also present such as campene, αpinene, a-limonene [10].

Betle leaves also comprise secondary metabolites like alkaloids, flavonoids, polyphenols, phenolic, steroids, saponins, tannin, triterpenoids, and vital oil [14]. Betle leaf has an enhanced source of carotene, niacin, vitamin C, thiamine, calcium, and riboflavin [15].

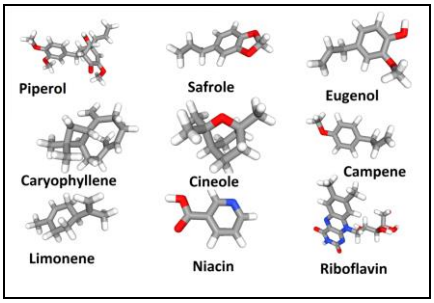

Fig 1: Ball and stick models of various major bioactive molecules from Piper betle.

Therapeutic Uses

The Piper betle contains secondary metabolites that have an essential role based on traditional use. Piper betle leaves are used as a mouth freshener and chewing for the prevention of bad breath due to their antibacterial activity, in wound healing, in enhancing digestion and pancreatic lipase stimulant activity, in the contracts and pulmonary diseases [14]. In Ayurveda, sometimes the extract of betle leaves is used as an adjuvant and gives a synergistic effect with other drugs besides role as a single drug. Betle leaf is a highly aromatic, laxative, appetizer. It also provides immunity to the liver and regulates blood flow. In Ayurveda, it is recommended as a heart-beat controller by relaxing blood flow in blood vessels. It also has higher activity against microbial and inflammation infection. The products or supplements of piper betle are cost-effective and easily reachable. Some parts of the betle plant particularly leave is used as a conventional medicine form for the treatment of health certain issues like abrasions, conjunctivitis, constipation, itches, rheumatism, etc [16]. The extracted oil from betle leaves also has bactericidal action. Betle leaves are usually taken as a feeling of freshness, improved saliva formation, sweating, and increased energy. The leaf of piper betle display many more medicinal properties such as antioxidant, anti-mutagenic, anti-microbial, wound healing, antifungal, and chemo-preventive activities.

Chemo-preventive effect of piper betle

Cancer is uncontrolled growth of cells due to mutation in the transcription factors and inhibition of suppressor genes expression [17, 18] According to the report of WHO, cancer accounts for the second major cause of death globally. Several studies have been reported that active molecules of piper betle such as hydroxychavicol displayed significant anti-proliferative potential against cancer. Bioactive molecules from piper are also known to show anti-mutagenic, inhibition of cyclooxygenase (COX), thromboxane B2 production, and platelet calcium signalling [15].

Piper betle's bioactive molecules are also known to decreases inflammatory molecules such as COX-2, and nitric oxide synthase via down-regulation of the NFκB signaling pathway. Aromatic compounds from piper betle are known to exhibit radioprotection and displayed the essential antitumor effect via free radical scavenging activities. Literature also suggested that bio active molecules of piper betle synergized and boost the anti-tumor effects of other chemotherapeutic drugs in various cancer cells. Similarly safrole is also present in betle leaves which known to be transformed into other bioactive and anti-mutagenic molecules such as eugenol and dihydroxychavicol. Chlorogenic acid another bioactive agent of betle leaves which selectively removes carcinogenic cells. The major chemo-preventive cell signalling mechanisms including activation of caspases, inhibition of cyclin, MMPs, COX, NFKB etc. has been shown in figure 2 [19, 16, 20, 21, 15].

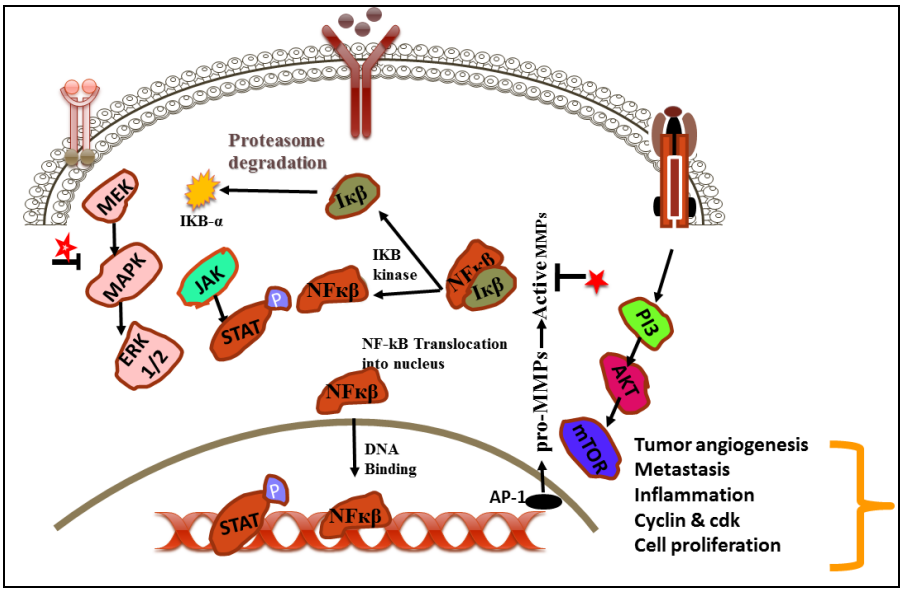

Fig 2: Schematic representations of various anti-cancer signalling pathways known to be modulated by piper betle molecules.

Pro-oxidants Activity of piper betle

The phytochemicals such as curcumin, resveratrol, epigallocatechingallate, caffeic acid, quercetin are classified under the phenol superfamily. Piper betle leaves are also known to have specific vital phenolic compounds including eugenol, hydroxychavicol, CHA, and piperol.[16,22] These compounds are known to work as defensive systems of the plant and provide them resistance against unfavourable conditions. Presence of such bioactive secondary metabolites provides chemo-preventive and chemotherapeutic properties to betle leaves extract. The pro-oxidant behaviour of the betle bioactive metabolites reduces the GSH level and enhances ROS concentrations. Numerous reports show the pro-oxidant activity of betle leaves compounds such as eugenol and hydroxychavicol. Hydroxychavicol has found to elevate ROS levels in cancer cells, and increase in a uniform manner to particularly kill them without affecting the normal cells. Literature suggests that quantity of hydroxyl groups determine the pro-oxidant behaviour of betle piper based.

Potential anti-diabetic

Evidences suggested that the piper betle leaves have potential to be used as nutraceutical for diabetes mellitus patients. Studies reported that piper betle can be utilized to formulate any therapy for type 2 diabetes patients. The ethanolic and aqueous extracts of piper betle leaves have revealed hypoglycemic action in abstained normoglycemic

rats. The extract displayed anti-hyper-glycemic action in the external glucose level for glucose tolerance test**.** [12] Researcher has also studied and found that crude extract of betle leave reduces glucose synthesis. The antioxidants compounds from piper belet are found to be very effective in modulating glucose levels. The ethanolic and water extracts of piper betle leaves are capable to inhibit **α** glucosidase activity in a concentration-dependent aspect [14].

Antiplatelet aggregation Activity

Bioactive constituents of Piper betle are also investigated as a promising source to inhibit platelet accumulation. Platelets aggregations are found to protect circulatory tumor cells from host immune system. Therefore, inhibition of platelet aggregation around tumor cells can lead to their destruction via body immune cells. Studies reported that bioactive molecules from piper betle act as free radicle scavenger, inhibits cyclooxygenase activity, and platelet calcium signaling, via thromboxane B2. Therefore such therapeutic strategies can prevent and treat platelets associated atherosclerosis, cardiovascular, and cancer**.** [10, 23]

Anti-microbial activity

Bioactive constituents from Piper betle was also investigated for antimicrobial activity against hundreds of microbial strains. For instance hydroxychavicol, a bioactive constituent displayed repressive effects on certain fungal species of clinical implication. Evidence suggested Piper betle as potential antifungal agent for certain candida infections [12]. The antifungal activity of six micro fractions (in various solvents) of piper betle was found by using the diffusion antimicrobial assays [24].

Similarly, Piper betle leaves are used for oral hygiene too by reducing the endogenous infection caused by oral microorganism.

Antihistaminic Activity

Histamine is known as common mediators in a variety of inflammation associated signalling cascade. Evidence suggested that piper betle possessed strong anti-histaminic potential in dose-dependent manner. A study conducted in guinea pig demonstrates anti-histamine potential of bioactive constituents of Piper betle in induced bronchoconstriction animal models. Results showed that ethanolic extract and essential oil of piper betle remarkably protected the Guinea pigs against histamine-induced bronchospasm. The piper betle leaves oil remarkably extend the period of spasm as compared to control followed by histamine aerosol. [25]

Conclusion

Evidence suggested that piper betle plant can be used to treat a variety of malignancies in various diseases including cancer and cardiovascular. Such natural therapeutic formulations may open new doors to the scientific world to come forward and explore other medicinal action. However future studies should also be initiated to extend clinical trials to investigate and explore translational role of piper betle. In addition the utilization of nano-based drug delivery systems using bioactive metabolites from piper betle can also be explored by the researchers.

Conflict of interest

Authors declare no conflict of interest.

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