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REVIEW ON THE PHARMACOLOGICAL ACTIVITIES OF PIPER SPECIES

Neethu M A, Kavitha MP, K. Krishnakumar*

Department of Pharmaceutical Analysis, St. James College of Pharmaceutical Sciences, Chalakudy, Thrissur, Kerala, India.
St. James hospital trust Pharmaceutical Research Center (DSIR certified), Chalakudy, Thrissur, Kerala, India.

ABSTRACT

A large number of natural products are being used as traditional medicine in several countries for the treatment of various diseases . The genus Piper belongs to the family Piperaceae and has over 2000 species. It is a well known spice considered as *''The King of spices''* among various spices. It contains a pungent alkaloid ''piperine'' which is known to possess many pharmacological actions. Piperine increases bioavailability of many drugs and nutrients by inhibiting various metabolising enzymes. The plants of genus Piper are also used for many other purposes such as foods and spices, fish bait, fish poison, hallucinogens, insecticides, oils, ornaments, perfumes etc. Piper species are of high commercial and economical importance such as *Piper nigrum*, it has world-wide spice market. The phytoconstituents obtained from Piper species are characterized by the production of typical classes of compounds such as amides, benzoic acids, chromenes, terpenes, phenylpropanoids, lignans, other phenolics and a series of alkaloids. They have shown antihypertensive, antiplatelet, antioxidant, antitumor, anti-asthmatics, analgesic, anti-inflammatory, anti-diarrheal, antispasmodic, antidepressants, immunomodulatory, anticonvulsant, anti-thyroids, antibacterial, antifungal, hepato-protective, insecticidal and larvicidal activities etc. This review article explains the pharmacological activities of Piper species.

Keywords: Piper species, Phytoconstituents, Piperaceae.

INTRODUCTION

It is widely accepted that there is an increasing use of herbal remedies or phytomedicines by the general public to replace or complement conventional medicines. Recently, the World Health Organization (WHO) estimated that 80% of the people worldwide rely on herbal medicines for some part of their primary healthcare [1]. Of the 250,000 to 300,000 plant species, only 5000 have been studied exhaustively for possible medical application. Hence our medicinal future is bright if the integrity of these plants and their growing conditions can be maintained. Also the WHO has emphasized the need to ensure the quality of medicinal plant products using modern controlled techniques and applying suitable standards. The goal of modern phytochemical research is to develop preparations derived from herbal drugs of traditional medicine to meet present day international standards of quality, safety and efficacy [2].

The genus *Piper*, the largest in the family Piperaceae consisting of more than 1000 species, occurs throughout the tropical and subtropical regions. The distribution of *Piper* ranges from sea level to the high ranges of Andes and Sub Himalayas Trans-Gangetic region and the South Deccan are considered to be the two independent centres of origin of the genus *Piper* in India. The sub mountainous tracts of the Western Ghats are believed to be the centre of origin of black pepper, *Piper nigrum* L. More than 1000 species are included in the genus *Piper*, of which 110 are of Indian origin [3].

The greatest diversity of *Piper* species is in the Neotropics, where about two thirds of the described species are found. Some 300 species are endemic to Southeast Asia, including the East Indian islands and northern Australia. Only two species are native to Africa. Most *Piper* species grow in wet, warm, lowland rain forests. Both diversity and abundance of *Piper* typically decrease with increasing elevation or with decreasing precipitation. *Piper* is the nominate genus of the family Piperaceae, a pantropical family composed of five to eight or more genera, depending upon the treatment. The two largest genera are *Piper* and *Peperomia*, each containing about 1,000 species. Peperomias are mostly small, succulent, often epiphytic herbs; pipers are woody and more diverse in habit, including shrubs (the great majority), climbing vines, and small trees [4].

Corresponding Author: **K. Krishnakumar Email:-** stjamespharmacyproject@gmail.com

PHYTOCONSTITUENTS OF DIFFERENT SPECIES OF PIPER

Piper nigrum contains piperine, pipereidine, chavicin, starch, protein, phellandrene, caryophyllene, cineole, p-cymene and carvoneThe presence of volatile oil consisting of terpenes, phellandrene, caryophyllene, piperonal-dihydrocarbeol and caryophyllene oxidesabenene, myrecene, limonene, ∝& β pinenes, ∝-benganotene, humulene, p-cymene and ∝-selinene was also reportedLignans cubebin was found only in *Piper cubeba*. Vitexin and marginatoside were found in the leaves of *Piper marginatum* . Myristicin, asarinin, sesamin and fargesin were found in *Piper mullesua* . The presence of hydroxychavicol acetate, allylprocatechol-piperbetol, eugenol, isoeugenol, safrol, anethole, stearic acid, methyl eugenol, carvacrol, polyphenol, alkaloids, saponin, tannin, steroids and other compounds like chavicol, chavibetol, allylpyrocatechol, chavibetol acetate in *Piper betle* were mentioned . The compound such as piperlotine A, piperlotine C, cinnamoylpyrrolidine, sermentine, pellitorine were found in *Piper lolot* . The presence of new benzoic acid derivatives crassinervic acid, aduncumene, hostmaniane and gaudichaudianic acid in *P. crassinervium*, *P. aduncum*, P. hostmania-num and *P. gaudichaudianum* were reported. The presence of tembamide acetate and alatamide into aerial parts of *Piper guayranum* were well documented. The compounds such as pyridine alkaloid, piplartine and piplartine dimer were found in *Piper aborescens* The presence of volatile oil, resin, alkaloids, calcium, phosphorous and iron into fruits of Piper were reported . The components such as taboganic acid, pinocembrin, pinocembrin chalcone, lanceaefolic acid methyl ester in *Piper lanceafolium* were mentioned. The presence of sakuranetin, anodendroic acid methyl ester and carotenoid lutein in *Piper aduncum* were reported [5].

EVIDENCE BASED PHARMACOLOGICAL ACTIVITIES

Antihypertensive Activity

Taqvi *et al* studied on the Blood Pressure Lowering and Vasomodulator Effects of Piperine. Intravenous administration of piperine caused a dose-dependent (1 to 10 mg/kg) decrease in mean arterial pressure (MAP) in normotensive anesthetized rats; the nexthigher dose (30 mg/kg) did not cause any further change in MAP. Thefall in blood pressure (BP) was followed by small increase in MAP after each dose. In Langendorrf 's rabbit heart preparation, piperine caused partial inhibition and verapamil caused complete inhibition offorce and rate of ventricular contractions and coronary flow. In rabbitaortic rings, piperine inhibited high K+ (80 mM) precontractions and partially inhibited phenylephrine (PE), suggesting Ca2+ channel blockade (CCB), which was further confirmed when pretreatment of tissues with piperine caused rightward shift in Ca2+ concentration response curves, similar to verapamil. In Ca2+-free medium, piperine (1 to 30 mM) exhibited vasoconstrictor effect. In rat aorta, piperine demonstrated endothelium-independent vasodilator effect and was more potent against high K+ precontractions than PE. In bovinecoronary artery preparations, piperine inhibited high K+ precontractions completely. These data indicate that piperine possesses a blood pressure–lowering effect mediated possibly through CCB, while consistent decrease in BP was restricted by associated vasoconstrictor effect [6].

Anti Asthmatic Activity

Kaushik *et al* studied on the In vivo and In vitro anti asthmatic studies of plant Piper longum Linn. and found that the fruits of Piper longum Linn are used in allergic skin disorder and asthma. The effect of petroleum ether, alcoholic and decoction of the fruits of *P.longum* was studied for anti histaminic activity using Guinea pig ileum preparation (in vitro),histamine induced bronchospasm in Guinea pig and haloperidol induced catalepsy in mice (in vivo).Its antiallergic activity was evaluated using milk induced leucocytosis in mice and passive paw anaphylaxis in rats(in vivo). The extracts (100µg/ml) significiantly ($p<0.01$) inhibited the histamine induced contraction of isolated Guinea pig ileum preparation.The extracts(50,100,200mg/kg)showed the significiant ($p<0.01$)activity and increase in dose of extract ,increased the % protection in histamine induced bronchospasm and also showed significant ($p<0.01$)activity in haloperidol induced catalepsy and passive paw anaphylaxis. In milk –induced leukocytes,petroleum ether and decoction extract (200mg/kg)showed significiant ($p<0.05$)decrease in number of leukocytes and alcoholic extract didn't show any significiant effect [7].

Anti Microbial Activity

Khan *et al* studied on the antimicrobial activity of piper fruits and found that Twenty eight extracts prepared from the fruits of four species viz *Piper cubeba Linn.f., P.retrofractum Vahl syn, P.chaba Hunter non Blume, P.longum Linn and P.nigrum Linn*. were evaluated against bacterial pathogens, such as *Staphylococcus albus, Salmonella typhi, Pseudomonas aeroginosa, Escherichia coli* and *Bacillus megaterium* and one fungus, *Aspergillus niger*. Compared to Streptomycin all the extracts exhibited a good antibacterial activity. Some of the extract showed antifungal activity as well [8].

Anticancer Activity

Manoharan *et al* studied on the Chemopreventive efficacy of curcumin and piperine during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis by the method Oral squamous cell carcinoma was developed in the buccal pouch of Syrian golden hamsters, by painting them with 0.5 percent DMBA in liquid paraffin, three times a week for 14 weeks. The tumour incidence, tumour volume and burden were determined in the buccal pouches. The status of phase II detoxification agents, lipid peroxidation and antioxidants were estimated by specific colorimetric methods and found that 100 percent tumour formation in DMBA-alone painted hamsters. Disturbances in the status of lipid peroxidation, antioxidants and phase II detoxification agents were

noticed in DMBA-alone painted hamsters. Oral administration of curcumin (80 mg/kg body weight) and piperine (50 mg/kg body weight) to DMBA-painted hamsters on alternate days to DMBA painting for 14 weeks completely prevented the formation of oral carcinoma. Also, curcumin and piperine restored the status of lipid peroxidation, antioxidants and detoxifying agents in DMBA-painted hamsters [9].

Selvendiran *et al* studied on the Chemopreventive effect of piperine on modulating lipid peroxidation and membrane bound enzymes in benzo(a)pyrene induced lung carcinogenesis.and to evaluate the effects of orally supplemented piperine on lung tumour initiation by B(a)p, its effects on ATPase enzymes were first evaluated. Lung cancer bearing mice showed an increase in erythrocyte membrane and tissues ATPase enzymes (Na(+)/K(+)-ATPases, Mg(2+)-ATPases and Ca(2+)-ATPases). Na(+) K-ATPase and Mg-ATPase enzyme activities were decreased and calcium ATPase increased ($P < 0.05$) in erythrocyte membrane and tissues of lung cancer bearing animals compared with control groups. The elevation of these enzyme activities in membrane and tissues were indicative of the persistent deteriorating effect of B(a)p in cancer bearing animals. These enzyme activities were reversed to near normal control values in animals treated with piperine (50 mg/kg body weight). It is apparent that the beneficial effect of piperine is primarily exerted on the during initiation phase and post-initiation stage of B(a)p induced lung carcinogenesis. Overall, these data indicative that piperine has chemopreventive effects when administered orally on lung cancer bearing animals [10].

Cognitive Action

Wattanathorn J *et al* studied on the Piperine, the potential functional food for mood and cognitive disorders and observed that The effect of piperine, the main alkaloid from piper nigrum, on the central nervous system is not clearly known until now. In the present study, male Wistar rats were administered piperine at various doses ranging from 5, 10 and 20mg/kg BW once daily for 4 weeks and the animals were determined the neuropharmacological activity after single, 1, 2, 3 and 4 weeks of treatment. The results showed that piperine at all dosage range used in this study possessed anti-depression like activity and cognitive enhancing effect at all treatment duration. Therefore, piperine may be served as the potential functional food to improve brain function [11].

Anti-inflammatory Activity

Bang J S *et al* studied on the in vitro anti-inflammatory activity of piperine was tested on interleukin 1beta (IL1beta)-stimulated fibroblast-like synoviocytes derived form patients with rheumatoid arthritis. The levels of IL6, matrix metalloproteinase (MMPs), cyclo-oxygenase 2 (COX-2), and prostaglandin E2 (PGE2) were investigated by ELISA and RT-PCR analysis. The analgesic and antiarthritic activities of piperine were investigated on rat models of carrageenan-induced acute paw pain and arthritis. The former were evaluated with a paw pressure test, and the latter by measuring the squeaking score, paw volume, and weight distribution ratio. Piperine was administrated orally to rats at 20 and 100 mg/kg/day for 8 days and found that Piperine inhibited the expression of IL6 and MMP13 and reduced the production of PGE2 in a dose dependant manner at concentrations of 10 to 100 microg/ml. In particular, the production of PGE2 was significantly inhibited even at 10 microg/ml of piperine. Piperine inhibited the migration of activator protein 1 (AP-1), but not nuclear factor (NF) kappa B, into the nucleus in IL1beta-treated synoviocytes. In rats, piperine significantly reduced nociceptive and arthritic symptoms at days 8 and 4, respectively. Histological staining showed that piperine significantly reduced the inflammatory area in the ankle joints [12].

Hepatoprotective Activity

H Matsuda *et al* studied on the Protective effects of amide constituents from the fruit of Piper chaba on D-galactosamine/TNF-alpha-induced cell death in mouse hepatocytes and concluded that the methanolic extract from the fruit of Piper chaba (Piperaceae) was found to have a hepatoprotective effect on D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced liver injury in mice. From the ethyl acetate-soluble fraction, a new amide constituent named piperchabamide E together with twenty known amide constituents (e.g., piperine, piperchabamides A-D, and piperanine) and two aromatic constituents were isolated as the hepatoprotective constituents. With regard to structure-activity relationships, the amide moiety and the 1,9-decadiene structure between the benzene ring and amide moiety were suggested to be important for strong inhibition of D-GalN/tumor necrosis factor-alpha (TNF-alpha)-induced death of hepatocytes. Furthermore, a principal amide constituent, piperine, dose-dependently inhibited increase in serum GPT and GOT levels at doses of 2.5-10 mg/kg (p.o.) in D-GalN/LPS-treated mice, and this inhibitory effect was suggested to depend on the reduced sensitivity of hepatocytes to TNF-alpha [13].

Anti Diarrhoeal Activity

Shamkuwar *et al* studied on the topic Evaluation of antidiarrhoeal effect of Black pepper (Piper nigrum L.) and found that Aqueous black pepper extract (75, 150, 300 mg/kg, po) was tested for its antidiarrhoeal, antimotility and antisecretory activity in mice. The methods of castor oil and magnesium sulphate induced diarrhoea were used to evaluate antidiarrhoeal activity, while charcoal meal test and castor oil induced intestinal secretions were used for testing antimotility and antisecretory activity in mice. Aqueous Black pepper extract (ABPE) produced a significant and dose dependent antidiarrhoeal, antimotility, and antisecretory effect. Preliminary phytochemical screening of ABPE showed the presence of carbohydrates, and alkaloids. It can be concluded that ABPE possesses antidiarrhoeal effect may be due to its antimotility and antisecretory effect. Antimotility and antisecretory effect of Black pepper may be due to the presence of carbohydrates and alkaloids [14].

Antidepressant Activity

Mao QQ *et al* studied on the Piperine reverses the effects of corticosterone on behavior and hippocampal BDNF expression in mice and found that A mouse model of depression has been recently developed by exogenous corticosterone administration. The present study aimed to examine the antidepressant-like effect and the possible mechanisms of piperine, a major alkaloid of black pepper (Piper nigrum Linn.) and long pepper (Piper longum Linn.), in corticosterone-induced depression in mice. The results showed that 3-weeks corticosterone injections caused depression-like behavior in mice, as indicated by the significant decrease in sucrose consumption and increase in immobility time in the forced swim test and tail suspension test. Moreover, it was found that brain-derived neurotrophic factor protein and mRNA levels in the hippocampus were significantly decreased in corticosterone-treated mice. Treating the animals with piperine significantly suppressed behavioral and biochemical changes induced by corticosterone. The results suggest that piperine produces an antidepressant-like effect in corticosterone-treated mice, which is possibly mediated by increasing brain-derived neurotrophic factor expression in the hippocampus [15].

Li *et al* studied on the Antidepressant like effects of piperine in chronic mild stress treated mice and its possible mechanismsand found that In this study, we investigated the antidepressant-like effect of piperine in mice exposed to chronic mild stress (CMS) procedure. Repeated administration of piperine for 14 days at the doses of 2.5, 5 and 10 mg/kg reversed the CMS-induced changes in sucrose consumption, plasma corticosterone level and open field activity. Furthermore, the decreased proliferation of hippocampal progenitor cells was ameliorated and the level of brain-derived neurotrophic factor (BDNF) in hippocampus of CMS stressed mice was up-regulated by piperine treatment in the same time course. In addition, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactic dehydrogenase (LDH) assays showed that piperine (6.25-25 microM) or fluoxetine (FLU, 1 microM) dose-dependently protected primary cultured hippocampal neurons from the lesion induced by 10 microM corticosterone (CORT). Reverse transcription-polymerase chain reaction (RT-PCR) was used to detect the messenger ribonucleic acid (mRNA) level of BDNF in cultured neurons. Treatment with piperine (6.25-25 microM) for 72 h reversed the CORT-induced reduction of BDNF mRNA expression in cultured hippocampal neurons. In summary, up-regulation of the progenitor cell proliferation of hippocampus and cytoprotective activity might be mechanisms involved in the antidepressant-like effect of piperine, which may be closely related to the elevation of hippocampal BDNF level [16].

Immunomodulatory Activity

Sunila *et al* studied on the Immunomodulatory and antitumor activity of Piper longum Linn. and piperine and found that Alcoholic extract of the fruits of the plant Piper longum and its component piperine was studied for their immunomodulatory and antitumor activity. Alcoholic extract of the fruits was 100% toxic at a concentration of 500 microg/ml to Dalton's lymphoma ascites (DLA) cells and 250 microg/ml to Ehrlich ascites carcinoma (EAC) cells. Piperine was found to be cytotoxic towards DLA and EAC cells at a concentration of 250 microg/ml. Alcoholic extract and piperine was also found to produce cytotoxicity towards L929 cells in culture at a concentration of 100 and 50 microg/ml, respectively. Administration of alcoholic extract of Piper longum (10 mg/dose/animal) as well as piperine (1.14 mg/dose/animal) could inhibit the solid tumor development in mice induced with DLA cells and increase the life span of mice bearing Ehrlich ascites carcinoma tumor to 37.3 and 58.8%, respectively. Administration of Piper longum extract and piperine increased the total WBC count to 142.8 and 138.9%, respectively, in Balb/c mice. The number of plaque forming cells also enhanced significantly by the administration of the extract (100.3%) and piperine (71.4%) on 5th day after immunization. Bone marrow cellularity and alpha-esterase positive cells were also increased by the administration of Piper longum extract and piperine [17].

Anti Convulsant Activity

Chen CY *et al* studied on the Piperine exerts anti-seizure effects via the TRPV1 receptor in mice and found that The mechanisms involved in the anti-seizure property of piperine (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-(E,E)-piperidine, C17H19NO3) are still unclear. Piperine could activate transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, and the rapid activation of whole-cell currents is antagonized by the competitive TRPV1 antagonist capsazepine. Interestingly, recent studies have reported that TRPV1 may be a novel anti-epileptogenic target which led us to hypothesize that the anti-seizure property of piperine involves the TRPV1 receptor. To test this hypothesis, we examined the effect of piperine on seizures induced in mice and identified the receptors involved in the suppression of seizure caused by maximal electroshock (MES) and pentylenetetrazol (PTZ) models. Piperine, administered at doses of 40 and 80 mg/kg, significantly delayed the onset of myoclonic jerks and generalized clonic seizures, and decreased the seizure stage and mortality compared with the vehicle-treated animals. Piperine also significantly reduced the incidence of MES-induced tonic hindlimb extension (THE) and PTZ-induced Fos immunoreactivity in the dentate gyrus. The anti-seizure effects of piperine were blocked by a TRPV1-selective antagonist capsazepine. Taken together, these data support the further investigation of piperine as a TRPV1 agonist for anti-seizure therapy [18].

CONCLUSION

It was revealed from these articles that Black Pepper possesses significant *in vitro* and *in vivo* pharmacological potential for the treatment of different ailments and diseases and found to be safe. Piperine has also been found to increase the absorption of many drugs and shown bioavailability enhancing activity of many

drugs and nutrients. This important property of piperine may be very helpful to enhance the therapeutic efficacy of many therapeutically important drugs. It is therefore concluded that Black pepper and its bioactivecompound Piperine exhibited wide spectrum therapeutic potential and also emerged as an excellent adjuvant to enhance the therapeutic efficacy of the concurrently administered drugs and nutrients. Further detailed research studies are needed to obtain more scientific data on this miraculous King of spices.

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None

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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