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PHARMACOTHERAPEUTIC PROPERTIES OF BLACK PEPPER: A SYSTEMATIC REVIEW

Y. Suvarna*¹ and SK. Abdul Rahaman¹

¹*Department of Pharmaceutical Analysis, Nirmala College of Pharmacy, Mangalagiri, Andhra Pradesh, India.

ABSTRACT

Alkaloids are the natural products that are produced during secondary metabolism in living organisms. Alkaloids are classified into different types. Among them Piperidine and pyrrolidine alkaloids form one of the largest groups of alkaloids. *Piper nigrum* (family Piperaceae) is one of the most commonly used spices and considered as "The King of spices". It contains major pungent alkaloid Piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological actions like antihypertensive, antiplatelets, antioxidant, antitumor, antiasthmatic, antipyretic, anti-inflammatory, anti-diarrheal, antispasmodic, anxiolytic, hepato-protective, immuno-modulatory, antibacterial, antifungal, anti-thyroids, antiapoptotic, antimutagenic, anti-spermatogenic, anti-colon toxin, insecticidal and larvicidal activities etc. Along with the pharmacologically diversified activities, piperine can also act as bioavailability enhancer.

KEYWORDS

Piperine, Alkaloids, *Piper nigrum* and Pharmacological activity.

Author for Correspondence:

Suvarna Y,
Department of Pharmaceutical Analysis,
Nirmala College of Pharmacy,
Mangalagiri, Andhra Pradesh, India.

Email: suvarna.ph52@gmail.com

INTRODUCTON

A natural product is a chemical compound or substance produced by a living organism that is, found in nature. Natural products can also be synthesized by chemical methods and have plays a major role in the development of the field of organic chemistry by providing challenging synthetic targets. The term natural product can also be referred to cosmetics, natural food products and dietary supplements without any added artificial ingredients.

In organic chemistry, the definition of natural products is restricted to purified organic compounds isolated from natural sources and are produced as metabolites in primary or secondary

metabolism¹. Within the field of medicinal chemistry, the definition is often further restricted to secondary metabolites. Secondary metabolites are not essential for survival, but nevertheless provide organisms that produce them an evolutionary advantage. Most of the secondary metabolites that were selected and optimized through evolution are used as "chemical warfare" agents i.e. against competing organisms, prey and predators.

Natural products which have pharmacological or biological activity can be used for therapeutic benefits. Therefore, natural products are the active components of most traditional medicines and in many modern medicines too. In addition to this, the structural diversity of natural products can be achieved by chemical synthesis and so synthetic analogs are prepared with improved potency and safety. Natural products are generally considered as starting points for drug discovery and most of the drugs approved by U.S. Food and Drug Administration are inspired from natural products.

Fruits of *Piper longum* Linn. Commonly called as black pepper have a long history in Indian traditional medicine like Ayurveda for treating of gastro intestinal and respiratory complications (Johri and Zutshi, 1992). Piperine (1-piperoyl piperidine) (Meghwal and Goswami, 2013) is an amide alkaloid extracted from the black pepper fruits have a number of pharmacological activities reported such as analgesic, hypertensive, anti-cancer, neuro protective, anti-inflammatory. Piperine has also been proved for stimulation of gastric acid secretion, intestinal lipase and pancreatic lipase, increased bio-availability and absorption of other drugs, decreased metabolism by inhibiting cytochrome 450/CYP 3YP3A4 etc.

Based on the above pharmacological activities it is demonstrated that piperine has a vast pharmacological scope for treating several diseases and also piperine increases the bio-availability and absorption of different drugs.

BRIEF HISTORY OF ALKALOIDS

Alkaloids are the natural compounds that are synthesized by the secondary metabolism of living organisms. These molecules play important roles in

the species that synthesize them but are not essential for life, unlike products of primary metabolism, e.g. nucleosides, amino acids, carbohydrates or lipids.

Alkaloids mainly found as carboxylic acid salts of their nitrogen heterocycles, e.g. citric, lactic, oxalic, acetic, maleic or tartaric acid salts as well as fumaric, benzoic, aconitic acid salts. Thus, just as some plants are noted for containing certain alkaloids, they may be equally noted for containing high levels of the particular acid that forms a salt with the alkaloid. However, because of the polar and basic nature of alkaloids, most of these occur dissolved in plant saps as cations, and it is on evaporation of the sap that the organic acid is formed. The general physical properties of alkaloids are colourless, crystalline solids slightly soluble in neutral or alkaline aqueous solution and readily soluble in acid or in organic solvents such as ether, chloroform, or ethanol. Some alkaloids such as coniine and nicotine are liquid at room temperature, and few (e.g. sanguinarine) are coloured².

Alkaloids are classified into different types. Among them Piperidine and pyrrolidine alkaloids form one of the largest groups of alkaloids known, and as their name indicates, they include piperidine or pyrrolidine rings in their structures, which are derived from the amino acids lysine and ornithine respectively Figure No.1. These two heterocyclic structures differ only in carbon-nitrogen skeleton length, piperidines, have six membered and pyrrolidines have five membered rings. Irrespective of the difference in one carbon length, the biosynthesis of these units is identical, and so the report mainly points on piperidine alkaloids only, because it is the main theme throughout the present project.

PHARMACOGNOSY OF THE PIPER NIGRUM

Piper nigrum (family Piperaceae) is a valuable medicinal plant, the most commonly used spices and regarded as "The King of spices" among various spices. Black pepper is mainly cultivated in many tropical countries like Brazil, India and Indonesia. *Piper nigrum* is commonly known as Kali Mirch in Urdu and Hindi, Pippali in Sanskrit,

Milagu in Tamil and Peppercorn, White pepper, Green pepper, Black pepper, Madagascar pepper in English. Hot and pungent pepper corns are obtained from Black pepper which is the most famous and one of the commonly used spices throughout the world. Black pepper is used as medicinal agent, as preservative and in perfumery. Peppercorn of *Piper nigrum* or its active constituents are generally used in different types of foods and as medicine. Pepper is used in various types of dishes like meat dishes and also in sauces. It contains Piperine (1-piperoylpiperidine), major pungent alkaloid Figure No.2 that shows many pharmacological actions³. It is widely used in different traditional systems of medicine like Ayurvedic and Unani System of medicines. Piperine possess diversified pharmacological activities like antihypertensive, antioxidant, antitumor, anti-platelets, anti-asthmatics, anti-inflammatory, antipyretic, analgesic, antispasmodic, anti-diarrheal, antidepressant, anxiolytic, hepato-protective, immuno-modulatory, antibacterial, antifungal, anti-thyroids, anti-metastatic, antimutagenic, antiapoptotic, anti-spermatogenic, anti-colon toxin, insecticidal and larvicidal activities etc. Piperine has been found to enhance the therapeutic efficacy of many drugs, vaccines and nutrients by increasing oral bioavailability by inhibiting various metabolizing enzymes⁴. It is also found to elevate fertility and cognitive action. Piperine also found to stimulate the pancreatic and intestinal enzymes which aid to digestion. Many therapeutic activities of this spice are attributed to the presence of piperine apart from other chemical constituents. The *Piper nigrum* fruits are used to produce white and green peppers. *Piper nigrum* is also used as a flavorant.

TAXONOMICAL CLASSIFICATION OF PIPER NIGRUM

Kingdom: Plantae
Class: Equisetopsida
Sub class: Magnoliidae
Super order: Magnolianae
Order: Piperales
Family: Piperaceae

Genus: Piper

Species: nigrum

PHARMACOGNOSTIC CHARACTERISTICS

Piper nigrum (Black pepper) plant is a woody perennial climbing flowering vine and belongs to the family Piperaceae. Pepper plants easily grow in the shade on supporting trees, trellises or poles up to maximum height of 13 feet or 4 meters and roots may come out from leaf nodes if vine touch to the ground. The plants have heart shape as long as the leaves. The spikes length goes up to 7-15 cm. The fruits of black pepper (drupe) are small with 3 to 4 mm in diameter and the dried unripe fruits of *Piper nigrum* are called peppercorn. The fully matured fruits of black pepper are dark red in color and approximately 5 mm in diameter. A fruit contains a single seed. The plants starts bearing fruits from 4th or 5th year, and continues up to seven years. A single stem contains 20-30 spikes of fruits. The spikes are collected, sun dried and peppercorns are separated from the spikes. The fresh unripe green fruits are harvested and freeze-dried to make green pepper and some are sun-dried to make black pepper. From the ripen fruits, red skin is removed and the seeds are sun-dried to make white pepper.

CHEMICAL COMPOSITION OF PIPER NIGRUM

The phytochemical investigations of *P. nigrum* revealed that it contains variety of phytochemicals. Piperine was the first pharmacologically active compound isolated from different members of Piperaceae family. Various types of compounds like Phenolics, flavonoids, alkaloids, amides and steroids, lignans, neolignans, terpenes, chalcones etc were isolated. Some of the chemical constituents are Brachyamide B, (2E, 4E)-N-Eicosadienoyl-piperidine, Guineensine, Dihydro-pipericide, N-trans-Feruloyltryamine, N-Formylpiperidine, pentadienoyl as piperidine, (2E, 4E)-Nisobutyldecadienamide, Tricholein, Trichostachine, isobutyl-eicosatrienamide, isobutyl-eicosadienamide, Isobutyl-octadienamide, Piperamide, Piperine, Piperamine, Piperettine, Pipericide, Piperolein B, Sarmentine, Sarmentosine,

Retrofractamide . The different pharmacological activities were reported due to the presence of these phytochemicals. Piperine reported to have four isomers viz; Piperine, Isopiperine, Chavicine and Isochavicine (Figure No.3). Among all isolated compounds isolated from *P. nigrum*. Piperine, pipene, piperamide and piperamine were found to possess diverse pharmacological activities

EVIDENCE BASED PHARMACOLOGICAL ACTIVITIES

An attempt has been made to collect updated research information on *Piper nigrum* from the internet using Google search engine and Pub Med. Many researchers carried out their researches on *Piper nigrum* and its active constituent "piperine" using latest sophisticated scientific technologies and Important Pharmacological activities of *Piper nigrum* and piperine are summarized in Table No.1.

ANTIMICROBIAL ACTIVITY OF BLACK PEPPER

In 2007, Khan and Siddiqui evaluated the antibacterial activity of aqueous decoction of *Piper nigrum* L. (black pepper), *Laurusnobilis* L. (bay leaf), *Pimpinella anisum* L. (aniseed), and *Coriandrum sativum* L. (Coriander) against different bacterial isolates from oral cavity of two hundred individual volunteers. Aqueous decoction Black pepper showed strong antibacterial activity when compared with aqueous decoction of *Pimpinella anisum* and *Laurusnobilis* at a concentration of 10µL/disc. In a recent study, the silver nanoparticles from leaf and stem extract of *Piper nigrum* were synthesized and then antibacterial activity of the synthesized silver nanoparticles of *Piper nigrum* was evaluated against agricultural plant pathogens. These silver nanoparticles showed the excellent antibacterial activity against plant pathogens. Authors concluded that the antibacterial activity of silver nano-particles is a beneficial application in crop improvement and protection in agricultural nanotechnology⁵.

ANTIOXIDANT ACTIVITY OF BLACK PEPPER

Free radicals cause many diseases. Various free radicals that attack on membranes cause oxidation of lipids, loss of different enzyme activities and may even cause cancer. Antioxidants completely stop or delay the process of oxidation. Antioxidant protection system includes enzymes like Ascorbate, Catalase, Peroxidase and Superoxide dismutase which scavenge both radicals and related non radical oxygen species. Plants are important source of antioxidants. Some in vitro studies reports that Piperine inhibits free radicals and reactive oxygen species, hence possess protective effects against oxidative damage. Piperine also found to decrease lipid per oxidation *in vivo*.

Piper nigrum reported to possess antioxidant activity that might be due to the presence of flavonoids and phenolic contents. *Piper nigrum* was found to prevent the oxidative stress by inhibiting lipid per oxidation, human lipoxygenase and arresting hydroxyl and superoxide free radicals, decrease lung carcinogenesis in animal studies. The memory enhancing and antioxidant proprieties of the methanolic extract of *Piper nigrum* L. fruits at a doses of 50 and 100 mg/kg, orally, for 21 days in amyloid beta (1-42) were investigated in Alzheimer's disease model in rats⁶⁻⁸. The memory-enhancing activity of the extract was studied by means of *in vivo* (Y-maze and radial arm-maze tasks) methods. While, the antioxidant activity was evaluated by measuring activities of glutathione peroxidase, catalase, superoxide dismutase, and by measuring the total content of reduced glutathione, malondialdehyde, and protein carbonyl levels in the hippocampus. The amyloid beta (1-42)-treated rats showed the diminishing of spontaneous star variation percentage within Y- maze task and enhancement of work memory and reference memory errors within radial arm-maze task. Methanolic extract of *Piper nigrum* showed significant improvement in memory performance and showed antioxidant potential on administration. These studies suggest that methanolic extract of *Piper nigrum* ameliorates amyloid beta (1-42)-induced spatial memory deterioration by depletion

of the oxidative stress in the hippocampus of rats. The antioxidant activity of the three Piper species (*P. nigrum*, *P. guineense* and *P. umbellatum*) was studied for the protection of renal, cardiac, and hepatic antioxidant status in atherogenic diet fed hamsters. Animals were fed atherogenic diet addition with different doses of Piper species like *P. nigrum*, *P. guineense* and *P. umbellatum* at doses of 1 g/kg and 0.25 g/kg for 12 weeks. Piper species showed significant inhibition of the atherogenic diet induced increased lipid profile and altered the antioxidant enzymes activities. This study revealed an antioxidant role of the extracts of Piper species against atherogenic diet induced oxidative stress in renal, hepatic and cardiac tissues.

ANTI-CANCER ACTIVITY OF BLACK PEPPER

Piper nigrum had been reported to inhibit tumors formation indifferent experimental models. Many studies revealed the antitumor activity of *P. nigrum* or *Piperine* by the oral administration. Piperine and the alcoholic extract of peppercorn showed an effective antitumor and immunomodulatory activities. Piperine is also reported to reduce the lung cancer by altering lipid peroxidation and by antioxidant protection enzymes activation. Piperine has distinct pharmacological activities along with Anti-cancer activity.

Piperine was reported to inhibit G1/S transition and the proliferation of human umbilical vein endothelial cells (HUVECs), migration of HUVECs and in vitro formation of tubule and angiogenesis induced by collagen and breast cancer cell in chick embryos. Piperine also inhibits the phosphorylation of Thr 308 residues of Akt of protein kinase B as well as Ser 473⁹.

Since phosphorylation of these residues is a necessary controller of angiogenesis and for proper functioning of endothelial cells. Therefore, Piperine may be used as an inhibitor of the angiogenesis for the treatment of cancer as angiogenesis plays a key role in the progression of tumor¹⁹. Docetaxel (a cytotoxic agent) is an FDA approved drug, used for the treatment for castration-resistant prostate cancer. Its metabolism occurs in the liver by hepatic

CYP3A4, and it was revealed that piperine inhibits the hepatic CYP3A4 enzymatic activity.

Therefore, the administration of docetaxel in combination with piperine was investigated for both in vitro and in vivo pharmacokinetic activity of docetaxel. It was also reported that nutritional use of piperine increased the efficacy of docetaxel in a xenograft model devoid of any side effects on the mice.

The cytotoxic activity of piperine against many cancer cell lines was reported earlier. Therefore, the mechanisms of anticancer activity of piperine against both androgen independent and dependent cells of prostate cancer were investigated. The proliferation of 22RV1, LNCaP, PC-3, and DU-145 prostate cancer cells was found to be inhibited by piperine in a dose dependent manner. Piperine treatment was also found to induce apoptosis, by the activation of caspase-3 and by the cleavage of PARP-1 proteins in different prostate cancer cells like PC-3, DU-145 & LNCaP prostate cancer cells. Treatment with piperine also found to disrupt the androgen receptor expression in LNCaP prostate cancer cells and cause significant diminution in the level of Prostate Specific Antigen in LNCaP cells¹⁰. The phosphorylated STAT-3 and Nuclear factor- κ B transcription factors expression were reduced in LNCaP, DU-145 and PC-3 prostate cancer cells on treatment with piperine. These results suggested that there was a significant reduction in the androgen dependent and independent growth of tumor in a naked mice model of xeno-transplanted with prostate cancer cells after treatment with piperine. Piperine is non-genotoxic and found to possess anti-mutagenic and anti-tumor influences.

HEPATOPROTECTIVE ACTIVITY OF BLACK PEPPER

It was found that piperine inhibited the increased level of serum GPT and GOT in a dose-dependent manner in a hepato-toxicity model of mice caused by D-galactosamine. The methanolic extract of *Piper nigrum* fruits was utilized to evaluate the hepatoprotective activity in ethanol- CCl₄ induced hepatic damage in Wistar rats. Ethanol-CCl₄ was used to induce hepatotoxicity in the rats.

Prophylactic treatment with methanolic extract of *Piper nigrum* at a dose of 100 and 200 mg/kg body weight, p.o. and piperine at a dose of 50 mg/kg body weight for pre-treatment, p.o. for 15 days with Ethanol- CCl₄ treated rats showed significant liver protection as proved from the triglycerides levels, Alanine transaminase, Aspartate transaminase, alkaline phosphatase, bilirubin and superoxide dismutase, Catalase, Glutathione reductase and Lipid per oxidation levels to assess the liver functions. In this study, administration of Ethanol-CCl₄ exhibited significant boost in triglycerides, Alanine transaminase, Aspartate transaminase, alkaline phosphatase, and bilirubin levels while there was significant decrease in the superoxide dismutase, catalase, and glutathione reductase levels which were restored to normal level after pre-treatment of methanolic extract of *Piper nigrum* and Piperine. Lipid per oxidations were also markedly decreased on pretreatment with the methanolic extract of *Piper nigrum* and Piperine at given doses. The results were close to that of reference standard-Liv52 at a dose of 1 mL/kg, p.o. treated for 15 days¹¹.

The Morphological and histopathological studies of liver also supported the biochemical parameters. Thus it is concluded that *Piper nigrum* possesses potential hepato-protective activity due to the presence of piperine alkaloids and have great therapeutic potential in treatment of liver ailments

ANTI-DIARRHEAL ACTIVITY OF BLACK PEPPER

Aqueous black pepper extract (ABPE) at a dose of 75, 150, 300mg/kg, po was evaluated for anti-diarrheal, anti-motility and anti-secretory activity in mice¹². The castor oil and magnesium sulphate were used to induce diarrhea for the evaluation of anti-diarrheal activity and gastrointestinal motility was assessed by charcoal meal, while castor oil was used for the evaluation of anti-motility and anti-secretory activities.

ABPE showed a significant and dose dependent anti-diarrheal, anti-motility and anti-secretory effect. Anti-motility and anti-secretory activities of *Piper nigrum* might be due to the presence of

carbohydrates and alkaloids, and anti-diarrheal activity of ABPE may be due to its anti-motility and anti-secretory activities.

IMMUNO-MODULATORY ACTIVITY OF BLACK PEPPER

Piperine at a concentration of 250µg/mL was reported to be cytotoxic to Dalton's lymphoma ascites and Ehrlich as cites carcinoma cells. Piperine of 50µg/mL concentration showed cytotoxic activity on L929 cells in culture. Piperine administration also causes an increase in the total WBC counts in Balb/c mice. On administrations of piperine there was an increase the bone marrow cellularity and alpha-esterase positive cells

In vitro immunomodulatory activity of piperine was evaluated to enhance the efficacy of rifampicin in a murine model of Mycobacterium tuberculosis infection. Mouse splenocytes were used to evaluate *in-vitro* immune modulation of piperine for cytokine production, macrophage activation and lymphocyte proliferation. Mouse splenocytes when treated with piperine showed an increase in the Th-1 cytokines (IFN-γ and IL-2) secretion, increased macrophage activation and proliferation of T and B cell. Protective efficacy of piperine and rifampicin (1 mg/kg) combination against Mycobacterium tuberculosis was reported due to immunomodulatory activity¹³.

DIGESTIVE ACTIVITY OF BLACK PEPPER

Many spices are known for their digestive stimulant action. Dietary piperine enhances digestion by stimulation of the pancreatic enzymes and considerably decreases the food transit time of gastrointestinal tract. Piperine has been reported to increases the saliva production and gastric secretions, and increases the production and activation of salivary amylase¹⁴.

ANTI-CONVULSANT ACTIVITY OF BLACK PEPPER

The oral administration of Piperine or *P. nigrum* showed a delayed onset of myoclonic jerks and generalized clonic at 40 and 80mg/kg doses and Piperine also diminishes the seizure stage and

mortality when compared with vehicle treated animals. A significant reduction was also observed in the incidence of MES-induced tonic hind limb extension (THE) and PTZ-induced Fos immune reactivity in the dentate gyrus after of piperine administration. Capsazepine, a TRPV1-selective antagonist blocked the anti-convulsant effects of piperine. These data reveals the anti-convulsant activity of piperine. An alternative study was done to evaluate in vivo anticonvulsant activity of piperine was in pentylenetetrazole (PTZ) and picrotoxin (PIC)-induced seizures models of epilepsy in mice. A significant ($P < 0.01$) delayed in the onset of PTZ-and PIC-induced seizures was observed after intra-peritoneal injection of piperine at a dose of 30, 50 and 70 mg/kg (i.p.), valproic acid at a dose of 200 mg/kg, Carbamazepine at a dose of 30 mg/kg and diazepam at a dose of 1 mg/kg in mice. These results revealed the anti convulsant effects of piperine which possibly mediated via GABA ergic Pathways¹⁵. In another study, in vivo anticonvulsant activity of piperine was evaluated in pentylenetetrazole (PTZ) and picrotoxin (PIC) induced seizures models of epilepsy in mice.

ANTIDEPRESSANT ACTIVITY OF BLACK PEPPER

The antidepressant-like effect of piperine and its possible mechanisms were evaluated in corticosterone-induced model of depression in mice¹⁶. Depression-like response was developed in mice after 3 weeks of corticosterone injections. The depression was revealed by the significant reduction in sucrose utilization and augmentation in immobility time in the forced swim test and tail suspension test. Further, the brain-derived neurotropic factor protein and mRNA levels in the hippocampus were also significantly decreased in corticosterone-treated mice. Corticosterone induced the behavioral and biochemical changes were significantly diminished after treatment to animals with Piperine. These results showed that piperine produces an antidepressant-like effect in corticosterone-induced model of depression in mice. Piperine produces an antidepressant-like effect in

corticosterone-induced model of depression in mice mediated via GABA ergic pathways.

CYTOTOXIC ACTIVITY

Duh CY *et al*, reported cytotoxic activity of chloroform extracts of *Piper aborescens* leaves. Cyclobutanoid amides with trans-trans-trans configurations such as piperarborenine C, piperarborenine D and piperarborenine E and new furanoid lignan, (+) arborone, along with twelve known compounds were isolated from the stems of *Piper arborescens*. The structures of these new compounds were determined by means of spectral analysis. Piperarborenines A-E, aristolactam BIII, goniothalactam showed significant cytotoxic activity against P-388, HT-29 and A549 cell lines *in vitro*¹⁷. Tang GH *et al*, reported the cytotoxic activity of amide alkaloid which was obtained from methanolic extract of *Piper boehmeriaefolium*¹⁸. Pan L *et al*, reported cytotoxic activity of chloroform extract of *Piper sermentosum*¹⁹.

ANTIPLATELET ACTIVITY

Lei D *et al*, reported antiplatelet activity of aqueous extract of inflorescence *Piper betle*, where inflorescence *Piper betle* inhibited the arachidonic acid induced and collagen-induced platelet aggregation²⁰. Li CY *et al*, also mentioned that the methanolic extract of *Piper lolot* showed potent inhibitory activity on platelet aggregation.

CYP3A4 INHIBITORY EFFECT

Usia T, Watabe T, Kadota S, *et al*, mentioned the potent inhibitory activity of aqueous extract of *Piper cubeba* on the metabolism mediated by CYP3A4 enzyme. Human liver microsome was used for CYP inhibitory assay. The inhibitory activity on the metabolism mediated by CYP3A4 in vitro was determined using a radiometric measurement²¹.

ANTI-INFLAMMATORY ACTIVITY

Lin LC *et al*, mentioned anti-inflammatory activity of methanolic extract of *Piper kadsura stem*. Among the constituents that were isolated from the stems of *Piper kadsura* futoquinol, piperlactam S,

and N-p-coumaroyl tyramine showed potent inhibition of PMA-induced ROS production in human polymorphonuclear neutrophils²².

ANTI-PLASMODIAL ACTIVITY

Flores N *et al*, reported anti plasmodial activity against Plasmodium falciparum of ethanolic extract of *Piper glabratum* leaves. Among the evaluated compounds, methyl-3,4-dihydroxy-5-(3'-methyl-2'-butenyl) benzoate exhibited leishmanicidal effect (IC₅₀ 13.8-18.5 µg/mL) against the three Leishmania strains used, and methyl 3,4-dihydroxy-5-(2-hydroxy-3-methylbutenyl)benzoate, methyl 4-hydroxy-3-(2-hydroxy-3-methyl-3-butenyl)benzoate, and methyl 3,4-dihydroxy-5-(3-methyl-2-butenyl) benzoate showed significant trypanocidal activity²³.

ANT-REPELLENT ACTIVITY

Capron M A *et al*, reported ant repellent activity of chloroform fraction of hexane extract of *Piper tuberculatum* leaves. Green TP *et al*. also reported ant repellent activity of leaves²⁴.

ANTIFUNGAL ACTIVITY

The essential oil of the fruits of *P. longum* L exhibits fungicidal activity²⁵. The substances derived from fruit was tested against six phytopathogenic fungi, *Pyricularia oryzae*, *Rhizoctonia solani*, *Botrytis cineria*, *Phytophthora infestans*, *Puccini are condita*, and *Erysiphe graminis* using a whole plant in vivo method. Pipernonaline, a piperidine alkaloid was isolated from the hexane fraction of *P. longum* showed a potent fungicidal activity against *P. recondita* at the concentration of 0.5 and 0.25 mg /ml, with 91% and 80% control values respectively.

ANTI-ASTHMATIC ACTIVITY

An extract of the fruits in milk reduced passive cutaneous anaphylaxis in rats and protected guinea pigs against antigen-induced bronchospasm²⁶.

ANTI-DIABETIC ACTIVITY

The antihyperglycemic and anti-lipid per oxidative effects of ethanolic extract of *Piper longum* dried

fruits in alloxan induced diabetic rats were studied. The blood glucose level, carbohydrate metabolizing enzymes and the status of lipid per oxidation and antioxidants were assayed using specific colorimetric methods. Oral administration of dried fruits has shown significant anti-hyperglycemic, antilipid per oxidative and antioxidant effects in diabetic rats comparable to that of the standard reference drug glibenclamide²⁷.

HYPOCHOLESTEROLAEMIC ACTIVITY

Methyl piperine significantly inhibited the elevation of total serum cholesterol, and the total cholesterol to HDL cholesterol ratio, in rats fed with a high cholesterol diet. The unsaponifiable fraction of the oil of *P. longum* also significantly decreased total serum cholesterol and hepatic cholesterol in hypercholesterolaemic mice²⁸.

ANTIULCER ACTIVITY

The aqueous extract of ginger, one of the constituents of Mahakasyaya drugs along with aqueous extract of *P. longum* and also the colloidal solution of *Ferula asafoetida* were reported to protect against CRS-ASP and PL- induced gastric ulcers in rats. Piperine, an alkaloid of long peppers, inhibited gastric emptying (GE) of solids/liquids in rats and gastrointestinal transit (GT) in mice in a dose and time dependent manner. GE inhibitory activity of piperine is independent of gastric acid and pepsin secretion²⁹.

ANALGESIC ACTIVITY

Roots of *P. longum* was evaluated for opioid type analgesia using rat tail-flick method as well as for NSAID type analgesia using acetic-acid writhing method by using pentazocine and ibuprofen as drug controls³⁰. An aqueous suspension of root powder of *P. longum* was administered orally to rat and mice. The study revealed that *P. longum* root shows weak opioid and potent NSAID type of analgesic effect.

Table No.1: Pharmacological Activities

S.No	PHARMACOLOGICAL ACTIVITIES
1	Anti-hypertensive
2	Anti-asthmatic
3	Cognitive action & fertility activity
4	Anti-microbial
5	Anti-oxidant
6	Anti-cancer
7	Anti-inflammatory
8	Hepatoprotective
9	Anti-diarrheal activity
10	Digestive activity
11	Antidepressant activity
12	Immunomodulatory activity
13	Anticonvulsant activity
14	Analgesic activity
15	Effect of piperine on metabolism

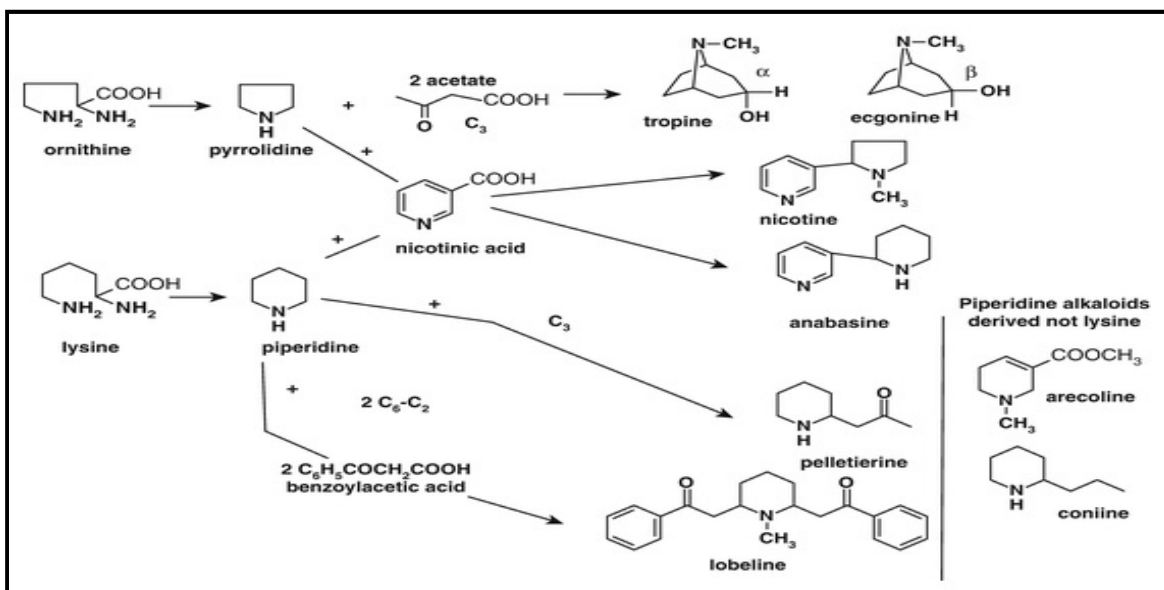


Figure No.1: Biosynthesis of Piperidine alkaloids

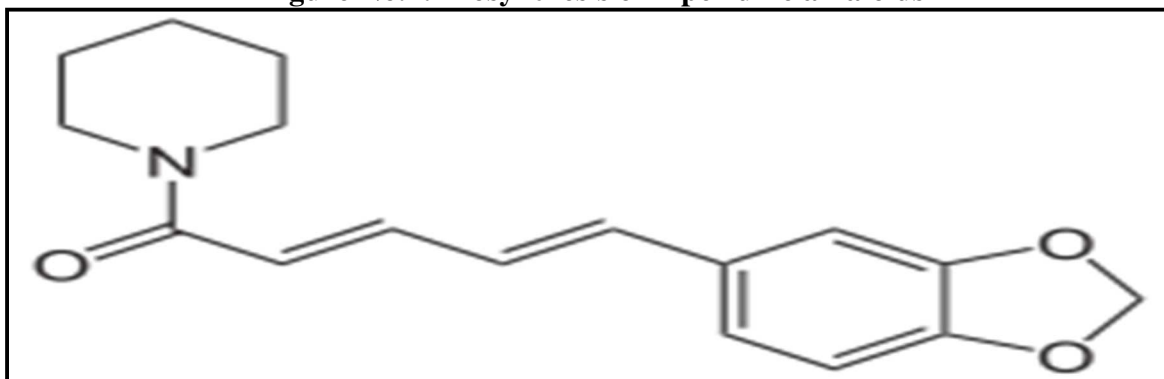


Figure No.2: Structure of Piperine

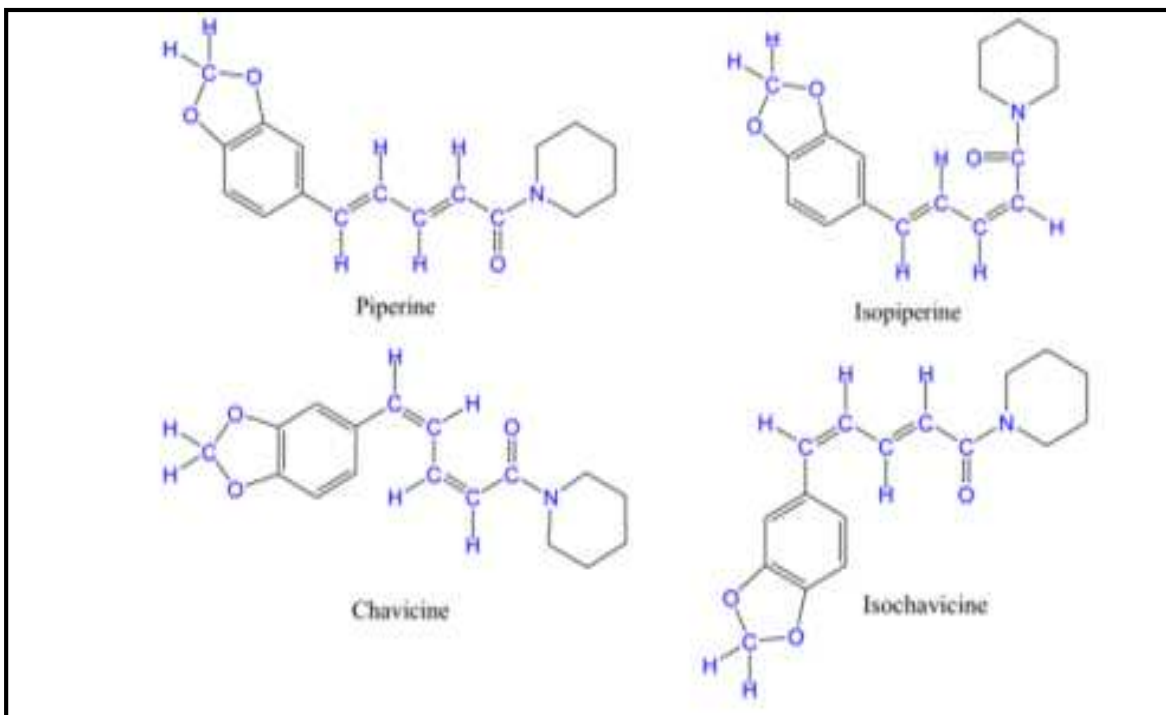


Figure No.3: Isomers of Piperine

CONCLUSION

Natural products are used as medicines for many years and they are the main sources of drugs for many treatments. Drugs obtained from natural sources are efficacious with fewer side effects when compared with synthetic drugs. Black pepper, the king of spices has piperine alkaloid as a major chemical constituent and it is showing wide range of pharmacological activities which raises the importance of black pepper and a preferable one for regular intake with food. Piperine formulations are available in market for treating different disease conditions and also piperine is used in combination with other drugs to enhance the bioavailability.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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