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RESEARCH ARTICLE

Piper nigrum: An Overview of effects on Human Health

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ABSTRACT:
Piper nigrum (family Piperaceae) is a valuable medicinal plant. It is one of the most commonly used spices and considered as "The King of spices" among various spices. Black pepper is grown in many tropical regions like Brazil, Indonesia and India. Hot and pungent peppercorns are obtained from Black pepper which is the most famous and one of the commonly used spices throughout the world. Pepper is used worldwide in different types of sauces and dishes like meat dishes. One study reported that piperine is widely used in various herbal cough syrups for its potent anti-tussive and bronchodilator properties. It is used in anti- inflammatory, anti-malarial, anti-leukemia treatment. Recent medical studies have shown that it is helpful in increasing the absorption of certain vitamins, selenium, β-cartene, also increase the body's natural thermogenic activity.

KEYWORDS: Piper nigrum, antioxidant, antitumor, anti-inflammatory, anti-diarrheal, antidepressants, anti-thyroids, medicinal herbs.

INTRODUCTION:
Piper nigrum (family Piperaceae) is a valuable medicinal plant. It is one of the most commonly used spices and considered as "The King of spices" among various spices. Black pepper is grown in many tropical regions like Brazil, Indonesia and India. *Piper nigrum* is commonly known as kali Mirch in Urdu and Hindi, Pippali in Sanskriti, Milagu in Tamil and peppercorn, White pepper, Green pepper, Black pepper, Madagascar pepper in English. Hot and pungent peppercorns are obtained from Black pepper which is the most famous and one of the commonly used spices throughout the world. Black peppercorn of piper nigrum or its active components are being used in different types of foods and as medicine. Pepper is used worldwide in different types of sauces and dishes like meat dishes. It contains major pungent alkaloid Piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological actions. It is widely used in different traditional systems of medicine like Ayurvedic and Unani System of medicines (1, 2). Piperine exhibits diverse pharmacological activities like antihypertensive and antiplatelets (3), antioxidant, antitumor (4), antiasthamatics (5), antipyretic, analgesic, anti-inflammatory, anti-diarrheal, antispasmodic, anxiolytic, antidepressants (6), hepatoprotective (7), immuno-modulatory, antibacterial, antifungal, anti-thyroids, antiapoptotic, anti-metastatic, antimutagenic, 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 metabolising enzymes (8). It is also known to enhance cognitive action and fertility (9). 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 fruits of Piper nigrum are used to produce white and green peppers. *Piper nigrum* is also used as flavouring agents (1). The alkaloids, of which some 5,500 are known, comprise the largest single class of secondary plant substance. Alkaloids are often toxic to man and many have dramatic physiological activities; hence their wide use in medicine. They are usually

colorless, often optically active substances, most crystalline but a few (e.g. nicotine) are liquids at room temperature. Piperine is an alkaloids found naturally in plants belonging to the pyridine group of Piperaceae family, such as piper nigrum and piper longum. Piperine is the Tran stereoisomer of 1-piperoylpiperidine. It is also known as (E, E)- 1-piperoylpiperidine and (E,E)-1-[5- (1,3-benzodioxol-5-yl)-1-oxo-2,4-pentdienyl] piperidine. Piperine is the alkaloid responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine). It has also been used in some forms of traditional medicine and as an insecticide. One study reported that piperine is widely used in various herbal cough syrups for its potent anti-tussive and bronchodilator properties. It is used in anti-inflammatory, anti-malarial, anti leukemia treatment. Recent medical studies have shown that it is helpful in increasing the absorption of certain vitamins, selenium, β-cartene, also increase the body's natural thermogenic activity (10).

Taxonomical Classification of *Piper nigrum*:

Kingdom	Plantae
Class	Equisetopsida
Sub class	Magnoliidae
Super order	Magnolianae
Order	Piperales
Family	Piperaceae
Genus	*Piper*
Species	*Nigrum*

Figure 1: Piper nigrum (a) plant with mature pepper corn (b) black pepper corn (c) mature dried corn of long pepper

Phytochemicals 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. Many investigators isolated different types of compounds viz. Phenolics, flavonoids, alkaloids, amides and steroids, lignans, neolignans, terpenes, chalocones etc and many other compounds. Some of the compounds are Brachyamide B, Dihydro-pipericide, (2E, 4E)-N-Eicosadienoyl- pereidine, N-trans-Feruloyltryamine, N-Formylpiperidine, Guineensine, Pentadienoyl as piperidine, (2E, 4E)-Nisobuty-Idecadienamid, isobutyl-eicosadienamide, Tricholein, Trichostachine, Isobutyl-eicosatrienamide, Isobutyl-octadienamide, Piperamide, Piperamine, Piperettine, Pipericide, Piperine, Piperolein B, Sarmentine, Sarmentosine, Retrofractamide A (figure 1). 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. Among all isolated compounds isolated from P. nigrum. Piperine, pipene, piperamide and piperamine were found to possess diverse pharmacological activities (1,11).

Pharmacological activity of *Piper nigrum:*

Important Pharmacological activities of *Piper nigrum* and piperine are summarized in Table 1. Some of the pharmacological activities of *piper nigrum* are discussed below.

Antimicrobial activity of *black pepper:*

Khan and Siddiqui in 2007 evaluated the antibacterial potential of aqueous decoction of *Piper nigrum L.* (black pepper), *Laurus nobilis L.* (bay leaf), *Pimpinella anisum L.* (aniseed), and Coriandum sativum L. (corinder) against different bacterial isolates from oral cavity of two hundred individual volunteers. Black pepper (aqueous decoction) showed strongest antibacterial activity comparable to aqueous decoction of *Laurus nobilis* and *Pimpinella anisum* at the concentration of 10L/disc (12). 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 nano-particles 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 nanotechnology (13).

Figure 2: Chemical constituents of *Piper nigrum*

Properties	Values
Oleoresin	10.6wt %
Piperine content	5.8 wt %
Essential oil	1.7 (v/w) %
Water content	11 wt %
Real density	1545 kg/m3
Bulk density	793 kg/ m3
Bed porosity	0.49

Table 1: Pharmacological activities of *Piper nigrum L.* (Black Pepper)

S. No.	Activities	References
1.	Antihypertensive activity	(3)
2.	Anti-asthmatic activity	(5)
3.	Cognitive action and Fertility activity	(9)
4.	Antimicrobial activity	(12, 13)
5.	Antioxidant activity	(14-18)
6.	Anti-cancer activity	(4,15 ,19 -23)
7.	Anti-inflammatory activity	(24)
8.	Hepatoprotective activity	(7,25)
9.	Anti-diarrheal activity	(26)
10.	Digestive activity	(13,23,27-29)
11.	Antidepressant activity	(6,30)
12.	Immunomodulatory activity	(31,32)
13.	Anticonvulsant activity	(33,34)
14.	Analgesic activity	(34)
15.	Effect of Piperine on metabolism	(2,8)

Antioxidant activity of black pepper:

Free radicals cause many diseases. Different free radicals attack on membranes causing oxidation of lipids, loss of different enzyme activities and may 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 revealed that Piperine inhibited free radicals and reactive oxygen species, therefore known to possess protective effects against oxidative damage. *Piper nigrum* or piperine also found to decrease lipid peroxidation 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 peroxidation, human lipoxygenase and arresting hydroxyl and superoxide free radicals, decrease lung carcinogenesis in animal studies. The memory enchancing and antioxidant properties of the methanolic extract of Piper nigrum L. Fruits at doses of 50 and 100 mg/kg, orally, for 21 days in amyloid beta (1-42) were investigated in Alzheimer's disease model in rats (14,15,19). The memory-enhancing effects of the extract were studied by means of in vivo (Y- maze and radial arm-maze tasks) approaches. While, the antioxidant activity was evaluated by measuring activities of glutathione peroxidise, 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 performance and exhibited antioxidant potential. 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 (16). The antioxidant effect of three Piper species viz P. nigrum, P. guineense and P. umbellatum was evaluated for the protection of renel, cardiac, and hepatic antioxidant status in artherogenic diet fed hamsters. Animals were fed artherogenic diet addition with different doses of Piper species viz., *P. nigrum, P. guineense* and *P. umbellatum* at a dose of 1 g/kg and 0.25 g/kg for 12 weeks. Piper species significantly inhibited the artherogenic diet induced increased lipid profile and alteration in antioxidant enzymes activities. This study showed an antioxidant protective role of the extracts of Piper species against artherogenic diet induced oxidative stress in renal, cardiac and hepatic tissues (17).

Anti-cancer activity of black pepper:

Piper nigrum had been reported to inhibit tumors formation in different experimental models. Many studied revealed the antitumor activity of *P. Nigrum* or Piperine by the oral administration. The alcoholic extract of peppercorn and piperine exhibited effective immunomodulatory and antitumor activities. Piperine is also reported to reduce the lung cancer by altering lipid peroxidation and by antidative protection enzymes activation (1, 15, 19). 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 473. Since phosphorylation of these is an essential controller of angiogenesis and function 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 tumor (20). Docetaxel (a cytotoxic chemotherapeutic agent) is a FDA approved drug for the treatment for castration-resistant prostate cancer. The metabolism of docetaxel occurs in the liver by hepatic CYP3A4, and piperine is reported to inhibit 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 docetaxl in a xenograft model devoid of any side effects on the mice (21). The anticancer activity of piperine against many cancer cell lines has been 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 LNCaP, 22RV1, PC-3 and DU-145 prostate cancer cells was found to be dose dependently inhibited by piperine. 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 and LNCaP prostate cancer cells. Treatment with piperine also found to disrupt the androgen receptor expression in LNCaP prostate cancer cells and cause significant diminutionin the level of Prostate Specific Antigen in LNCaP cells. The expression of phosphorylated STAT-3 and Nuclear factor-KB transcription factors were reduced in LNCaP, PC-3 and DU-145 prostate cancer cells after treatment of with piperine. These results suggested that there was a significant reduction in the androgen dependent and independent growth of tumor in naked mice model of xeno- transplanted with prostate cancer cells after treatment of piperine (22). Piperine is non-genotoxic and found to possess anti-mutagenic and anti-tumor influences.

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 have been reported to increases the saliva production and gastric secretions and increases the production and activation of salivary amylase. The orally administration of piperine or *P.nigrum* stimulate the liver to the secret bile acids which in turn play key role in the absorption and digestion of fats. The oral administraton of active compounds like piperine, pipene, piperamines and piperamides significantly increases the activities of enzymes like pancreatic amylase activity, protease activity, lipase activity and chymatrypsin activation (18,23). An influence on digestive enzymes of intestinal mucosa was examined in experimental rats by Platel K and Srinivasan. The animals were fed with piperine (20%) mg which significantly increased the activity of intestinal lipase, disaccharidases sucrose and maltase enzymes (29). In another study, Patel K and Srinivasan evaluated the influence of piperine (20%) mg on digestive enzymes of pancreas 28in experimental rats. Dietary piperine (20%) mg significantly stimulated the activities of pancreatic lipase, amylase, trypsin and chymotrypsin (). The influence of some spices included in the diet, on food transit time was examined in adult female Wistar rats. Animals were maintained for 6 weeks on diets containing piperine (0.02%) g. The ferric oxide (0.5%) was included in the diet as an un-absorbable marker to monitor the food transit time. Time of extra creation of colored stool was noted to follow the time of consumption of the diet with the marker. The piperine (0.02%)g significantly shortened the food transit time (29).

Anti-inflammatory activity of black pepper:

The piperine was evaluated for the anti-inflammatory, analgesic, and anti-arthritic activities. The in vitro anti-inflammatory activities were evaluated on interleukin 1β stimulated fibroblast like synoviocytes obtained from rheumatoid arthritis, while anti-arthritic including analgesic activities was evaluated on carrageen an induced acute paw model of pain and arthritis in rats. The prostaglandin E_2, cyclooxygenase 2, interleukin 6 and matrix

metallo-proteinase levels were evaluated by ELISA and RT-PCR methods of analysis. Piperine treated groups were found to reduce the synthesis of prostaglandin E_2 in a dose dependent comportment at the concentrations of 10-100g/mL. It significantly inhibited the synthesis of prostaglandin E_2 even at 10g/mL. The expression of interleukin 6 and matrix metallo-proteinase 13 were also inhibited. The migration of activator protein 1 into the nucleus in interleukin 1β treated synoviocytes was inhibited by piperine while migration of nuclear factor kB was not affected by piperine. The pain ad arthritic symptoms in rats were significantly reduced by piperine. It was concluded that piperine showed anti-inflammatory, analgesic and anti-arthritic activities in arthritis model of rats (24).

Antidepressant activity of black pepper:
The antidepressant-like effect of piperine and its possible mechanisms was evaluated in corticosterone-induced model of depression in mice. Depression like behaviour in mice was developed after 3 weeks 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 neurotrophic factor protein and mRNA levels in the hippocampus were also significantly decreased in corticosterone-treated mice. Corticosterone induced the behavioural 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 (30).

Anti-diarrheal activity of black pepper:
Aqueous black pepper extract (ABPE) at a dose of 75,150,300mg/kg was evaluated for anti-diarrheal, anti-motility and anti-secretory activity in mice. 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, antimotility and anti-secretary effect. Antimotility 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 (26).

Anticonvulsant activity of black pepper:
The anticonvulsant activity of piperine in maximal electroshock (MES) and pentylenetetrazol (PTZ) models of convulsions in mice was examined and further participation of transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor was acknowledged in the inhibition of convulsion caused by pentylenetetrazol and maximal electroshock models. A significant was observed after administration of piperine at doses of 40 and 80mg/kg and Piperine also diminish the seizure stage and mortality as compare to the animals treated with vehicle. 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 (TRPV1-selective antagonist) blocked the anti-seizure effects of piperine. These data reveals the anti-convulsant activity of piperine (33). In another study, in vivo anticonvulsant activity of piperine was evaluated in pentaylenetetrazole (PTZ) and picrotoxin (PIC)-induced seizures models of epilepsy in mice. A significant ($P<0.01$) delaydin the onset of PTZ and PIC-induced seizures was observed after intra-peritoneal injection of piperine at a dose of 30,50 and 70mg/kg (i.p), valproic acid at a dose of 200mg/kg , Carbamazepine at a dose of 30mg/kg and diazepam at a dose of 1mg/kg in mice. These results revealed the anticonvulsant effects of piperine which possibly mediated via GABAergic pathways (34).

Hepatoprotective activity of black pepper:
It was found that piperine inhibited the increased level of serum GPT and GOT in dose-dependent manner in a hepato-toxicity model of mice caused by D-galactosamine. The hepatoprotective activity of methanolic extract of Piper nigrum fruits was evaluated in ethanol-CC14 induced hepatic damage in Wistar rats. Ethanol-CC14 was used to induce hepatotoxicity in the rats. Prophylactic treatment with methanolic extract of piper nigrum at a dose of 100 and 200mg/kg body weight, p.o and pre-treatment with piperine at a dose of 50mg/kg body weight, p.o for 15 days with Ethanol-CC14 treatment rats showed significant liver protection as evidenced from the triglycerides levels, Alanine transaminase, Aspartate transaminase, Alkaline phosphate, and bilirubin and superoxide dismutase, Catalase, Glutathione reductase and lipid peroxidation levels to assess the liver functions. In this study, administration of Ethanol-CC14 exhibited significant boost in triglycerides, Alanine transaminase, Aspartate transaminase, alkaline phosphatise, 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 peroxidations were also significant decreased after pre-treatment with methanolic extract of *Piper nigrum* and Piperine at given doses. The results were similar to that of reference standard-Liv52 at a dose of 1mg/kg p.o for 15 days. The morphological and histopathoogical studies of liver were also supportive of 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 activity due to the presence of piperine alkaloids and have great therapeutic potential in treatment of liver ailments (25).

Analgesic activity of black pepper:
In vivo analgesic activity of piperine in mice was evaluated. The acetic acid- induced writhing and tail flick assay models in mice were used to evaluate the analgesic activity of piperine. There was a significant ($P<0.01$) inhibition in the acetic acid-induced writhing in mice after intra-peritoneal (i.p.) administration of piperine at a dose of 30,50 and 70mg/kg as compared with in domethacin at a dose of 20mg/kg (i.p). Intra-peritoneal injection of piperine at dose of 30 and 50mg/kg and intra-peritoneal injection of morphine at dose of 5mg/kg significantly ($P<0.01$) increase in the rejection time of mice in the tail flick assay. The analgesic activities of both piperine and morphine in the tail flick assay were reversed on pre-treatment of animals with naloxone at dose of 5mg/kg (i.p). These results revealed the analgesic activity of piperine which possibly mediated via opioid pathway (34).

Immuno-modulatory activity of black pepper:
Immune-modulatory and antitumor activity of piperine was evaluated. Piperine (250g/mL) was reported to be cytotoxic to Ehrlich ascites carcinoma cells and Dalton's lymphoma ascites. Piperine at a concentration of 50g/mL showed cytotoxicity to L929 cells in culture. Piperine administration also causes an increase in the total WBC counts in Bal b/c mice. Administrations of piperine were also increase the bone marrow cellularity and alpha-esterase positive cells (31). 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 immunomodulation of piperine for cytokine production, macrophage activation and lymphocyte proliferation. Piperine treated mouse splenocytes demonstrated an increase in the secretion of Th-1 cytokines (IFN-and IL-2), increased macrophage activation and proliferation of T and B cell. Protective efficacy of piperine and rifampicin (1mg/kg) combination against Mycobacterium tuberculosis was reported due to immune-modulatory activity (32).

Effect of Piperine on metabolism: a bioavailability enhancer:
Piperine has shown bioavailability enhancing effects on many therapeutically important drugs and nutrients. Piperine increases the absorption of many drugs and nutrients from the gastrointestinal tract by various mechanisms. It alters the membrane dynamics and increases permeability at site of absorption. Piperine increases the serum half-lives of some substances like beta-carotenene and coenzyme Q10 and decreases metabolism of many drugs by inhibiting various metabolizing enzymes like cytochrome BS, CYP3A4, NADPH cytochrome, UDP glucuronyl transferase, UDP-glucose dehydrogenase (UDP-GDH), and aryl hydrocarbon hydroxylase (AAH). These enzymatic inhibition by piperine resulted in increased bioavailability of many drugs and nutrients e.g., amoxicillin, amphicillin, acefotaxime, carbamazepine, ciprofloxacin, norfloxacin, metronidazole, oxytetracyclin, nimesulide, pentobarbitone, phenyyoin, resveratrol, beta-carotene, curcumin, galic acid, tiferron, nevirapine, and sparteine by different types of mechanisms. Therefore, piperine is known as bioavailability enhancer and a potent drug's metabolism inhibitor (2). Besides the above discussed activities of Black pepper, Piper nigrum or pure compound "Piperine" exhibits many more Pharmacological activities like antihypertensive, antiplatelets, antipyretic, antispasmodic, antifungal, anti-apoptotic, anti-metastatic, antimutagenic, anti- spermatogenic, anti-colon toxin, anti-asthamatics, anti-anxiety, antithyroids, antifungal, insecticidal and larvaicidal activities etc (1-5).

CONCLUSION:

The scientific research on Tinospora cordifolia suggests a huge biological potential of this plant. It is strongly believed that detailed information as presented in this review

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