International Journal of Food Science and Nutrition
ISSN: 2455-4898
Impact Factor: RJIF 5.14
www.foodsciencejournal.com
Volume 3; Issue 2; March 2018; Page No. 84-88

Protective role of *Piper nigrum* in health and healing of diseases

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Abstract
India is called as "Spice bowl of the World". Black pepper (*Piper nigrum*) is the "king of spices". It is the most significant and broadly used spice in the world. The use of black pepper is not only limited in human diet but also used in medicinal purposes, as preservatives & as biological pest control agents. The colour of the pepper depends upon the kind and distribution of phenolic compounds. The enzymatic oxidation of ethanol glycoside in the presence of enzyme o-diphenol oxidase leads to the conversion of fresh green pepper into black pepper. 3, 4-dihydroxy-6-(N-ethylamino) benzamide acts as a substrate for o-diphenol oxidase. *Piper nigrum* inhibits lipid peroxidation, arrests hydroxyl and superoxide free radicals to prevent oxidative stress. The secretion of saliva and the activity of salivary amylase increased with the intake of black pepper. Fat digestion and absorption also enhanced by the spices as they stimulate liver to produce and secrete bile. Many such benefits of pepper leads to encourage us to write a Review about the benefits of Indian herbs and spices present in our kitchen.

Keywords: *Piper nigrum*, black pepper, peroxidation

Introduction
Black pepper (*Piper nigrum*) is the "king of spices". It is the most significant and broadly used spice in the world [1]. The use of black pepper is not only limited in human diet but also used in medicinal purposes [2], as preservatives & as biological pest control agents [6]. The nutritional composition of black pepper per 100g is 400kcal, 10g protein, 10.2g fat, 66.5g carbohydrate, 4.6g ash, 0.4g calcium, 160mg phosphorous, 10mg sodium, 1200mg potassium, 17mg iron, 0.07mg thiamine, 0.210mg riboflavin, 0.07mg thiamine, 0.210mg riboflavin and 0.8mg niacin [3]. India, Vietnam, Brazil, Indonesia, Malaysia, Sri Lanka, China, and Thailand are the countries where black pepper cultivation is more [13]. South India is the main producer of black pepper. Black pepper which we commercially use is the matured dried fruits of the tropical plant *P. nigrum* L. of the family *Piperaceae* [3]. The dried fruit is called as peppercorn which becomes dark red after maturation and 5mm in diameter with a single seed [3]. The maximum height of the plant is 4 metres or 13 feet and the leaves of plant are heart shaped of length 5-10 cm and width of 3-6 cm [10]. The climatic conditions which are most appropriate for pepper cultivation are elevated rainfall, constant temperature, and high relative humidity. The soil of pH 4.5-6.9 is more preferable for the growth of pepper [1].

Black pepper has two main constituents – the volatile oil and pungent compounds. [3] The Dutch chemist Hans Christian Orstedt first identified and isolated the piperine which is a bioactive and pungent ingredient of black pepper [5]. The IUPAC name of piperine is Trans, Trans-5-(3, 4-methylenedi-oxyphenyl) - 2, 4-pentadienoic acid piperidide [3]. The chemical formula of piperine is $C_{17}H_{19}O_3N$. Piperine is a weak base which upon alkali hydrolysis yields a volatile base piperidine [11]. The melting point of piperine is 128-130 degree celcius. Other than piperine, five more pungent alkaloids are present in pepper that are piperettine, piperylin A, piperanine, piperolein B, and pipericine [3]. But their involvement in pungency of black pepper is very low. The solubility of piperine in water is very low due to which its pharmaceutical activities are less. Central nervous system and reproductive system can be affected due to the toxicity by high level of piperine [11].

The aroma of black pepper is due to the presence of mixture of volatile chemical compounds which varies between 2 – 5% in berries [3]. Some of them are monoterpene hydrocarbons and oxygenated compounds (70-80%), sesquiterpene hydrocarbons and oxygenated compounds (20-30%) and many others [7]. It was found tha t glucose was the major polysaccharide of black pepper berries which constituted about 88% of total polysaccharides followed by galactose, arabinose, galacturonic acid and rhamnose in a very little amount [3].

The colour of the pepper depends upon the kind and distribution of phenolic compounds. The enzymatic oxidation of ethanol glycoside in the presence of enzyme o-diphenol oxidase leads to the conversion of fresh green pepper into black pepper. 3, 4-dihydroxy-6-(N-ethylamino) benzamide acts as a substrate for o-diphenol oxidase [3].

Black pepper was reported to have digestive power, improves

appetite, cures cold, cough, dyspnoea, diseases of the throat, intermittent fever, colic, dysentery, worms and piles. Also, a wide range of antimicrobial activity was possessed by black pepper. Black pepper along with one of its active compound piperine shows analgesic, antipyretic and anti-inflammatory actions. It does not bring out any type of hepatic toxicity [4]. Some researchers also stated that black pepper consumption in humans increased orocecal transit time [6]. Trans-dermal delivery of active drugs through skin membrane intensifies with the help of piperine. Gastric acid secretion in rats increased with the intake of black pepper. The intake of black pepper increases the secretions of digestive enzymes which further enhance the secretion of bile acid from liver [6]. The effects of physiological conditions like pain, rheumatism, chills, cold, exhaustion, muscular aches, fevers, etc can be reduced with use of black pepper oil [3]. Black pepper shows anti-cancer properties probably by altering the metabolic activity of various enzymes [9]. Toxic symptoms after the intake of piperine have not been observed [16].

Review of literature

This paper provides a review on the black pepper and its major alkaloid piperine with their therapeutic uses.

Antioxidant activity of black pepper

Many diseases can be caused by free radicals. They can lead to the loss of different enzyme activities, loss of receptor activities, reduced fluidity of bio-membranes, cell inactivation by damaging proteins present in the membrane and cancer due to mutation. So there is a requirement of antioxidants to prevent these conditions. Antioxidants are the substances which inhibit oxidation. Antioxidants can be natural or synthetic but synthetic oxidants are cancer causing. Antioxidants present in plants are more of interest due to their nontoxic and environmental friendly nature. Enzymes like peroxidase, catalase, superoxide dismutase, and ascorbate are included in antioxidant protection system by scavenging both radicals and their associated non-radical oxygen species. Flavonoids and phenolic contents present in the regenerated tissues like callus, in vitro shoots, roots, in vitro plantlets, peppercorn and acclimated plantlets of black pepper are responsible for its antioxidant activity. It was reported that the intake of black pepper avert induced stress such as oxidative stress, inhibit peroxidation, arresting different radicals such as hydroxyl and super oxides radicals and decrease induced lung carcinogeneisis and inhibit human lipoxygenase [6]. *Piper nigrum* inhibits lipid peroxidation, human lipoxygenase, and arresting hydroxyl and superoxide free radicals to prevent oxidative stress [10].

In a study of antioxidant properties of three species of black pepper i.e, *Piper nigrum*, piper guineense and piper umbellatum on cardiac, renal and hepatic antioxidant atherogenic diet fed hamsters. *Piper nigrum* and Piper guineense were fed with a dose of 1 g/kg while Piper umbellatum with a dose of 0.25g/kg for 12 weeks. The intake of black pepper inhibits the effects of atherogenic diet like increased lipid profile and alteration in the antioxidant enzymes. Hence atherogenic diet induced oxidative stress in renal, cardiac, and hepatics tissues can pe prevented by the antioxidant role of the extracts of the black pepper [10].

Antibacterial activity of black pepper

In a study which was done to explore the antibacterial activity of black pepper by using disc diffusion method, it was shown that gram positive bacteria is more susceptible to the black pepper than gram negative bacteria. Black pepper performs this action by affecting the cell membrane permeability of bacteria which leads to the loss of intracellular material in the extracellular material. Gram positive bacteria like *Staphylococcus aureus* shows significant inhibition followed by *Bacillus cereus* and *Streptococcus faecalis.* Gram negative bacteria like *Pseudomonas aeruginosa* followed by *Salmonella typhi* and *E. coli also* show inhibition in presence of black pepper [8].

Antibacterial activity of aqueous extraction of *Piper nigrum* L. (black pepper), *Laurus nobilis* S. (bay leaf), *Pimpinella anisum* L. (aniseed), and *Coriandum sativum* L. (coriander) against different types of bacteria isolated from oral cavity of two hundred individuals. In comparison to *Laurus nobilis* and *Pimpinella anisum* black pepper showed strongest antibactertial activity at the concentration of 10μL/disc [10]. A study done on the silver nanoparticles from leaf and stem extract of *Piper nigrum* to evaluate the antibacterial activity of the synthesized silver nanoparticles against agricultural plant pathogens. Antibacterial activity shown by these silver nano particles is significant against plant pathogens [10].

Antimutagenic and antitumor activity

Many experimental studies showed that the tumor formation is inhibited by the black pepper. The growth of androgen dependent and independent tumor in naked mice model of xeno-transplanted with prostate cancer cells is inhibited under the effect of piperine [10].

A study in which mutations are induced in *Drosophila melanogaster* by promutagen-ethyl carbamate using the wing Somatic Mutation and Recombination Test show that black pepper reduces the chances of mutation. The mechanism which is involved in the inhibition of mutation by black pepper is the interaction of black pepper with the active groups of mutagens [2].

It was also found that the intake of piperine in case of lung metastasis induced by B16F-10 melanoma cells in C57BL/6 mice produced a significant reduction (95%) in tumor nodule formation. Animals treated with piperine have reduced levels of serum sialic acid and serum γ -GT activity than the untreated animal [2].

In mice with induced experimental lung cancer it was observed that piperine increase its chemopreventive effect by modulating lipid peroxidation and augmenting antioxidant defense system. 100 mg/kg body weight of piperine restrain lung cancer initiated by B(alpha)p. Chemopreventive effects are also shown by piperine on lung cancer suffering animals [2].

In a study it was found that in presence of aqueous extracts of black pepper proliferation of splenocytes enhanced. It explains that the aqueous extracts of black pepper contain some factors that are able of stimulating the proliferative signalling pathways in splenocytes [9].

Black pepper also enhances macrophage pro-inflammatory responsiveness by increasing the release of the pro-inflammatory cytokines IL-6 and TNFa by macrophages.

Cytotoxic activity of NK cells intensifies by the aqueous extracts of black pepper by its immunostimulatory effects [9].
Apoptosis is also induced by the intake of piperine by activating caspase-3 and by the cleavage of PARP-1 proteins in different prostate cancer cells like PC-3, DU-145 & LNCaP prostate cancer cells [10].The effectiveness of docetaxel is also enhanced by use of black pepper in mice [10].

Anti-inflammatory activity

Inflammation is a complicated immune response to destructive foreign substances like pathogens, damaged cells, or irritants by the vascular tissues of the body to reduce pain. Black pepper possesses anti-inflammatory activtity. It inhibits the synthesis of two significant proinflammatory mediators IL6 and PGE. PGE_2 plays a main part in giving rise to pain so its inhibition is required [13].
Piperine was tested for its anti-inflammatory activity in rat models of carrageenan-induced rat paw edema, cotton pellet-induced granuloma, and a croton oil-induced granuloma pouch. The enzymes required in the biosynthesis of leukotriene and prostaglandin that are 5-lipoxygenase and COX-1 respectively showed less activity in the presence of *Piper nigrum* in vitro. The diseases which involve immense pain like rheumatoid arthritis show some positive effects in presence of piperine [12].
In a study done on the samples of the ankle joints from an experimental group showed that the area of lymphocyte infiltration was smaller in case of piperine treatment (100 mg/kg) than corn oil treatment [12].
Three different pathologists examined the expanse of inflammation on five specimens and found out that the inflammation induced by carrageenan was lessened by piperine up to a large extent [12].In a study it was shown that adhesion of endothelial monolayer to neutrophils get inhibited due to piperine which leads to the blockage of tumor necrosis factor induced expression of cell adhesion molecules.
Collagen matrix invasion of melanoma cells was also blocked by piperine in a variety of concentrations and in a dependent amount of dose.Intake of piperine also decreases the pro-inflammatory cytokines [6].
The concentration of 10 ug/ ml is enough for the inhibition of the synthesis of prostaglandin E2. Piperine lowered the extent of pain and also the symptoms due to arthritis significantly [10].

Effect of black pepper on digestion

The secretion of saliva and the activity of salivary amylase increased with the intake of black pepper. Fat digestion and absorption also enhanced by the spices as they stimulate liver to produce and secrete bile.
A study was done on experimental rats to see the effect of spices on the secretion of bile in two conditions. First after the regular intake of spices in diet and the second condition was the single exposure of it. It was found that the dietary piperine had no significant effect on the secretion of bile while a one-time dose increased the bile secretion up to a greater extent that is about 30%.
A complete study on animals was done to evaluate the effect of different spices on the activity of digestive enzymes. It was found that the dietary intake of piperine increased the activity of pancreatic lipase. The activity of pancreatic amylase was also increased by the intake of piperine in diet up to an extent of 87%. It was also found that the activity of trypsin was also increased by the piperine up to 150%. Also high level of chymotrypsin was found in animals fed with piperine. The activity of intestinal lipase is significantly increased by piperine when given in a single dose. Also the activity of intestinal amylase is enhanced by it [2].
It was observed that food transit time is lessened by the intake of piperine when a study was done on adult female Wistar rats in which animals were kept on diet containing 0.02g % piperine for six weeks and ferric oxide (0.5 %) as a marker was added in the diet which could not be absorbed so that the food transit time can be known. Then the time of the intake and excretion of food was recorded [10].
Absorption of selenium, vitamin B, beta – carotene and curcumin and other nutrients is also increased by the piperine. Piperine can also enhance the digestion by increasing the release of saliva which further sends signals to stomach to stimulate the release of hydrochloric acid that aids in protein digestion. Symptoms like poor digestion, heartburn, constipation, or diarrhea can be caused in the absence of hydrochloric acid in stomach. The health of the digestive tract is improved by the intake of black pepper. It also keeps the human body fit by breakdown of fat [13].

Antidiarrhoeal Property

Pepper is one of the constituent of the conventional formulations used for preventing diarrhoea. An experiment was done in mice to evaluate the antidiarrhoeal property of black pepper. In mice diarrhoea was induced by three substances that accelerate diarrhoea are castor oil, MgSO4 and arachidonic acid and the effect of piperine was examined against these substances. Diarrhoea induced by these substances was prevented by the piperine at 8 and 32 mg/kg p.o. dose. Also, castor oil induced intestinal fluid accumulation was lessened by the effect of piperine in a particular dose of 2.5–20 mg/kg. Capsaicin-sensitive neurons were involved in the mechanism of decreasing castor oil induced intestinal fluid accumulation. Capsazepine sensitive vanilloid receptors are comparatively less effective during castor oil induced situation [2].
Castor oil shows significant laxative effect. It reduces the fluid absorption, leads to the rise in the secretions of small intestine and colon and alters smooth muscle contraction in intestine. A constituent of castor oil called ricinoleic acid is responsible for causing diarrhoea and the mechanism behind this is increase in prostaglandin biosynthesis so aqueous extract of black pepper suppress castor oil induced diarrhoea by inhibiting prostaglandin synthesis. On the other hand magnesium sulphate induces diarrhoea by increasing the volume of intestinal contents and by blocking the reabsorption of water and sodium chloride. Release of cholecystokinin from the mucosal lining of small intestine is also enhanced by $MgSO_4$ which leads to the rise in the secretion and motility of small intestine. Black pepper extract inhibits diarrhoea by increasing the absorption of water and electrolytes from intestine [14].
Aqueous extract of black pepper was examined at a dose of 75, 150, 300 mg/kg, po for its anti-darrheal, anti-motility and anti-secretory activity. It was found that the presence of carbohydrates and alkaloids is responsible for its anti-motility

and anti-secretory activities and hence these activities of piperine are the main cause of preventing diarrhoea [10].

Effect of piperine on bioavailability of drugs

Piperine significantly increases the bioavailability of various drugs by enhancing the absorption of drugs from GI tract or by inhibiting its metabolism after absorption from liver or by both of these [2]. It changes the membrane activity to increase absorption. The serum half-lives of some substances like beta-carotene and coenzyme Q10 is enhanced by piperine. The metabolism of some drugs is decreased as piperine lessened the activity of various enzymes which help in digestion like cytochrome BS, CYP3A4, NADPH cytochrome, UDPglucuronyl transferase, UDP-glucose dehydrogenase (UDP-GDH), and aryl hydrocarbon hydroxylase (AAH) and this inhibition increases the bioavailabilty of certain drugs and some nutrients [10].

(-)-Epigallocatechin-3-gallate (EGCG) present in green tea show chemopreventive activity in animal models having cancer. It was found that the treatment of EGCG with piperine increases the bioavailability of EGCG. The mechanism involved in this process is the inhibition of EGCG glucuronidation in mice gastrointestinal tract. The rate of excretion of EGCG in piperine treated mice was slower than the mice provided with EGCG only.

In a study Propranolol (40 mg) and theophylline (150 mg) were given alone and along with piperine and it was observed that piperine improved the bioavailability of these oral doses. Systemic availability of β-lactam antibiotics, amoxycillin trihydrate, and cefotaxime is increased when given with piperine. Bioavailability of curcumin is also examined under the influence of piperine in rats and human subjects. In rats a dose of 2 g/kg curcumin when given alone then moderate serum concentration were found for 4 hours but when 20 mg/kg piperine was given curcumin serum concentration became high for 1-2 hours. While in humans curcumin dose of 2 g was not found in serum but when 20 mg piperine was provided curcumin serum levels became high for 0.25 to 1 hour post drug. This is very beneficial as curcumin has a number of health benefits [2].

Hepatoprotective Activity

In a study done on mice in which hepato toxicity was induced by D-galactosamine it was observed that high levels of serum GPT and GOT can be controlled by the intake of piperine.

Methanolic extract of *Piper nigrum* was examined for its hepatoprotective property in ethanol-carbon chloride induced hepatic toxicity in experimental rats. To prevent hepato-toxicity a dose of 100 and 200 mg/kg body weight, p.o. was given and to pre-treat a dose of 50 mg/kg body weight, p.o. for 15 days was given to rats. It was found that methanolic extract of *Piper nigrum* exhibit a great antihepatotoxic activity as evaluated by the triglycerides levels, Alanine transaminase, Aspartate transaminase, alkaline phosphatase, bilirubin and superoxide dismutase, Catalase, Glutathione reductase and Lipid peroxidation levels to examine the functioning of liver [10].

CCl_4 induced hepatic toxicity by boosting the activity of NADPH-cytochrome C reductase enzyme. This enzyme accessed in the biotransformation of CCl_4 and hence causes rise in the lipid peroxidation and elevate hepato-toxicity [2].

Antihypertensive effect of *P. nigrum*

Antihypersensitivity effect of piperine was examined when anesthesia given rats show decrease in arterial pressure after piperine is given in a particular dose by veins. In vitro study on rabbits show that epinephrine and contractions are inhibited by piperine. Vasoconstrictor effect is shown by piperine in Ca^{2+} free conditions [6].

Antithyroid activity of *P. nigrum*

The functioning of thyroid gland is inhibited under the influence of piperine. A study done on Swiss albino mice in which thyroid gland activity was examined when piperine was given to them for 15 days and it was observed that piperine reduced the concentration of both the thyroid hormones, thyroxine (T4) and triiodothyronine (T3) in the same way as antithyroid drugs [2].

Piperine also decreased the glucose concentration with a concomitant decrease in hepatic 5_D enzyme and glucose-6-phospatase (G-6-Pase) activity [6].

Antipyretic effect of *P. nigrum*

The drugs that lower the increased body temperature are called antipyretic is induced by yeast, it leads to release of prostaglandins which increased body temperature controlled by thermoregulatory centre of hypothalamus. Inhibition of prostaglandin synthesis is done by antipyretic drugs. Then mice were treated with 20 – 30 mg/kg piperine and 10 mg/kg indomethacin. It was found that mice treated with piperine had reduction in fever in the same manner as the standard drug indomethacin [15].

Antiasthmatic Property

Antiasthmatic property of piperine was observed when mice treated with piperine showed less infilteration of eosinophil, hyper responsiveness, and reduced synthesis of histamine, IL-5, IgE, and IL-4 [6].

Antidepressant Property

Depression is induced in mice by corticosterone to evaluate the antidepressant activity of piperine. After 3 weeks of corticosterone intake mice showed depression like symptoms. Depression was confirmed by decreased sucrose utilisation and increase immobility time in the forced swim test and tail suspension test. Reduction in the neurotrophic factor protein and mRNA levels in hippocampus region of brain took place in these mice. But treatment with piperine lessened the corticosterone induced symptoms and it was concluded that piperine has an antidepressant like activity [10].

Conclusion

Various research articles had been published so far on the therapeutic potential of *Piper nigrum* and its bioactive compound piperine. People at present time prefer natural food items instead of synthetic items and black pepper is one natural source which has various health benefits like antioxidant, anti-inflammatory, antipyretic, antidiarrhoeal, increases digestibility, enhances bioavailability of various drugs and curcumin, anti-hypersensitive and hepatoprotective

properties. Several researches on animals and cell lines confirmed its anti-tumor activity. The use of black pepper is completely safe as it is proved by different animal studies.

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