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Overview on Pharmacological Properties of *Piper Nigrum* (Black Pepper)

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Abstract

Piper nigrum (Black pepper) is an important medicinal plant. It is one of the most popular spices and known among other spices as "The King of spices." Many tropical countries like Brazil, Indonesia, and India grow black pepper. The "King of spices," black pepper, is a common spice with a strong pungent aroma. From time immemorial, plant sources were used in traditional systems of medicine and day-to-day common use, such as in meal preparation and cosmetic purposes. This is due to their vast pharmacological potential with minimum side effects. Among the various species of the Piperaceae family, black pepper is one of the most popular due to its principle pharmacological component, piperine. Piperine is an alkaloid that has diverse

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pharmacological activities like antioxidant, anticonvulsant, antimicrobial, hepatoprotective, anti-inflammatory, antidiarrheal, immunomodulator, anticancer, etc. Due to some religious value of black pepper, its being popular from ancient time to modern generation. In the current narrative review of literature, we aimed to describe and delineate on the pharmacological properties of black pepper.

Keywords: *Piper nigrum*, Antioxidant, Anti-inflammatory, Antidiarrheal.

Introduction

Spices have a definition of plants used to improve the taste of food, including the skin, flowers, fruit, roots, leaves, rhizomes, seeds, tubers, and other plant parts. Spices are aromatic or intensely flavored parts of plants used in small quantities in foods as preservatives or flavoring in cooking. Black peppers, probably nature's most potent food is a spice belongs to the Piperaceae a class of bulb-shaped plants belongs to the family. It is an important condiment crop in the country. It is not only an herb used as spice and food but also possess medicinal properties. This perennial creeper has wide adaptability in the backyard arecanut & coconut gardens of Assamese household and it is gaining popularity as commercial crop. The crop is highly valued for its contents of Oleoresin, Piperine and essential oil.[1]

Black pepper is one of the most 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.

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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.[2,3]

Piperine exhibits diverse pharmacological activities like antihypertensive and antiplatelets,[4] antioxidant, antitumor,[5] antiasthamatics,[6] antipyretic, analgesic, anti-inflammatory, anti-diarrheal, antispasmodic, anxiolytic, antidepressants,[7] hepatoprotective,[8] 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.[9] It is also known to enhance cognitive action and fertility.[10]

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 flavoring agents. 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. In recent pasts, different therapeutic potentials of *Piper nigrum*, its extracts, or its important active chemical constituent ‘’piperine’’ have been published in different international research journals. 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

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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-carotene, also increase the body's natural thermogenic activity.[11] In the current narrative review of literature we aimed to describe and delineate on the pharmacological properties of black pepper.

Taxonomy of *Piper nigrum*

Kingdom: Plantae

Class: Equisetopsida

Sub class: Magnoliidae

Super order: Magnolianae

Order: Piperales

Family: Piperaceae

Genus: *Piper*

Species: *nigrum*

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Figure 1: Showing *Piper nigrum* plant

Antimicrobial activity

The antimicrobial activity of black pepper remains unclear till date. According to Rani et al.,[12] piperine had potential antimicrobial as well as antifungal effects against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Aspergillus niger, A. flavus, Alternaria alternata* and *Fusarium oxysporum*. Phenolic compounds obtained from fresh black pepper seed extracts have the potential to inhibit the growth of *Bacillus*, *Escherichia coli* and *Staphylococcus aureus*, *S. faecalis and B. cereus*.[13,14] Zhang et al.[15] showed that 1.0 µl/ml of BPEO was the effective minimum inhibition concentration against meat-borne *E. coli*, and suggested that black pepper essential oil has potential as a natural antibacterial agent in the meat industry. Similarly, BPEO displayed substantial activity against *E. coli, B. substilis*, and *S. aureus*.[16] Besides, most of the studies focusing on the antimicrobial effects of BPEO have been conducted disc diffusion method[17] though; given its intrinsic limitations, the technique requires to be improved through more relevant MIC assays.[18]

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Antioxidant activity

Oxidative stress is the main factor for initiation of various degenerative and chronic diseases, including cancer, immune dysfunction, diabetes, and Parkinson's.[19] Antioxidants are natural or synthetic constituents that can be used for inhibition of free radical formation by scavenging and suppression of degenerative and chronic diseases. A polyphenolic compound hydroxytyrosol (HT), has a potent antioxidant effect on hydrogen donation and improved radical stability. Supplementation with HT improves the white adipose tissue (WAT) dysfunction induced by high-fat diet (HDF) fed in mice through the modulation of transcription factors NF-κB, Nrf2, SREBP-1c and PPAR-γ as well as their target genes, involved in inflammation, antioxidant defences and lipogenesis.[20] Vijayakumar et al.[21] noted that piperine has potential protection activity against lipid peroxidation and antioxidant activity in rats fed a high-fat diet which induced oxidative stress to cells. Piperine has greatest antioxidant potential and was utmost effective with minimum inhibitory concentration (MIC) < 325 mg/ml against all assessed gram positive and negative strains.[22] Under *in vitro* conditions, Jeena et al.[23] recorded that essential oil of black pepper scavenged superoxide, and inhibited tissue lipid peroxidation.

Anti-cancer activity

Piperine was found to possess antimutagenic potential since it inhibits the mutagenicity of the three food mutagens (3-Amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), 2-Amino-3-methylimidazo[4,5-f]quinoline (IQ) and 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MelQx)).[24] At a dose of 100 mg/kg, piperine gave a statistically significant reduction in cyclophosphamide-induced chromosomal aberrations in rat bone marrow cells.[25] Hepatic and renal cadmium levels were significantly decreased in mice when treated with piperine, demonstrating its protective action to this type of renal and hepatic toxicity.[26] When orally

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administered for three days prior the treatment with mitomycin C, piperine inhibited the frequency of sister chromatid exchanges (up to 41.82%), as well as the number of chromosomal aberrations in mouse splenocytes and spermatocytes (50% and 40.78% of inhibition, respectively).[27] Another study found that piperine inhibits aflatoxin B1-induced cytotoxicity and genotoxicity in V79 Chinese hamster cells.[28] The results of Kumar et al.'s[29] in vitro experiments on deltamethrin (DLM, a pyrethroid insecticide, and a potent immunotoxicant)-induced thymic apoptosis in primary murine thymocytes demonstrated the protective role of piperine (1, 10 and 50 μg/mL). Its administration led to increased cell viability in a concentration-dependent manner and reduced levels of early activated markers of apoptosis (reactive oxygen species and caspase-3), as well as GSH depletion, all induced by DLM.

Anti-inflammatory activity

Piperine decreases liver marker enzymes activity (aspartate transaminase (AST), alanine, transaminase (ALT), and alkaline phosphatase (ALP)) in acetaminophen-challenged mice, indicating its hepatoprotective and antioxidant effects.[30] Piperine decreases blood urea nitrogen (BUN), creatinine, and malondialdehyde (MDA), and increases superoxide dismutase (SOD), glutathione peroxidase (GPx) in the kidney of lead acetate-treated nephrotoxic rats.[31] Similar results were observed in cadmium-induced oxidative stress in cultured human peripheral blood lymphocytes in a HFD and antithyroid drug-induced hyperlipidemic rats. These enzymatic studies also revealed the anti-inflammatory activity of piperine. The administration of piperine to rats before irradiation significantly abolished the radiation-induced alleviation in lungs catalase (CAT) and GPx activities, reduced GSH content and significantly limited the elevation in serum tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) levels, which demonstrated its protective function from ɣ-rays. Piperine inhibits LPS-induced expression

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interferon regulatory factor (IRF)-1 and IRF-7 mRNA, phosphorylation of IRF-3, type 1 IFN mRNA, and reduces the activation of signal transducer and activator of transcription (STAT)-1. The results indicate that piperine is a potential molecule for treating lipopolysaccharide-induced inflammation.[32] Similarly, Wang-Sheng et al.[33] reported that piperine inhibits LPS-induced TNF-α, IL-6, IL-1β, and prostaglandin E2 (PGE-2) production in BV2 microglial cells. In the human peripheral blood mononuclear cells (PBMCs), piperine was found to inhibit IL-2 and interferon gamma (IFN-ɣ).[34] Piperine inhibits the production of PGE2 and NO induced by LPS while decreasing TNF-α, inducible NO synthase (iNOS) and cyclooxigenase-2 (COX-2) in RAW264.7 cells, resulting in anti-inflammatory activity.[35] In the model of LPS-induced inflammation of nucleus pulposus cells, piperine inhibited IL-1β, TNF-α, IL-6, expression of iNOS, activities of matrix metalloproteinases MMP-3 and MMP-13, ADAMTS-4 mRNA, and ADAMTS-5 mRNA.[36]

In an arthritis animal model, at doses of 10 and 100 µg/mL, piperine inhibits the IL-6, MMP-13, activator protein 1 (AP-1) and reduces PGE2 in a dose-dependent manner, and significantly reduced nociceptive and arthritic symptoms in piperine-treated rats. Histological investigation revealed reduced inflammatory area in the ankle joints.[37] Piperine downregulates IL-1, MMP-8, and MMP-13 in periodontitis, leading to protective effects on inflammation, alveolar bone loss, bone microstructures, and collagen fiber degradation in experimental periodontitis.[38] Son et al.[39] reported that piperine suppresses cytosolic phospholipase A2 (cPLA2) and inhibits thromboxane A2(TXA2) synthase, but not of COX-1, in collagen-stimulated platelets. It also inhibits the lipopolysaccharide-induced generation of PGE2 and PGD2 in RAW264.7 cells by suppressing the activity of COX-2, without effect on cPLA.[39] Piperine reduces proinflammatory cytokines IL-1β, IL-6 and TNF-α, COX-2, nitric oxide

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synthase (NOS-2), and nuclear factor kappa B (NF-κB) in the cerebral ischemia-reperfusion-induced inflammation rat model.[37] Piperine was found to reduces SOD, CAT, GPx, and GR, and increases hydrogen peroxide generation and lipid peroxidation in the epididymis, thus having a negative effect to redox state and affecting fertility.[40]

Antidepressant activity

In this globalized world, people are more stressed. Suicide and mental sub-activity is a big problem in today's society. Many herbs are used as a memory enhancer. Among which, black pepper has been used for a long time in herbal and ethnomedicinal practice.[41,42] Today's more scientific experimental model findings prove it is useful. Anxiolytic and antidepressant activity of the methanolic extract of *P. nigrum* fruits in beta-amyloid treated rat model of Alzheimer's disease showed increase in immobility and decrease in swimming time within forced swimming test. Whereas decreases in % of time spent, exploratory activity and number of entries in open arm within elevated plus-maze test. This showed the methanolic extract significantly exhibited antidepressant and anxiolytic effects by attenuation of oxidative stress.[43] Another study was done in corticosteroid induced depression model of mice. After 3-week corticosterone injection mice showed depression like behavior observed by tail suspension test and immobility time in forced swim test. These depression behaviors are significantly diminished after piperine administration.[44] Those finding proves the potent anxiolytic and antidepressant activity of black pepper.

Anti-diarrheal activity

Along with above described antimicrobial activity of black pepper, against some bacteria which are also responsible for causing diarrhea.[45] Other research signifies its great potency in controlling diarrhea. As we know, diarrhea is a leading cause of morbidity and mortality globally,

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especially among the children in developing countries. Aqueous extract of black pepper at a dose of 75, 150, 300 mg/kg, produces a significant dose-dependent antimotility, anti-secretory and anti-diarrheal effects. The author concluded that this effect is due to the presence of carbohydrates and alkaloids in black pepper.[46]

Anticonvulsant activity

The mice model for anticonvulsant activity of piperine was evaluated by inducing seizure with pentylenetetrazol (PTZ)-and picrotoxin (PIC) in mice. On administering piperine (30, 50 and 70 mg/kg, i.p.) and reference standard drugs, valproic acid (200 mg/kg, i.p.), diazepam (1 mg/kg, i.p.) and carbamazepine (30 mg/kg, i.p.) which showed significantly ($P<0.01$) delayed onset of PTZ-and PIC-induced seizures in mice. Which indicate that piperine exhibits anticonvulsant effects possibly mediated via GABA-ergic pathways.[47] Another experiment on anticonvulsant activity of piperine in pentylenetetrazol (PTC) and maximal electroshock (MES) model of convulsion in mice showed a delay in onset of generalized chronic seizure and myoclonic jerks with administering piperine (40- 80 mg/kg) and a significant reduction of PTZ-induced Fos immune reactivity in dentata gyrus and MES-induced tonic hind limb extension after piperine administration. The capsazepine, a selective TRPV1 antagonist blocked the anti-seizure effect of piperine.[48] These findings reveal the potent anti-convulsant activity of piperine.

Hepatoprotective activity

Many experimental findings show the hepatoprotective effect of P. nigrum in animal and human model.[49] The methanolic extract from black pepper (MEPN) fruits (100 and 200 mg/kg, p.o. for 15 days) and piperine (50 mg/kg, p.o. for 15 days) were tested against ethanol-CCl4 induced hepatotoxicity Wistar rats, which reveals the significant activity of black pepper in decreasing the hepatic biomarker level like TG, AST, ALT, ALP, and bilirubin, which were increased on

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ethanol-CCl4 administration. The significantly decreased level of SOD, GSH and CAT after ethanol-CCl4 administration were restored with MEPN and piperine. Another study where liver toxicity in mice was induced with D-galactosamine and exposed to dose dependent piperine, which inhibited increase in serum GOT and GPT levels and suggested that this effect dependent on hepatocytes reduced sensitivity towards tumor necrosis factor-α.[50] Those study reveals that the *P. nigrum* possesses potent hepatoprotective properties which can be used as therapeutic potential in liver disorder. The pungent properties of *P. nigrum* specially the piperine increases production of the saliva, activate salivary amylase, and promote gastric secretion, more over decrease GI transit time.[51] The use of black pepper as spicy is more. Black pepper 1.5g/meal administration in healthy human volunteer via intragastrical administration significantly increases pepsin and parietal secretion, gastric cell exfoliation and potassium loss. In rat model administration of piperine 20 mg% for 8 weeks along with fed significantly enhanced intestinal lipase activity and disaccharidases the maltase and sucrose, thus promote digestion.[52]

Analgesic activity

In-vivo analgesic activity of piperine was evaluated in mice. The analgesic activity was tested by using acetic acid-induced writhing, tail flick assay. After intraperitoneal (i.p.) injection of piperine (30, 50 and 70 mg/kg), the acetic acid-induced writhing in mice was observed and found to be significantly inhibited ($P<0.01$), like the effect of indomethacin- an NSAID drug (20 mg/kg, i.p.). In the tail flick assay, morphine (5 mg/kg, i.p.) and piperine (30 and 50 mg/kg, i.p.) showed a significant increase ($P<0.01$) in the reaction time of mice. Animals with naloxone pre-treatment (5 mg/kg i.p.), reversed the analgesic effects of both morphine and piperine. All these findings reveal that piperine exhibits analgesic effects possibly mediated via opioid pathway.[53] Analgesic activity of piperine was tested in mice (20 and 30 mg/kg, i.p.); acetic acid and hot

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plate reaction test was used. Indomethacin (10 mg/kg) was taken as reference standard. Piperine showed significant ($p<0.5$) dose dependent delayed response towards pain. The antipyretic activity of piperine was observed by using yeast-induced pyrexia in mice model. The rectal temperature was measured in piperine (20 and 30 mg/kg) treated mice as compared to the control group. Where the significant ($p<0.5$) increase in temperature in the control group mice was observed.[54] The experiment revealed that anti-inflammatory, analgesic, and anti-arthritic activity of piperine in arthritis model of rat. For measuring in-vitro anti-inflammatory activity, the interleukin 1β stimulated synoviocytes taken from rheumatoid arthritis was used. While the anti-arthritic including analgesic potency was carried out on carrageen, an induced acute paw model or arthritis and pain in rat. The cyclooxygenase 2, interleukin 6, prostaglandin E2 and matrix metalloprotease levels were tested by RT-PCR and ELISA analysis method. At concentration of 10-100µg/mL, piperine treated group were found to reduce synthesis of PGE2 in a dose dependent manner. Even at 10 µg/mL it significantly inhibits the synthesis of PGE2. The expression of metalloproteinase 13 and interleukin 6 were also inhibited.[55] Which concludes the potency of piperine for the titled topic.

Immunomodulatory activity

Black pepper exhibits immunomodulatory effect on human body. It is able of boost and supports the number and the efficiency of white cells and assists the body to raise a powerful defense against invading microbes and cancer cells. Lianzhong et al.[56] found that the analysis of component PN-IIa showed a different monosaccharide composition, which contained a significant proportion of galactose, arabinose, galacturonic acid and rhamnose; and PN-IIa did react with *β-glucosyl* Yariv reagent, which indicated that PNIIa might be an arabinogalactan; and

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purified anti-complementary polysaccharides from *Piper nigrum* is suggested as a supplement for immune enhancement.

Conclusion

Pepper is one such product that can offer natural nutritional and medicinal benefits. Today's consumers are health conscious and prefer natural food items free of synthetic additives, colorants, and adhesives. Numerous scientific analyses of its volatile components, including monoterpenes, sesquiterpenes, and particularly piperine, have expanded the field of research testing its medicinal and other uses. Additionally, synthetic alterations were made to create a more potent drug candidate with low toxicity and significant significance.

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