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REVIEW ARTICLE

Review on the Pharmacological Activities of Black Pepper

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Abstract

Black pepper (*Piper nigrum* (L.), Family: Piperaceae) which is considered as the king of spices is well known for its pungent odour and has gained a global consideration. Traditional uses of pepper include the treatment of piles, worms, diarrhoea, intermittent fever, cough, cold, dyspnea, and throat conditions. The bioactive components of pepper like pungent alkaloid piperine as well as its essential oil possess numerous pharmacological properties, including hypolipidemic, antibacterial, neuroprotective, anticancer, anticonvulsant, analgesic, with anti-inflammatory effects and so on. This review focuses on the research that has been carried out on black pepper's chemical content, recent advancements in chemistry and its pharmacological effects.

Keywords: Black Pepper, Piperine, Pharmacological Activity

1. Introduction

Black pepper, with the botanical name *Piper nigrum* L., is commonly referred to as the ″King of Spices″. Black pepper, despite its use in enhancing taste and unique flavour, has undergone extensive investigation for its biological characteristics and bioactive plant components. In the past, *P. nigrum* was utilized in India for treating throat, nasal, and stomach problems. Additionally, it was discovered that *P. nigrum* and its bioactive components, like piperine, possess significant pharmacological traits. However, the plant also contains other bioactive substances, including piperine, piperic acid, piperlonguminine, piperamide, piperolein B, and (-)-kusunokinin. Given its status as the king of spices, it also has strong nutraceutical and medicinal uses with its pharmacological properties, including hypolipidemic, antibacterial, neuroprotective, antioxidant, anticancer, anticonvulsant, hypoglycaemic, analgesic, with anti-inflammatory effects. This review deals with the pharmacological properties of piperine and its biological activities[1].

1.1 Anti-microbial Activity of Piperine

Piperine in pepper has antimicrobial properties due to the phenolic compounds which help in inhibiting the growth of *S. aureus*, *Salmonella typhimurium*, *Bacillus*, and *E. coli*[2]. The accumulation of pyruvic acid and the reduction of ATP proved that chloroform extracts of black pepper can change cell membrane permeability, destroy bacterial respiratory metabolism, and ultimately lead to pyknosis and death. Although the antibacterial mechanism of pepper is unknown, there are several experimental results which provide an approach for utilizing pepper as a safe natural antimicrobial agent with applications in the food industry[3].

1.2 Pharmacokinetic Activity of Black Pepper

The pharmacokinetic activity of Piperine, a bioavailability booster in the clinical setting, has big effects on the way metabolic enzymes work in the liver and intestine. These effects can change depending on the dose, method of administration, and species. Piperine taken by mouth may have a significant effect

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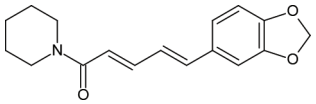

Figure 1. Chemical structure of Piperine.

on pharmacokinetic drug-food interactions with both natural and man-made drugs. As one of the most potential bioavailability enhancers, piperine may provide a therapeutic benefit to improve the pharmacokinetics of poorly bioavailable drugs. Piperine taken by mouth may have a significant effect on pharmacokinetic drug-food interactions with both natural and man-made drugs. As one of the most potential bioavailability enhancers, piperine may provide a therapeutic benefit to improve the pharmacokinetics of poorly bioavailable drugs.

1.3 Hepatic Biotransformation

The effect of black pepper on the hepatic biotransformation system has been studied in mice for 10 and 20 days by giving 0.5, 1 and 2% dosages of black pepper. It was identified that glutathione S-transferase and sulfhydryl levels went up in a dose-dependent way in mice fed black pepper-containing diets for 10 days, except for a 0.5% black pepper diet. Cytochrome b5 and cytochrome P450 levels were also significantly and dose-dependently raised. As a possible way to get the body's detoxification system going, black pepper has been mentioned as a possible way to stop chemical carcinogenesis. Several studies have looked at how black pepper or piperine affects the digestive enzymes in the liver and intestines. This suggests that there could be food-drug interactions with prescription drugs through changes in biotransformation pathways[4].

1.4 Antioxidant Activity of Piperine Essential Oils

The essential oil or extract of black pepper displays various pharmacological activities. Essential oils are made up of different organic compounds that have conjugated carbon double bonds and hydroxyl groups, which can give hydrogen to stop free radicals and reduce oxidative stress it was found that flavonoids, phenols and piperine are important for the antioxidant properties in black pepper. The antioxidant activities of pepper were mainly due to catechin, rutin, epicatechin, and resveratrol. However, other compounds like ascorbic acid could also contribute to the antioxidant activity[5].

1.5 Tobacco Withdrawal

Small clinical studies suggest that the essential oil of black pepper may help in treating nicotine withdrawal and cravings. The exact reason how it acts, is not known. Researchers proved that inhaling combusted black pepper may have helped in tobacco withdrawal and cravings by reducing the automatic motor desire to smoke, calming the anxiety that comes with withdrawal, and giving the same sensorimotor experience as smoking tobacco cigarettes. The vaporized black pepper essential oil may be an effective way to help individuals quit smoking even though black pepper that has been burned is probably not appealing outside[6].

1.6 Metabolic Action of Piperine on Mitochondria

Piperine has been found to exhibit inhibitory effects on various enzymatic processes involved in the biotransformation of drugs, which play a crucial role in both the creation of energy in mitochondria and the metabolism of toxins. Studies have provided evidence for the suppression of bioenergetic processes, such as ATPase activity, oxidative phosphorylation, and calcium transport, in isolated rat liver mitochondria with the application of piperine in an *in vitro* setting. The observed effects are associated with concentration, exhibit specificity to sites, and impact the functioning of mitochondria. The inhibitory half-life (I50) values of piperine on oxidative phosphorylation were determined to be 22, 12 mcg and 1mg of mitochondrial protein in the presence of glutamate, malate, and succinate, respectively. Thus, it indicates that piperine can hinder mitochondrial oxidative phosphorylation, bioenergetics, and enzymes involved in energy metabolism[7].

1.7 Anti-inflammatory and Anti-nociceptive Effects

Balb/C mice exhibited pronounced anti-inflammatory and anti-nociceptive properties after the administration of black pepper essential oil via intraperitoneal injection over a consecutive period of five days. The extracts of *P. nigrum* exhibited inhibitory effects on the generation of pro-inflammatory nuclear factor (NF-B),

cyclooxygenase-1 (COX-1), and cyclooxygenase-2 (COX-2), as well as the proliferation of tumour cells. The administration of *P. nigrum* essential oil through inhalation for 15 minutes was found to exhibit analgesic properties[8]. Ethanolic extract of *Piper nigrum* novels amide alkaloids such as pipernigramides, pipernigrester, and seven other compounds are extracted, which shows anti-inflammatory properties in the carrageenan-induced paw oedema test[9].

1.8 Nutritional and Biomedical Properties

Piperine essential oils of black pepper and ginger in combination have extensively been reported for their nutritional and biomedical properties. *Bacillus cereus*, *Salmonella typhimurium*, *S. aureus* and *E. coli* growth were strongly suppressed by piperine and they also act as promising substitutes for food packaging materials and bandages[10].

1.9 Cholesterol-lowering Activity

Piperine has been utilized to potentially mediate these effects due to its observed ability to decrease blood lipids in living organisms and inhibit cholesterol absorption in laboratory settings. The experiment revealed that the uptake of cholesterol into CaCo-2 cells exhibited a reduction that was dependent on the dosage of piperine and black pepper extract. Notably, both substances contained an equivalent amount of piperine. The study utilized differentiated CaCo-2 cells to investigate the impact of black pepper extract and piperine on the absorption of cholesterol in the intestinal lumen. This finding demonstrates that piperine exerts an influence on the process of cholesterol metabolism[11].

2. Combined Effects of Piperine

2.1 Iron and Piperine

The potential of piperine to enhance bioavailability could potentially facilitate the absorption of iron by the human body. Research conducted on the iron content of black pepper has demonstrated advantageous effects on markers related to iron metabolism, without any observed adverse reactions[12].

2.2 Curcumin and Piperine

Both curcumin and piperine work in a synergistic way. The combination of piperine and curcumin (in a 1:1 ED50 ratio) resulted in a synergistic interaction, as seen by the significantly lower experimental ED50 values compared to the theoretical ED50 values. This effect was observed in the formalin, tail-flick, and cold plate tests. The combination of curcumin and piperine exhibits significant synergistic antinociceptive benefits in mice models, while also lacking any discernible detrimental effects on the central nervous system[13].

The potential impact of co-supplementation with curcumin and piperine on the severity, duration, and clinical manifestations of coronavirus illness (COVID-19), as well as on inflammatory mediators in affected patients. Experimental trial of a randomized, placebo-controlled, double-blind, and parallel-arm design encompass the efficacy of co-supplementation with curcumin-piperine about the clinical manifestations, duration, intensity, and inflammatory mediators associated with coronavirus disease, as observed over two weeks[14]. Combining curcumin and piperine can considerably increase its effects, avoiding the formation of gallbladder stones, and lowering blood lipid and cholesterol bile saturation. The bioavailability of curcumin can be increased by piperine, which will elevate curcumin's effectiveness[15]. Dietary bioactive compounds that possess the potential to improve metabolic profiles would be highly beneficial for those who are overweight and following a Calorie Restriction (CR) plan. It includes the regulation of body fat, metabolism, and low-grade inflammation encompassing curcumin (Cur), a promising chemical compound with possible anti-obesity properties, and piperine, a plausible enhancer of curcumin's bioavailability and effectiveness. There is a potential for the acceleration of fat reduction and reduction of inflammation induced by a High-Fat Diet (HFD) in mice subjected to caloric restriction by the addition of curcumin + piperine. The concomitant administration of such drugs may potentially enhance the efficacy of CR in mitigating the onset of metabolic syndrome[16].

3. Cardioactive Effects

The primary terpene of black pepper, such as humulene, caryophyllene, limonene, pinene, and sabinene, have demonstrated cardioprotective properties using anti-inflammatory, antioxidant, anti-hypertensive, and anti-atherosclerotic mechanisms. These terpenes are

present in PhytoCann BP. To address the prevalence of cardiovascular diseases, researchers are currently exploring natural interventions aimed at reducing risk factors associated with cardiovascular disease[17]. Alterations in the architecture and functionality of the vascular wall coincide with an elevation in blood pressure. Piperine showed the ability to reduce the myofibril content while moderately increasing actin levels. Additionally, curcumin effectively prevented the depletion of elastin. The effects of the mixture of spices on aorta morphology were found to be like those of curcumin. Piperine can modify the remodelling process of the aorta's wall that is induced by hypertension and curcumin therapy is more effective in preventing the adverse changes in blood vessel structure that are commonly observed in individuals with hypertension[18].

Gemfibrozil is an antihyperlipidemic drug that is primarily used for lowering high Triglyceride and cholesterol content. Gemfibrozil also has a strong ability to increase levels of high-density lipoprotein. The half-life of this medicine is around 2 hours, and an increase in dosage has been observed to result in liver damage. Piperine is a pharmacological agent that possesses the ability to enhance the bioavailability of co-administered medicinal compounds, without changing the inherent characteristics and therapeutic effects. Piperine as a bio-enhancer was employed to augment the bioavailability of gemfibrozil and mitigate its potential adverse effects, hence enhancing its efficacy. The concurrent administration of piperine and gemfibrozil was conducted on rats to evaluate the antihyperlipidemic effects in the context of a high-fat diet. The results indicated that the combined administration of gemfibrozil and piperine had a significantly enhanced efficacy in normalizing elevated levels of triglycerides and cholesterol, compared to their administration[19].

4. Myocardial Infarction

The treatment of Myocardial Infarction/Ischemia (MI) involves the use of many pharmacological therapeutic strategies. However, the effectiveness of these treatments is hindered by their toxicity and lack of selectivity in their pharmacological effects. In this work, the protective effects of piperine against Myocardial Infarction (MI) induced by isoproterenol (ISO) were demonstrated. In this study, rats were employed as experimental subjects to simulate isoproterenol (ISO)-induced myocardial ischemia. The efficacy of piperine in preventing this condition was evaluated by modulating mitochondrial activity. The results indicate that the administration of piperine before treatment prevents the alterations generated by ISO in the antioxidant status of mitochondria, as well as in the Krebs cycle and the activity of Mitochondrial Respiratory Chain Enzymes (MRCEs). The experimental group that received pretreatment with piperine before injection with ISO exhibited a significant decrease in the structural changes induced by ISO in the mitochondria of the heart. It shows that piperine could be used as a nutritional intervention against ISO-induced myocardial ischemia[20].

The impact of black pepper on blood pressure in a rat model was studied and it was found that piperine found in black pepper, has the potential to generate a notable reduction in blood pressure in rats with normal blood pressure levels. During the study, Wistar rats were subjected to several treatments including the administration of clear water, L-NAME, and piperine in maize oil. The rats were orally gavaged with L-NAME (LP) or without it (P) for Piperine for 6 weeks. Piperine exhibited a reduction in the elevation of blood pressure starting from the third week of therapy. Additionally, it shows an impact on the production of elastin as well as the percentage and absolute content of PTAH-positive myofibrils. The administration of piperine through oral means has demonstrated the ability to partially mitigate the rise in blood pressure resulting from the chronic administration of L-NAME[21].

5. Piperine for Atherosclerosis and Aortic Inflammation

The effects of Piperine on the proliferation and migration of vascular smooth muscle cells triggered by platelet-derived growth factors were assessed by various experimental techniques and were observed to be significant. This was achieved through the upregulation of p27kip1 expression, modulation of mRNA expression of cell cycle enzymes (cyclin D, cyclin E, and PCNA), and reduction in the phosphorylation of extracellular signal-regulated kinase (ERK)1/2. Notably, these effects were observed within a concentration range of

30-100 μM, without inducing cytotoxicity. Piperine in a specific concentration and dose-dependent inhibits cell proliferation and decreases cell migrations and production of Reactive Oxygen Species (ROS) by inducing cell cycle arrest. On behalf of these findings, piperine can be used for treating vascular-related disorders and diseases[22].

Atherosclerosis, a condition characterized by immunoinflammatory processes, is widely acknowledged as a leading contributor to cardiovascular and peripheral artery disorders, significantly impacting global death rates[23]. Curcumin, a highly strong polyphenol found in the plant *Curcuma longa*, has demonstrated significant efficacy in combating atherosclerosis through its anti-inflammatory and anti-oxidative characteristics. Because of the low solubility and bioavailability, the clinical translational applications of curcumin are limited[24]. Bioperine, a bioactive component of piperine can be co-administered along with curcumin in polymeric nano drug formulation which induces rapid absorption and elevates curcumin's bioavailability since it is used as a potent bioenhancer, it will easily target the atherosclerotic plaque site and decrease the foam cell formation[25].

The circulatory system assumes a vital part in the regulation and sustenance of several biological processes. Vascular injury is responsible for the development of various aortic pathologies, including atherosclerosis, aortic dissection, and aneurysm. Sudden deaths can be attributed to various aortic illnesses, underscoring the importance of timely diagnosis and proper management in those afflicted with aortic diseases[26].

Aortic malfunctioning is mostly due to smoking which causes chronic aortic inflammation[27]. B-caryophyllene, a natural bioactive terpene, present in essential oil, is obtained from Black pepper and several other spices[28]. The act of smoking is a significant risk factor for the development of vascular illnesses. According to reports, BCP has strong pharmacological properties in mice and rats by effectively reducing nicotine reward and nicotine addiction, while without inducing any sedative effects. B-caryophyllene effects on nicotine-induced degeneration of the aortic wall were studied with mice and cultured aorta wall, in which group of mice inhaled B-caryophyllene showed a decrease in nicotine-induced aortic wall degeneration and cultured aorta, the effect is inhibited by blocking the CB2 receptor dependant pathway[29].

5.1 Anti-tumour Activity

Extracts of black pepper having a high mitotic index, high rate of metastasis, poor prognosis, and triple-negative breast cancer have gained attention, and essential oils of black pepper show good Anti-cancer activity. Due to its poor stability, nanoparticles containing black pepper essential oil were created using nanoprecipitation, employing Eudragit L100 as the carrier, which inhibited the expression of cancer cell lines[30].

5.2 Osteosarcoma (Bone Cancer)

Survival of patients with metastasis has been stabilized, with a broad-spectrum medication doxorubicin, which shows a restricted therapeutic window because of its cardiotoxicity. Piperine can cause the death of some cancer cells, and it increases the chemosensitivity of doxorubicin. Combined therapy of piperine and doxorubicin has reduced tumour growth and cell proliferation which is proved by *in vivo* and *in vitro* studies[31].

5.3 Mesothelioma Cancer

A combination of curcumin-C3 complex and bioperine (A bioactive form of piperine) has shown significant effects in *in vitro* studies as it inhibits the mesothelioma cells forming tumour growth by limiting cell motility, proliferative cell rate, and self-renewal, and also slows tumour growth in a xenograft mice model by decreasing angiogenesis and boosting apoptosis[32].

5.4 Stomach Carcinogen

Helicobacter pylori is designated as a stomach carcinogen. The effects of piperine on *H. pylori* adhesion and growth were studied by using the broth macro dilution method and the urease assay to confirm adherence to gastric cancer cells, it was possible to measure the amount of *H. pylori* growth inhibition. The motility test by motility agar beside piperine administration was evaluated by RT-PCR and immunoblotting. Piperine on administration in dose dependant has reduced adhesion to gastric adenocarcinoma cells and inhibition was statistically significant by student T-test[33].

5.5 Anti-cancer Activity of Natural Piperine Derivatives

Two series of piperine-derived amides and ureas have been synthesized, utilizing the native piperine molecule, with potential applications as anti-cancer agents. The anti-cancer efficacy was assessed against ovarian A2780CP, Triple-Negative Breast Cancer (TNBC) MDA-MB-231, and HepG2 cancer cell lines derived from the liver. These actions have undergone clinical evaluation and have been demonstrated to show that modifying natural piperine can potentially have significant anti-cancer effects[34]. Due to its ability to induce cell cycle arrest, promote autophagy and apoptosis, and disrupt redox homeostasis, piperine has a high potential for chemopreventive effects. An alkaloid derivative of piperine has a direct and indirect impact on tumour cell survival and inhibits normal cells. Piperine has a good therapeutic index for administering anti-cancer medications[35].

5.6 Anti-malarial Activity

The antimalarial efficacy of piperine is considered limited but the concurrent administration of piperine and curcumin demonstrated *in vivo* antimalarial activity in a mouse model infected with *Plasmodium chabaudi* has shown moderate activity when administered orally. Piperine, administered concurrently at a lesser dose for the same duration, was found to enhance the bioavailability of curcumin, hence augmenting its antimalarial activity[36,37].

6. Piperine on Neuroprotective Activity

Neurological illnesses have a significant impact on about one billion individuals globally, with advancing age being a prominent risk factor. The current age-related neurological disorders medications just relieve symptoms by altering neurotransmission[38-42]. Natural products have efficiently evolved in treating age-related neurological disorders with multiple medicinal values and with a multi-targeted approach[43]. Piperine owing to its chemical composition, is an effective drug in treating neurological disorders which will enhance efficacy, solubility, and bioavailability along with neuroprotective properties, proving vital in animal modules and clinical trials[44]. Black pepper contains pungent alkaloids like piperine, piperlonguminine, piperazine, piperocaine, pipercallosine, guineensine, dehydropipernonaline, retrofractamide A and B, carbamide, piperazine, etc., amide alkaloids, and alkamides like pellitorine, piperettyline, piperidine, and feruperine that protects the brain[45].

6.1 Activity on Alzheimer's Disease

Alzheimer's disease resulted due to the alteration in neural region[46] on treatment with black-pepper fruit extract at a concentration of 35 µg/mL has demonstrated the ability to decrease the levels of phosphorylated forms of pro-apoptotic proteins. Pepper extract inhibits the working of acetylcholinesterase (AChE) and the aggregation of amyloid-beta (Aβ) in SH-SY5Y cells produced by hydrogen peroxide (H_2O_2)[47]. In $AlCl_3$-induced AD rats, supplementation by black pepper orally reduced amyloidal plaque development and cholinesterase levels and improved memory performance[48].

6.2 Activity on Parkinson's Disease

Parkinson's Disease (PD) primarily arises from the progressive degeneration of dopaminergic neurons and is closely linked to the development of motor deficits and cognitive decline in individuals[49]. The findings from the *in vitro* experiments indicate that the administration of piperine promotes the survival of cells and mitigates their toxicity. Furthermore, administration of the therapy demonstrated a protective effect on SK-N-SH cells that were experiencing impaired autophagy flux because of the expression of SNCA, through the activation of the purinergic receptor P2X 4 (P2RX4). The observed protective benefits were achieved by promoting autophagy flux through the enhancement of autophagosome-lysosome membrane fusion[50].

6.3 Activity on Huntington's Disease (HD)

HD is a complicated neurodegenerative disorder caused by striatal neuron degeneration that causes motor function impairment and mental irregularity[51]. The occurrence of HD may be instigated by oxidative stress and mitochondrial malfunction since they give rise to the generation of ROS. These ROS can induce protein misfolding, subsequently resulting in the aggregation of inclusion bodies that impede neurotransmission[52]. The protective effects of piperine were observed in rats treated with 3-nitro propionic acid (3-NP) and piperine

demonstrated its protective action by restoring the levels of 5-HT (5-hydroxytryptamine), improving neurobehavioral performance as assessed by various tests like grip strength, narrow-beam walk, rotarod, gait analysis and elevated plus maze test. Additionally, piperine enhanced the activity of Monoamine Oxidase (MAO) and reduced neuron degeneration in the striatal tissue of the rats. Additionally, there have been reports indicating that the administration of piperine results in a considerable decrease in Glial Fibrillary Acidic Protein (GFAP) staining. This treatment also serves to protect against neuronal malfunction and mortality in animals subjected to toxin-induced insults[53]. A combination of curcumin with piperine with defined doses can be used to treat Huntington's disease by reducing the effects caused by quinolinic acid moiety[54].

6.4 Activity on Multiple Sclerosis

Multiple Sclerosis (MS) stands as the prevailing chronic immune-mediated neurodegenerative disorder of the Central Nervous System (CNS)[55]. Rats were subjected to immunization using a suspension consisting of guinea-pig spinal cord homogenized in complete Freund's adjuvant and toxin, to induce Experimental Autoimmune Encephalomyelitis (EAE). The examination of lumbar spinal cord cross-sections revealed that the administration of piperine resulted in a notable decrease in inflammation, immune cell infiltration, and demyelination, as well as the activation of microglia and astrocytes[56].

6.5 Activity on Epilepsy

Neurological disorder (epilepsy) defined by chronic and persistent neuronal activity in the Central Nervous System (CNS), resulted from a decreased seizure threshold[57]. Essential oil extracts of several natural species have become an alternate way to treat epilepsy[58]. The potential anticonvulsant effects of piperine on inflammation, memory function, and oxidative stress in a rat model of epilepsy produced by pilocarpine resulted in a decrease in status epilepticus and memory impairment. This effect was attributed to the enhancement of catalase and superoxide dismutase (SOD) activities, as well as an increase in glutathione (GSH) content. Additionally, in the pilocarpine-induced rat epilepsy model, piperine supplementation was found to reduce levels of proinflammatory cytokines, malondialdehyde as well as caspase-3 activity. Additionally, it was found to modulate the expression of Bax and Bcl-2, key proteins involved in apoptosis[59] and reduce the onset and increase of the electroshock-induced Epilepsy model[60].

6.6 Activity on Stroke

Ischemic brain injury, resulting from either stroke or cardiac arrest, is a significant contributor to neurological disability in the human population. Acute ischemic stroke occurs when a cerebral vessel is obstructed by thrombosis or embolism, leading to a sudden deprivation of blood flow to a specific region of the brain[61]. Black pepper and its derivatives can be used to treat cerebral ischemic injury by modulating the signalling pathways. The administration of 100 or 200 mg/kg/b.w of dichloromethane fraction derived from black-pepper fruit extracts demonstrated a mitigating effect on neurological deficits. Additionally, it resulted in elevated levels of calmodulin, p-CaMKII (phosphorylated calmodulin-dependent protein kinase II), PSD-95 (postsynaptic density protein 95) and NR2B (N-methyl D-aspartate receptor subtype 2B). Furthermore, it exhibited a protective effect against cellular damage induced by ischemia. In addition, the immuno-histochemical study resulted in a notable elevation of SYN-I (synapsin-I) and PSD-95 protein levels, while concurrently reducing the expression of α-synuclein in the brains of rats with produced ischemia[62,63]. The experimental findings of the neuroprotective impact on cerebral ischemia injury upon administration of dichloromethane fraction of piperine at varying doses exhibited over 14 days suggested that piperine can lead to enhanced neurological recovery and improved neuronal morphological structure in rats afflicted with ischemic stroke[64]. Piperine formulated in nanoparticle carriers can easily deliver the drug with enhanced bioavailability and cross-blood-brain barrier[65,66].

7. Conclusion

The various pharmacological activities of the pungent alkaloid piperine from pepper and its essential oil have been reviewed. In conclusion, *P. nigrum* is not only a popular spice but also a significant medicinal plant that has the potential to be used in pharmaceutical and nutraceutical products.

8. References

1. Takooree H, Aumeeruddy MZ, Rengasamy KRR, Venugopala KN, Jeewon R, Zengin G, Mahomoodally MF. A systematic review on black pepper (*Piper nigrum* L.): from folk uses to pharmacological applications. Crit Rev Food Sci Nutr. 2019; 59(sup1):S210-43. https://doi.org/10.1080/10408398.2019.1565489 PMid:30740986
2. El-Hack ME, El-Shall NA, El-Kasrawy NI, El-Saadony MT, Shafi ME, Zabermawi NM, Alshilawi MS, Alagawany M, Khafaga AF, Bilal RM, Elnesr SS, Aleya L, Qamar SF, El-Tarabily KA. The use of black pepper (*Piper guineense*) as an eco-friendly antimicrobial agent to fight foodborne microorganisms. Environ Sci Pollut Res Int. 2022;29(8):10894-907. https://doi.org/10.1007/s11356-021-17806-7 PMid:35000164
3. Kathiravan MK, Salake AB, Chothe AS, Dudhe PB, Watode RP, Mukta MS, Gadhwe S. The biology and chemistry of antifungal agents: a review. Bioorganic and Medicinal Chemistry. 2012; 20(19):5678-98. https://doi.org/10.1016/j.bmc.2012.04.045
4. Han HK. The effects of black pepper on the intestinal absorption and hepatic metabolism of drugs. Expert Opin Drug Metab Toxicol. 2011; 7(6):721-9. https://doi.org/10.1517/17425255.2011.570332 PMid:21434835
5. JoonGoo L, Chae Y, Shin Y, Kim Y. Chemical composition and antioxidant capacity of black pepper pericarp. Appl Biol Chem. 2020; 63:35. https://doi.org/10.1186/s13765-020-00521-1
6. Weleffs J, Dore S, Anand A, Barnett BS. Black Pepper (*Piper nigrum*) for tobacco withdrawal: A case report. Case Rep Psychiatry. 2022; 2022:5908769. https://doi.org/10.1155/2022/5908769 PMid:36530582 PMCid: PMC9757938
7. Meghwal M, Goswami TK. *Piper nigrum* and piperine: An update. Phytother Res. 2013; 27(8):1121-30. https://doi.org/10.1002/ptr.4972 PMid:23625885
8. Dosoky NS, Satyal P, Barata LM, da Silva JKR, Setzer WN. Volatiles of black pepper fruits (*Piper nigrum* L.). Molecules. 2019; 24(23):4244. https://doi.org/10.3390/molecules24234244 PMid:31766491 PMCid: PMC6930617
9. Pei H, Xue L, Tang M, Tang H, Kuang S, Wang L, Ma X, Cai X, Li Y, Zhao M, Peng A, Ye H, Chen L. Alkaloids from black pepper (*Piper nigrum* L.) exhibit anti-inflammatory activity in murine macrophages by inhibiting activation of NF-κB pathway. J Agric Food Chem. 2020; 68(8):2406-17. https://doi.org/10.1021/acs.jafc.9b07754 PMid:32031370
10. Amalraj A, Haponiuk JT, Thomas S, Gopi S. Preparation, characterization, and antimicrobial activity of polyvinyl alcohol/gum arabic/chitosan composite films incorporated with black pepper essential oil and ginger essential oil. Int J Biol Macromol. 2020; 151:366-75. https://doi.org/10.1016/j.ijbiomac.2020.02.176 PMid:32084477
11. Duangjai A, Ingkaninan K, Praputbut S, Limpeanchob N. Black pepper and piperine reduce cholesterol uptake and enhance translocation of cholesterol transporter proteins. J Nat Med. 2013; 67(2):303-10. https://doi.org/10.1007/s11418-012-0682-7 PMid:22736065
12. Fernández-Lázaro D, Mielgo-Ayuso J, Córdova Martínez A, Seco-Calvo J. Iron, and physical activity: Bioavailability enhancers, properties of black pepper (Bioperine®) and potential applications. Nutrients. 2020; 12(6):1886. https://doi.org/10.3390/nu12061886 PMid:32599787 PMCid: PMC7353321
13. Boonrueng P, Wasana PWD, Hasriadi, Vajragupta O, Rojsitthisak P, Towiwat P. Combination of curcumin and piperine synergistically improves pain-like behaviours in mouse models of pain with no potential CNS side effects. Chin Med. 2022; 17(1):119. https://doi.org/10.1186/s13020-022-00660-1 PMid:36274168 PMCid: PMC9590184
14. Miryan M, Bagherniya M, Sahebkar A, Soleimani D, Rouhani MH, Iraj B, Askari G. Effects of curcumin-piperine co-supplementation on clinical signs, duration, severity, and inflammatory factors in patients with COVID-19: A structured summary of a study protocol for a randomized controlled trial. Trials. 2020; 21(1):1027. https://doi.org/10.1186/s13063-020-04924-9
15. Li Y, Li M, Wu S, Tian Y. Combination of curcumin and piperine prevents the formation of gallstones in C57BL6 mice fed on lithogenic diet: whether NPC1L1/SREBP2 participates in this process? Lipids Health Dis. 2015; 14:100. https://doi.org/10.1186/s12944-015-0106-2 PMid:26335572 PMCid: PMC4557223
16. Miyazawa T, Nakagawa K, Kim SH, Thomas MJ, Paul L, Zingg JM, Dolnikowski GG, Roberts SB, Kimura F, Miyazawa T, Azzi A, Meydani M. Curcumin and piperine supplementation of obese mice under caloric restriction modulates body fat and interleukin-1β. Nutr Metab (Lond). 2018; 15:12. https://doi.org/10.1186/s12986-018-0250-6 PMid:29445415 PMCid: PMC5801844
17. Swiderski J, Sakkal S, Apostolopoulos V, Zulli A, Gadanec LK. Combination of taurine and black pepper extract as a treatment for cardiovascular and coronary artery diseases. Nutrients. 2023; 15(11):2562. https://doi.org/10.3390/nu15112562 PMid:37299525 PMCid: PMC10255510
18. Hlavačková L, Janegová A, Uličná O, Janega P, Cerná A, Babál P. Spice up the hypertension diet - curcumin and piperine prevent remodeling of aorta in experimental L-NAME induced hypertension. Nutr Metab (Lond). 2011; 8:72. https://doi.org/10.1186/1743-7075-8-72 PMid:22005253 PMCid: PMC3214182

19. Mohanalakshmi S, Bhatt S, Kumar ACK. Enhanced antihyperlipidemic potential of gemfibrozil under co-administration with piperine. Curr Res Pharmacal Drug Discov. 2021; 2:100021. https://doi.org/10.1016/j.crphar.2021.100021 PMid:34909656 PMCid: PMC8663971
20. Viswanadha VP, Dhivya V, Somasundaram B, Beeraka NM, Huang CY, Mikhaleva LM, Achkasov E, Bondarev S, Gridin L, Nikolenko VN, Aliev G. The role of mitochondria in piperine mediated cardioprotection in isoproterenol-induced myocardial ischemia. Curr Pharm Des. 2021; 27(26):2975-89. https://doi.org/10.2174/1381612826666200909125750 PMid:32912121
21. Hlavackova L, Urbanova A, Ulicna O, Janega P, Cerna A, Babal P. Piperine, active substance of black pepper, alleviates hypertension induced by NO synthase inhibition. Bratisl Lek Listy. 2010; 111(8):426-31.
22. Lee KP, Lee K, Park WH, Kim H, Hong H. Piperine inhibits platelet-derived growth factor-BB-induced proliferation and migration in vascular smooth muscle cells. J Med Food. 2015; 18(2):208-15. https://doi.org/10.1089/jmf.2014.3229 PMid:25384161
23. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N. Engl. J. Med. 2005; 352:1685-95. https://doi.org/10.1056/NEJMra043430 PMid:15843671
24. Del Prado-Audelo ML, Caballero-Florán IH, Meza-Toledo JA, Mendoza-Muñoz N, González-Torres M, Florán B, Cortés H, Leyva-Gómez G. Formulations of curcumin nanoparticles for brain diseases. Biomolecules. 2019; 9:56. https://doi.org/10.3390/biom9020056 PMid:30743984 PMCid: PMC6406762
25. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PSSR. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Medica. 1998; 64:353-6. https://doi.org/10.1055/s-2006-957450 PMid:9619120
26. Aoka Y, Sakai A, Ishizuka N, Kasanuki H. Diagnosis of aortic dissection and aneurysm. Angiol. Front. 2007; 6(4):312-9.
27. Sakalihasan N, Limet R, Defawe DO. Abdominal aortic aneurysm Lancet. 2005; 365:1577-89. https://doi.org/10.1016/S0140-6736(05)66459-8 PMid:15866312
28. He Y, Galaj E, Bi GH, Wang XF, Gardner E, Xi ZX. β-Caryophyllene, a dietary terpenoid, inhibits nicotine taking and nicotine seeking in rodents Br. Pharm. Soc. 2020; 177(9):2058-72. https://doi.org/10.1111/bph.14969 PMid:31883107 PMCid: PMC7161544
29. Kishi C, Higashihara M, Takemoto Y, Kamei M, Yoshioka Y, Matsumura S, Yamada K, Kobayashi T, Matahira Y, Moriyama T, Zaima N. Inhaled volatile β-caryophyllene is incorporated into the aortic wall and attenuates nicotine-induced aorta degeneration via a CB2 receptor-dependent pathway. Biomed Pharmacother. 2022; 153:113423. https://doi.org/10.1016/j.biopha.2022.113423 PMid:36076543
30. Gopinath P, Kathiravan MK. Molecular insights of oxadiazole benzene sulfonamides as human carbonic anhydrase IX inhibitors: Combined molecular docking, molecular dynamics, and 3D QSAR studies. Journal of the Indian Chemical Society. 2022; 99(2):100339. https://doi.org/10.1016/j.jics.2022.100339
31. Qi Y, Yao L, Liu J, Wang W. Piperine improves the sensitivity of osteosarcoma cells to doxorubicin by inducing apoptosis and inhibiting the PI3K/AKT/GSK-3β pathway. J Orthop Surg Res. 2023; 18(1):180. https://doi.org/10.1186/s13018-023-03642-7 PMid:36895009 PMCid: PMC9996932
32. Di Meo F, Filosa S, Madonna M, Giello G, Di Pardo A, Maglione V, Baldi A, Crispi S. Curcumin C3 complex®/Bioperine® has antineoplastic activity in mesothelioma: an *in vitro* and *in vivo* analysis. J Exp Clin Cancer Res. 2019; 38(1):360. https://doi.org/10.1186/s13046-019-1368-8 PMid:31419989 PMCid: PMC6698046
33. Tharmalingam N, Kim SH, Park M, Woo HJ, Kim HW, Yang JY, Rhee KJ, Kim JB. Inhibitory effect of piperine on *Helicobacter pylori* growth and adhesion to gastric adenocarcinoma cells. Infect Agent Cancer. 2014; 9(1):43. https://doi.org/10.1186/1750-9378-9-43 PMid:25584066 PMCid: PMC4290101
34. Elimam DM, Elgazar AA, El-Senduny FF, El-Domany RA, Badria FA, Eldehna WM. Natural inspired piperine-based ureas and amides as novel antitumor agents towards breast cancer. J Enzyme Inhib Med Chem. 2022; 37(1):39-50. https://doi.org/10.1080/14756366.2021.1988944 PMid:34894962 PMCid: PMC8667897
35. Zadorozhna M, Tataranni T, Mangieri D. Piperine: role in prevention and progression of cancer. Mol Biol Rep. 2019; 46(5):5617-29. https://doi.org/10.1007/s11033-019-04927-z PMid:31273611
36. Thiengsusuk A, Muhamad P, Chaijaroenkul W, Na-Bangchang K. Antimalarial activity of piperine. J Trop Med. 2018; 9486905. https://doi.org/10.1155/2018/9486905 PMid:30631371 PMCid: PMC6304611
37. Emon NU, Alam S, Rudra S, Riya SR, Paul A, Hossen SMM, Kulsum U, Ganguly A. Antidepressant, anxiolytic, antipyretic, and thrombolytic profiling of methanol extract of the aerial part of *Piper nigrum*: *In vivo, in vitro*, and *in silico* approaches. Food Sci Nutr. 2021; 9(2):833-46. https://doi.org/10.1002/fsn3.2047 PMid:33598167 PMCid: PMC7866625
38. Wyss-Coray T. Aging, neurodegeneration, and brain rejuvenation. Nature. 2016; 539: 180-6. https://doi.org/10.1038/nature20411 PMid:27830812 PMCid: PMC5172605
39. Mattson MP, Arumugam T V. Hallmarks of brain ageing: Adaptive and pathological modification by metabolic

states. Cell Metab. 2018; 27:1176. https://doi.org/10.1016/j.cmet.2018.05.011 PMid:29874566 PMCid: PMC6039826
40. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK. Natural phytochemicals as novel therapeutic strategies to prevent and treat Parkinson's disease: Current knowledge and future perspectives. Oxid Med Cell Longev. 2021. p. 1-32. https://doi.org/10.1155/2021/6680935 PMid:34122727 PMCid: PMC8169248
41. Hajali V, Moradi HR, Sahab Negah S. Neurotransmitters play as a key role in adult neurogenesis. Neurosci J Shefaye Khatam. 2018; 6:61-74. https://doi.org/10.29252/shefa.6.4.61
42. Di Paolo M, Papi L, Gori F, Turillazzi E. Natural products in neurodegenerative diseases: A great promise but an ethical challenge. Int J Mol Sci. 2019; 20:1-12. https://doi.org/10.3390/ijms20205170 PMid:31635296 PMCid: PMC6834164
43. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov. 2015; 14:111-29. https://doi.org/10.1038/nrd4510 PMid:25614221
44. Zhu F, Mojel R, Li G. Physicochemical properties of black pepper (*Piper nigrum*) starch. Carbohydr Polym. 2018; 181:986-93. https://doi.org/10.1016/j.carbpol.2017.11.051 PMid:29254063
45. Yu L, Hu X, Xu R, Ba Y, Chen X, Wang X, *et al.* Amide alkaloids characterization and neuroprotective properties of *Piper nigrum* L.: A comparative study with fruits, pericarp, stalks, and leaves. Food Chem. 2022; 368:130832. https://doi.org/10.1016/j.foodchem.2021.130832 PMid:34474242
46. Chen XQ, Mobley WC. Alzheimer disease pathogenesis: Insights from molecular and cellular biology studies of oligomeric Aβ and tau species. Front Neurosci. 2019; 13: 1-21. https://doi.org/10.3389/fnins.2019.00659 PMid:31293377 PMCid: PMC6598402
47. Deture MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019; 141(14):1-18. https://doi.org/10.1186/s13024-019-0333-5 PMid:31375134 PMCid: PMC6679484
48. Subedee L, Suresh RN, Jayanthi MK, Kalabharathi HL, Satish AM, Pushpa VH. Preventive role of Indian black pepper in animal models of Alzheimer's disease. J Clin Diagnostic Res. 2015; 9:FF01-4. https://doi.org/10.7860/JCDR/2015/8953.5767 PMid:26023568 PMCid: PMC4437082
49. Balakrishnan R, Vijayraja D, Mohankumar T, Manimaran D, Ganesan P, Choi DK, *et al.* Isolongifolene mitigates rotenone-induced dopamine depletion and motor deficits through anti-oxidative and anti-apoptotic effects in a rat model of Parkinson's disease. J Chem Neuroanat. 2021; 112:1-12. https://doi.org/10.1016/j.jchemneu.2020.101890 PMid:33220427
50. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK. Natural phytochemicals as novel therapeutic strategies to prevent and treat Parkinson's disease: Current knowledge and future perspectives. Oxid Med Cell Longev. 2021. p. 1-32. https://doi.org/10.1155/2021/6680935 PMid:34122727 PMCid: PMC8169248
51. Li R, Lu Y, Zhang Q, Liu W, Yang R, Jiao J, *et al.* Piperine promotes autophagy flux by P2RX4 activation in the SNCA/α-synuclein-induced Parkinson's disease model. Autophagy. 2022; 18:559-75. https://doi.org/10.1080/15548627.2021.1937897 PMid:34092198 PMCid: PMC9037522
52. Islam MT. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. Neurol Res. 2017; 39(1):73-82. https://doi.org/10.1080/01616412.2016.1251711 PMid:27809706
53. Xu X, Tay Y, Sim B, Yoon SI, Huang Y, Ooi J, *et al.* Reversal of phenotypic abnormalities by CRISPR/Cas9-mediated gene correction in Huntington disease patient-derived induced pluripotent stem cells. Stem cell reports. 2017; 8:619-33. https://doi.org/10.1016/j.stemcr.2017.01.022 PMid:28238795 PMCid: PMC5355646
54. Salman M, Tabassum H, Parvez S. Piperine mitigates behavioural impairments and provides neuroprotection against 3-nitro propionic acid-induced Huntington disease-like symptoms. Nutr Neurosci. 2022; 25:100-9. https://doi.org/10.1080/1028415X.2020.1721645 PMid: 32093571
55. Singh S, Kumar P. Neuroprotective activity of curcumin in combination with piperine against quinolinic acid-induced neurodegeneration in rats. Pharmacology. 2016; 97:151-60. https://doi.org/10.1159/000443896 PMid:26828892
56. Rezapour A, Almasian Kia A, Goodarzi S, Hasoumi M, Nouraei Motlagh S, Vahedi S. The impact of disease characteristics on multiple sclerosis patients' quality of life. Epidemiol Health. 2017; 39:e2017008. https://doi.org/10.4178/epih.e2017008 PMid:28231687 PMCid: PMC5434226
57. Nasrnezhad R, Halalkhor S, Sadeghi F, Pourabdolhossein F. Piperine improves Experimental Autoimmune Encephalomyelitis (EAE) in Lewis rats through its neuroprotective, anti-inflammatory, and antioxidant effects. Mol Neurobiol. 2021; 58:5473-93. https://doi.org/10.1007/s12035-021-02497-5 PMid:34338970
58. Stafstrom CE, Carmant L. Seizures and epilepsy: An overview for neuroscientists. Cold Spring Harb Perspect Med. 2015; 5:1-19. https://doi.org/10.1101/cshperspect.a022426 PMid:26033084 PMCid: PMC4448698
59. Bahr TA, Rodriguez D, Beaumont C, Allred K. The effects of various essential oils on epilepsy and acute seizure: A systematic review. Evid Based Complement Alternat Med. 2019. p. 1-14. https://doi.org/10.1155/2019/6216745 PMid:31239862 PMCid: PMC6556313
60. Mao K, Lei D, Zhang H, You C. Anticonvulsant effect of piperine ameliorates memory impairment, inflammation, and oxidative stress in a rat model of pilocarpine-induced epilepsy. Exp Ther Med. 2017; 13:695-700. https://doi.

org/10.3892/etm.2016.4001 PMid:28352353 PMCid: PMC5348653
61. Mishra A, Punia JK, Bladen C, Zamponi GW, Goel RK. Anticonvulsant mechanisms of piperine, a piperidine alkaloid. Channels. 2015; 9:317. https://doi.org/10.1080/19336950.2015.1092836 PMid:26542628 PMCid:PMC4826125
62. Hinkle JL, Guanci MMK. Acute ischemic stroke review. J Neurosci Nurs. 2007; 39:285-310. https://doi.org/10.1097/01376517-200710000-00005 PMid:17966295
63. Hua S, Wang B, Chen R, Zhang Y, Zhang Y, Li T, *et al*. Neuroprotective effect of dichloromethane extraction from *Piper nigrum* L. and *Piper longum* L. on permanent focal cerebral ischemia injury in rats. J Stroke Cerebrovasc Dis. 2019; 28:751-60. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.018 PMid:30528673
64. Zhang Y, He Q, Yang M, Hua S, Ma Q, Guo L, *et al.* Dichloromethane extraction from *Piper nigrum* L. and *P. longum* L. to mitigate ischemic stroke by activating the AKT/mTOR signalling pathway to suppress autophagy. Brain Res. 2020; 1749:147047. https://doi.org/10.1016/j.brainres.2020.147047 PMid:32781091
65. Zhang Y, Yang M, Yuan Q, He Q, Ping H, Yang J, *et al.* Piperine ameliorates ischemic stroke-induced brain injury in rats by regulating the PI3K/AKT/mTOR pathway. J Ethnopharmacol. 2022; 295:115309. https://doi.org/10.1016/j.jep.2022.115309 PMid:35597410
66. Mirza AZ, Siddiqui FA. Nanomedicine and drug delivery: A mini-review. Int Nano Lett. 2014; 4:1-7. https://doi.org/10.1007/s40089-014-0094-7