*Annals of Science and Allied Research* Vol. 2 (1) June, 2024: 10-25.
https://doi.org/10.5281/zenodo.12596886
ISSN – 2584-2307 (Online)

# BLACK PEPPER: *A SPICE OF ENDLESS POSSIBILITIES* - A MINI REVIEW

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*(Received on April 20, 2024; Revised on June 9, 2024; Accepted on June 21, 2024)*

**ABSTRACT**

Black pepper is widely considered the most esteemed spice among all others. It has gained global recognition for its exceptional flavor, alluring aroma, and medicinal properties. Phytochemists heavily utilize a variety of compounds found in black pepper, such as terpenes, alkaloids, lignans, amphetamines, and more, due to their profound therapeutic effects. Black pepper is a rich source of various natural substances, including antioxidants, antibacterial, antifungal agents, anticancer compounds, anti-inflammatory properties, analgesics, antipyretics, remedies for gastrointestinal disorders, bioavailability enhancers and enzyme inhibitors. In this article, we aim to provide a succinct overview of the chemical composition and pharmacological characteristics of this notable spice.

**Keywords:** Piperine*, immunomodulatory, anti-inflammatory*, antimicrobial, anticancer activities.

## INTRODUCTION

There are a few spices in the world of culinary arts that command as much respect and admiration as black pepper. Appreciated for its unique taste, aroma, and many uses, black pepper is an indispensable ingredient in cuisines around the world. Its journey from ancient civilizations to modern cuisine is of endless importance and culinary mastery. The origins of black pepper can be traced back thousands of years to the tropical regions of South Asia, where it was not only a food but also a valuable commodity traded like ancient spices. The Malabar Coast of India is the original homeland of black pepper, cultivated along with other tropical regions, and is described in Hajeski and Nancy [1], and has been called the king of spices by Sen [2]. According to the International Trade Centre's Global Spice Import Report, black pepper is a popular spice used in cuisines worldwide [3]. The nitrogenous alkaloid piperine, was first reported in 1820 by Danish chemist H. C. Orstedt [4]. Piperine, yellow crystalline compound, has the molecular composition $C_{17}H_{19}NO_3$, melting range 128-130 °C, (2E,4E)-5-{2H-1,3-benzodioxol-5-yl)-1-(Piperidin-1-yl)}penta-2,4-dien-1-one, IUPAC name. In water, its alkaline content is 40 mg/litre, but it is more soluble in organic solvents. The solubility of piperine was determined in different organic solvents with the following results-ethanol - 1 gram per 15 millilitres, ether - 1 gram per 36 millilitres, and chloroform - 1 gram per 1.7 millilitres. Aziz et al. [5] conducted a study on the utilization of both traditional and innovative biotechnology techniques in white pepper production. According to the findings of Baker et al. [6], variations were observed in the oils of white pepper, green and black pepper. Thakur et al. [7] examined the medicinal uses of black pepper. Tiwari et al. [8] found that alkaloids such as piperine, piperonin A, and piperonal B were present in black pepper extract. Black pepper still commands the respect of the culinary world today, creating many dishes with its flavour and warmth. In addition, black pepper also has many health benefits. Derosa et al. [9] explored about the use of piperine in chronic diseases, such as reducing insulin resistance, preventing diseases, and improving hepatic steatosis. Meghwal and Goswami [10] presented a scientific review on the main effects of piperine on part of ABC transporter family, i.e. p-glycoprotein with several enzymes. This study focussed to chemoprevention, detoxification, and biotransformation related to enhancing the absorption and bioavailability of herbal and routine medicines. Singletary [11] investigated black pepper as a folk remedy with antioxidant, anti-inflammatory, and anti-inflammatory properties. Zorica and colleagues [12] have identified various components in aetheroleum of black pepper as α-pinene, β-pinene, sabinene, phellandrene, β-caryophyllene, linalool, citral, limonene etc. According to their work, weakly alkaline compound, piperine can hydrolyze to piperic acid or piperidine, depending on whether the hydrolysis is alkaline or

acidic. It serves the community not only by being productive but also as a symbol of general prosperity. These findings warrant towards the biopotentials of black pepper. Drawing upon a synthesis of historical theory, scientific research, and culinary expertise, our study aims to explore the intricate realm of black pepper. Through this brief investigation, we will reassess its potential health benefits as well as its cultural significance, chemical makeup, and biological properties in the hopes of uncovering untapped dimensions of this spice.

**Botanical traits of Black Pepper (*Piper nigrum*)**

Black pepper, scientifically known as *Piper nigrum*, is a flowering vine in the family Piperaceae, widely cultivated for its fruit, which is usually dried and used as a spice and seasoning. Here, we explore the key botanical traits of black pepper.

*Plant Description*

*Growth Habit: Piper nigrum* is a perennial climbing vine that can grow up to 10 meters in height, using trees, poles, or trellises for support.

*Stem:* The stem is woody, flexible, and can form adventitious roots at nodes, which help the vine cling to supports.

*Leaves:* The leaves are alternate, simple, and broadly ovate to heart-shaped, with a leathery texture. They are dark green, glossy, and have a pointed tip and a rounded base, with prominent veins.

*Flowers*

*Inflorescence*: Black pepper plants produce flowers in dense, slender, spike-like inflorescences that can grow up to 15 cm long. Each spike consists of numerous tiny flowers.

*Flower type*: The flowers are small, white to yellowish, and lack petals. They are unisexual or bisexual, depending on the variety.

*Pollination*: Piper nigrum is primarily pollinated by insects, although some self-pollination can occur.

*Fruit*

*Type*: The fruit of black pepper is a drupe (berry-like), known as a peppercorn.

*Appearance*: The drupes are small, about 5 mm in diameter, and start green, turning red as they mature.

*Ripening*: When dried, the fruit shrinks and darkens, forming the familiar black peppercorns. If left to mature fully and dried, they become white pepper; harvested green and preserved, they can be used as green pepper; and preserved when fresh, they are used as red pepper.

*Seed*s

*Structure*: Each drupe contains a single seed, which is the actual spice. The seed is spherical, with a wrinkled surface.

*Propagation*: Black pepper is typically propagated through cuttings rather than seeds to maintain desirable traits and ensure uniformity.

**Habitat and Cultivation**

*Climate*: Black pepper thrives in tropical climates with warm temperatures (25-30°C) and high humidity (70-90%).

*Soil*: It prefers well-drained, fertile soils rich in organic matter, with a pH range of 5.5 to 6.5.

*Water Requirements*: Consistent rainfall or irrigation is essential, as the plant requires a lot of water, but waterlogging can damage the roots.

**Growth Cycle**

*Lifespan*: Piper nigrum plants can remain productive for up to 20 years.

*Harvesting*: Peppercorns are typically harvested when they are still green but have started to mature. Multiple harvests can occur within a year, depending on the growing conditions and the desired pepper type

**Crystals of piperine**

**Pharmacology of piperine**

Piperine, the primary bioactive compound found in black pepper (Piper nigrum), has garnered significant attention in the field of pharmacology due to its wide range of therapeutic properties. Its pharmacological effects are diverse, impacting various physiological and biochemical processes in the human beings. Here, we have tried to explore the pharmacokinetic and pharmacodynamic aspects of piperine under the light of literature study. ***Immunomodulatory and anti-allergic property***

Bezerra et al. [13] asserted that incubating cell lines of the tumour with 5-FU i.e. 5-fluorouracil where piperine showed increased growth inhibition, thereby yielding a reduced IC value of 5-FU. Bernardo et al. [14] investigated for the first time the effect of piperine on B cell functions in vitro and its effects on the humoral immune response to T-dependent and T-independent antigens was noted with different concentrations of 1 μM, 3 μM, and 15 μM. Lee et al. [15] reported a combinatory effect of piperine and GABA (gamma-aminobutyric acid) on functional erythropoietin and erythropoietin receptor gene

*Annals of Science and Allied Research* Vol. 2 (1) June, 2024: 10-25.
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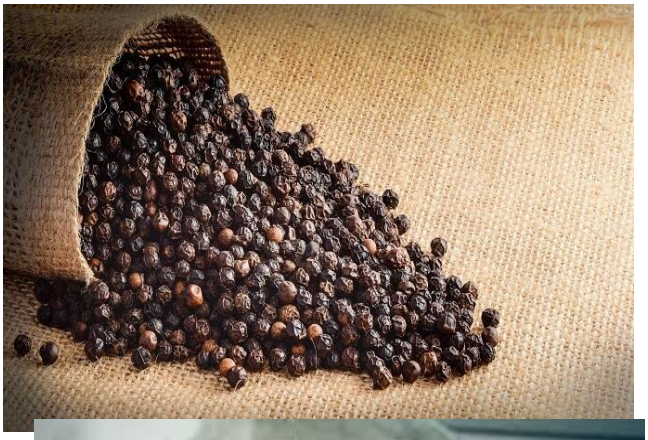
expression in kidney epithelial cells. Piperine may improve allergic symptoms such as sneezing, chafing, rash, and tenderness of blood vessels caused by the release of histamine from the antigen-antibody reaction. According to the results of study of Aswar et al. [16], administration of piperine has demonstrated significant efficacy in reducing inflammation causing redness, and harm in the alveoli and bronchioles. Furthermore, this compound also exhibits therapeutic effects in the treatment of asthma by inhibiting T cell activity and suppressing the production of Th2 cytokines [17]. Overall, these findings suggest that piperine may be a valuable tool in managing respiratory conditions characterized by inflammation.

**Hans Christian Orste**

**Antimicrobial property**

Different researchers have studied the antibacterial properties of piperine and confirmed its overall effects. Aldaly [18] explored the antimicrobial properties of piperine at concentrations ranging from 3.12 to 100 mg/ml, demonstrating its efficacy against Candida albicans. The microbial inhibition calculated by Umadevi et al is 100-600 µg/mL. [19] and has been proven to have the best inhibitory effect on Pseudomonas aeruginosa.


**Image-1**

Maitra J. [20] observed a synergistic effect of piperine, extracted from *P. nigrum*, with ciprofloxacin on *Escherichia coli* and *Bacillus subtilis*. Piperine enhances the inhibitory effect of ciprofloxacin on *E. coli* and *B. subtilis* [20-21]. In the same continuation, Jin et al. [21] claimed the potency of pierine by inhibition of ethidium bromide efflux in *Mycobacterium smegmatis*. Amperayani et al. [22] synthesized different piperine derivatives featuring the pyridine moiety and tested vitro and in silico antimicrobial properties against selected pathogens. They subjected to antimicrobial testing against *B. subtilis, Streptobacillus, Staphylococcus aureus, E. coli,* and *Salmonella typhi* and fungal strains *Aspergillus niger, A. flavus,* and *A. fumigatus* respectively (Image-1). Several studies have also elucidated the antibacterial activity of piperine in food samples. Hugas et al. [23] proposed examining the impact of piperine, an ingredient in fermented sausages, on the antilisterial activity of bacteriocin-producing *Lactobacillus sakei* CTC494 in both in vitro and model fermented sausages. Masatcioglu and Avsar [24] studied the effects of different flavourings, storage conditions, and storage duration on the survival of S. aureus in Sürk cheese. They found a significant decrease in the viability of S. aureus ($P < 0.05$). Martínez et al. [25] looked at the effects of red and hot cayenne pepper powders from Capsicum annuum and black and white pepper powders from Piper nigrum on fresh pork sausages stored in a modified atmosphere. Sausages were made with different concentrations of the peppers and stored at 2 °C for 16 days. The use of black and white pepper resulted in a delay in discoloration and inhibited lipid oxidation, with black pepper being particularly effective. All spices were able to inhibit microbial growth at higher concentrations. Krumov et al. [26] designed four sets of processed cheese using *P. nigrum* and *Satureja hortensis* L. extracts. Samples were stored at 5±1ºC for 10 days and analyzed for various factors. Microbiological assessment was conducted on spices, extracts, and cheese samples, with lower colony counts in test samples. Processed cheeses with spice extracts had higher sensory scores. The study found that using spice extracts improved the microbiological and sensory quality of the cheese. Agbabiaka et al. [27] conveyed storage and microbial inhibition on selected moon fishes. 36 oven-dried moonfishes, weight range from 850 to 900 g, divided into three groups and stored at room temperature. After, the first group was soaked in a 3% brine solution without black pepper, serving as the control followed by second and third groups, soaked in a mixture of 3% brine with 1.5% and 3% black pepper extract, respectively. After being oven-dried for 5 hours at 80°C–90°C, the samples were stored for 7 days. Microbial analysis showed that the control group

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had the highest microbial count, while the groups treated with black pepper had lower counts. S. aureus was found in the control group, while *Klebsiella* spp. and *Bacillus* spp. were found in the other groups. Results recommend that using brine with black pepper can reduce microbial load and improve the shelf-life of oven-dried fish.

***Anti-Inflammatory potential of piperine***

Sabina et al. [28] disclosed that piperine can suppress the activity of enzyme of liver activity (AST, ALT, ALP) and showed antioxidative potential also. In a study conducted by Sujawo et al. [29], it was discovered that piperine can lower BUN, creatinine, and MDA levels while concurrently augmenting the renal antioxidant functionality of SOD and glutathione in lead acetate-treated nephrotoxic rats through GPx intervention. In their research, Verma et al. [30] investigated the potential of piperine to mitigate oxidative stress caused by cadmium. They examined the beneficial effects of piperine using different biomarkers, including comet and lipid peroxidation (LPA) assays, in cultured human peripheral blood lymphocytes obtained from healthy individuals. The results showed that piperine at concentrations of 35 and 50 µM significantly decreased the tail moment and lipid peroxidation. Vijayakumar et al. [31] also documented comparable findings, where they investigated the effectiveness of piperine, an alkaloidal component derived from Piper nigrum, on the antioxidant status of erythrocytes in rats with high-fat diets and hyperlipidemia induced by antithyroid drugs. Elkadi et al. [32] showed that piperine had an anti-inflammatory effect on lung injury caused by gamma-ray antithyroid drugs in hyperlipidemic rats. Bae et al. (33) found that piperine suppresses lipopolysaccharide-induced inflammation by inhibiting IRF-1, IRF-7, IRF-3, type 1 IFN, and phosphorylating STAT-1 mRNA. Piperine shows potential as a therapeutic agent for treating this type of inflammation. Wang-Sheng et al. [34] detected piperine's role as a reductase in the generation of inflammatory markers in BV2 microglia. Discovery of Chuchawankul et al. [35] reported that IL-2 and IFN-γ are key cytokines involved in the immune response. By inhibiting these cytokines, piperine may have potential therapeutic applications in autoimmune diseases, inflammatory conditions, and other immune-related disorders. Further research is needed to fully understand the mechanisms by which piperine exerts its effects on IL-2 and IFN-γ, as well as to explore its potential as a novel immunomodulatory agent. In RAW264.7 cells, Ying et al. [36] suppressed LPS-induced PGE2, NO, TNF-α, iNOS, and COX-2 levels thus producing the antidote. Li et al. [37] reported LPS-induced intervertebral disc inflammation and catabolism in rats under the influence of piperine. [37]. In their study, Bang et al. [38] created an arthritis animal model at concentrations of 10 and 100 µg/ml. Piperine caused inhibition in levels of IL-6, MMP-13, AP-1, and reduced PGE2 in a dose-dependent manner. Piperine also inhibited alkali and effectively reduced nociceptive and arthritis pain in the rats. Study of Dong et al. [39] cleared protective effects of piperine against inflammation, alveolar bone loss, and collagen fiber degradation in periodontitis. Analysis of IL-1β, TNF-α, MMP-8, and MMP-13 expression levels revealed insights into these mechanisms. Both doses of 50 mg/kg, 100mg/kg piperine reduced degraded collagen fibers, significantly suppressing IL-1β, MMP-8, and MMP-13 expressions. TNF-α expression was not affected. Piperine shows promise in protecting against periodontitis by targeting specific inflammatory markers to mitigate various aspects of the disease. Son and colleagues [40] showed that piperine suppressed cPLA2 and TXA2 synthase in platelets, with no effect on COX-1.

**Gastrointestinal tract response of Piperine**

When testing bioactivity, it was also found that piperine's ability to increase bioavailability was associated with a delay in product and liquid delivery, resulting in a longer time for the drug to be absorbed in the stomach from chewable rice. Bajjad et al. [41] found that piperine reduced gastric emptying and gastric emptying in mice and rats. In research conducted by Sabina et al. [42], rats afflicted with rheumatoid arthritis underwent treatment with varying combinations of piperine and indomethacin, leading to decreased dosage requirements for the treatment. Bai and Xu [43] conducted experiments with different doses of piperine (25, 50, and 100 mg/kg) and observed stress-induced intestinal inflammation, with inhibition rates ranging from 16.9% to 48.3%. Piperine was also effective in reducing inflammation caused by Indomethacin (4.4 - 64.4%), HCl (19.2 - 59.6%), and pyloric ligation (4.8 - 26.2%) in rats.

**Anti-Cancer property of Piperine**

This suggests that piperine may have potential as a natural anti-cancer agent. Studies have shown that piperine can induce apoptosis, or programmed cell death, in cancer cells, while leaving normal cells unharmed. Additionally, piperine has been found to inhibit the growth and spread of cancer cells by interfering with various signalling pathways involved in cancer progression. These findings highlight the potential of piperine as a promising therapeutic agent for the treatment of cancer. Further research is needed to fully understand the mechanisms underlying piperine's anti-cancer effects and to determine its efficacy and safety in clinical settings.

**Breast cancer and piperine**

Minh et al. [44] elucidated the molecular pathways through which piperine exerts its anti-cancer effects on HER2-gene expression. The results demonstrated that piperine strongly inhibited cell growth and induced apoptosis in these cells. Greenshields et al. [45] demonstrated the impact of piperine on the proliferation and movement of triple-negative breast cancer (TNBC) cells. Piperine was found to suppress the growth of TNBC cells in laboratory settings, as well as hormone-sensitive breast cancer cells, while leaving normal mammary epithelial cell growth unaffected. Treatment with piperine led to a reduction in the proportion of TNBC cells in the G2 phase of the cell cycle. Kakarala et al. [46] targeted concentrations of 5 microM by applying both curcumin and piperine, which exhibited a 50% inhibition of mammosphere formation, serial passaging, and the percentage of ALDH+ cells in both normal and malignant breast cells. They find curcumin and piperine effectively suppress breast stem cell self-renewal without harming differentiated cells, showing promise for cancer prevention. Abdulhamed et al. [47] reported the effectiveness of piperine on TNBC cells. Various piperine-carboximidamide hybrids (VIa-k) have been developed as a new cytotoxic agent targeting EGFR, BRAF, and CDK2 by Umadevi and colleagues [48]. Among the drivatives VIa-k, compound Vik was the most efficient derivative as an antiproliferative agent, which exhibited strong anti-CDK2 activity with an IC50 value of 12 nM, showing 1.5 times greater potency compared to the standard dinaciclib.

**Lung Cancer and piperine**

Numerous research studies have demonstrated the beneficial impact of piperine on lung cancer. The cytotoxic and apoptotic effects of piperine on human lung cancer A549 cells were assessed by Lin et al. [49], with the aim of investigating its mechanisms. Piperine demonstrated a significant cytotoxic impact on A549 cells in a dose-dependent manner, while no effect was observed on WI38 human lung fibroblasts. The inhibition of cell growth could potentially be linked to DNA damage and cytotoxic effects. Selvindillan and colleagues [50] conducted a study using thirty Swiss albino mice, which were divided into five groups consisting of six animals each. The researchers observed that the administration of piperine resulted in a significant reduction in the levels of lipid peroxidation, protein carbonyls, nucleic acid content, and polyamine synthesis. These levels were found to be elevated in mice with lung cancer. Based on their findings, the researchers concluded that piperine effectively inhibits B(a)P-induced lung carcinogenesis in albino mice. This inhibition is achieved by providing protection against protein damage and suppressing cell proliferation. Chu et al. [51] observed a decrease in GST and UDP-GT due to piperine-induced BaP cytotoxicity in V-79 lung fibroblasts. Chu et al. [51] observed under various experimental conditions that piperine enhanced the DNA damage and cytotoxicity caused by benzo[a]pyrene (B[a]P) in cultured V-79 lung fibroblast cells. The V-79 cells were exposed to a non-toxic dosage of piperine (ranging from 1 to 20 microM) in combination with 10 microM B[a]P, or they were pre-treated with piperine for either 30 minutes or 2 hours before the administration of 10 microM B[a]P. Piperine significantly intensified the cytotoxic effects of B[a]P in all tested scenarios. Selvindillan et al. [52] elucidated the correlation between piperine's anti-peroxidative properties and its ability to inhibit cancer development. Administering piperine at a dosage of 50 mg/kg body weight resulted in increased activity of detoxification enzymes and decreased DNA damage, as evidenced by single cell electrophoresis. Additionally, supplementation with piperine was shown to regulate the levels of DNA-Protein cross links, which were elevated in animals with lung cancer.

**Prostate cancer and piperine**

Scientific studies have shown that piperine can control the growth of cancer cells. Ba and Malhotra [53] found that piperine's anticancer effects may be due to its inhibition of voltage-gated K+ current (IK). Piperine

*Annals of Science and Allied Research* Vol. 2 (1) June, 2024: 10-25.
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ISSN – 2584-2307 (Online)

showed a dose-dependent inhibition of IK, with an $IC_{50}$ of 39.91 µM. It also caused a positive shift in the relative activation curve in both cell types. Ouyang and colleagues [54] detailed the antitumor effects of piperine on human prostate cancer cells DU145, PC-3, and LNCaP, both *in vitro* and *in vivo*. Their study revealed that piperine triggered apoptosis at low levels and enhanced autophagy, as demonstrated by the rise in LC3B-II levels and the appearance of LC3B puncta in PC-3 and LNCaP cells. The autophagic process induced by piperine was further validated through the assessment of LC3-II accumulation and LC3B puncta formation in the presence of chloroquine, a widely recognized autophagy inhibitor. Samykutty et al. [55] conducted a study to explore the therapeutic benefits of piperine, a bioactive compound found in pepper spice, on prostate cancer cells that are both androgen-dependent and androgen-independent. The researchers observed a noteworthy decrease in the levels of prostate-specific antigen (PSA) after administering piperine treatment to LNCaP cells. Previous studies have indicated that NF-kB and STAT-3 transcription factors contribute to the angiogenesis and invasion of prostate cancer cells. Similarly, findings of Zeng and Yang [56] indicated that piperine significantly inhibited cancer cell growth and movement, and triggered programmed cell death in PCa DU145. Furthermore, LY294002, a protein kinase B (Akt) blocker, effectively reduced the levels of phospho (p)-Akt, matrix metalloproteinase (MMP)-9, and p-mammalian target of rapamycin (mTOR).

**Enzymatic action of piperine**

Huang et al. [57] examined the collective impact of trans-resveratrol and piperine on depression in mice. Transresveratrol exhibited a decrease in immobility during tests, albeit limited to a maximum of 60% even with higher doses. On the other hand, piperine displayed relatively weak effects. However, when these two substances were combined, they demonstrated a synergistic effect. The involvement of the serotonergic system was verified, and the combination also alleviated symptoms induced by reserpine, highlighting the significance of noradrenaline. According to Lee et al. [58] piperine showed inhibitory activity against both MAO-A (IC50: 20.9 microM) and MAO-B (IC50: 7.0 microM). Lineweaver-Burk plot analysis indicated competitive inhibition, with Ki values of 19.0+/-0.9 microM for MAO-A and 3.19+/-0.5 microM for MAO-B. Lee et al. [59], Li EJ et al. [60] and Mu et al. [61] further carried out a similar study on the activity of monoamine oxidase using piperine derivatives. Ferulic acid, also known as 4-hydroxy-3-methoxy-cinnamic acid (Fig. 1a), serves as a primary polyphenolic compound in Radix angelicae Sinensis, a Chinese herb. Lee et al. [62] discovered that it exhibits antidepressant-like properties by modulating serotonergic and noradrenergic activity. Dalvi and Dalvi [63] compared the properties of intragastric and intraperitoneal administration of piperine on rat liver and hepatic mixed-function oxidases; Piperine decreased cyt-P-450, amphetamine N-demethylase, amino ratio decreased Lin N-demethylase, and aniline hydroxylase. Beltran et al. [64] studied piperine's effect on human K2P channels, we used Xenopus laevis oocytes to express TREK-1, TASK-1, TRAAK, TASK-3, TREK-2, and TRESK and found that 300 µM piperine significantly suppressed TASK-1, TASK-3, and TRESK currents. Chen et al. [65] conducted a study to investigate the impact of piperine on seizures induced in mice. They were able to identify the receptors responsible for the suppression of seizures triggered by maximal electroshock (MES) and pentylenetetrazol (PTZ) models. The administration of piperine at doses of 40 and 80 mg/kg resulted in a significant delay in the onset of myoclonic jerks and generalized clonic seizures. Moreover, it led to a decrease in seizure stage and mortality when compared to the animals treated with the vehicle alone. Additionally, piperine was found to notably reduce the occurrence of MES-induced tonic hindlimb extension (THE) and PTZ-induced Fos immunoreactivity in the dentate gyrus. Male Sprague-Dawley rats, aged 35 days, were given piperine orally at doses of 0, 5, or 10 mg/kg for 30 days by Chen et al. [66] and observed that piperine improves the development of Leydig cells in pubertal rats by increasing their numbers and promoting maturation, while also inhibiting spermatogenesis. This enhancement of Leydig cell development may be linked to the ERK1/2 and AKT pathways.

**Neuroprotective effects of piperine**

In a study, mice were treated with rotenone for 6 weeks by Liu et al. [67], and afterward, PIP was given at doses of 25 mg/kg and 50 mg/kg for 4 weeks. The results showed that PIP reduced motor impairments

caused by rotenone and prevented the loss of dopaminergic neurons in the substantia nigra. PIP also improved cell viability and mitochondrial function in SK-N-SH cells and primary neurons. Interestingly, PIP triggered autophagy by blocking mTORC1 through the activation of PP2A. When PP2A activity was inhibited, the protective effects of PIP were diminished, highlighting the importance of PP2A as a target of PIP. Piperine co-treatment had varying effects on cytotoxicity, with the most significant inhibition observed at 1 μM by Mao et al. [68]. Piperine co-treatment also reduced reactive oxygen species levels, increased superoxide dismutase activity and total glutathione levels, and reversed the decline in BDNF mRNA levels caused by corticosterone. These findings suggest that piperine can protect against corticosterone-induced neurotoxicity by reducing oxidative stress and enhancing BDNF mRNA expression. Singh et al. [69] studied the neuroprotective effects of QC and piperine against MPTP-induced neurotoxicity in rats. They injected MPTP intranigrally on days 1, 4, and 7 and administered QC (25 and 50 mg/kg) and QC (25 mg/kg) with piperine (2.5 mg/kg) for 14 days. The treatments improved behavioral abnormalities, neurotransmitter changes, oxidative stress, and inflammation in the striatum. Neuroprotective effects of piperine on primary cultured hippocampal neurons were reported by Fu et al. [70]. Unchern and colleagues claim that piperine inhibits neurite extension in developing neurons. [71]. In a study conducted by Khalili et al. [72], it was found that a daily intake of 2.5 mg/kg of piperine had a positive impact on cognitive function. This was evidenced by an increase in correct arm entries and a decrease in revisiting arms. Interestingly, the cognitive improvement was observed regardless of the dosage of memantine administered. Furthermore, piperine was found to contribute to maintaining redox balance by reducing malonaldehyde levels in both the cerebrospinal fluid and hippocampus. Additionally, the levels of CSF ferric reducing ability of plasma (FRAP) were like those of the control group, providing further support for the cognitive-enhancing effects of piperine at this dosage. Hu et al. [73] studied the effects of piperine on rats and its potential as an antidepressant and neuroprotective agent in rats. They found that piperine effectively reduced moderate depression by modulating the hypothalamic-pituitary-adrenal axis, revealing its neuroprotective process.

**Vitiligo and piperine**

Skin discoloration occurs due to vitiligo. Discoloured spots usually grow larger over time. Any part of the body's skin can be affected by the disease. Melanin mainly determines skin and hair colour. Vitiligo occurs when melanin-producing cells are killed or stop working. Anyone can get vitiligo, but it is more likely to occur in people with brown or black skin. It is the most common depigmentation condition, affecting 0.5–2.0% of the population, regardless of gender or race reported by Ezzedine et al. [74]. This disease is not contagious, but it can cause stress or make you feel unwell. Silverberg et al. [75] studied on patients with vitiligo also have a higher incidence of psychological disorders, including depression and low self-esteem. In a 3-month trial, Shafiee et al. [76] studied 63 individuals possessing facial vitiligo, splitting them into two groups to examine the effects of piperine. Results showed that 45% of those receiving piperine treatment experienced mild and temporary side effects like skin burning and redness. Notably, significant regrowth was observed at 1, 2, and 3-month intervals when piperine was topically applied with NB-UVB. Mikhail et al. [77] treated three patients with vitiligo by combining piperine extract with different topical creams and applying it to different areas of the skin for 12 weeks. The results showed reduced recovery time and fewer side effects. Rofes [78] conducted a videofluoroscopic examination to evaluate the indications of compromised safety and effectiveness of swallowing, as well as the swallowing response, in 40 dysphagic affected peoples, divided into two groups. Significant results were obtained by giving 150 μM piperine to group 1 and 1 mM piperine to group 2. Cristina and colleagues [79] studied re-pigmentation in localized vitiligo using NB-UVB and piperine-based topical treatment on eight patients. Treatment involved topical application twice daily and NB-UVB twice weekly for two cycles of two months each. Clinical changes were assessed using the VNS and measuring repigmentation percentage. RCM findings confirmed morphological alterations from the combined treatment for localized vitiligo. Panahi et al. [80] conducted a study to assess the effectiveness of short-term supplementation with curcuminoids (combined with piperine) in reducing oxidative stress and improving quality of life in individuals with chronic pulmonary complications caused by exposure to SM. The results showed that the combination of curcuminoids and piperine had a significantly greater -impact compared to a placebo in increasing GSH levels, reducing MDA levels, and improving CAT and

*Annals of Science and Allied Research* Vol. 2 (1) June, 2024: 10-25.
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ISSN – 2584-2307 (Online)

SGRQ scores ($p < 0.001$). These findings suggest that curcuminoids can be considered as safe adjuncts for patients undergoing standard treatments for chronic SM-induced pulmonary complications, offering potential benefits in terms of oxidative stress, symptoms, and quality of life. Panahi et al. [81] conducted their research on the impact of supplementing with curcuminoids on oxidative stress and inflammation in MetS patients through four randomized double-blind placebo-controlled trials. The combination of curcuminoid and piperine led to increased serum SOD activities and decreased MDA and CRP levels compared to the placebo group. A quantitative analysis showed a significant reduction in circulating CRP levels with curcuminoids compared to placebo. This effect remained consistent in the sensitivity analysis. Donata et al. [82] focussed on cow's urine and mixtures of selected herbs along black pepper to ferment it. Fermented herbal mixture given orally as drink twice a day before meals for six months. Symptoms improved in 40% of patients.

**Thyroid and piperine**

Many researchers have investigated the antithyroid effects of black pepper in various ways. Panda and Kar [83] observed Swiss albino rats and noticed a decrease in serum thyroxine and triiodothyronine levels, thyroid hormones, and glucose after piperine treatment. Vijayakumar and Nalini [84] claimed that the combination of carbimazole and piperine lowered lipoprotein, altered serum lipids and also increased HDL levels. In Singh and Duggal's study [85] piperine supplementation reduced TSH and apo B but improved testosterone levels, apo A-I, T4 and T3 levels.

**Anti-platelet activity and piperine**

Srinivasan found that the most potent compound in black pepper was piperine [86]. Nair and Gupta [87] described somatic embryogenesis and plant development in black pepper. Ahmed et al. [88] described the beneficial effects of black pepper on tissue regeneration and its antioxidant capacity. Park et al [89] demonstrated the antibacterial effect of piperidine base. In rabbit experiments, they examined the toxic effects of piperine on platelet aggregation, which is caused by many factors that cause platelets, such as collagen and thrombin.

**Chemistry of black pepper**

Aleksandra and Ljiljana [90] claimed that the chemical composition of black pepper is divided into three groups viz. piperine, oleoresin and essential oils. According to them, black pepper has a distinct aroma and spicy flavour due to piperine, the main alkaloid in peppercorns. Spice oleoresins come in various forms, including oils and pastes, and contain essential oils, fixed oils, pigments, and pungent alkaloids. The essential oil content of black pepper, which is a colorless to yellow-green liquid with a spicy and unique scent, is usually 1% to 3%, but can reach up to 9% according to some studies (Table 1).

**Table-1: Different components of black pepper**

| Component | % | Reference |
|---|---|---|
| Piperine | 2-9 | 13 |
| | 3.90 | 14 |
| Oleoresin | 4.4-12 | 13 |
| | 3.8 | 15 |
| Essential oils | 0.4-7 | 13 |
| | 2.81 | 17 |
| Starch | 50 | 12 |
| | 28-49 | 13 |
| Fatty acids | 1.9-9 | 13 |
| | 5.34 | 20 |

While in another study, Chen et al. and Plessi et al. [91 claimed different aromatic and volatile compounds existing in black pepper (Table-2) as-

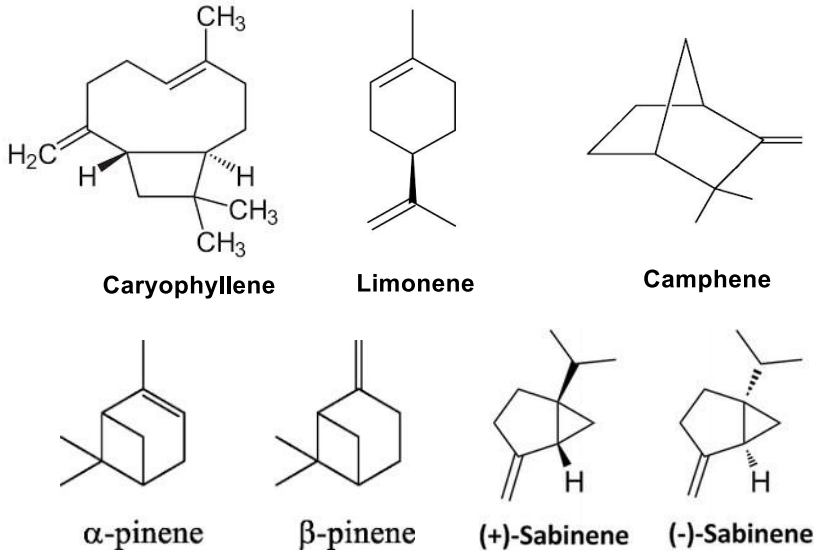
| **Table 2: aromatic and volatile compounds present in *P. nigrum*.** | | |
|---|---|---|
| Monoterpene | Caryophyllene oxide | Cinnamic acid |
| Sesquiterpenes | Limonene | alpha-cis-Bergamotene |
| Sabinene | Benzaldehyde | 1,8-cineole |
| Eugenol | Terpinolene | p-methyl acetophenone |
| Acetophenone | gamma-Terpinene | alpha-cubebene |
| gamma-cadinene | alpha-phellandrene | curcumene |
| m-methyl acetophenone | alpha-selinene | safrole trans-Anethole |
| Camphene | alpha-trans-Bergamotene | |

Kapoor et al. [92] reported the Chemistry and *in vitro* antioxidant activity of volatile oil and oleoresins of black pepper. Gas Chromatography-Mass Spectrometry (GC-MS) analysis of pepper essential oil found 54 components, making up 96.6% of the total weight. Percent amount of main component viz. beta-Caryophyllene, limonene, beta-pinene sabinene was found 29.9%, 13.2%, 7.9%, and 5.9% respectively. The antioxidant properties of the oil and oleoresins were tested against mustard oil using various methods. They showed strong antioxidant activity compared to BHA and BHT, but lower than PG. Morshed and colleagues [93] conducted a study on the physiological characteristics of black pepper essential oil (EO) sourced from Chittagong, Bangladesh. The essential oils were extracted using the Clevenger apparatus and steam distillation method. The results revealed that the components caryophyllene, limonene, and camphene were present in percentages of 19.12%, 9.74%, and 8.44% correspondingly. Additionally, the black pepper samples were found to contain moisture (2.20%), dry matter (96.12%), protein (12.66%), fatty oil (14.41%), ash (12.49%), carbohydrate (42.56%), and crude fiber (5.55%). A comparative study on the essential oil composition and insecticidal effect of different tissues of Piper capense L., Piper guineense Schum. et Thonn., Piper nigrum L. and Piper umbellatum L. grown in Cameroon was made by Tchoumbougnang et al. [94]. They adopted hydrodistillation of different tissues of selected plants. GC and GC/MS analyses showed qualitative and quantitative differences between the collected essential oils of targeted plants. Jirovetz et al. [95] produced a novel approach using SPME was used to identify key odorous components in spices and food flavoring products. GC-FID and GC-MS with different columns were used to determine primary compounds in P. nigrum (black) and P. guineense (black and white). In P. nigrum (black), major compounds included germacrene D, limonene, beta-pinene, alpha-phellandrene, beta-caryophyllene, alpha-pinene, and cis-beta-ocimene. P. guineense (black) had beta-caryophyllene, beta-elemene, bicyclogermacrene, and alpha-humulene as predominant components. P. guineense (white) contained beta-caryophyllene, cis-beta-ocimene, limonene, beta-pinene, linalool, and alpha-humulene. The essential oil composition of black, green, and white pepper was analyzed Orav et al. [96] using a micromethod for oil isolation and gas chromatography techniques. The main compounds found in pepper oils were (E)-beta-caryophyllene, limonene, beta-pinene, Delta-3-carene, sabinene, alpha-pinene, eugenol, terpinen-4-ol, hedycaryol, beta-eudesmol, and caryophyllene oxide. Green pepper corn obtained through sublimation drying method had higher oil yield and monoterpenes content compared to air-dried green pepper corn. The oil from ground black pepper had more monoterpenes and less sesquiterpenes and oxygenated terpenoids than green and white pepper oils. Storage of pepper samples for a year resulted in decreased oil yield, reduced terpene content, and increased oxygenated terpenoids. Green pepper corn showed a significant increase in oil yield after 1 year of storage, unlike other pepper samples. The essential oil composition of black, green, and white pepper was analyzed Orav et al. [96] by adopting a micromethod for oil isolation and gas chromatography techniques. The main compounds found in pepper oils were (E)-beta-caryophyllene, limonene, beta-pinene, Delta-3-carene, sabinene, alpha-pinene, eugenol, terpinen-4-ol, hedycaryol, beta-eudesmol, and caryophyllene oxide. Green pepper corn obtained through sublimation drying method had higher oil yield and monoterpenes content compared to air-dried green pepper corn. The oil from ground black pepper had more monoterpenes and less sesquiterpenes and oxygenated terpenoids than green and white pepper oils. Storage of pepper samples for a year resulted in decreased oil yield, reduced terpene content, and increased oxygenated terpenoids. Green pepper corn showed a significant increase in oil yield after 1 year of storage, unlike other pepper samples.

*Annals of Science and Allied Research* Vol. 2 (1) June, 2024: 10-25.
https://doi.org/10.5281/zenodo.12596886
ISSN – 2584-2307 (Online)

**Chemical manipulation, structure hierarchy of piperine**

Amit and colleagues [97] introduced the hierarchical structure of black pepper, which includes piperine. Piperine is an alkaloid that consists of three subunits: a butadiene chain, 1,3-benzo meta dioxolyl (also referred to as pepper core), and an amide functional group composed of a piperidine ring with an α-β-unsaturated carbonyl moiety (Figure-2).




**Toxicology and piperine**

The use of spices and herbs as food or medicine has a long history. Some studies suggest that black pepper may have toxic effects. Guldiken et al. [98] found that high doses of phytochemicals in medicinal plants and spices can be toxic, but lower doses can provide health benefits. Piyachaturawat et al. [99] found that piperine had higher acute toxicity levels in mice, rats, and hamsters compared to other methods of administration. The $LD_{50}$ values varied between different species and age groups, with animals typically succumbing to respiratory paralysis within minutes. In subacute toxicity tests, rats died within days post-treatment, showing severe histopathologic changes in various organs. These findings suggest that piperine can cause organ dysfunctions leading to fatalities in animals. Chonpathompikunlert et al. [100] aimed their study to investigate the antioxidant properties and mechanism of nitroxide radical-containing nanoparticles (RNPs) combined with piperine (PI) in human neuroblastoma SH-SY5Y cells. Various assays were used to assess the effects of RNP/PI on SH-SY5Y cells, showing that the combination significantly reduced reactive oxygen species levels compared to RNPs alone. Additionally, RNP/PI treatment increased catalase and glutathione peroxidase activity. In Alzheimer's model experiments, RNP and PI together had a stronger antioxidant effect. The study concluded that the combination therapy protected cells by reducing reactive oxygen species production and preventing apoptosis through enzyme scavenging pathways.

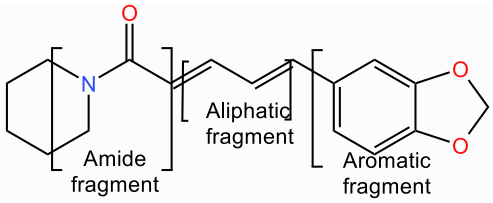
**Conclusion**

Black pepper, often dubbed the "king of spices," boasts a rich history and an array of applications that extend far beyond its culinary uses. Its significance is underscored not only by its role in enhancing the flavour of countless dishes but also by its impressive medicinal and therapeutic benefits. Black pepper's active compound, piperine, contributes to its potential in aiding digestion, improving nutrient absorption, and exhibiting antimicrobial, anti-inflammatory, neuroplastic and antioxidant properties.

Furthermore, the spice's versatility is reflected in its integration into traditional medicine practices and modern scientific research, which continues to explore

its potential in areas such as cancer prevention, cognitive health, and weight management. The diverse uses of black pepper in food preservation and its versatile pharmacological potentials as further highlighted its broad spectrum of applications. It is yet unclear how piperine is combined with other naturally occurring bioactive substances in varying dosages or how it works as a medication against various health risks.

In essence, black pepper's endless possibilities make it an invaluable spice in both the culinary and medicinal worlds. As research continues to unveil new benefits and uses, black pepper remains a testament to the profound impact that a single natural product can have across various domains of human health and wellbeing.




(2E,4E)-5-(2H-1,3-Benzodioxol-5-yl)-1(piperidin-1-yl)penta-2,4-dien-1-one

**Structure of piperine**

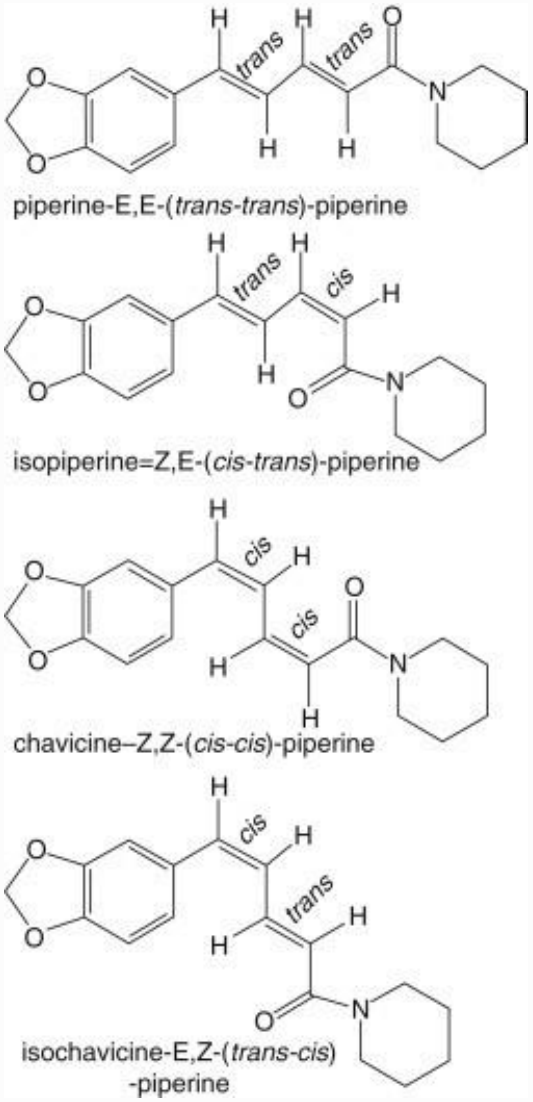



**Figure-2**

**Acknowledgement**

This article consists of the dissertation work of a final semester M.Sc. student, Madhu.

**Conflicts of interest**

The author states there are no conflicts of interest

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