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REVIEW ARTICLE

Piper nigrum L.: A Systematic Review of its Botanical Characteristics, Phytochemistry, and Pharmacological Activities

Aditya Jain, Tanvi Jangid, Gauri Shankar Bhardwaj and Ram Niwas Jangir*

Department of Zoology, University of Rajasthan, Jaipur - 302004, Rajasthan, India; ramanjangir@gmail.com

Abstract

Piper nigrum L., commonly known as black pepper, is a globally recognized spice with a long history of traditional medicinal use and a growing body of scientific research supporting its pharmacological potential. This review aims to provide an in-depth analysis of global research on *P. nigrum* by examining literature from databases such as PubMed, Scopus, Web of Science, and Google Scholar, including studies published up to 2025. The article explores the plant's botanical profile, rich phytochemical composition- including key bioactive compounds such as piperine, flavonoids, and essential oils- and its extensive traditional and modern medicinal applications. *P. nigrum* has demonstrated a wide range of pharmacological activities, including antidiabetic, antioxidant, anticancer, antimicrobial, anticonvulsant, analgesic, antidepressant, anti-inflammatory, hypolipidemic, hepatoprotective, neuroprotective, antidiarrheal, insecticidal, antipyretic, anti-asthmatic, and antiulcer effects. The review also delves into the underlying mechanisms of action that support these therapeutic effects, offering insights into how these phytochemicals exert biological activity at the molecular level. In addition, the toxicity profile of *P. nigrum* is discussed to highlight considerations for its safe use in pharmacological applications. By integrating traditional knowledge with current scientific evidence, this review highlights the broad therapeutic potential of *P. nigrum* and provides direction for future research and clinical application.

Major Findings: This review provides an extensive overview of *P. nigrum*'s pharmacological relevance, highlighting its rich phytochemical makeup and diverse therapeutic applications. It also addresses mechanisms of action and safety considerations, supporting its potential in evidence-based medicine.

Keywords: Black Pepper, Pharmacological Activities, Phytochemistry, *P. nigrum*, Piperine

Abbreviations: ABTS: 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); ALP: Alkaline phosphatase; ALT: Alanine Aminotransferase; ALX: Alloxan; AST: Aspartate Aminotransferase; *B. cereus: Bacillus cereus; B. subtilis: Bacillus subtilis;* BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; *C. albicans: Candida albicans*; CAT: Catalase; COR: Clove Oleoresin; DPPH: 2,2-diphenyl-1-picrylhydrazyl; *E. cloacae: Enterobacter cloacae*; *E. coli: Escherichia coli*; *E. faecalis: Enterococcus faecalis*; *E. faecalis: Enterococcus faecalis;* FRAP: Ferric reducing ability of plasma; GPx: Glutathione Peroxidase; GSH: Glutathione; GST: Glutathione S- transferase; HbA1C: Glycated haemoglobin; HDL: High density lipoprotein; HRS: Hydroxyl radical scavenging; HSP: Heat shock protein; IL: Interleukin; *K pneumoniae: Klebsiella pneumoniae; L. monocytogenes: Listeria monocytogenes;* LD: Lethal dose; LDH: Low density lipoprotein; LDL: Low density lipoprotein; MBC: minimum bactericidal concentration; MIC: minimum inhibitory concentration; NORS: Nitric oxide radical scavenging; *P. aeruginosa: Pseudomonas aeruginosa*; *P. mirabilis: Proteus mirabilis*; *P. vulgaris: Proteus vulgaris*; *P.stuartii: Providencia stuartii*; *S. aureus: Staphylococcus aureus*; *S. boydii: Shigella boydii; S. dysenteriae: Shigella dysenteriae; S. enterica: Salmonella enterica; S. epidermidis: Staphylococcus epidermidis; S. flexneri: Shigella flexneri; S. paratyphi – Salmonella Paratyphi; S. pyogenes: Streptococcus pyogenes*; *S. saprophyticus: Staphylococcus saprophyticus*: *S. sonnei: Shigella sonnei; S. typhi: Salmonella typhi; S. typhimurium: Salmonella typhimurium;* SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; SOD: Superoxide Dismutase; SORS: Superoxide radical scavenging; STZ: Streptozotocin; TAA: Total antioxidant activity; TBARS: Thiobarbituric acid reactive substances; TBHQ: Tertiary Butyl Hydro Quinone; VLDL: Very low density lipoprotein; γ GT: Gamma glutamyl transferase

*Author for correspondence

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1. Introduction

Black pepper (*P. nigrum* L.), often referred to as the "King of Spices," is a widely used seasoning across the globe. It belongs to the *Piperaceae* family and originates from the southern region of India[1]. The diverse genus *Piper* comprises 4,166 scientifically recorded plant names at the species level. Among these, 1,457 are recognized as accepted species, 1,376 are considered synonyms, and 1,333 remain unassessed[2]. Black pepper is a key pungent ingredient in culinary preparations, particularly throughout Asia. In addition to its culinary importance, it holds promising uses in traditional medicine, fragrance production, food preservation, and as a natural insect repellent[3]. White and black pepper differ primarily in their harvest timing and methods of processing. White pepper is derived from fully ripened berries after the outer layer is removed, whereas black pepper is made by drying unripe berries with the outer skin intact, resulting in its characteristic wrinkled appearance. Despite these differences, both forms are widely used- not only as culinary spices but also for their roles in natural preservation, pest control, and traditional medicinal practices[4]. Black pepper contains the primary pungent alkaloid piperine (1-peperoyl piperidine), which is recognized for its wide range of pharmacological properties. It plays a significant role in various traditional medicinal systems, including Ayurveda and Unani[5,6]. Research has shown that piperine can boost the effectiveness of numerous drugs, vaccines, and nutrients by enhancing their oral bioavailability. This is achieved through the inhibition of certain metabolic enzymes[7].

Piperine has garnered significant interest from medicinal chemists and healthcare professionals because of its wide array of therapeutic properties. These include antioxidant, antitumor, anti-asthmatic, analgesic, antipyretic, anti-diarrheal, anti-inflammatory, anxiolytic, antispasmodic, hepatoprotective, antidepressant, antibacterial, immunomodulatory, antifungal, antiapoptotic, antithyroid, antimutagenic, and antimetastatic activities[8].

While numerous reviews have explored the pharmacological potential of black pepper and its key bioactive compound, piperine, they often present the information in a scattered or narrative format. A significant limitation of these previous works is the lack of a systematically organized, tabular presentation of pharmacological activities. This absence makes it difficult for researchers and healthcare professionals to quickly access, compare, and interpret the diverse therapeutic effects of black pepper across studies. Thus, there remains a need for a comprehensive and structured compilation that fills this informational gap.

This review stands out by offering a well-organized and consolidated account of *P. Nigrum*'s pharmacological and medicinal potential. It uniquely compiles the botanical profile, phytochemical constituents, traditional medicinal uses, and a wide range of pharmacological effects- including antidiabetic, antioxidant, anticancer, antimicrobial, anticonvulsant, analgesic, antidepressant, anti-inflammatory, hypolipidemic, hepatoprotective, neuroprotective, antidiarrheal, insecticidal, antipyretic, anti-asthmatic, and antiulcer properties- in an accessible tabular format. Additionally, the review includes a detailed toxicity profile, enhancing its practical utility for future pharmacological research and clinical applications.

2. Materials and Methods

This review was conducted through a systematic literature survey to collect and analyze scientific data on *P. nigrum* L. A comprehensive search was performed across databases including PubMed, Scopus, Web of Science, Google Scholar, PubChem, and the AYUSH Research Portal, covering all English-language publications up to 2025.

Search terms included "*P. nigrum*," "black pepper," "phytochemicals," "medicinal uses," "piperine," and various pharmacological activities such as "antioxidant," "anti-inflammatory," and "toxicity." Boolean operators were used to refine results.

Studies were screened by title and abstract, with full texts reviewed when relevant. Inclusion focused on phytochemical composition, ethnopharmacological use, pharmacological activity, and mechanisms of action. Non-English papers, duplicates, and irrelevant studies were excluded.

Data from eligible peer-reviewed articles and reviews were qualitatively analyzed and thematically synthesized to assess the therapeutic potential and safety of *P. nigrum*.

3. Botanical Profile

Black pepper is derived from the ripe fruits of *P. nigrum*, a perennial woody climber that thrives in shaded environments and can grow up to 4 meters tall, often using trees or trellises for support (Figure 1)[9]. The plant develops 10-12 adventitious roots at the stem base for stability and nutrient uptake, and exhibits dimorphic branching with orthotropic (vertical) and plagiotropic (horizontal) shoots that support climbing and fruiting[9,10]. Orthotropic stems grow indeterminately, producing lateral fruiting branches from leaf axils, while each node forms clinging roots for anchorage[10].

Leaves are simple, alternate, with grooved petioles (2-5 cm), and leaf blades ranging from 8-20 cm long and 4-12 cm wide[11]. In India, flowering begins 2-3 years post-planting during the monsoon season (May-July), with fruiting spikes 3-15 cm long. Flowers bloom 10-15 days after spike emergence and complete flowering in 6-10 days[12]. Wild varieties are dioecious, while cultivated ones are monoecious, with self-pollination being common; protogyny is also observed[13].

Each stem bears 20-30 fruit spikes (peppercorns), which are harvested and sun-dried to produce black pepper[14]. Before drying, the berries are boiled for about 10 minutes to disinfect and initiate fermentation, leading to their black color[15].

The fruit, commonly called a berry, is a small, spherical, single-seeded drupe with a fleshy pericarp and a hard endocarp. Mature fruits are about 5 mm in diameter and retain their round shape. After harvest, they are sun-dried for various uses[16]. The seeds, 3-4 mm in diameter, have a smooth white to brown coat rich in oil, with the embryo located near the micropyle[17].

Below is the botanical hierarchy of *P. nigrum* L., starting from the kingdom *Plantae* down to its species level[18].

Kingdom: *Plantae*
Class: *Equisetopsida*
Subclass: *Magnoliidae*
Superorder: *Magnolianae*
Order: *Piperales*
Family: *Piperaceae*
Genus: *Piper*
Species: *nigrum*

4. Nutritional Composition

Black pepper contains a variety of essential nutrients, including carbohydrate, fat, vitamins (like vitamin K and vitamin C), minerals (such as iron, calcium, and potassium), dietary fiber, and beneficial bioactive compounds like piperine, which enhances nutrient absorption and offers antioxidant and anti-inflammatory properties[19-21]. Most of these nutrients are reported on a per 100 g basis (Figure 2).

5. Phytochemical Composition

Several researchers have reported that black pepper contains a diverse range of bioactive phytochemicals



Figure 1. Botanical features of black pepper (*P. nigrum* L.).



Figure 2. Major nutritional components of black pepper (*P. nigrum* L.).

such as alkaloids, flavonoids, steroids, phenols, terpenes, tannins, and amides (Figure 3)[22,23]. Black pepper contains a variety of biochemical compounds, including piperine (ranging from 2.1% to 8.9%), oleoresin (2.31% to 12%), essential oils (0.4% to 6.9%), starch (28% to 51%), and fatty acids (1.8% to 15%). Among its most prominent bioactive constituents are β-caryophyllene (30%), limonene (13.4%), β-pinene (8%), α-pinene (4.6%), sabinene (6%), caryophyllene oxide (9%), 3-carene (30%), and camphene (11%)[24-26].

The chemical composition of *P. nigrum* (black pepper) is remarkably diverse, with both essential oils and petroleum ether extracts revealing a wide range of bioactive compounds. Essential oils from black pepper seeds originating in South India are predominantly composed of β-caryophyllene, along with notable amounts of limonene, sabinene, α-pinene, β-bisabolene, α-copaene, α-cadinol, α-thujene, and α-humulene. In contrast, the leaves are particularly rich in nerolidol, with significant levels of α-pinene and β-caryophyllene also present[27,28]. A similar profile was observed in seeds from Bangladesh, which contained high concentrations of β-caryophyllene (18.39%), α-pinene (16.68%), limonene (16.16%), and β-pinene (13.61%), along with δ-3-carene (9.23%), β-phellandrene (3.16%), copaene (3.13%), 1-naphthalenol (3.0%), and β-myrcene (2.89%)[29]. Complementing this, the petroleum ether extract of *P. nigrum* has been extensively studied for its phytochemical richness. In the dried whole fruits, several phytosterols such as stigmastanol, β-sitosterol, and stigmasterol were identified, along with their glycosylated forms- stigmastanol 3-O-β-D-glucopyranoside and β-sitosterol 3-O-β-D-glucopyranoside. A broad array of amide alkaloids was also detected, including [(2E, 4E)-octadienoyl]-N-isobutylamide, sarmentine, [(2E, 4E)-dodecadienoyl] pyrrolidine, 1-[(2E, 4E, 12Z)-octadecatrienoyl]-N-isobutylamide, and [(2E, 4E)-dodecadienoyl]-N-isobutylamide. Other significant components included

pellitorine, hexadecanoylpyrrolidine, [(2E)-octadecanoyl] pyrrolidine, piptaline, and fatty acid derivatives such as hexadecenoic ethyl ester and octadecanoic acid. Aromatic amides like 1-[7-(3, 4-methylenedioxyphenyl)-(2E, 4E)-heptadienoyl]-N-isobutylamide and 1-(3, 4-methylenedioxyphenyl)-(1E)-tetradecene were also found. Further phytochemical investigations led to the identification of three novel amide alkaloids-pipgulzarine, pipzorine, and piptahsine- alongside nine previously known compounds such as (2E, 4E, 8Z)-N-isobutyl eicosatrienamide, pellitorine, pipercide, piperine, stigmastanol, stigmasterol, decurrenal, stigmasterol 3-O-β-D-glucopyranoside, and 5, 10 (15)-cadinen-4-ol[30]. Additionally, a crystalline compound identified as [{(1, 5-(1, 3)-benzodioxol-5-yl)-1-oxo-2, 4-pentadienyl}-piperidine] was isolated, along with fifteen sesquiterpenes including linalool, 4-terpineol, α-terpineol, δ-elemene, α-copaene, β-elemene, β-caryophyllene, α-caryophyllene, gurjunene, β-bisabolene, δ-cadinene, elemol, caryophyllene oxide, murrolene, and β-eudesmol[31].

Investigations into the roots of *P. nigrum* have similarly revealed significant alkaloid content. Lim *et al.* reported the presence of piperdine, pelliterine, piperidine, piperine, and pellitorine in the dried roots collected from Malaysia. Complementing these findings, Wei *et al.* isolated seven structurally diverse alkaloids from the roots: N-isobutyl-4-hexanoyl-4-hydroxypyrrolidin-1-one; erythro-1-(1-oxo-4,5-dihydroxy-2E-decaenyl) piperidine; threo-1-(1-oxo-4,5-dihydroxy-2E-decaenyl) piperidine; threo-N-isobutyl-4,5-dihydroxy-2E-octaenamide; 1-(1,6-dioxo-2E,4E-decadienyl) piperidine; 1-[1-oxo-3-(3,4-methylenedioxy-5-methoxyphenyl)-2Z-propenyl] piperidine; and 1-[1-oxo-5-(3,4-methylenedioxyphenyl)-2Z,4E-pentadienyl] pyrrolidine[32,33].

6. Traditional Medicinal Uses

Piper nigrum (black pepper) offers a wide range of health benefits across various systems. It enhances digestion by stimulating hydrochloric acid production and helps prevent constipation, gastric problems, diarrhea, flatulence, and dyspepsia[34,35]. For respiratory health, it relieves cough, cold, and chest congestion, and is often used in steam inhalation therapies[36,37]. Its application in skin care includes treatment of acne, rashes, pigmentation disorders such as vitiligo, allergies, and reduction of wrinkles, dark spots, and premature aging[38]. Black pepper

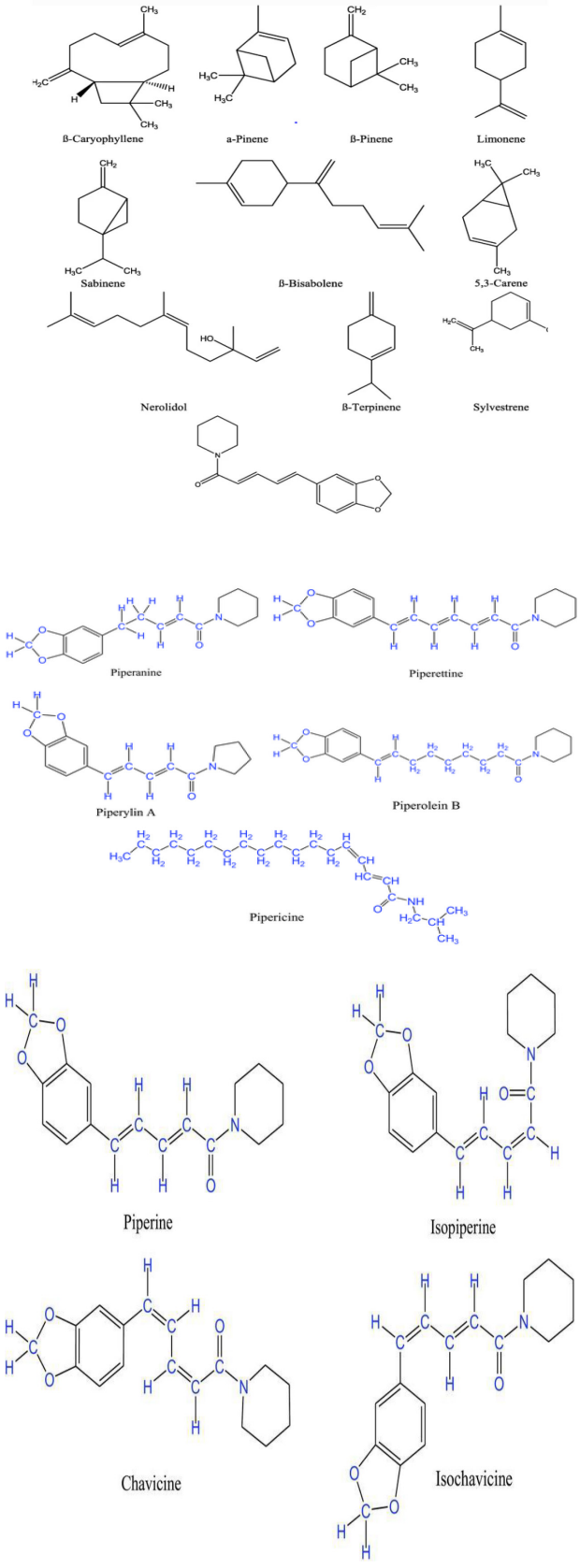


Figure 3. Structures of major phytochemicals in black pepper (*P. nigrum*).

is also beneficial for hair care, treating dandruff and hair loss, promoting hair growth and shine[39]. It supports weight loss by boosting metabolism and burning excess fat, aided by its phytonutrients[39]. In mental and neurological health, it is used to alleviate depression and enhance mood, with external applications assisting in paralysis and treatment of epilepsy[40]. For joint and bone support, black pepper provides relief from arthritis, gout, and spinal pain[34]. Regarding sexual and reproductive health, black pepper acts as an aphrodisiac and is used in treating erectile dysfunction; it also serves as a contraceptive when used during the first seven days of the menstrual cycle and postpartum birth control, with effects extending up to 3-4 months of pregnancy spoiling[41,42]. Additionally, it is traditionally used to treat infections such as cholera, gonorrhea, syphilis, and dysentery, and is applied to boils and piles[43]. It is known as an antidote for snake bites and is used in managing night blindness and dog bite treatment[44,45]. For dental health, black pepper combined with vinegar is used in oral care[38].

7. Pharmacological Activities of *P. nigrum*

The main pharmacological characteristics of this plant are displayed in Table 1. The plant's various activities are arranged in the table based on the year of publication, the plant part used for treatment, the type of extract used, the doses used, the mode of administration, experiment duration, the study model, and the effects observed.

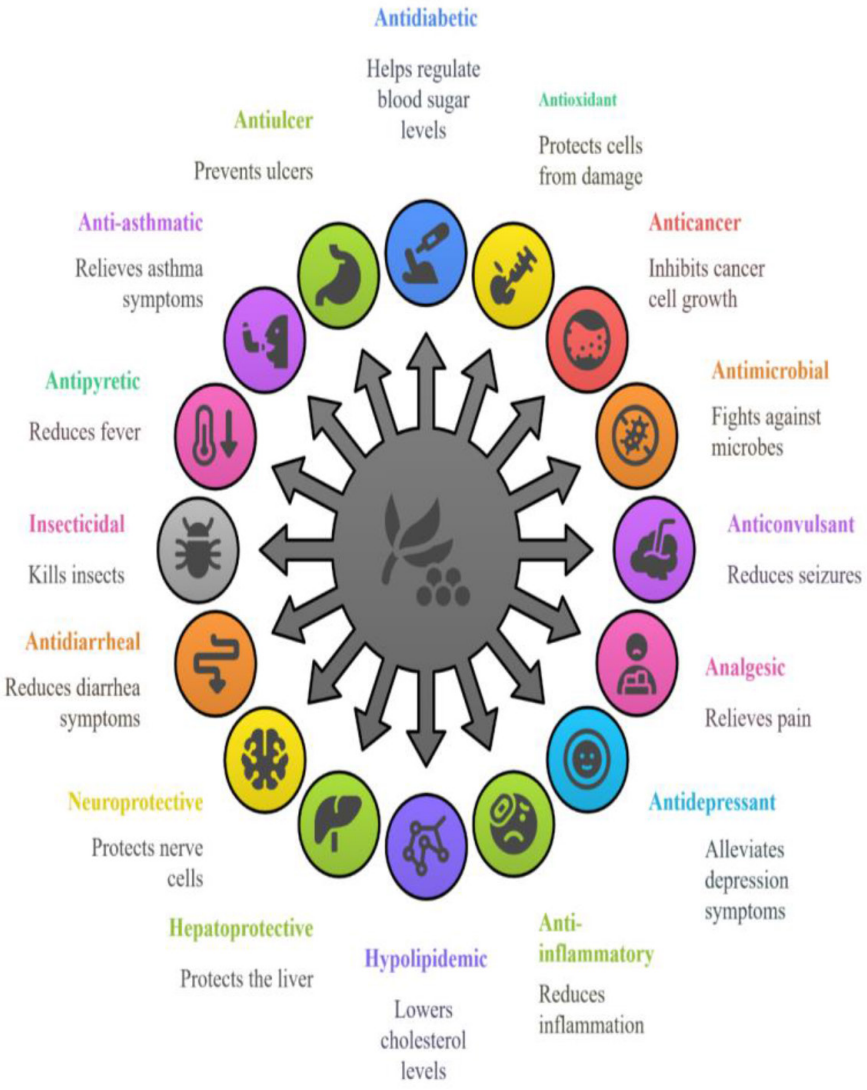


Figure 4. Various pharmacological activities of black pepper (*P. nigrum*).

Table 1. Various pharmacological activities of *P. nigrum*

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
Antidiabetic activity	Seeds	Aqueous extract	0.5 ml/day, 28 days, orally	ALX induced male Wistar rats	After four weeks of treatment with an aqueous seed extract of *Piper nigrum*, diabetic rats exhibited a significant reduction in blood glucose levels, decreasing to 129 mg/dL, compared to 270 mg/dL observed in untreated diabetic controls.	46
	Leaves	Ethanolic Extract	100, 200, 300 mg/kg, BW/Day, 21 days	ALX induced male Wistar rats	Administration of extract at various doses significantly reduced fasting blood glucose level and Hba1c at day 7, 14, 21.	47
	Seeds	Piperine from Ethanolic extract	20, 50 mg/kg, BW/Day, 14 days	STZ induced male Wistar rats	In the subacute study, piperine administered at a dose of 50 mg/kg produced a notable reduction in blood glucose levels by day 14, achieving statistical significance ($p < 0.05$).	48
	-	Extract purchased	25%, 50%, 75%	ALX induced male Wistar rats	Blood glucose level reduced significantly in the extract treatment.	49
	Seeds	Methanolic Extract and its Aqueous (AQF), Petroleum ether (PEF), Chloroform fraction (CHF)	0.3125-5 µg/ml	*In vitro*	In the α-amylase inhibition assay, PEF demonstrated a potent inhibitory effect with an IC_{50} value of 1.191 µg/mL, compared to 3.591 µg/mL for the CHF. Similarly, in the α-glucosidase inhibition assay, PEF showed a stronger inhibitory activity with an IC_{50} of 1.47 µg/mL, while CHF recorded an IC_{50} of 2.95 µg/mL. Acarbose was used as the benchmark for this test. Glucose uptake by yeast cells was assessed at varying glucose concentrations using a constant extract concentration of 5 mg/mL. At 5 mM glucose, the PEF facilitated 76% uptake, while the CHF achieved 69%. When the glucose concentration was increased to 10 mM, uptake levels decreased to 57% for PEF and 43% for CHF. A further increase to 25 mM glucose resulted in a more pronounced reduction in uptake, with PEF and CHF showing 30% and 28% uptake, respectively.	50
Antioxidant activity	Pods	Ether	0.02, 0.5, 0.35 g/kg, BW/Day, orally	Male Wistar rats	Supplementation with black pepper or piperine led to a decrease in TBARS and conjugated dienes (CD) levels, while preserving the activities of antioxidant enzymes—such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST)—and maintaining reduced glutathione (GSH) levels comparable to those of control rats.	51

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Seeds	Water extract of black pepper (WEBP)and Ethanolic extract of black pepper (EEBP)	75 µg/ml	*In vitro*	WEBP exhibited stronger DPPH radical scavenging activity than EEBP. At 75 µg/mL, the scavenging activities followed the order: BHA (79%) ≈ α-tocopherol (78%) > BHT (76%) > WEBP (55%) > EEBP (48%). The scavenging activity ranked as follows: BHT (82.2%) > α-tocopherol (75.4%) > BHA (69.6%) > WEBP (64.2%) > EEBP (22.6%) . At 75 µg/mL, WEBP and EEBP inhibited linoleic acid peroxidation by 95.5% and 93.3%, respectively. In comparison, standard antioxidants showed inhibition rates of 95.0% (BHT), 92.1% (BHA), and 70.4% (α-tocopherol). At 75 µg/mL, the metal chelating capacities were 84% for WEBP and 83% for EEBP, higher than those of α-tocopherol (75%), BHA (69%), and BHT (66%). At 75 µg/mL, WEBP and EEBP showed hydrogen peroxide scavenging activities of 83% and 63%, respectively. In comparison, BHT, α-tocopherol, and BHA exhibited higher activities at 97%, 93%, and 88%, respectively. The scavenging effectiveness ranked as: BHT > α-tocopherol > BHA > WEBP > EEBP. EEBP showed a stronger reducing power than WEBP, though the difference was not statistically significant ($P > 0.05$). The overall reducing power ranked as: BHA > BHT > α-tocopherol > EEBP > WEBP.	[52]
	-	-	40 mg/kg BW/ Day in 1% carboxymethyl cellulose, p.o	Hyperli pidemic male Wistar rats	Piperine supplementation alongside a high-fat diet and antithyroid drug treatment decreased lipid peroxidation and enhanced antioxidant status (plasma vitamin C, erythrocyte vitamin E, GSH, CAT, GPx) compared to rats that did not receive piperine.	[53]
	Peppe rcorn	Acetone and Methanol extract	-	*In vitro*	Acetone extract showed stronger antioxidant activity than methanol extract across several assays: higher Trolox equivalents (39.8 vs. 23.3 mmol/g), greater ORAC values (395 vs. 363 mmol/g), and better FRAP results (1.09 vs. 0.54 mg EDTA equivalents/g). It also had a lower DPPH ED_{50} (1.20 mg/mL vs. 1.46 mg/mL), indicating more effective free radical scavenging.	[54]

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Fruits	Pet ether and ethyl acetate Fractions R1, R2, R3	50-500 µg/ml (TAA), 50-200 µg/ml (DPPH), 20-100 µg/ml (NORS and SARS), 50-1000 µg/ml (HRS)	*In vitro*	The free radical scavenging activity of various fractions of the petroleum ether extract of *Piper nigrum* (PEPN) increased in a dose-dependent manner. At 500 µg/mL, the R3 and R2 fractions inhibited linoleic acid peroxidation by 60.48 ± 3.33% and 58.89 ± 2.51%, respectively. In the DPPH assay, both fractions showed nearly identical activity. At 100 µg/mL, the R3 fraction inhibited nitric oxide radicals by 55.68 ± 4.48%, compared to 84.27 ± 4.12% inhibition by curcumin. Additionally, PEPN effectively scavenged superoxide radicals generated by the xanthine/xanthine oxidase system, with R3 and R2 inhibiting 63.56 ± 4.17% and 61.04 ± 5.11% at 1000 µg/mL, respectively. In hydroxyl radical scavenging activity R2 and R3 fractions of PEPN effectively reduced DNA damage across all tested concentrations, while the R1 fraction exhibited negligible or no protective effect.	55
	Fruit	Essential oil and Oleoresins (extracted by ethanol and ethyl acetate)	5-20 µg/ml	*In vitro*	In DPPH, FRAP, and lipid peroxidation assay the inhibitory effects followed the order: essential oil > ethyl acetate oleoresin > ethanol oleoresin. Both the oil and oleoresins exhibited strong antioxidant activity, surpassing that of BHA and BHT, but remaining lower than propyl gallate (PG).	56
	Leaves	Ethyl acetate, Acetone, Aqueous extract	100 µg/ml	*In vitro*	Among the tested extracts, the ethyl acetate extract showed the highest antioxidant activity in DPPH (84.75%), ABTS (72.75%), and superoxide inhibition (58.50%) assays. Acetone extract was most effective in nitric oxide (42.80%) and hydrogen peroxide scavenging (14.40%). In the phosphomolybdenum assay, acetone showed the highest inhibition (0.95%), while the aqueous extract exhibited the strongest activity in the FRAP assay (1.256 mg BHT eq/g).	57
	Berries	Methanol, Ethanol, ethyl acetate, chloroform, water	50-300 µg/ml	*In vitro*	In the DPPH assay (50 µg/mL), ethanol extract showed the highest inhibition (65.59%), followed by piperic acid (29.5%) and piperine (10.28%). In the phosphomolybdenum assay, antioxidant activity (in α-tocopherol equivalents) was 48.2 µmol/mL for ethanol extract at 25 µg/mL, while piperine and piperic acid showed 58.8 and 64.1 µmol/mL at 100 µg/mL, respectively.	58

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Seeds	Essential oil extracted by Co_2 and hydro distillation	-	*In vitro*	In the DPPH assay, the supercritical CO_2 extract showed stronger antioxidant activity (EC_{50}: 103.28 µg/mL) than the hydrodistilled extract (EC_{50}: 316.27 µg/mL), indicating greater potency.	59
	Fruit	Essential Oil	50-200 µg/ml (SORS, HRS, LPO) 100-1000 µg/ml (DPPH) 100, 500, 1000 mg/kg, BW/ Day	*In vitro* *In vivo* (Balb/C mice)	Essential oil effectively scavenged superoxide and hydroxyl radicals and inhibited tissue lipid peroxidation. The IC_{50} values for superoxide and hydroxyl radical scavenging were both above 200 µg/mL, while lipid peroxidation was inhibited at an IC_{50} of 196 µg/mL. At 50 µg, the essential oil demonstrated a ferric reducing activity equivalent to 1.3 mM. However, its DPPH radical scavenging ability was relatively mild. Treatment with 500 mg/kg BW of oil significantly enhanced the levels of antioxidant enzymes—including catalase, superoxide dismutase, glutathione reductase (GRx)—as well as glutathione in both liver and blood samples.	60
	Leaves	Methanolic extract (Hot and cold extraction)	50-200 µg/ml	*In vitro*	Cold extraction showed slightly higher antioxidant activity (78.81% at 200 µg/mL) compared to heat extraction (77.62%), both increasing with concentration. The IC_{50} values were 61.28 µg/mL for cold extract and 55.28 µg/mL for heat extract.	61
	Pericarp	Ethanolic extract	-	*In vitro*	The antioxidant activities measured using DPPH and ABTS assays were found to be 392.46 ± 6.84 and 1366.82 ± 25.14 mg vitamin C equivalents (VCE) per 100 g fresh weight (FW) in the pericarp, respectively. In comparison, black pepper exhibited lower activities, with 225.33 ± 6.84 and 793.97 ± 39.83 mg VCE/100 g FW for DPPH and ABTS assays, respectively. This indicates that the pericarp had significantly greater radical scavenging capacities than black pepper, with increases of approximately 42.5% for DPPH and 41.9% for ABTS assays.	62
	Seeds	n-hexane (Essential oil (EO) extracted)	-	*In vitro*	The extracted essential oil demonstrated notable antioxidant activity, with an IC_{50} value of 35.83 ± 2.92 µg/mL, which is comparable to that of the standard ascorbic acid (27.34 ± 1.86 µg/mL).	63
Anticancerous activity	Piperine	-	50 mg/kg, BW/ Day, orally	Male Swiss Albino mice	Benzo(a)pyrene [B(a)p]-induced lung cancer in mice was suppressed by piperine treatment, as evidenced by a significant reduction in total protein levels and protein-bound carbohydrate components, including hexose, hexosamine, and sialic acid.	64

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Piperine	-	12.5, 25, 50 µM	*In vitro* Cell Lines (Doxoru bicin resistant MCF-7 and A-549)	Piperine has been shown to enhance the efficacy of anticancer drugs in drug-resistant cancer cell sublines, such as MCF-7/DOX and A-549/DDP, which are derived from MCF-7 and A-549 cells, respectively. At a concentration of 50 µM, piperine significantly reversed resistance to doxorubicin, increasing drug sensitivity by 32.16-fold in MCF-7/DOX cells and 14.14-fold in A-549/DDP cells. It also re-sensitized resistant cells to mitoxantrone by 6.98-fold. Furthermore, prolonged exposure to piperine was found to suppress the transcription of ABC transporter genes responsible for drug efflux, suggesting a potential mechanism for overcoming multidrug resistance in cancer therapy.	65
	Piperine	-	0-160 µM (LNCaP, PC-3), 0-320 µM (DU145)	*In vitro* Prostrate cancer Cell Lines (LNCaP, PC-3 and DU145)	Piperine treatment led to a dose-dependent inhibition of cell proliferation across prostate cancer cell lines, with the most pronounced effect observed in LNCaP cells (IC_{50} = 74.4 µM), followed by PC-3 (IC_{50} = 111.0 µM) and DU145 (IC_{50} = 226.6 µM) after 48 hours. The antiproliferative effect was associated with G0/G1 cell cycle arrest, accompanied by downregulation of cyclin D1 and cyclin A. Additionally, piperine treatment upregulated the cell cycle inhibitors p21^Cip1 and p27^Kip1 in LNCaP and DU145 cells, but not in PC-3 cells, correlating with a stronger cell cycle arrest in the former two lines. While piperine induced only modest levels of apoptosis, it significantly promoted autophagy, as indicated by increased LC3B-II expression and the formation of LC3B puncta, particularly in LNCaP and PC-3 cells.	66

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Piperine	-	10-200 µM	*In vitro* HER2-over expressing breast cancer cells (SKBR3 and MCF-7 cell)	Piperine demonstrated potent anti-cancer effects in HER2-overexpressing breast cancer cells by significantly inhibiting cell proliferation and inducing apoptosis, as evidenced by caspase-3 activation and PARP cleavage. It suppressed HER2 gene expression at the transcriptional level and disrupted the ERK1/2 signaling pathway, leading to reduced expression of SREBP-1 and fatty acid synthase (FAS). Additionally, piperine inhibited EGF-induced MMP-9 expression by blocking AP-1 and NF-κB activation through interference with ERK1/2, p38 MAPK, and Akt pathways, thereby reducing cell migration. Notably, piperine pretreatment enhanced the cytotoxic effect of paclitaxel in HER2-positive breast cancer cells. After 48 hours of exposure, piperine exhibited greater potency in SKBR3 cells (IC_{50} = 50 µM) compared to MCF-7 cells (IC_{50} = 200 µM), indicating its selective effectiveness against HER2-overexpressing subtypes.	67
	Pepper corn	Dichloro methane extract	100, 200, 400 mg/kg, BW/Day, orally	*In vitro* Various cancer cell lines (MCF-7, ZR75-1, MDA-MB-23) *In vivo* Female Sprague Dawley rats	The piperine-free *Piper nigrum* extract exhibited differential cytotoxic effects across various cancer cell lines. It showed the highest potency against the MCF-7 breast cancer cell line (IC_{50} = 7.45 µg/mL), followed by ZR75-1 (13.85 µg/mL), MDA-MB-468 (18.19 µg/mL), and MDA-MB-231 (22.67 µg/mL), indicating strong activity particularly against hormone receptor-positive breast cancer. Moderate cytotoxicity was observed in colorectal cancer cells, HT-29 (27.74 µg/mL) and SW-620 (29.56 µg/mL), while lung cancer cell lines A-549 (30.77 µg/mL) and H-358 (34.69 µg/mL) were less sensitive. Overall, the extract demonstrated selective anticancer potential, with the most pronounced effects seen in breast cancer cells. The tumor growth rate in PFPE-treated groups was significantly slower compared to both the control and vehicle-treated groups.	68

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	-	Piperine	Cell Viability (0, 50, 100, 150, and 200 µM) 50, 100 mg/kg, BW/Day, orally, 28 days	*In vitro* (A375SM, A375P) *In vivo* Tumour xenograft model (Male BALB/c nude mice)	Piperine demonstrated significant anti-melanoma activity by inhibiting the proliferation of melanoma cells and inducing apoptosis. At the molecular level, piperine upregulated pro-apoptotic markers such as BAX, cleaved PARP, cleaved caspase-9, phosphorylated JNK, and phosphorylated p38, while downregulating anti-apoptotic proteins including BCL-2, XIAP, and phosphorylated ERK1/2 in a concentration-dependent manner. *In vivo*, a 4-week piperine treatment regimen significantly suppressed tumor growth in mice without inducing observable toxicity. Tumor analysis further confirmed enhanced expression of cleaved caspase-3 and increased apoptotic cell presence, alongside reduced levels of phosphorylated ERK1/2.	69
	Fruit	Methanolic, Ethanolic and Water extract	50, 100 and 200 µg/ml	*In vitro* Human leukemia cell line, K-562 cells	The methanolic extract (BP-M) and its active compound, piperine (PIP), demonstrated significant cytotoxic activity against K-562 cells. Both BP-M and PIP induced apoptotic features, including the formation of apoptotic bodies and nuclear condensation, as observed through fluorescence microscopy. These findings were further validated using flow cytometry. Additionally, treatment with BP-M and PIP led to increased generation of reactive oxygen species (ROS) in the K-562 cells. Gene expression analysis revealed an upregulation of pro-apoptotic markers Bax, caspase-3, and caspase-9, accompanied by a downregulation of the anti-apoptotic gene Bcl-2. The anti-proliferative effects of BP-M and PIP were confirmed by trypan blue exclusion assays and supported by the observed decrease in the expression of proliferating cell nuclear antigen (PCNA).	70
	Fruit	Piperine treatment *Piper nigrum* extract (PFPE)	50, 100, 150 mg/kg, BW/Day, orally	Female Sprague-Dawley rats	PFPE treatment at 50, 100, and 150 mg/kg reduced tumor incidence to 20%, 20%, and 0%, respectively. The low dose transiently suppressed early-stage cancer cytokines (s-ICAM, L-selectin, CX3CL1, CXCL7, VEGF and TIMP-1), while the intermediate dose significantly inhibited multiple cancer-related cytokines and chemokines (CXCL7, VEGF, TIMP-1, CCL5, CXCL1, CXCL9 and IL-1β). All doses increased IFN-γ levels at three months; intermediate and high doses promoted a Th1 response and reduced Th2 levels, with the high dose also lowering Tregs. Additionally, PFPE downregulated ER-α and NF-κB, and upregulated IL-6R and STAT3 in tumor tissues.	71

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	-	-	0-200 µM	*In vitro* Cell lines (NB-4, MOLT-4)	Piperine exhibited potent cytotoxic effects on NB4 and MOLT-4 leukemia cells, as evidenced by a significant reduction in cell viability in the MTT assay. Mechanistically, piperine promoted autophagy, marked by elevated expression of LC3, Beclin-1, and ULK1, alongside a downregulation of mTOR and NF-κB1. Additionally, piperine induced cellular senescence, as indicated by increased senescence-associated β-galactosidase activity. This effect was accompanied by upregulation of p21 and IL-6, and a concurrent decrease in CDK2 expression. These findings suggest that piperine suppresses leukemia cell growth through the induction of autophagy and senescence pathways.	[72]
	-	Methanol, Ethanol, Ethyl acetate, Acetone, n-hexane, Petroleum ether	-	*In silico*	Molecular docking analysis exhibited that piperine, various piperidine derivatives, and piperettin demonstrated notable potential to inhibit cancer cell proliferation by targeting the epidermal growth factor receptor (EGFR), showing higher binding affinity than the reference drug erlotinib. Notably, the compound *(2E,4E,8E)-9-(benzo[d][1,3]dioxol-5-yl)-1-(piperidine-1-yl) nona-2,4,8-trien-1-one* exhibited the highest binding affinity across multiple critical targets, including EGFR, monoamine oxidase B (MAO-B), apoptosis-inducing factor, and cytochrome P450 enzymes. These findings suggest its potential as a multi-target anticancer agent.	[73]
Analgesic activity	Piperine	-	30, 50, 70 mg/ kg, BW/Day, intraperitoneally	Male mice	In the writhing test, administration at a dose of 70 mg/kg resulted in an 89% inhibition of acetic acid-induced nociception. In the tail-flick assay, a dose of 50 mg/kg significantly increased the reaction time latency from 3.7 seconds (control) to 17.2 seconds.	[74]

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Fruit	Ethanol and Hexane extract	5, 10, 15 mg/kg, BW/Day	Swiss Albino mice	In the tail immersion test, piperine showed the highest analgesic activity with a reaction time of 11.658 seconds at 5 mg/kg after 120 minutes. Hexane extract peaked at 8.284 seconds (10 mg/kg, 60 min), while ethanol extract reached 9.602 seconds (15 mg/kg, 120 min). In the analgesy-meter test, the ethanol extract showed the strongest effect with a reaction time of 20.900 seconds at 10 mg/kg after 60 minutes. Hexane and piperine followed with 13.000 seconds (5 mg/kg) and 9.400 seconds (15 mg/kg), respectively. The hot plate test showed piperine to be most effective, with a reaction time of 12.870 seconds at 10 mg/kg after 30 minutes. Hexane (2.738 s at 15 mg/kg) and ethanol (2.486 s at 5 mg/kg) showed weak activity. In the writhing test, piperine and ethanol extracts both achieved 100% protection at doses of 10 mg/kg and 15 mg/kg, respectively. Hexane extract provided 99.71% protection at 5 and 10 mg/kg.	[75]
	Fruit	Piperine Ethanol and Hexane extract	5, 10, 20 mg/kg, BW/Day	Swiss Albino male mice	Piperine exhibited strong analgesic effects at doses of 5 and 10 mg/kg compared to the control and standard treatments, with the maximum effect observed at 10 mg/kg after 120 minutes. In contrast, both hexane and ethanol extracts showed weak analgesic activity at all tested doses (5, 10, and 20 mg/kg) in the hot plate method. However, using the tail immersion method, significant pain relief was noted with piperine at 5 mg/kg and ethanol extract at 20 mg/kg after 120 minutes, and with hexane extract at 10 mg/kg after 60 minutes. In the writhing test, the ethanol extract significantly reduced the number of writhes at 20 mg/kg, while piperine at 20 mg/kg completely eliminated the writhes in mice.	[76]
Anti convulsant activity	-	Piperine	30, 50, 70 mg/kg, BW/Day	Pentyle netetrazol (PTZ)- and Picrotoxin-induced seizures in male mice	In the pentylenetetrazol (PTZ)-induced seizure model, piperine at a dose of 50 mg/kg was more effective than 70 mg/kg in preventing seizures, suggesting optimal anticonvulsant activity at the lower dose. In the picrotoxin-induced seizure model, the highest tested dose of piperine (70 mg/kg) significantly prolonged the onset of convulsions, increasing the latency to 878.5 seconds compared to 358.4 seconds in the control group.	[74]

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	-	Ethyl alcohol, n-hexane	500 mg/kg	Male Wistar Rats Pentyle netetrazol (PTZ) and Maximal electro shock seizure (MES) induced model	*Piper nigrum* effectively reduced both the onset and duration of seizures in PTZ- and MES-induced seizure models.	77
Antimicrobial activity	Berries	Acetone and Dichlorom ethane extract	-	*In vitro*	The acetone extract exhibited greater antibacterial activity than the dichloromethane extract, with *S. aureus* showing the highest sensitivity, indicated by a 20 mm zone of inhibition.	78
	Seeds	Methanolic extract	25-100 µl	*In vitro* *S. aureus, B. subtilis*, *P. aeru ginosa, E. coli*	At a concentration of 50 mg/mL, the methanolic extract exhibited inhibitory effects against all tested bacteria, with zones of inhibition ranging from 9.75 to 12.25 mm.	79
	Berries	Methanol, Ethanol, ethyl acetate, chloroform, water	-	*In vitro* *E. coli* (ATCC 25922), *K. pneu monia* (ATCC 27853), *S. enterica* (ATCC 43972), *S. aureus* (ATCC 25923), *S.epidermidis* (ATCC 14990), *E. faecalis* (ATCC 29122), and *B. subtilis* (ATCC 6633).	The MIC values for all tested strains were below 325 mg/ml. *Staphylococcus aureus* and *Bacillus subtilis* were the most susceptible to the ethanol extract, each exhibiting an MIC of 156.25 mg/ml.	58
	Fruit	Water (Cold and Hot), Methanol extract	-	*In vitro*	All extracts inhibited the tested bacteria. The cold-water extract showed the largest zone of inhibition against *E. coli* (23 mm). The hot water extract was most effective against *S. typhi* and *S. aureus*, each with a 22 mm inhibition zone. The methanolic extract demonstrated maximum inhibition against *E. coli*, *S. typhi*, and *P. aeruginosa* (21 mm), but showed no activity against *S. aureus*.	80
	Fruit	Methanol	-	*In vitro* clinical strains of *P. stuartii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *E. aerogenes* and *E. cloacae*	The methanolic extract of *Piper nigrum* exhibited inhibitory activity against all tested microorganisms, with the highest efficacy observed against *Pseudomonas aeruginosa* PA01, showing a MIC of 32 µg/ml.	81

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Fruit	Ethanol, Chloroform extract	1-4 mg/ml	*In vitro* *S. aureus, S. typhi, E. coli, Proteus* sp. and *P. aeruginosa.*	At its highest tested concentration (4 mg/mL), the ethanol extract exhibited strong antibacterial activity against *E. coli*, producing a zone of inhibition measuring 22 mm. In comparison, the chloroform extract showed notable effectiveness against both *E. coli* and *Proteus* spp., each with a zone of inhibition of 18 mm.	[82]
	Powder	Aqueous, Ethanol, Methanol	-	*In vitro* *S. aureus, B. subtilis, B. cereus, E. coli, S. typhi, P. aeruginosa*	The aqueous extract showed selective antibacterial activity, inhibiting only Gram-positive bacteria with zones of inhibition ranging from 12 to 17 mm. The methanolic extract was effective against all tested bacteria except *Bacillus subtilis*, with inhibition zones between 11 and 18 mm. The ethanolic extract demonstrated the strongest overall activity, producing zones of inhibition ranging from 16 to 22 mm.	[83]
	Seeds	Black Pepper Chloroform Extract (BPCE)	-	*In vitro* *E. coli* and *S. aureus*	BPCE disrupted the tricarboxylic acid (TCA) cycle in bacteria and a significant reduction in intracellular ATP levels. Additionally, BPCE compromised the integrity of the bacterial cell membrane, resulting in impaired permeability. This disruption caused metabolic dysfunction, hindered energy production, and ultimately led to bacterial cell death.	[84]
	Fruit	Methanol	-	*In vitro*	The extract showed the greatest antibacterial activity against *Proteus mirabilis* (zone of inhibition: 5.00 mm), followed by *Escherichia coli* (4.90 mm) and *Klebsiella pneumoniae* (4.63 mm).	[85]
	-	Black Pepper essential oil (BPEO)	0.0-8.0 µl/ml	*In vitro* *E. coli*	The results demonstrated that the minimum inhibitory concentration (MIC) of BPEO was 1.0 µl/ml. The inhibition zone diameters ranged from 17.12 to 26.13 mm. Treatments at 2× MIC resulted in lower membrane potential and shorter kill times compared to 1× MIC, with the control group showing the highest values. Morphological analysis of *E. coli* treated with BPEO revealed significant structural damage, including deformation, pitting, shrinkage, adhesion, and cell rupture. At 2× MIC, BPEO induced the highest electrical conductivity at 1, 3, 5, 7, 9, 11, and 13 hours, and caused substantial leakage of intracellular contents: DNA (at 4, 8, 12, 16, 20, 24, and 28 hours), proteins (at 4, 6, 8, 10, 12, 14, and 16 hours), potassium ions (at 0, 0.5, 1, 1.5, and 2 hours), phosphate ions (at 0.5, 1, 1.5, and 2 hours), and ATP ($P < 0.05$). Although 1× MIC also caused leakage, the effects were less pronounced than at 2× MIC but still greater than the control. Overall, BPEO compromised cell membrane integrity, leading to cellular leakage, structural disorganization, and ultimately, bacterial cell death.	[86]

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Seeds	Benzene, Methanol, Acetone extract	25, 50, 100 µg/ ml	*In vitro* *S. aureus* (NCIM-2079), *B. subtilis* (NCIM-2124), *E. coli* (NCIM-2064) and *P. aeruginosa* (NCIM-5210).	During the analysis, *P. aeruginosa* and *S. aureus* exhibited the highest sensitivity to the benzene extract, each showing a 16 mm zone of inhibition at a concentration of 100 µg/mL. In contrast, the acetone and methanol extracts demonstrated the least antibacterial activity.	87
	Plant	Methanol	25 mg/ml	*E. coli* isolated from chickens	In vitro antimicrobial sensitivity testing revealed that combining methanolic black pepper extract with antibiotics enhanced their efficacy against *E. coli* isolates. The combination improved the activity of amoxicillin, doxycycline, gentamicin, erythromycin, and cefotaxime, as demonstrated by both disc diffusion and MIC assays.	88
	Leaf	Ethanol, Diethyl ether, chloroform, Water	-	*In vitro* *S. aureus, Bacillus sp., E. coli* and *Klebsiella* sp.	The ethanol extract exhibited the strongest antimicrobial activity among all tested pathogens, with the highest effect observed against *Bacillus* species.	89
	Seeds	Aqueous, Methanol, Ethanolic, Acetone, Petroleum ether	0.5 mg/µl	*E. coli, K. pneumoniae, Proteus sp., P. aeruginosa*, and *B. subtilus*	All extracts demonstrated inhibitory effects against the tested bacteria. At a concentration of 50% v/v, the methanol extract showed notable antibacterial activity, with zones of inhibition ranging from 10 to 14 mm. In contrast, the petroleum ether extract exhibited the weakest activity, producing inhibition zones of only 4 to 6 mm across all microorganisms.	90
	Seeds	Black pepper petroleum ether extract (BPPE)	-	*In vitro* *S. typhimurium* (ATCC 14028), *L. monocytogenes* (ATCC 19115)	BPPE demonstrated strong antimicrobial activity against *Listeria monocytogenes* and *Salmonella typhimurium*. BPPE inhibited the breakdown of hydroperoxides and suppressed the activities of antioxidant enzymes POD and CAT. Additionally, it disrupted key metabolic enzymes, significantly altering organic acid levels and impairing the energy metabolism of both bacterial species, contributing to inhibited cell growth.	91
	Seeds	Ethanolic extract	0.3905, 0.781, 1.565, 3.125, 6.25, 12.5, 25, 50, 100 mg/ml	*In vitro*	Antibacterial testing demonstrated that black pepper seed extract exhibited activity against *Escherichia coli* ATCC 25922, with a minimum bactericidal concentration (MBC) of 50 mg/ml.	92

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Seeds	n-hexane (Essential oil (EO) extracted)	-	*In vitro Gram-positive* bacteria (*S. aureus* and *B. magneterium)* Eight Gram-negative bacteria (*S. paratyphi, E. coli, S. typhi, S. flexneri, S. sonnei, S. boydii, S. dysentery)*	The extracted black pepper essential oil (BPEO) exhibited moderate antibacterial activity relative to the standard antibiotic, Ceftriaxone. Among the tested strains, *S. boydii* was the most susceptible, with BPEO producing a zone of inhibition measuring 20.7 ± 0.6 mm, compared to 24.7 ± 0.6 mm observed for Ceftriaxone.	63
	Seeds	Ethanol extract	100-1000 µg/ml	*In vitro* *S. aureus* (ATCC 0538), *P. aeruginosa* (ATCC no code), *Salmonella* sp. (ATCC 4029), *P. mirabilis* (ATCC 1353), and *C. albicans* (ATCC 10635).	The extract obtained through maceration demonstrated high efficacy in inhibiting *Salmonella* spp., with a MIC of less than 100 µg/mL. The Soxhlet-derived extract exhibited strong inhibitory activity against nearly all tested microorganisms, with the exception of *P. aeruginosa*, which showed minimal response. The extract obtained through the stepwise purification process also showed favorable inhibition against *S. aureus* and *Salmonella* spp. (MIC < 100 µg/mL). Piperine exhibited excellent antimicrobial activity against most microorganisms, although it was ineffective against *P. aeruginosa*.	93
Anti-inflammatory activity	Piperine	-	10-100 µg/ml	Interleukin 1β (IL1β)-stimulated fibroblast-like synoviocytes derived from patients with rheumatoid arthritis	Piperine suppressed the expression of IL-6 and MMP-13 and reduced the production of prostaglandin E2 (PGE2) in a dose-dependent manner across concentrations ranging from 10 to 100 µg/mL. Additionally, piperine inhibited the nuclear translocation of activator protein-1 (AP-1) in IL-1β-treated synoviocytes, while having no effect on nuclear factor kappa B (NF-κB) migration.	94
	Piperine	-	50 mg/kg, BW/ Day, orally, 10 days	Albino Wistar rats	Compared to controls, the piperine demonstrated significant anti-inflammatory effects, with 56% inhibition observed in the carrageenan-induced paw edema model and 40% in the formalin-induced arthritis model. However, in the cotton pellet-induced granuloma model, the inhibition was minimal at only 10%.	95
	-	Viphyllin (extract of β-cary ophyllene from black pepper)	5-50 µg/ml	Inflammtion induced by lipopol ysaccharide in RAW 264.7 cells	Viphyllin exhibited notable anti-inflammatory activity by inhibiting the release of pro-inflammatory mediators such as nitric oxide (NO), cytokines, and interleukins. It also reduced the expression levels of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Furthermore, Viphyllin suppressed the phosphorylation of key signaling molecules, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK).	96

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
Neuroprotective activity	Piperine	-	10 mg/kg, BW/ Day, 15 days	1-methyl-4-phenyl-1,2,3,6tetra hydropyridine (MPTP)-induced Parkinson's mouse model (Male C57BL/6 mice)	Piperine pretreatment effectively protected against MPTP-induced motor and cognitive impairments in Parkinson's disease mice. It preserved motor coordination (rotarod test), improved learning and memory (Morris water maze), and increased platform crossings during the probe trial. Piperine also maintained tyrosine hydroxylase-positive neurons in the substantia nigra, reduced microglial activation, downregulated IL-1β, and alleviated oxidative stress, highlighting its neuroprotective potential.	97
	Fruits	Cold pressed oil	100 mg/kg, BW/ Day	Alzheimer-type Dementia induced Sprague dawley male rats	CPO administration significantly enhanced cognitive performance in rats, as demonstrated by the Morris water maze test. Treated rats showed a 262.9% increase in time spent in the platform quadrant compared to the scopolamine group, along with an 18.18% increase in platform crossings relative to the control group. In the passive avoidance test, CPO also prolonged step-through latency, indicating improved memory retention compared to controls.	98
	Fruits	Methanolic extract	30 mg/kg	Ischemic Reperfusion-induced Cerebral Injury in the Wistar albino rats	A significant reduction in the infarct area within the hippocampal region was observed in the *Piper nigrum* L. treatment group compared to the disease control. Moreover, the infarct area was further reduced when compared to the quercetin-treated group, indicating superior neuroprotective effects. The *Piper nigrum* L. treatment group showed a significant reversal of damage induced by ischemia-reperfusion injury in the hippocampal region.	99
	Fruits	Hexane and Ethyl acetate	-	H_2O_2-induced oxidative stress in SH-SY5Y cells	The extracts demonstrated neuroprotective effects by significantly reducing oxidative stress and restoring mitochondrial membrane potential in cells. They also exhibited strong anti-glycation activity and effectively inhibited Aβ fibril formation. Additionally, the extracts acted as competitive inhibitors of acetylcholinesterase (AChE). These multitarget neuroprotective actions suggest *Piper nigrum* as a promising candidate for the treatment of neurodegenerative diseases (NDs).	100

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
Anxiolytic and Antidepressant activity	Piperine	-	2.5, 5, 10 mg/kg, BW/Day, 14 days	Adult male Kunming mice and *In vitro*	Fourteen days of repeated piperine treatment effectively reversed chronic mild stress (CMS)-induced changes, including reduced sucrose consumption, elevated plasma corticosterone, and decreased open field activity. Piperine also restored hippocampal progenitor cell proliferation and upregulated hippocampal BDNF levels. In vitro, piperine (6.25–25 *μM*) and fluoxetine (1 *μM*) dose-dependently protected primary hippocampal neurons from corticosterone (10 *μM*)-induced damage, as shown by MTT and LDH assays.	101
	Fruits	Methanolic extract	50, 100 mg/kg, BW/Day, orally, 21 days	Beta-amyloid (1–42) rat model of Alzheimer's disease	The methanolic extract, particularly at 100 mg/kg, significantly improved anxiety-related and locomotor behaviors in Aβ (1–42)-treated groups. It increased time spent in open arms, open-arm entries (notably at 50 mg/kg), crossings (especially at 100 mg/kg), and enhanced swimming time while reducing immobility (notably at 50 mg/kg), compared to the Aβ (1–42) group alone.	102
	-	Ethyl alcohol	10 mg/kg, BW/ Day, oral as well as i.p	Adult Swiss Albino mice	In the Tail Suspension Test, piperine alone (via both oral and i.p. routes) reduced immobility time. However, both oral and i.p. piperine-sertraline combination groups showed significantly greater antidepressant activity than the respective sertraline-only groups.	103
	Piperine	-	10, 20 mg/kg, BW/Day, i.p	Swiss Albino mice	Piperine and fluoxetine significantly reduced immobility time in stressed mice, indicating notable antidepressant-like effects without affecting locomotor activity. Both treatments also significantly lowered plasma corticosterone levels. However, the antidepressant-like effects of piperine in the Forced swim test and Tail Suspension Test were significantly attenuated by Antalarmin, a CRF-1 receptor antagonist.	104
	Fruits	*Piper nigrum* Essential oil (PNEO)	5, 10, 50 mg/kg, BW/Day, orally, 21 days	Mice	Acute and repeated treatments with PNEO did not affect overall locomotor activity but significantly reduced rearing (at 10, 50 mg/kg acutely and 5, 10, 50 mg/kg repeatedly) and grooming behaviors at all doses. Acute administration of PNEO (10 and 50 mg/kg) and diazepam significantly increased open arm entries and time spent in open arms. Additionally, PNEO 10 and 50 mg/kg significantly reduced immobility time, while PNEO 5 and diazepam had no effect in the tail suspension test (TST).	105

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
Insecticidal activity	Aerial part	Methanolic extract	100, 200, 400 mg/kg, orally, BW/Day	Swiss Albino mice	MEPN administration significantly increased mobility in both the Forced Swim Test and Tail Suspension Test enhanced head-dipping behavior, and reduced latency time in the Hole Board Test. These effects were dose-dependent, indicating the plant extract's potential antidepressant and anxiolytic activities.	106
	Seeds	Powder and piperine	10-100%	*Anopheles arabiensis, An. coluzzii, An. gambiae, An. quadriannulatus* and *An. funestus*.	Mixtures of black pepper and piperine caused high mortality in *An. gambiae* complex strains, with black pepper being significantly more toxic than piperine. In contrast, *An. funestus* strains showed considerably lower sensitivity, likely due to differences in feeding behavior or metabolic processes related to their distinct breeding habitats compared to the *An. gambiae* complex.	107
	Berries	Methylene chloride, Methanol, Ethanol, water	-	Pepper whitefly, *Aleurodicus dispersus*	The results indicated that pepper whitefly adults and nymphs were most susceptible to the methanol extract, with survival rates dropping to 17.1% for adults and 50% for nymphs at 10% (w/w) concentration after 72 hours. In contrast, leaf and stem extracts showed little to no effectiveness against adult and nymphal stages, respectively.	108
Hypolipidemic activity	Powder	Alcoholic extract	200, 500 mg/kg, BW/Day BP and 20 mg/kg piperine	Male Wistar rats	Treatment with *Piper nigrum* extracts and piperine led to reduced levels of total cholesterol, free fatty acids, phospholipids, and triglycerides. Both treatments also increased plasma HDL cholesterol while decreasing LDL and VLDL cholesterol levels.	109
	Piperine	-	40 mg/kg BW/ Day in 1% carboxymethyl cellulose, p.o	High fat diet induced male Wistar rats	Piperine supplementation significantly reduced plasma total cholesterol, LDL, VLDL, and tissue HMG-CoA reductase levels, while increasing antioxidant levels compared to rats not receiving piperine.	53
	Fruits	Ethanol	-	*In vitro*	Both piperine and black pepper extract effectively reduced cholesterol absorption in Caco-2 cells in a dose-dependent manner. This reduction was associated with decreased localization of NPC1L1 and SR-BI proteins at the cell membrane, without affecting their overall cellular levels. Cholesterol solubility in micelles remained largely unchanged, except at a high concentration (1 mg/mL) of black pepper extract, which showed a noticeable effect.	110
Antiulcer activity	Fruits	Pet Ether	200 mg/kg, BW/ Day, orally, 14 day	Swiss Albino mice	Both PEPN and the standard drug ranitidine significantly reduced the incidence and severity of ulcers in the ethanol-induced ulcer model.	111
	Piperine	-	20-30 mg/kg, BW/Day, i.p	Swiss Albino mice	A dose-dependent reduction in the ulcer index was observed in mice treated with piperine at doses of 20 and 30 mg/kg.	112

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
Hepato protective activity	Fruits	Methanolic extract and Piperine	100, 200 mg/kg (Extract) and 50 mg/kg (Piperine) BW/Day, orally, 15 days	Ethanol-CCl_4 induced male Wistar rats	Ethanol–CCl_4 administration elevated hepatic biomarkers (TG, AST, ALT, ALP, SGPT, SGOT, bilirubin) and LPO, indicating liver damage. Pretreatment with extract and piperine significantly reduced these levels. Histopathology showed liver damage (fatty degeneration, necrosis, infiltration), which was notably reversed by extract and piperine after 15 days of treatment.	113
	Fruits	Methanolic extract of *Piper nigrum* (MPN)	50, 100, 200 mg/kg, BW/Day, orally, 20days	Albino Rats	MPN administration was found to significantly ($p<0.05$) reduce serum and tissue levels of malondialdehyde, along with AST and ALT activities, in a dose-dependent manner.	114
	Piperine	-	P20, P40 mg/kg, BW/Day, orally NAC (N-acetylcysteine) APAP (high dose of paracetamol)	Paracetamol induced hepatotoxicity in C57BL/6 male mice	The NAC+P20 and NAC+P40 treatment groups exhibited a reduction in necrotic area, MMP-9 activity, and Casp-1 expression. Notably, the NAC+P20 group significantly lower alanine ALT levels while increasing sulfhydryl group (-SH) content. In the NAC+P40 group, NLRP-3 expression was also reduced. Compared to the APAP group, levels of AST, TBARS, and IL-1β were decreased in the NAC, NAC+P20, and NAC+P40 groups. Additionally, liver necrosis area, TNF levels, protein carbonylation, and IL-18 expression were significantly reduced in the P40, NAC, NAC+P20, and NAC+P40 groups. All treatment groups also showed a reduction in IL-6 levels.	115
	Fruits	Black pepper Essential oil (BPEO)	0.5, 1 ml/kg, BW/ Day, 4 days	Dexamethasone-induced hepatotoxicity in male Wistar rats	BPEO mitigated signs of toxicity, as evidenced by decreased monocyte infiltration, reduced hepatocyte degeneration and vacuolation, and lower ALT and AST levels. Additionally, compared to dexamethasone-treated rats, BPEO reduced the number of PGC-1α-positive hepatocytes and enhanced the expression of PPAR-α in the liver.	116
	Stems	Hydroethanolic extract	200, 400, 800 mg/kg, BW/Day, orally, 28 days	Tenofovir/ lamivudine/ efavirenz (TLE)-induced hepatotoxicity in male Wistar rats	A significant reduction in AST, ALT, ALP and triglyceride levels was observed in both the silymarin and *Piper nigrum* stem groups compared to the TLE-only group.	117
	Piperine	-	30 mg/day, BW/ Day	CCl_4 induced male Wistar Rats	Piperine treatment in CCl_4-exposed rats led to a significant reduction ($p < 0.05$) in liver enzyme (AST, ALT, ALP) levels. Moreover, it significantly improved lipid profiles by lowering total triglycerides, total cholesterol, LDL, and VLDL levels, while increasing HDL levels.	118
Antidiarrheal activity	Piperine	-	1-10 mg/kg, BW/ Day	Balb/c mice	Piperine provided protection in a dose-dependent manner.	119

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Fruits	Aqueous Black pepper extract (ABPE)	75, 150, 300 mg/ kg, BW/Day, p.o	Castor oil and magnesium sulphate induced Swiss Albino mice	Pretreatment of mice with varying doses of ABPE resulted in a significant, dose-dependent reduction in purging frequency, evidenced by a decrease in both the number of wet stools and the total stool count, as well as a reduction in the weight of wet stools. ABPE demonstrated dose-dependent inhibition of diarrhoea induced by castor oil in albino mice, with a significant effect observed at 300 mg/kg compared to the control group. Similarly, ABPE exhibited dose-dependent inhibition of magnesium sulphate-induced diarrhoea, showing a significant effect at the 300 mg/kg dose relative to controls.	120
Anti-asthmatic activity	Fruits	Crude (Pn. Cr), Aqueous (Pn.Aq), Chloroform (Pn.$CHCl_3$), Ethyl acetate (Pn.EtAc), petroleum ether (Pn.Pet)	-	*In vivo* (Sprague dawley rats) *In vitro* (Isolated trachea of Guinea Pig)	Pn.Cr produced dose-dependent relaxation of CCh-induced bronchospasm in anesthetized rats, with up to 37.3% relaxation at 100 mg/ kg. Piperine also showed bronchodilatory effects, though less potent, achieving 26.7% relaxation at the same dose. Among the fractions tested, Pn.Pet was the most effective, causing 60.3% relaxation at 100 mg/kg, followed by Pn.Aq (40.8%), Pn.EtAc (24%), and Pn.$CHCl_3$ (21.4%), all demonstrating dose-dependent responses. Pn.Cr and piperine inhibited K^+ (80 mM)-induced contractions with IC_{50} values of 0.28 mg/mL and 30.4 µM, respectively, showing similar potency to their effects on CCh-induced contractions. Papaverine exhibited comparable inhibition for both stimuli, while verapamil was more potent against K^+-induced contractions. Among the P. nigrum fractions, Pn.Aq and Pn.$CHCl_3$ showed similar inhibitory profiles to the crude extract on both CCh and K^+ contractions. Pn.EtAc was more effective against K^+-induced contractions (IC_{50}: 0.2 mg/ mL), resembling verapamil's pattern. Pn.Pet showed greater potency than the crude extract on both CCh and K^+ contractions, with IC_{50} values of 0.24 mg/mL and 0.22 mg/ mL, respectively.	121
Antipyretic activity	Piperine	-	20-30 mg/kg	Swiss Albino mice	Piperine-treated mice exhibited a dose-dependent reduction in rectal temperature compared to the control group.	112
	Piperine	-	50 mg/kg, BW/ Day	Albino Wistar rats	Piperine significantly reduced rectal temperature only at the 4-hour mark compared to the control group, whereas aspirin showed a significant reduction at both 3 and 4 hours.	95

Table 1. Continued...

Plant activity	Part used	Extract	Dose/Mode/ Duration	Animal Model	Effects observed	References
	Aerial part	Methanolic extract	100, 200, 400 mg/kg, BW/Day	Swiss Albino mice	Paracetamol and MEPN produced a significant ($p < .01$, 0.001), dose-dependent reduction in pyrexia compared to the control group. The highest level of pyrexia inhibition was observed with MEPN at 400 mg/kg, showing an effect comparable to that of the standard drug paracetamol at 100 mg/kg.	106

Different Pharmacological activities of *P. nigrum* are also shown in Figure 4.

8. Possible Mechanisms of Various Pharmacological Activities

A comprehensive summary of the underlying mechanisms responsible for the various pharmacological activities described in Table 1, offering a visual representation to enhance understanding of their mode of action (Figure 5).

9. Toxicity Profile of *P. nigrum*

To evaluate its safety, various studies involving rodents such as rats, mice, and hamsters have examined the potential hepatotoxic, genotoxic, immunotoxic, and reproductive toxicities of *P. nigrum* L., often through exposure to clinically relevant acute doses. The estimated oral LD_{50} was found to be over 5 g/kg, while the intraperitoneal (ip) LD_{50} of *P. nigrum* was reported as 3.714 g/kg[122]. Piperine, the principal bioactive component of black pepper and widely used as a nutraceutical, has been shown to pose health risks when consumed in excessive amounts. According to subacute toxicity assessments, piperine is non-toxic at doses up to 100 mg/kg body weight (b.w.). However, more acute toxicity data report the median Lethal Dose (LD_{50}) for a single Intravenous (IV) administration in adult mice to be 15.1 mg/kg b.w., while oral LD_{50} values are 330 mg/kg b.w. for mice and 514 mg/kg b.w. for rats[123].

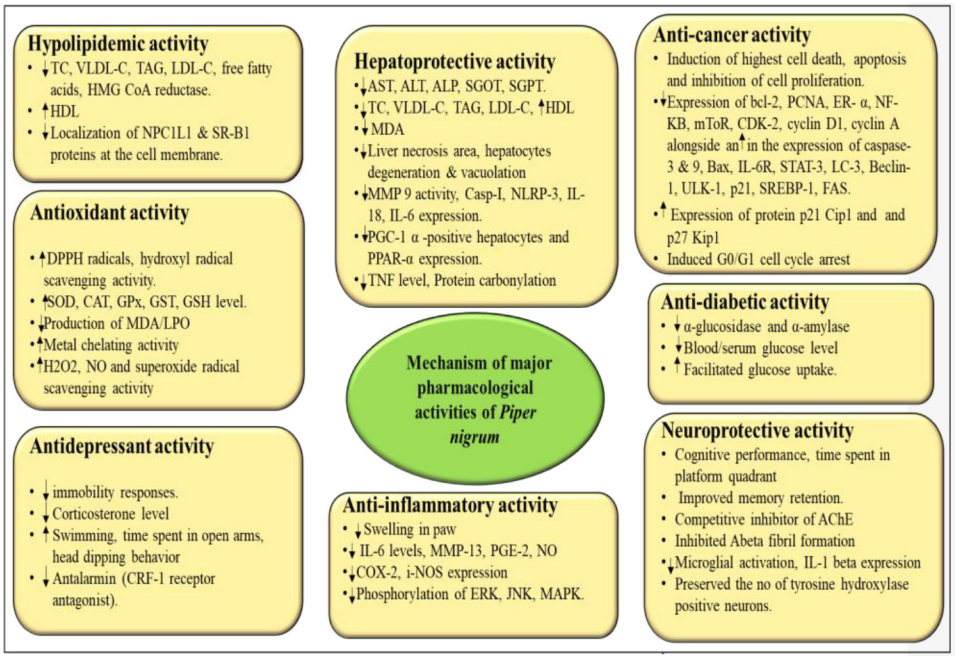


Figure 5. Mechanisms of Major pharmacological activities.

Given that black pepper oleoresins contain approximately 40% piperine, average human intake-based on typical dietary consumption- is estimated to be around 1 picogram per kilogram of body weight per day (pg/kg/day)[124]. Furthermore, the European Food Safety Authority (EFSA) has established a No Observed Adverse Effect Level (NOAEL) for piperine at 5 mg/kg/day[125]. Immunotoxicity studies conducted in Swiss male mice over 5 consecutive days showed that piperine is immunologically safe at 1.12 mg/kg b.w., supporting this dose as a NOAEL[126].

Reproductive toxicity evaluations also suggest that piperine is safe at low doses; administration of up to 75 mg/kg b.w. did not adversely affect male reproductive function, including germ cells, spermatogenesis, and epididymis enzyme activity[127,128].

10. Conclusion

Piper nigrum is a pharmacologically versatile medicinal plant with a rich ethnobotanical heritage and significant modern therapeutic relevance. Its diverse bioactive constituents, particularly piperine, are responsible for a wide array of pharmacological activities, including antidiabetic, antioxidant, anticancer, antimicrobial, and neuroprotective effects, among others. This review not only highlights these therapeutic properties but also elucidates the underlying mechanisms of action, offering insights into how these compounds interact at molecular and cellular levels to produce pharmacological effects. Despite its promising potential, there remains a need for more extensive toxicological assessments and well-designed clinical trials to confirm its efficacy and safety in human populations. Continued research focusing on mechanistic pathways, standardized formulations, and translational studies will be essential to fully harness the therapeutic value of *P. nigrum* in evidence-based medicine.

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12. Author Contribution

AJ: Conceptualization, writing original draft, review and editing, visualization. TJ: Review and editing. GSB: editing. RNJ: Writing original draft, review and editing. All authors have read and agreed to the published version of the manuscript.

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