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REVIEW

Piperine: A review of its biological effects

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Medicinal plants have been used for years as a source of food, spices, and, in traditional medicine, as a remedy to numerous diseases. *Piper nigrum*, belonging to the family *Piperaceae* is one of the most widely used spices all over the world. It has a distinct sharp flavor attributed to the presence of the phytochemical, piperine. Apart from its use as a spice, *P. nigrum* is frequently used for medicinal, preservation, and perfumery purposes. Black pepper contains 2–7.4% of piperine, varying in content is associated with the pepper plant. Piperine displays numerous pharmacological effects such as antiproliferative, antitumor, antiangiogenesis, antioxidant, antidiabetic, anti-obesity, cardioprotective, antimicrobial, antiaging, and immunomodulatory effects in various in vitro and in vivo experimental trials. Furthermore, piperine has also been documented for its hepatoprotective, anti-allergic, anti-inflammatory, and neuroprotective properties. This review highlights and discusses the medicinal and health-promoting effects of piperine, along with possible mechanisms of its action in health promotion and disease prevention. In addition, the present review summarizes the recent literature related to piperine as a therapeutic agent against several diseases.

KEYWORDS

black pepper, cancer prevention, metabolic syndromes, *Piper nigrum*, piperine

1 | INTRODUCTION

In recent years, functional compounds from food sources have attracted much attention owing to their disease prevention and health-promoting benefits (Ul-Haq et al., 2019). In this context, black pepper (*Piper nigrum*), belonging to the family *Piperaceae*, has drawn significant attention due to its rich phytochemistry and bioactivity (Zadorozhna, Tataranni, & Mangieri, 2019). It is cultivated in tropical regions of Indonesia, Brazil, and India. In this respect, the popularity of peppercorns is due to the presence of flavoring compounds, which possess hot and pungent characters. Black pepper is a widely used spice around the globe in various types of sauces and other culinary items like meat products. Principally, black pepper contains piperine, which is an alkaloid with multiple health benefits (Acharya, Momin, & Gajjar, 2012; Ahmad et al., 2012).

Chemically, piperine (Figure 1) is an alkaloid principally isolated from the plant, *P. nigrum*, and Piper. This compound has attracted the attention of medicinal chemists and health professionals due to its numerous benefits including antioxidant, antitumor, antihypertensive, anti-asthmatics, analgesic, antipyretic, anti-diarrheal, anti-inflammatory, anxiolytic, antispasmodic, hepato-protective, antidepressant, antibacterial, immunomodulatory, antifungal, antiapoptotic, antithyroid, antimutagenic, antimetastatic, and anti-spermatogenic (Smilkov et al., 2019). It additionally inhibits various metabolizing enzymes, thus increasing the oral bioavailability of multiple drugs, nutrients, and vaccines. Furthermore, it boosts the cognitive actions and fertility as well (Wattanathorn, Chonpathompikunlert, Muchimapura, Priprem, & Tankamnerdthai, 2008). It has also been indicated that piperine facilitates the digestion process via stimulation of intestinal and pancreatic enzymes (Ahmad et al., 2012).

Piperine is isolated from several members of the *Piperaceae* family including *P. nigrum* (Kanaki, Dave, Padh, & Rajani, 2008), *Piper longum* (Mohapatra & Basak, 2015), *Piper chaba* (Khan, 2015; Rameshkumar, Aravind, & Mathew, 2011), *Piper guineense* (Juliani et al., 2013), and *Piper sarmentosum* (Hussain, Ismail, Sadikun, & Ibrahim, 2009) as listed in Table 1. Plants of this family are also prominent sources of other

bioactive compounds such as flavonoids, phenolics, amides, alkaloids, steroids, neolignans, lignans, chalcones, terpenes, and various other phytochemicals. These plants exhibit numerous pharmacological activities due to the presence of phytochemicals. Research findings showed the presence of three geometrical isomers of piperine (Figure 1): isopiperine, isochavicine, and chavicine (Ahmad et al., 2012). Owing to the numerous bioactivities and pharmacological effects of piperine, it has been used in traditional medicines to alleviate various illnesses as antiseptic, digestion improvement, diuretic, antibacterial, and insecticidal (Meghwal & Goswami, 2013). Based on studies related to nutraceutical properties of piperine, various mechanisms have been proposed to understand its therapeutic effects.

Different reviews have appeared in the literature dealing with different therapeutic aspects and health perspectives of piperine. In this context, Acharya et al. (2012) published a review that dealt with piperine as an absorption enhancer and a potent inhibitor of drug metabolism. Similarly, a recent review by Christodoulou, Tchoumtchoua, Skaltsounis, Scorilas, and Halabalaki (2019) discussed concepts on the anti-diabetic effect of certain alkaloids, including piperine, with special reference to their molecular targets throughout the insulin-signaling pathway. In addition, reviews related to the anti-tuberculosis (Hegeto et al., 2019), autophagy regulators (Liang et al., 2019), chemoprevention, and anticancer (Mokbel, Wazir, & Mokbel, 2019; Zadorozhna et al., 2019) effects of piperine have been published. Furthermore, Joshi, Shrestha, and Adhikari (2018) published a review that aimed to provide the literature on recent advancement of the chemistry, pharmacognosy, pharmacological activities of piper, including new piperine-based formulations and other general use of *P. nigrum*. Based on the preceding discussion, this review focuses on the present knowledge related to the effects of piperine in preventing and/or treating different diseases, with emphasis on the mechanism of its action. In addition, this review summarizes the different bioactive properties of piperine and discusses its use as a bio-enhancer when combined with other nutraceutical agents. For this purpose, recent relevant references pertaining to the bioactivity and uses of piperine as a chemotherapeutic agent have been obtained from different databases and are compiled herein.

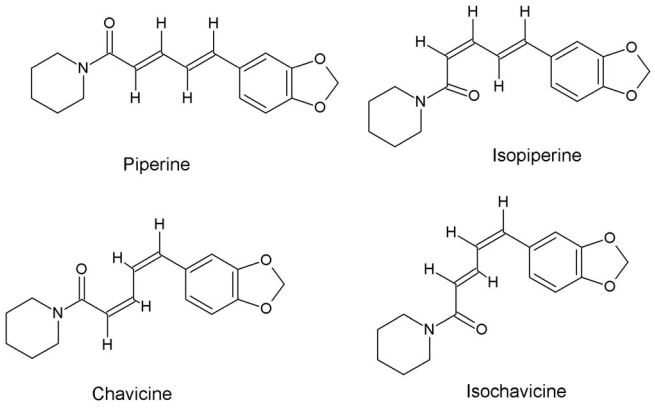

FIGURE 1 Structures of piperine and its isomers

2 | ABSORPTION AND METABOLISM

Absorption and metabolic transformations of piperine have been extensively studied to monitor its possible effects against various lifestyle-related disorders. Piperine given to male albino rats via gavage or intraperitoneal injection at a dose of 170 and 85 mg/kg, respectively, was absorbed (97%) and found to be independent of the mode of delivery of the administered dose. However, 3% of the dose given was excreted in feces as piperine with no traces in the urine. Furthermore, it was reported that 44–63% of piperine disappeared from the mucosal side when the everted sacs of rats' intestines were provided with 100–1,000 μg of piperine where maximum absorption (63%) was achieved (800 μg/10 ml). In addition, it has been demonstrated that the absolute amounts of absorbed piperine were comparatively higher as compared to its closer structural spice counterparts, such as curcumin (Suresh, Mahesha, Rao, & Srinivasan, 2007). Nevertheless, recent reports indicated that nano-encapsulation and resulting piperine-loaded nanoparticles enhance the bioavailability of piperine via oral administration (Ren et al., 2019; Zafar, Jahan, & Bhatti, 2019).

Interestingly, piperine does not undergo any metabolic alterations during absorption as it had been found in both intestinal tissues and serosal fluid, which supports the evidence that it remains unchanged during the absorption process. Moreover, higher absorption of

TABLE 1 Some plants containing piperine

Name of plant	Part of plant	Piperine content (%)	Reference
Piper nigrum	Fruit	1.7–7.4	(Kanaki et al., 2008)
Piper longum	Spikes and roots	5–9	(Mohapatra & Basak, 2015)
	Fruit	0.03	(Rameshkumar et al., 2011)
Piper chaba	Fruit	0.95–1.32	(Khan, 2015; Rameshkumar et al., 2011)
Piper guineense	Fruit	0.23–1.1	(Juliani et al., 2013)
Piper sarmentosum	Roots	0.20	(Hussain et al., 2009)
	Stem	1.59	
	Leaf	0.104	
	Fruit	2.75	

piperine was observed when it was mixed with micelles, which led to a significant increase in intestinal absorption as depicted by an in vitro everted intestinal model (Suresh & Srinivasan, 2007). In addition, research findings revealed that the passage of piperine can be tracked, and the highest concentration was found in the stomach and small intestine after 6 hr of exposure; from 30 min to 24 hr, only traces of piperine were found in serum, spleen, and kidney. It was also found that higher amounts of piperine were detected in the liver when the dose was administered via intraperitoneal injection as compared to an orally administered dose. Furthermore, major steps for piperine decomposition involves glucuronidation and sulfation, which can be correlated with the scission products of methylenedioxy group of piperine, as indicated by the increased excretion of conjugated sulfates, uronic acids, and phenols. Piperic acid was the major metabolite detected in the bile after 6 hr of oral administration of piperine (170 mg/kg), whereas vanillic acid, piperonal, piperonyl alcohol, and piperonylic acid were found in the urine of rats after 0–96 hr. Moreover, absorption dynamics of piperine, using everted intestinal sacs incubated without Na^+ salts and cycloheximide treatment, showed that piperine is quickly absorbed, possibly due to a nonpolar molecule across the intestinal barrier as evident from absorption rate, clearance, half-life, and apparent permeability coefficient (Bajad, Coumar, Khajuria, Suri, & Bedi, 2003). It was further suggested that piperine forms a nonpolar complex with drugs and solutes, which may promote permeability while modulating membrane dynamics via easy partitioning. After intestinal absorption, the transport of piperine may be assisted by serum albumin owing to its water-insoluble nature as revealed by the steady-state and time-resolved fluorescence techniques. The binding constant was found to be $0.5 \times 10^5\ M^{-1}$ for the interaction of piperine with human serum albumin. It was also suggested that piperine is bound to subdomain-IB of the serum albumin, which is a significant factor in understanding the transport of piperine in blood under physiological conditions (Suresh et al., 2007).

Piperine is known to enhance the biological effects of numerous therapeutically important nutrients and drugs. It increases the biological availability of nutrients and drugs via promoting absorption by various mechanisms. Recently, Cui and coworkers demonstrated that piperine inactivates cytochrome P450 (CYP) 3A (CYP3A), which plays a critical role in drug metabolism (Cui et al., 2020). It, in addition, enhances the anti-inflammatory effects when combined with resveratrol (Pannu & Bhatnagar, 2019). Piperine also modulates the membrane dynamics and increases the absorption site permeability. Furthermore, piperine enhances the serum half-life of coenzyme Q10 and beta-carotene that increases their contact time and efficacy. In contrast, it lowers the metabolism of various drugs via inhibition of multiple enzymes, such as UDP-glucuronyl transferase, UDP-glucose dehydrogenase, NADPH cytochrome, CYP3A4, cytochrome BS, and aryl hydrocarbon hydroxylase (AAH). Inhibition of these enzymes by piperine increases the bioavailability of various compounds such as ciprofloxacin, norfloxacin, metronidazole, oxytetracycline, nimesulide, pentobarbitone, phenytoin, resveratrol, beta-carotene, curcumin, gallic acid, tiferron, nevirapine, and sparteine (Acharya et al., 2012). Briefly, piperine may provide significant benefits only when it is better absorbed and transported to the host cells. In this regard, novel delivery systems like nanoparticles may be designed for potentiating the beneficial effects of piperine. Depicted in Figure 2 are absorption and metabolism routes of piperine.

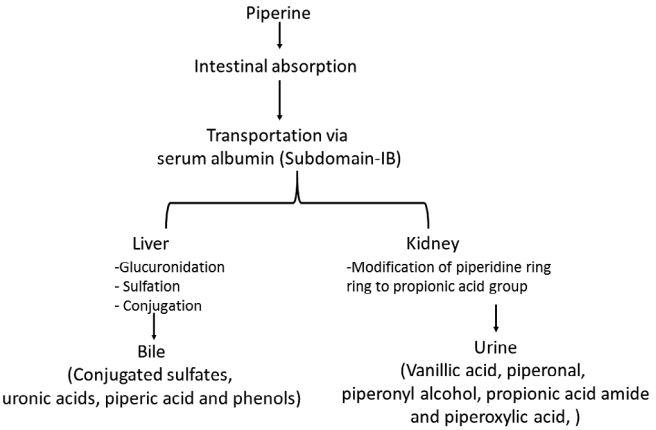

FIGURE 2 Absorption and metabolism routes of piperine

3 | TOXICOLOGICAL INSIGHTS OF PIPERINE

The primary route of exposure to piperine in humans is through diet. Thus, exposure to this compound may significantly vary depending upon one's dietary pattern and net consumption of piperine-containing diet. In Asian countries, a number of food items prepared at home or obtained from commercial bakeries, food chains, or local vendors, which consist of spices including black pepper as an integral part to introduce rich taste to the product. Recently, it was reported that piperine consists of 5.36% of black pepper on a dry weight basis (Morsy & Abd El-Salam, 2017); however, in foods and drinks, the content of piperine may vary from 0.4 to 6 ppm in candies, and to 640 ppm in baked products (Smilkov et al., 2019). Considering the piperine percentage in black pepper oleoresins as 40%, the human exposure to this compound can be estimated by calculating the amount of black pepper being consumed through different food products. Based on this approach, it was estimated that a person consumes about 1 pg kg^{-1} day^{-1} of piperine (Burdock, 2010). Furthermore, the no observed adverse effects level (NOAEL) of piperine has been established to be 5 mg kg^{-1} day^{-1} (EFSA Panel on Food Contact Materials & Aids, 2015). Therefore, regular consumption of black pepper in different foods may not cause any toxic effects, rather it may show irritant effects if it is consumed in higher amounts than normal.

Piperine as a nutraceutical agent can show negative impacts on the body if consumed in high amounts. For this purpose, tests for hepatotoxic, genotoxic, immune-toxic, and negative effects on the reproductive system have been conducted in studies involving rats, mice, or hamsters by exposing them to acute clinical doses of piperine. In this respect, subacute toxicity tests showed that piperine is nontoxic up to a dose of 100 mg/kg b.w. However, it was noticed that LD_{50}

value for a single intravenous (iv) administration was 15.1 mg/kg b.w. for adult mice, whereas oral doses of 330 and 514 mg/kg b.w. were reported as LD_{50} values for mice and rats, respectively (Piyachaturawat, Glinsukon, & Toskulkao, 1983). On the other hand, piperine administration has been linked with decreased serum protein, whereas elevated aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels are signs of a considerable liver damage in albino rats (Rao et al., 2015). Nonetheless, other studies have shown the protective role of piperine against liver damage (Choi et al., 2013; Sethiya, Shah, Rajpara, Nagar, & Mishra, 2015).

In genotoxicity tests, piperine has shown nontoxic effects, and was found to suppress the formation of micronucleus induced by benzo[*a*]pyrene and cyclophosphamide in mice (Selvendiran, Padmavathi, Magesh, & Sakthisekaran, 2005; Selvendiran, Singh, & Sakthisekaran, 2006). However, various studies have shown different results where a conflict may be observed between in vitro and in vivo results when high oral doses of piperine are administered. In this context, Thiel et al. (2014) conducted an experiment using in vivo (mice) and in vitro (Chinese hamster ovarian cells) studies and found that piperine is non-genotoxic. In addition, these researchers added mechanistic endpoints, such as core body temperature, organ weights, erythropoietin levels, and hematological indicators, to their study, and concluded that piperine is not genotoxic. Earlier, in vivo trials have shown that piperine increases the binding tendency of aflatoxin B1 to the calf thymus DNA. Nevertheless, findings showed that it is safe as feed additive due to its protective role against aflatoxin-induced genotoxicity (Allameh et al., 1992).

In reproductive toxicity studies, low doses (up to 75 mg/kg b.w.) of piperine did not cause any negative effects on reproductive functions and the male germ cells, spermatogenesis, and epididymis enzymes. However, higher doses caused significant reduction in epididymis enzymatic functions, sialic levels, and development of testis in pubertal rats (Chen et al., 2018; D'cruz & Mathur, 2005; Daware, Mujumdar, & Ghaskadbi, 2000). In an earlier report, researchers observed a partial to severe degeneration of germ cells when albino rats were fed with 5 and 10 mg/kg b.w. doses for 30 days, respectively. Furthermore, the dose of 10 mg severely affected the structural changes in seminiferous tubular and Leydig cell nuclear diameter alongside desquamation of spermatids and spermatocytes in rats. Moreover, caput and cauda epididymis sperm concentrations were significantly lowered (Malini, Manimaran, Arunakaran, Aruldhas, & Govindarajulu, 1999).

As far as the immunotoxicity trials are considered, piperine was tested for five consecutive days at doses of 1.12, 2.25, and 4.5 mg/kg b.w. in *Swiss* male mice. The results showed no explicit toxic effect and normal gain in liver weight. In addition, the results indicated that piperine is immunologically safe at 1.12 mg/kg b.w., which can be established as NOAEL dose. At higher doses, negative effects, such as suppression of mitogenic response of B-lymphocytes and decrease in primary antibody in serum and antibody-forming cells, were observed (Dogra, Khanna, & Shanker, 2004). Other reports have also indicated immunomodulatory functions and protective effects of piperine against cypermethrin (Sankar & Ramya, 2017), cadmium (Pathak & Khandelwal, 2007; Pathak & Khandelwal, 2008; Pathak & Khandelwal, 2009), and deltamethrin-induced immuno-toxicities (Kumar, Sasmal, & Sharma, 2015). One of the constraints to using piperine in pharmaceutical applications is its lipophilic nature and being insoluble in water (Rad & Hoskin, 2020). Thus, its bio-absorption, metabolism, and toxic effects may vary based on the delivery medium. Although comprehensive studies have been conducted to establish the safe limits of piperine administration for pharmaceutical benefits, research on consumption patterns is still needed to establish concrete grounds for post-consumption effects of piperine taken through diets by humans.

4 | HEALTH PERSPECTIVES

A plethora of scientific evidences are available on the various health effects of piperine. A detailed discussion about the documented activities related to the health-promoting perspectives of piperine and its potential against different diseases and disorders (Figure 3) along with the mechanisms of action are shown in Table 2. Below are details about the documented activities of piperine against different diseases and disorders.

4.1 | Anticancer

Cancer is a dreadful disease causing thousands of deaths per year and is the second leading cause of death worldwide. Chemotherapy remains an important option for the treatment of different cancers, although resistance, toxicity, and mutation of targets are major causes of chemotherapy's failure (Tiwari, Sodani, Dai, Ashby, & Chen, 2011). Therefore, more research is necessary in the area of discovery and development of novel anticancer agents that can circumvent these causes of chemotherapeutic failures. Undoubtedly, anticancer agents from natural origins are endorsed for clinical trials these days (Newman & Cragg, 2014). In this context, the anticancer effect of numerous natural compounds, including piperine, was extensively

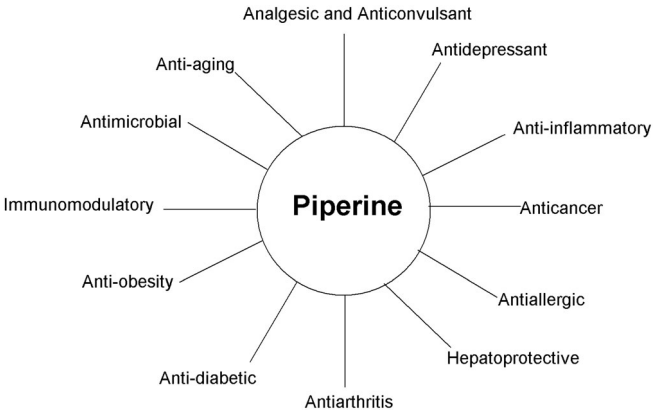

FIGURE 3 Health perspectives of piperine

TABLE 2 Piperine and its health perspectives

Disorders	Mechanisms	References
Cancer insurgence	Lowers the tumor growth and elevates survival time.	(De Souza Grinevicius et al., 2016)
	Exhibits cell cycle arrest and apoptotic cell death.	
	Increases the expressions of Bax and p53.	
	Inhibits Bcl-xL and cyclin A levels	
	Causes reduction in levels of lipid peroxidation and carbonyl proteins.	
	Downregulates the E-cadherin (E-cad), estrogen receptor (ER), matrix metalloproteinase 2 (MMP-2), matrix metalloproteinase 9 (MMP-9), vascular endothelial growth factor (VEGF) levels, and c-Myc.	(Dong, Huihui, & Li, 2015)
	Impairs IL-8 secretion and suppresses *H. pylori* protease which leads to reduction of E-cadherin cleavage and β-catenin expression	(Tharmalingam et al., 2016)
Diabetes mellitus	Decreases blood sugar level and increases the insulin secretion	(Kaur, Invally, & Chintamaneni, 2016)
	Reverses the HFD induced changes in adiposity index, blood pressure, plasma levels of glucose, insulin resistance, leptin, and adiponectin level.	(BrahmaNaidu et al., 2014)
	Decreases the alanine and aspartate aminotransferases and alkaline phosphatase, and kidney (urinary protein) dysfunction	(Arcaro et al., 2014)
	Decreases NLRP3 inflammasome and thioredoxin-interacting protein (TXNIP) expression	(Atal, Atal, Vyas, & Phadnis, 2016; Kharbanda et al., 2016; Samra et al., 2016)
	Lowers the increased IL-1β, TNF-α levels and NF-κB	
	Decreases blood glucose, serum creatinine, blood urea nitrogen, malondialdehyde, proteinuria, and kidney weight	
Obesity	Prevents from the HFD induced changes in body weight, body composition, fat percentage, adiposity index, blood pressure, leptin, adiponectin, plasma, and tissue lipid profiles.	(BrahmaNaidu et al., 2014)
	Protects from the changes in the activities of lipase, amylase, and lipid metabolic marker enzymes such as HMG-CoA reductase, fatty acid synthase (FAS), carnitine palmitoyltransferase (CPT), lecithin-cholesterol acyl transferase (LCAT), acetyl-CoA carboxylase (ACC), and lipoprotein lipase	
	Reduces the mRNA expression of the master adipogenic transcription factors, SREBP-1c, and C/EBPβ	(Park et al., 2012)
	Down-regulates the mRNA levels of PPARγ target genes, and represses the rosiglitazone-induced PPARγ transcriptional activity.	
	Decreases oxidative stress and inflammation.	(Diwan, Poudyal, & Brown, 2013)
	Shows improvement in glucose tolerance, liver functions. And reactivity of aortic rings.	

(Continues)

TABLE 2 (Continued)

Disorders	Mechanisms	References
Cardiovascular diseases	Protects from the reduction levels of pyruvate dehydrogenase and the Kreb's cycle enzymes.	(Dutta et al., 2014)
	Alters mitochondrial morphology, mitochondrial swelling, di-tyrosine level, and mitochondrial DNA damage.	
	Attenuates the proliferation of VSMCs by increasing the expression of p27(kip1) and regulating the mRNA expression of cell cycle enzymes (cyclin D, cyclin E, and PCNA).	(Hlavackova et al., 2010; Lee, Lee, Park, Kim, & Hong, 2015)
	Decreases the phosphorylation of extracellular signal-regulated kinase (ERK)1/2).	
	Inhibits cell migration, production of reactive oxygen species (ROS), and phosphorylation of the p38 mitogen-activated protein kinase (MAPK).	
	Increases high-density lipoprotein, lecithin-cholesterol acyltransferase (LCAT), protein expression, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), CYP7A1, and LDL receptor (LDLR) mRNA	(Bao, Bai, & Borijihan, 2012; Mair et al., 2015)
	Prevents from abnormalities of the cardiac action potential (AP)	(Liu et al., 2014)
Aging	Attenuates MPTP-induced deficits in motor coordination and cognitive functioning.	(Yang, Chen, Liu, & Qu, 2015)
	Protects from MPTP-induced decrease in the number of tyrosine hydroxylase-positive cells.	
	Lowers the number of cytokine IL-1β and maintains the balance of Bcl-2/Bax ratio.	
	Diminishes the cytochrome-c release from mitochondria and reduces caspase-3 and caspase-9 activation.	(Elnaggar, Etman, Abdelmonsif, & Abdallah, 2015; Shrivastava et al., 2013)
	Reduces contralateral rotations and improves the motor coordination and balance behavior.	
	Enhances the acetylcholinesterase, immobility, and plaques and tangles	(Yusuf, Khan, Khan, & Ahmed, 2013)
Allergy	Inhibits the expression of cytokines, and the release of both β-hexosaminidase and histamine.	(Huang et al., 2014)
	Lowers the levels of intracellular Ca^{2+}	
	Suppresses the mRNA expression levels of IL-4, IL-13, and TNF-α	
	Inhibits immunoglobulin (Ig) E-mediated signaling pathways, including the phosphorylation of Lyn, p38, Erk, and Ras.	
	Reduces the expression of IL-6, IL-1β, and IgE.	(Aswar, Shintre, Chepurwar, & Aswar, 2015)
	Inhibits the infiltration of eosinophils and hyperplasia.	
	Reduces MSD and paw edema.	

(Continues)

TABLE 2 (Continued)

Disorders	Mechanisms	References
Immune dysfunction	Prevents from alteration in apoptosis (mitochondrial membrane potential, caspase-3 activity, phosphatidylserine externalization, apoptotic DNA, and intranucleosomal DNA fragmentation), T- and B-cell phenotypes, and cytokine release	(Pathak & Khandelwal, 2009)
	Decreases ROS and caspase-3 activation	(Kumar et al., 2015)
	Restores cytokines levels in deltamethrin (DLM) induced rodents	
Inflammation	Causes reduction in overexpression of IL-1β, TNF-α, and IL-6, and enhancement in IL-10 expression	(Zhai et al., 2016)
	Causes reduction of TLR-2 and TLR-4 expressions that participate in inflammation.	
	Inhibits NF-κB and MAPKs, p65, I-κB, ERK, p38, and JNK levels	
	Lowers the oxido-nitrosative stress and malondialdehyde, nitrite	(Jangra et al., 2016)
	Shows reduction in pro-inflammatory cytokines level (IL-1β and TNF-α)	
Hepatic disorders	Decreases the levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total protein.	(Sethiya et al., 2015)
	Significantly increases the plasma adiponectin levels.	(Choi et al., 2013; Sehgal, Kumar, Jain, & Dhawan, 2013)
	Lowers the expressions of lipogenic target genes and increases the expression of carnitine palmitoyl transferase 1 (CPT1) gene.	
	Lowers the phosphorylation of insulin receptor substrate-1 (IRS-1)	

studied, and several research papers and reviews have appeared in the past few years. These articles support the use of natural compounds as chemopreventive and anticancer agents (Mokbel et al., 2019; Newman & Cragg, 2014; Tiwari et al., 2011).

Piperine has been recognized as a potential autophagy regulating anticancer agent. It showed excellent in vivo antitumor activities, and could be a potential drug candidate for antitumor therapy (Liang et al., 2019). Recent research indicated that piperine has been used as a sole agent and in combination with other drugs to boost the anticancer effects and effectively manage the carcinogenesis. Co-treatment with docetaxel (DTX) and piperine exerted synergistic effect, which augmented the cytotoxicity and improved the anticancer activity in HepG2 cell lines compared to free DTX (Ding et al., 2020). Recently, the role of piperine in prevention of cancer has been extensively discussed based on various relevant molecular and cellular mechanisms underlying the chemopreventive action of this natural alkaloid (Zadorozhna et al., 2019). In this respect, Yoo and coworkers have investigated the anticancer effects of piperine against human melanoma cells. These researchers found that piperine inhibits the growth of human melanoma cells through a mechanism that involves induction of apoptosis via the suppression of tumor growth of human melanoma cells and tumor xenograft models (Yoo et al., 2019).

In Ehrlich ascites carcinoma-bearing mice, *P. nigrum* ethanol extract (rich in piperamides) decreased the growth of tumor, increased survival time, caused cell cycle arrest, and induced apoptotic cell death. It also elevated the expressions of p53 and Bax and suppressed cyclin A and Bcl-xL expression. Furthermore, piperine induced oxidative stress verified by an increase in lipid peroxidation and carbonyl proteins content, and increased the activities of superoxide dismutase, catalase, and glutathione reductase. These results suggest that *P. nigrum* ethanol extract exhibit cytotoxic and antiproliferative effect on MCF-7 cells and in vivo antitumor effect possibly due to overproduction of reactive oxygen species (ROS) that causes oxidative stress, which eventually triggers apoptosis (De Souza Grinevicius et al., 2016). In a similar fashion, Tharmalingam and coworkers demonstrated that piperine diminishes IL-8 secretion in gastric epithelial cells infected by *Helicobacter pylori*. This could be due to the dwindling motility of *H. pylori*, which weakens its adhesion to gastric epithelial cells. This weakened adhesion lowered the toxin entry, resulting in

low secretion of IL-8. In addition, *H. pylori* protease was suppressed by piperine, leading to reduction of β-catenin expression and E-cadherin cleavage; this diminishes β-catenin translocation into the nucleus, thus lowering oncogenic risk (Tharmalingam et al., 2016).

Researchers have shown that piperine suppresses proliferation in N-nitroso-N-methylurea induced-mammary tumorigenesis rats and breast cancer cell lines ZR-75-1 and MCF-7 through multiple mechanisms, including down-regulating the E-cadherin (E-cad), estrogen receptor (ER), matrix metalloproteinases 2 and 9 (MMP-2 and 9), vascular endothelial growth factor (VEGF) levels, and c-Myc and up-regulating p53. In MCF-7 cells, it lowered the protein levels of c-Myc, E-cad, and VEGF. Furthermore, reduction of tumor size, suppression of cell proliferation, tumor cell invasion, migration, angiogenesis, and induction of cell cycle arrest in breast cancer lines indicate the anti-cancer and cancer prevention effects of piperine (Deng, Sriwiriyajan, Tedasen, Hiransai, & Graidist, 2016). Similarly, the protective role of piperine (from 20 to 100 μg/ml) against proliferation of HeLa cell lines via inhibiting the epidermal growth factor receptor (EGFR) tyrosine kinase-enzyme was also reported (Deepak, Kruger, Joubert, & Coetzee, 2015; Paarakh, Sreeram, & Ganapathy, 2015). In addition, a study conducted by Sriwiriyajan et al. (2016) concluded that piperine exerts an inhibitory effect on the growth of luminal-like breast cancer cells in female Sprague Dawley rats via inducing apoptosis (Sriwiriyajan et al., 2016). Along this line, the delivery module can significantly affect the bioactive properties of piperine. A recent investigation showed that piperine, being lipophilic, may not deliver significant cancer prevention properties, hence the use of thin-film hydration nanoparticles was better than a single emulsion solvent extraction. Furthermore, piperine-loaded nanoparticles significantly inhibited the growth of triple-negative breast cancer (TNBC) cells and induced apoptosis in cancer cells while sparing normal fibroblasts (Rad & Hoskin, 2020).

Interestingly, Hatab and colleagues have recently conducted a study that involved hepatocellular carcinoma (HCC) patients. Each patient was subjected to a treatment regime consisting of piperine with curcumin and taurine. The results revealed that this combined treatment caused a significant decrease in the levels of serum IL-10, and miR-21, and a non-significant upregulation of serum miR-141 expression level, thus increasing the overall survival rate. (Hatab et al., 2019). Previously, curcumin, in combination with piperine, suppressed the diethylnitrosamine (DENA)-induced hepatocellular carcinoma (HCC) in rats by supplying DENA (0.01%) in drinking water for 10 weeks. The DENA-induced HCC rats were then treated with curcumin (100 mg/kg) and curcumin with piperine (20 mg/kg) for 4 weeks. This combined treatment caused significant attenuation in the morphological and biochemical alterations in serum and liver (Patial et al., 2015). In *H. pylori* stimulated AGS gastric cancer cells, research findings indicated that piperine suppresses the infiltration of neutrophils and mononuclear cells. It, in addition, caused reduction of phospho-IκB-α in antrum and mRNA expression of tumor necrosis factor-alpha (TNF-α). Piperine also suppressed the expression of Ifn-γ, IL-1β & 6 and iNOS, whereas *H. pylori* urea and other factors involved in virulence were not significantly attenuated (Katiyar, Muntimadugu, Rafeeqi, Domb, & Khan, 2016; Sattarinezhad, Bordbar, & Fani, 2015; Toyoda et al., 2016).

Zhang and colleagues showed that piperine, in dose- and time-dependent fashion, inhibits the growth of HOS and U2OS cells. By using techniques such as scratch migration assays and transwell chamber tests, these researchers demonstrated that piperine inhibits osteosarcoma cell proliferation through mechanisms that involve G2/M phase cell cycle arrest, and the migration and invasion of HOS and U2OS cells, via increased expression of metalloproteinase (TIMP)-1/−2 tissue inhibitor (TIMP-1/−2) and downregulation of matrix metalloproteinase (MMP-2/−9). These findings suggest that piperine can be a promising therapeutic agent in the treatment of osteosarcoma (Zhang et al., 2015).

In TNBC cells, Greenshields et al. (2015) found that piperine exerts an inhibitory role on the motility and growth of these cells, as well as the hormone-dependent breast cancer cells, without affecting normal mammary epithelial cell growth. Piperine exerted its effect through G2 phase induction of cell cycle, reduction of G1- and G2-associated protein expression, enhancement of p21(Waf1/Cip1) expression, and suppression of survival-promoting Akt activation, thus causing caspase-dependent apoptosis via mitochondrial pathway (Greenshields et al., 2015). Thus, piperine may be useful in the treatment of TNBC by accelerated apoptosis and cell cycle arrest.

One of the important cytokines is interleukin-6 (IL-6) that activates the signal transduction, induces malignancy, and promotes metastasis in tumor cells. Research findings indicated that piperine inhibits the expression of IL-6 induced by IL-1β in a dose-dependent manner. It, in addition, inhibited the action of IL-6 promoter. Furthermore, piperine inhibited IL-1β induced p38 MAPK and STAT3 activation, subsequently blocking IL-6 expression in gastric cancer cells. Moreover, IL-1β-induced invasiveness in gastric cells was partially abrogated upon treatment with piperine (Xia et al., 2015). On the other hand, piperine is known to exhibit anti-inflammatory activity through suppression of cyclooxygenase (COX)-2 gene expression enzyme activity and exhibits antiplatelet activity. Son and coworkers studied the antiplatelet aggregation of piperine and the underlying mechanisms involving arachidonic acid (AA) metabolism. The results suggest that piperine inhibits platelet aggregation by attenuating $cPLA_2$ and TXA_2 synthase activities, rather than through the inhibition of COX-1 activity. However, piperine considerably inhibited lipopolysaccharide-induced generation of prostaglandin (PG)E_2 and PGD_2 in RAW264.7 cells by suppressing the activity of COX-2, without effect on $cPLA_2$ (Son et al., 2014).

Recently, Yaffe and colleagues showed that piperine, at a dose of 75–150 μM, inhibits the growth of several colon cancer cell lines but had little effect on the growth of normal fibroblasts and epithelial cells. It suppressed the growth of HT-29 colon carcinoma via cell cycle arrest at the G1 phase associated with a decrease in cyclin D1 and D3 expression along with their cyclin-dependent kinases-4 and 6. In addition, piperine caused hydroxyl radical production and apoptosis, partially dependent on the production of ROS. In HT-29 cells, treated with piperine, a loss of mitochondrial membrane integrity and reduced apoptosis were also observed. Taken all together, these researchers concluded

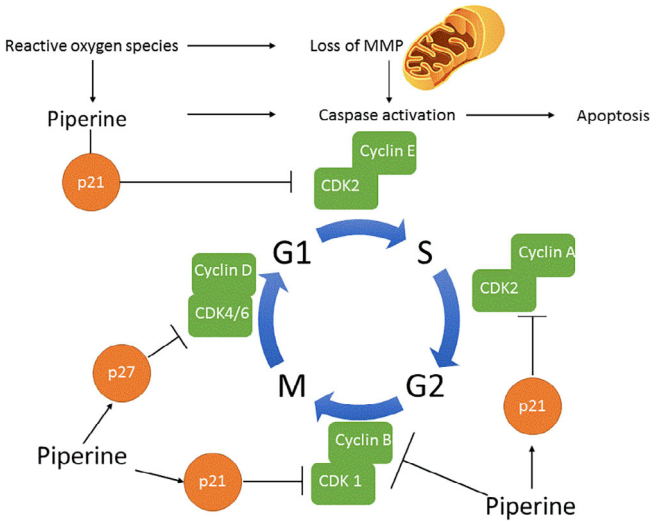

FIGURE 4 Apoptosis and cell cycle arrest mechanism of piperine [Colour figure can be viewed at wileyonlinelibrary.com]

that piperine treatment of HT-29 cells results in cell cycle arrest and endoplasmic reticulum stress-associated apoptosis, suggesting that piperine may be useful in the treatment of colon cancer (Yaffe, Power Coombs, Doucette, Walsh, & Hoskin, 2015). Figure 4 illustrates the apoptosis and cell cycle arrest mechanism of piperine.

4.2 | Antidiabetic

Diabetes mellitus is possibly the world's fastest-growing metabolic disease. Approximately 2.5–7% of the world's population suffer from diabetes mellitus, and is also one of the leading causes of illness and death in the world. Diabetes mellitus is associated with chronic hyperglycemia, caused by reduced utilization of glucose by various tissues, and by the increased release of glucose into the circulation by hepatic gluconeogenesis. It is, in addition, a main risk factor for cardiovascular disease, where diabetic patients can develop heart failure in the absence of hypertension and coronary heart disease, the so-called diabetic cardiomyopathy (Rauf et al., 2017). The use of compounds isolated from medicinal plants as hypoglycemic agents has been gaining momentum worldwide because of their natural origin and fewer side effects as compared to synthetic drugs (Alamgeer et al., 2014). In this respect, numerous plant species possessing hypoglycemic properties are employed to treat diabetes mellitus in the folk medicine of different cultures (Pushparaj, Tan, & Tan, 2000).

Natural alkaloids have been recognized for their beneficial effects to manage diabetes mellitus. This property of alkaloids is perceived as a promising hope for people suffering from diabetic conditions. In addition, recent research findings showed evidence that suggests the ability of some alkaloids to mediate in the insulin-signal transduction pathway, reverse molecular defects resulting in insulin resistance and glucose intolerance, and improve disease complications, in vitro and in vivo (Christodoulou et al., 2019). In this context, piperine promotes glucose uptake in skeletal muscles via ROS-dependent activation of CAMMK/AMPK signaling pathway (Maeda et al., 2018). Treatment of diabetic rats with piperine caused a significant decrease in the concentration of blood sugar and increased insulin secretion (Kaur et al., 2016). It has also been reported that piperine and curcuminoids control the energy metabolism via modulation of adipokines in type 2 diabetes mellitus (Panahi et al., 2017).

In hyperglycemic rats, piperine (30 mg kg^{-1} day^{-1}) significantly lowered NLRP3 inflammasome and thioredoxin-interacting protein (TXNIP) expression in kidneys. It also modulated the elevated levels of inflammatory biomarkers, such as IL-1β, TNF-α, and NF-κB, in addition to modulating levels of various blood parameters, including urea, creatinine, blood glucose, blood urea nitrogen (BUN), and malondialdehydes (MDA). In this regard, MDA are frequently used as markers of oxidative stress, whereas elevated levels of BUN are associated with an increasing risk of cardiovascular and renal conditions (Atal et al., 2016; Kharbanda et al., 2016; Samra et al., 2016). Similarly, an oral intake of piperine (20 mg/kg b.w.) showed promising effects to control hyperglycemia caused by streptozotocin in rats. Glycemic and dyslipidemic biomarkers were positively modified and antioxidant enzymes were upregulated in rats. Furthermore, lipid peroxidation was significantly reduced alongside (Arcaro et al., 2014). Similar findings have also been found by Kumar, Sharma, and Vasudeva (2013) and by Veeresham, Sujatha, and Rani (2012) who observed antihyperlipidemic and antidiabetic effects of piperine in streptozotocin-induced diabetic rats. Similar results were obtained by Atal and coworkers, and by Sama and coworkers who evaluated the effect of piperine on blood glucose level in alloxan-induced diabetic mice. Results revealed a significant blood glucose lowering effect with piperine at a dose of 20 mg/kg per day, suggesting a significant antihyperglycemic activity of this natural compound in subacute cases. (Atal, Agrawal, Vyas, Phadnis, & Rai, 2012; Sama, Nadipelli, Yenumula, Bommineni, & Mullangi, 2012).

4.3 | Anti-obesity

Obesity and type 2 diabetes affect a large fraction of the world's population. This is primarily due to overconsumption of food coupled with a reduction in physical activity. One approach to combat obesity is through healthy lifestyle, low-calorie diet, and increased physical activity, in addition to using pharmaceuticals (Ogden et al. 2015). In this context, Nogara and coworkers have recently developed a method that would treat obesity and type 2 diabetes by increasing the metabolic rate of resting skeletal muscles. These researchers found that piperine shows promising anti-obesity effects and could be a good lead compound for the development of therapies to combat these diseases (Nogara et al., 2016). On the other hand, piperine and curcuminoids have been found to modulate the adipokines in diabetes, which, in turn, regulate the energy homeostasis (Panahi et al., 2017). In addition, research findings showed that treatment of rats with piperine modulates adiposity index and obesity-related

biomarkers alongside antioxidant status of the body. Piperine also demonstrated anti-obesity effects by modifying the metabolic enzyme activities in a dose-dependent manner in diet-induced obesity in rats (BrahmaNaidu et al., 2014).

Park and coworkers examined the anti-adipogenic activity, along with the underlying mechanisms of action of black pepper extract and piperine in 3 T3-L1 preadipocytes cell line. These researchers showed that piperine and the extract strongly inhibit the adipocyte differentiation of 3 T3-L1 cells without affecting cytotoxicity. In addition, piperine attenuated fat cell differentiation through a mechanism that involves the downregulation of peroxisome proliferator-activated receptor-gamma (PPARγ) activity and suppression of PPARγ expression, thus suggesting a potential use of this natural compound in the treatment of obesity-related diseases (Park et al., 2012). Similarly, Diwan and colleagues demonstrated that piperine (30 mg kg^{-1} day^{-1}) given to carbohydrate, high fat (HCHF) diet-fed rats as food supplement (a) caused normalization of the blood pressure, (b) decreased inflammation and oxidative stress, (c) improved glucose tolerance, liver functions, and reactivity of aortic rings, and (d) attenuated cardiac and hepatic inflammatory cell infiltration and fibrosis, and improved liver function. These results suggest that piperine reduces symptoms of human metabolic syndrome in HCHF-fed rats by reducing inflammation and oxidative stress (Diwan et al., 2013). Furthermore, a combination of piperine and curcumin modulated body fat in obese mice under caloric restriction. This combination has the potential to prevent metabolic syndrome (Miyazawa et al., 2018).

In 3 T3-L1 adipocytes and L6 myocytes, research findings indicated that different doses of piperine (50–300 mg kg^{-1} day^{-1}) regulate the expression of lipid metabolism-related proteins and activated the PPARδ protein and the AMP-activated protein kinase (AMPK) signaling. It also decreased body weight gain, fat pad mass, and adipocyte size due to induction of obesity via high-fat diet. In addition, treatment with piperine caused reduction in the concentration of serum cholesterol, leptin, lipase, total lipids, and low-density lipoprotein cholesterol. Piperine also provided protection against non-alcoholic fatty liver by lowering hepatic triglyceride accumulation (Kim, Lee, Jo, & Hwang, 2011). Moreover, piperine (40 mg/kg) significantly decreased the body weight, triglycerides, cholesterol, and very low-density lipoprotein in high-fat diet-fed male Sprague Dawley rats (Shah et al., 2011). Figure 5 is a sketch showing the antidiabetic and anti-obesity effects of piperine.

4.4 | Cardioprotective

Increasing incidences of cardiac disorders attracted the attention of researchers in the search for preventive solution to promote cardiac health and reduce malfunctions. In this respect, various mechanisms have been identified in the cardioprotective role of piperine. Along this line, doxorubicin (DOX)-induced cardiac injury involves oxidative stress, inflammation, and cardiac apoptosis. Treatment of mice with piperine considerably relieved DOX-induced cardiac injury, improved cardiac function, and reduced myocardial oxidative stress, inflammation, and apoptosis. Piperine exerted its effect through a mechanism that involves PPAR-γ activation in mice (Yan et al., 2019). Likewise, PPAR-γ/Akt pathways are involved in the attenuation of pathological cardiac fibrosis when piperine is used as a therapeutic remedy (Ma et al., 2017). Furthermore, Chakraborty, Bhattacharjee, and Kamath (2017) reported on the preventive role of piperine in combination with curcumin against cardiotoxicity arising from cyclophosphamide. They found that curcumin alone could not function as efficiently as when combined with piperine, and the most effective combination was found to be piperine (20 mg/kg) and curcumin (50 mg/kg). This combination exhibited significant cardioprotective effect as compared with curcumin alone (Chakraborty et al., 2017). It also reversed the myocardial ischemia in male Wistar rats via its antioxidant and antidyslipidemic effects (Dhivya et al., 2017). Moreover, the post-piperine treatment showed inhibition of endothelial cells transformation to fibroblast as a potential mechanism to overcome myocardial fibrosis (Li et al., 2019).

Similarly, research by Dutta et al. (2014) revealed that piperine scavenges reactive species, including hydrogen peroxide, superoxide anion free radicals, hydroxyl radicals, and DPPH radicals. This indicates that piperine exerts protection to cardiac mitochondria against

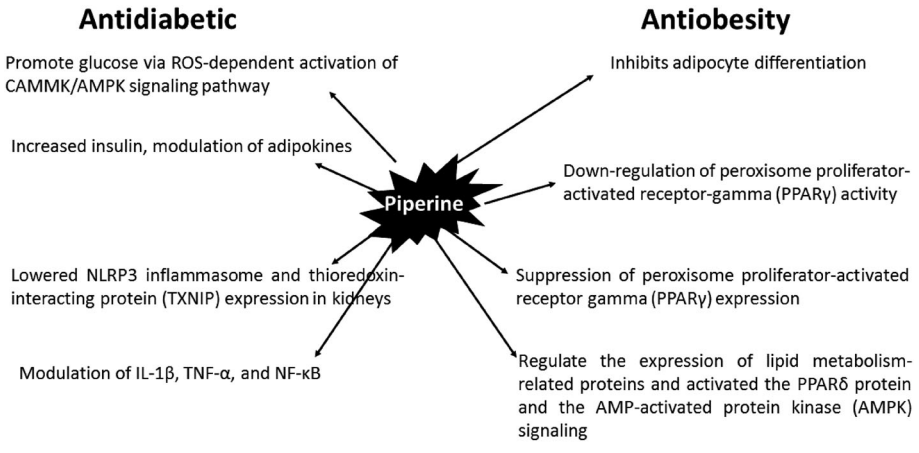

FIGURE 5 Antidiabetic and anti-obesity effects of piperine

copper-ascorbate induced toxic injury through its antioxidant activity. Thus, it may be used in the treatment of diseases associated with mitochondrial oxidative stress, via reduction in protein carbonylation and lipid peroxidation of mitochondrial membrane, enhancement in mitochondrial GSH, and increase in antioxidant enzymes (Dutta et al., 2014). Researchers also showed that piperine may protect ventricular myocytes from oxidative stress damage caused by hydrogen peroxide (H_2O_2), and prevented cardiac action potential (AP) abnormalities and numerous ion currents induced by H_2O_2 in single rabbit left atrial myocyte (Liu et al., 2014).

Several researchers and investigators have reported on the enhancement in the concentration of high-density lipoprotein, lecithin-cholesterol acyltransferase (LCAT), protein expression, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), CYP7A1, and LDL receptor (LDLR) mRNA after treatment of obese rats with piperine (2.5–10 mg/kg) (Bao et al., 2012; Mair et al., 2015). In blood vessels, migration and proliferation of vascular smooth muscle cells (VSMCs) are associated with atherosclerosis and restenosis. Piperine (30–100 μM) attenuated VSMCs proliferation via increasing p27 (kip1) expression, mRNA expression regulation in cell cycle enzymes (cyclin D and E, and PCNA), and decreasing extracellular signal-regulated kinase (ERK)1/2 phosphorylation in a noncytotoxic manner. In addition, piperine lowered cell migration, ROS production, and phosphorylation of p38 MAPK (Hlavackova et al., 2010; Lee et al., 2015).

In a similar fashion, Taqvi and coworkers showed that intravenous administration of piperine (1–10 mg/kg) caused a significant dose-dependent reduction in the mean arterial pressure (MAP) in normotensive rats. Furthermore, piperine inhibited high K^+ (80 mM) precontraction and partially inhibited phenylephrine (PE) in aortic rings, suggesting Ca^{2+} channel blockade (CCB), which was further confirmed when pretreatment of tissues with piperine caused a rightward shift in Ca^{2+} concentration-response curves, similar to verapamil. In Ca^{2+}-free medium, piperine (1–30 μM) exhibited vasoconstrictor effect. In addition, piperine demonstrated endothelium-independent vasodilator effect and was more potent against high K^+ precontraction than PE in rat's aorta. Piperine also inhibited high K^+ precontraction completely in bovine coronary artery model (Taqvi, Shah, & Gilani, 2008). The cardioprotective effects of piperine are shown in Figure 6.

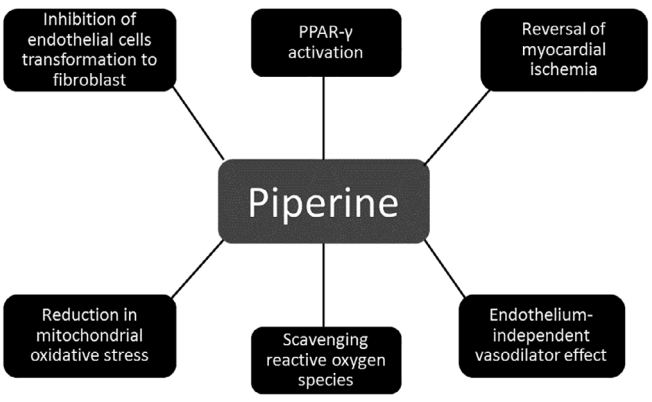

FIGURE 6 Cardioprotective effects of piperine

4.5 | Antiaging

Research findings indicated that piperine can be promising in controlling the effects of aging. Using Parkinson's mouse model, scientists showed that significant attenuation in cognitive function and motor coordination was attained when mice were treated with piperine (10 mg/kg). Furthermore, piperine prevented 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced decreases in the number of tyrosine hydroxylase-positive cells in the substantia nigra. In addition, it reduced activated microglia and cytokine IL-1β expression along with maintaining Bcl-2/Bax balance (Al-Baghdadi, Prater, Van Der Schyf, & Geldenhuys, 2012; Yang et al., 2015).

Recently, Wang and coworkers studied the protective effects of piperine against cognitive impairment in a senescent mouse model induced by D-galactose (D-Gal), along with the underlying mechanisms. These scientists found that piperine ameliorated the neurochemical, neuroinflammatory, and cognitive alterations caused by chronic exposure to galactose. In addition, piperine reversed D-Gal-induced GSK-3β activation through modulating PKC and PI3K/AKT pathways, suggesting that GSK-3β-related signaling might be involved in the benefits of piperine against D-Gal-induced cognitive decline in mice (Wang et al., 2020). Piperine stimulates glutathione levels in rats' striatum, reduced caspase-3 and 9 activation, and diminished release of cytochrome-c from mitochondria along with a reduction in lipid peroxidation induced by 6-hydroxydopamine (6-OHDA). Furthermore, piperine treatment markedly inhibited pro-apoptotic Bax levels, poly(ADP-ribose) polymerase activation, and elevation of Bcl-2 levels. Piperine also caused improvement in motor coordination and balance behavior along with reduction in contralateral rotations. Furthermore, various inflammatory biomarkers have also been controlled when piperine was administered to 6-OHDA-induced Parkinson's rats (Elnaggar et al., 2015; Shrivastava et al., 2013). A study by Yusuf and colleagues revealed that piperine in solid lipid nano-formulation (2 mg/kg) lowers superoxide dismutase, enhanced the acetylcholinesterase, and reduced immobility in Alzheimer's rats (Yusuf et al., 2013). In adult male Wistar rats, orally administrated piperine at a dose of (5–20 mg/kg BW) significantly amended impaired memory and hippocampus neurodegeneration and lowered lipid peroxidation and acetylcholinesterase enzyme (Chonpathompikunlert, Wattanathorn, & Muchimapura, 2010).

4.6 | Antimicrobial

Microbial population, inside and outside the human body, plays an important role in health since a number of these microbes cause diseases in humans. Along this line, many plant secondary metabolites exhibit potent antimicrobial activity against a number of strains. Thus,

different nutraceuticals positively influence the proportions of microbial population and inhibit harmful Bacteroidetes and Firmicutes (Lakes, Richards, & Flythe, 2019). Piperine acts as a potential agent to protect peritoneal macrophages (PM). Piperine-induced increase in mammalian target of rapamycin complex 1 (mTORC1) activity enhanced the production of IL-6 and boosted amino acid transporter, hence promoting amino acid metabolism and further production of cytokine and necrosis factors in bacterial cells. The correlated increase in mTORC1 activity in resident PM inhibited the mTOR signaling pathway. In addition, piperine treatment significantly enhanced the phagocytic ability of resident PM (Pan et al., 2015). In mice model, infected with *Mycobacterium tuberculosis*, piperine activated T cells differentiation into Th-1 subpopulation. Murine splenocytes showed proliferation of T and B cells and enhanced macrophage activation when exposed to piperine. Furthermore, increased secretion of Th-1 cytokines was associated with exposure to piperine. In immune-compromised TB patients, the therapeutic efficacy of rifampicin, an antibiotic used to treat several types of bacterial infections including tuberculosis, can be enhanced by synergistic treatment with piperine as it upregulates the Th-1 immunity (Khameneh et al., 2015; Sharma et al., 2014). Similarly, piperine has proven effective against the Argulus parasite in a study conducted by Kumar et al. (2012).

Mirza and colleagues have examined the effect of a combination of piperine and mupirocin for antimicrobial activity against *Staphylococcus aureus* strains, including methicillin-resistant *S. aureus*. These researchers demonstrated that the combination significantly reduced the minimal inhibitory concentration (MIC) of mupirocin and lowered the mutation frequency, since the inhibition of efflux in wild and mutant strains have been depicted as a possible mechanism of mupirocin activity potentiation by piperine (Mirza, Kumar, Kalia, Zargar, & Khan, 2011). Similarly, piperine exerted strong antimycobacterial activity in a research trial when *M. tuberculosis* and *M. smegmatis* have been exposed to piperine (Verma, Lobkovsky, Gange, Singh, & Prakash, 2011). Piperine significantly decreased the ethidium bromide efflux in *M. smegmatis*, suggesting its ability to inhibit mycobacterial infection (Jin et al., 2011; Sharma et al., 2010).

4.7 | Anti-allergic

With respect to anti-allergic effects, piperine has been found promising in reducing symptomatic allergic responses. A dose-dependent reduction in allergic responses, involving sneezing, redness of nose, and nasal rubbing, has been observed upon treatment with piperine. In addition, piperine caused dose-dependent reduction of histamine, nitric oxide (NO) concentration, and reduced expression of IL-6, IL-1β, and IgE. Furthermore, it exhibited inhibition of eosinophils infiltration and hyperplasia, and reduced paw edema. These results suggest that piperine exhibits immunomodulatory and anti-inflammatory activity, thus providing an effective treatment for allergic rhinitis (Aswar et al., 2015). Other researchers showed that piperine downregulates cytokine mRNA expression and inhibited IgE and necrosis factors that are involved with anti-allergic effects, suggesting that piperine can inhibit antigen-induced allergic reactions that control degranulation (Huang et al., 2014).

Research findings also revealed that piperine ameliorates the chronic asthma induced via ovalbumin in mice when combined with curcumin (Chauhan, Jaiswal, Subhashini, & Singh, 2018). In an asthma-induced model of mice via ovalbumin sensitization and inhalation, oral administration of piperine suppressed airway hyperresponsiveness, airway inflammation, production of histamine, IgE and IL-4 and IL-5, and eosinophil infiltration. It also lowered the polymerase chain reaction (PCR) products for thymus and lung cell chemokine and inflammation, hence reducing allergic effects in asthma-induced mice (Hirata et al., 2008; Kim & Lee, 2009).

4.8 | Immunomodulation

Published scientific research indicates that piperine improves immunological functions (Sunila & Kuttan, 2004). In an animal model consisting of cadmium-induced immunocompromised mice, piperine treatment showed considerable improvement in antioxidant enzymes and alterations in apoptosis. In addition, piperine significantly modulated the altered immune system response of cadmium-induced immunotoxicity in mice, thus suggesting immuno-protective efficacy of piperine (Pathak & Khandelwal, 2009). Similarly, piperine exhibited positive effects against cadmium-induced oxidative stress in cultured human peripheral blood lymphocytes (Verma, Bal, Gupta, Aggarwal, & Yadav, 2018). Furthermore, research by Santos and coworkers showed that the piperine analogue, N-(*p*-nitrophenyl)acetamide piperinoate, exhibits low toxicity and shows antitumor effects by Th1-based immunomodulation (Santos et al., 2018). Moreover, Kumar et al. (2015) indicated that piperine enhances antioxidant function by prevention of glutathione depletion and restoration of cytokine levels. Piperine also enhances cell viability and lowers ROS and caspase-3 activation (Kumar et al., 2015).

4.9 | Anti-inflammatory

Numerous scientific reports pertaining to the anti-inflammatory role of piperine have been published. Zhai and coworkers evaluated the effect and mechanism of piperine on *S. aureus* endometritis in a mouse model. These researchers indicated that piperine could significantly relieve inflammatory injury in *S. aureus* endometritis through various mechanisms. These mechanisms involve (a) effective reduction in IL-1β and IL-6, and TNF-α overexpression, (b) enhancement of the expression of IL-10, (c) lowering of the expression of TLR-2 and TLR-4, and (d) inhibition of NF-κB and MAPKs. Thus, piperine could be a potential anti-inflammatory agent both in endometritis and in other *S. aureus*-induced diseases (Zhai et al., 2016). Findings by Pannu and Bhatnagar (2019) highlighted the combinational effects of piperine with resveratrol in controlling inflammatory responses caused by systemic lupus erythematosus in the murine model. In addition,

piperine controls the inflammatory factors and oxidative damage in cardiomyocytes (Yan et al., 2019).

In lipopolysaccharide (LPS)-induced neurochemical and neurobehavioral deficits in mice hippocampus, recent findings demonstrated that piperine enhances the neuroprotective effect of curcumin against lipopolysaccharide (LPS)-induced neurobehavioral and neurochemical deficits (Jangra et al., 2016). In LPS-induced acute lung injury, piperine diminished myeloperoxidase (MPO) activity and inflammatory cytokine production. Furthermore, lung edema, inflammatory cytokines, and histological lung injuries were significantly attenuated by piperine (Lu, Liu, Li, & Gu, 2016). Similarly, piperine inhibited LPS-induced production of inflammatory factors and catabolic proteases in nucleus pulposus (NP) cells in NP cell culture model. Multiple oxidative stress-related genes and inflammatory factors were inhibited when NP cells were exposed to piperine. It was also observed that these effects were concentration-dependent and were directly related to the dose of piperine provided. Furthermore, piperine reversed the collagen-II and aggrecan gene expression inhibition induced by LPS. It could also inhibit the LPS-mediated phosphorylation of JNK and NF-κB activation (Li, Li, Hu, Xu, & Zhao, 2015).

Research by Hu et al. (2015) showed that piperine significantly increases PXR and CYP3A4 mRNA and protein. Its pre-administration was related to a decrease in the clinical pathology of colitis and histological changes in dextran sulfate sodium (DSS)-treated PXR mice. Similarly, an investigation by Dong et al. (2015) concluded that piperine inhibits alveolar bone loss. It reformed trabecula microstructures in linear fashion related to the dose of the piperine provided. Piperine also downregulated cytokine expressions, MMP-8 and 13 in periodontitis but not TNF-α. Its administration was clearly associated with protection from inflammation, alveolar bone loss, and changes in bone microstructures, as well as degradation of collagen fiber. In acetic acid-induced IBD ulcerative colitis mice model, Gupta, Motiwala, Dumore, Danao, and Ganjare (2015) showed that piperine effectively prevented from shortening of colon length and spleen size enlargement. Piperine administration was effective against harmful effects of acetic acid-induced ulcer via reduction of edema, hemorrhages, and cellular infiltration. In addition, abnormal secretion of pro-inflammatory mediators and inflammatory biomarkers were inhibited when mice were provided with piperine. The effects have been found to be directly linked to the dose of piperine administered (Gupta et al., 2015).

One of the features of piperine involves blockage of IL-2-induced phosphorylation of STAT 3 and 5 without affecting the upstream JAK 1 and 3 phosphorylation. It also inhibits the IL-2 induced phosphorylation of Akt and extracellular signal-regulated kinase 1/2 and suppresses cyclin-dependent kinases and protein phosphatase, indicating the G0/G1 and G2/M cell cycle arrest (Doucette, Greenshields, Liwski, & Hoskin, 2015). Furthermore, piperine administration has been linked to the decreased plasma CRP concentrations and lipid peroxidation markers along with significant improvement in superoxide dismutase activity (Panahi et al., 2015). In SW480 and HT-29 human epithelial-like cells stimulated by LPS, piperine inhibited cell proliferation in a dose-dependent manner. It also attenuated c-Jun N-terminal kinase (JNK) and p38 MAPK signaling; however, it did not affect the critical inflammatory NF-κB (Hou et al., 2015). Pretreatment of RBL-2H3 cells with piperine inhibited IgE-induced activation of type II phosphatidylinositol 4-kinase (s) and suppressed IgE-induced β-hexosaminidase release (Bojjireddy, Sinha, & Subrahmanyam, 2014).

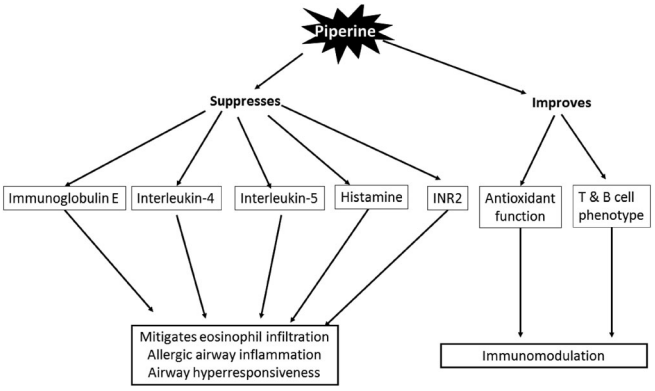

FIGURE 7 Anti-allergic, anti-inflammatory, and immunomodulatory effects of piperine

Inhibition of prostaglandin and nitric oxide (NO) by piperine in LPS-induced inflammatory responses in RAW264.7 cells showed its anti-inflammatory effects via control of TNF-α and gene expression, inducible NO synthase and COX-2. NF-κB inhibition is attained by suppression of degradation of inhibitor-κB proteins and p65 subunit of NF-κB translocation to nucleus from cytosol (Ying et al., 2013) in male Wistar rats, oral administration of piperine momentously lowered the pro-inflammatory mediators and arthritis scoring in collagen-induced arthritis rats (Umar et al. (2013). Furthermore, piperine inhibited the production of PGE2 and NO-induced by IL-1β in human osteoarthritis chondrocytes, suggesting the anti-inflammatory activity of piperine (Ying et al., 2013). Depicted in Figure 7 are the anti-allergic, anti-inflammatory, and immunomodulatory effects of piperine.

4.10 | Liver protection

The positive effects of piperine on liver health have been reported in various studies based on hepatic health biomarkers. Several researchers indicated that piperine lowers alanine aminotransferase (ALT), AST, and ALP levels in sera of cholesterol-fed albino mice (Rao et al., 2015; Rezaee et al., 2014; Sethiya et al., 2015). Similarly, piperine administration resulted in momentous elevation in plasma adiponectin in rats induced with hepatic steatosis via high-fat diet. In addition, piperine reversed the elevated glucose, insulin, and hepatic lipid levels as well. It also reversed the downregulation of AMPK signaling molecules, which are responsible for fatty acid oxidation, insulin signaling, and lipogenesis in mouse liver. Furthermore, administration of piperine to the high-fat diet-consuming mice caused reduction in the lipogenic gene expressions and a significant increase in fatty acid

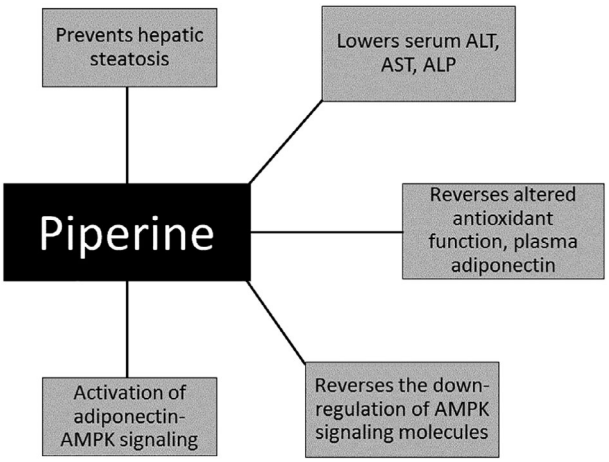

FIGURE 8 Hepatoprotective effects of piperine

oxidation. Piperine also reversed the insulin resistance and hepatic steatosis via activation of adiponectin-AMPK signaling (Choi et al., 2013; Sehgal et al., 2013). Moreover, coadministration of piperine with curcumin showed promising effects against benzo[a]pyrene-mediated toxicity in male *Swiss* albino mice. Treatment resulted in lowering of lipid peroxidation, frequency of bone marrow micronucleated polychromatic erythrocytes, and protein carbonyl content along with an increase in endogenous antioxidants like SOD, catalase, glutathione peroxidase, and reductase in the liver (Makhov et al., 2012; Sehgal, Kumar, Jain, & Dhawan, 2012). Interestingly, research findings indicated that piperine prevents the formation of cholesterol gallstone formation (Song et al., 2015). Shown in Figure 8 are the hepatoprotective effects of piperine.

4.11 | Miscellaneous properties

Apart from the aforementioned health perspectives, piperine displayed various other effects such as cerebral functioning and stress management. In this context, Hua et al. (2019) reported on the neuroprotective function of piperine in rats induced with cerebral ischemic injury. These researchers postulated that the protective effects of piperine in cortical ischemia are due to significant inhibition of caspase protein (Hua et al., 2019). In a recent investigation, piperine attenuated behavioral impairment along with significant neuroprotective effects against 3-nitropropionic acid-induced Huntington disease-like symptoms in rats (Salman, Tabassum, & Parvez, 2020). Previously, Mao and coworkers examined the biochemical and behavioral effects of piperine in rats subjected to chronic unpredictable mild stress (CUMS), which causes depression-like behavior, as shown by the substantial decrease in sucrose consumption and increase in immobility time in the forced swim test. In addition, it causes a significant decrease in serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) contents in the hippocampus and frontal cortex. However, treatment of rats with piperine suppressed the behavioral and biochemical changes induced by CUMS, suggesting that piperine can produce an antidepressant-like effect in CUMS-treated rats, possibly mediated by increasing 5-HT and BDNF contents in selective brain tissues (Mao, Huang, Zhong, Xian, & Ip, 2014). Earlier research by Wu and colleagues on rats with irritable bowel syndrome (IBS) showed that piperine enhances serotonin and synaptophysin expression in the hippocampus and colon of those rats. Thus, piperine can ameliorate the changes of the behavior and regulation of serotonin and synaptophysin expression in IBS rat model (Wu, Wang, Xue, & Pan, 2013). Similar results have been obtained in chronic unpredictable mild stress-induced rats, where piperine controls the behavioral change in stressed rats as well (Mao et al., 2014; Rinwa, Kumar, & Garg, 2013).

In a similar fashion, Mishra, Punia, Bladen, Zamponi, and Goel (2015) reported that piperine delays the onset of convulsions and decreases the mortality in maximal electroshock seizure (MES)-induced seizure model, suggesting an inhibitory effect of piperine on Na^+ channels. On the other hand, Bukhari, Alhumayyd, Mahesar, & Gilani, 2013 reported that piperine inhibits acetic acid-induced writhing in mice, and exhibits analgesic and anticonvulsant effects via opioid and GABAergic pathways (Bukhari et al. (2013). In addition, piperine delayed the myoclonic jerks and decreased the mortality and seizure stage in mice. It also reduced the tonic hindlimb extension induced via MES and PTZ-induced Fos immunoreactivity in dentate gyrus (Chen, Li, Qu, & Chen, 2013; Saraogi, Vohora, Khanam, & Pillai, 2013). On the other hand, da Cruz et al. (2013) indicated that piperine anticonvulsant effects result from its anti-inflammatory, antioxidant actions, and TNF-α reduction. In addition, piperine exerts inhibitory effects on amino acids and on the GABAergic system, which may certainly contribute to its anticonvulsant activity. Recent findings suggested that piperine (10 mg/kg b.w.) facilitates anticonvulsant effect of sodium valproate against pentylenetetrazol (PTZ)-induced seizure in *Swiss* albino mice. These results suggest a favorable interaction of piperine with sodium valproate against PTZ-induced seizures (Surendran, Babu, Joseph, & Padma, 2020)

Research findings also revealed that piperine could improve fertility through its positive effects on sperm count, viability and motility, weight of epididymis, caput, cauda, corpus, and seminal vesicles. However, some negative impacts, such as lowering of seminal fructose and an increase in malondialdehyde contents have also been observed by Chinta and Periyasamy (2016). Furthermore, piperine at a dose of 100 mg/kg decreased epididymis caput, cauda, and corpus weights (D'cruz & Mathur, 2005; Daware et al., 2000).

To potentiate the effectiveness against diseases, various derivatives of piperine have also been synthesized. Recently, Kim, Lee, Kim, Joshi, and Kwon (2020) published a patent dealing with a piperine derivative known as pentadienoyl compound (2E, 4E)-5-phenyl-penta-2,4-dien-1-one derivative that potentiates the prevention and curative effect of piperine against fatty liver disease via inhibition of lipogenesis, lipid accumulation in fat cells, and enhancing the fat metabolism. Furthermore, it may enhance the SIRT1 expression in cells and SIRT1 activity enhancing its potential to prevent SIRT1-mediated disease. In addition, it reduces the expression of CK2

and hence may potentially reduce the onset of CK2-mediated diseases (Kim et al., 2020). An earlier piperine derivative, developed by Hering, Erker, Schwarz, Baburin, and Schellmann (2011), showed promising effects in the treatment of anxiety, epilepsy, insomnia, and depression via $GABA_A$ receptor modulation. In addition, recent research findings indicated that piperine amino acid derivatives have a better potential to mitigate oxidative stress than piperine (Qin, Yang, & Cao, 2020). Some piperine derivatives have been found as potent monoamine oxidase inhibitors and free radical scavengers. It was noted that the IC_{50} values of some piperine derivatives were quite below the IC_{50} values of piperine in DPPH assay (Dhiman, Malik, & Khatkar, 2020). Similarly, some piperine derivatives have also been found as potential PPARγ agonists. One of the derivatives was reported to be two times more potent than rosiglitazone and 7.5 times than piperine (Wang et al., 2020). Other reports are also available for the development of piperine derivatives; however, potentiating the biological activities of piperine via its derivatives may pose some toxicological concerns as well for which stringent research trials and safety evaluation studies are necessary before their utilization as suitable drug ingredients.

5 | COMBINATIONAL THERAPY USING PIPERINE

Piperine exhibits numerous pharmacological effects and several health benefits, especially against chronic diseases, alone or in combination with other drugs and phytochemicals. It has also been employed to increase the pharmacokinetics (i.e., bioavailability and/or bioactivity) of certain other nutraceutical agents such as curcumin, quercetin, barbiturates, beta-carotene, resveratrol, coenzyme Q10, vitamin B-6, selenium, phyllanthin, propranolol, and theophylline (Derosa, Maffioli, & Sahebkar, 2016). In this context, several reports revealed the bio-enhancement effect of piperine on curcumin, metformin, and resveratrol (Arcaro et al., 2014; Atal et al., 2016; Chakraborty et al., 2017; Miyazawa et al., 2018; Pannu & Bhatnagar, 2019; Shoba et al., 1998). Furthermore, zein-carrageenan core-shell nanoparticles may effectively deliver and enhance the biological function of piperine and curcumin in co-delivery systems (Chen et al., 2020). Published research indicated that piperine is synergistic with other compounds such as curcumin. A combination with curcumin shows better control over metabolic disorders than piperine alone. In DENA-induced hepatocellular carcinoma (HCC), curcumin (100 mg/kg) in combination with piperine (20 mg/kg) suppressed HCC in rats as evident from the significant attenuation in morphological and biochemical changes in serum and hepatic tissue (Patial et al., 2015). Recently, Ding et al. (2020) showed the suitability of docetaxel and piperine for combinational therapy against liver cancer. Furthermore, use of piperine, curcumin, and taurine for the treatment of HCC has also depicted promising effect in altering the IL-10 and miR-21 levels (Hatab et al., 2019). Piperine also boosts the anticancer effect of curcumin by targeting breast stem cells (Kakarala et al., 2010). In Dalton's lymphoma ascites bearing mice, the combinational therapy of curcumin and piperine significantly potentiated anticancer effects than curcumin alone (Danduga, Kola, & Matli, 2020).

Similarly, a combined therapy of curcuminoids and piperine was effective against nonalcoholic fatty liver disease (Panahi et al., 2019). In type 2 diabetes mellitus, piperine and curcuminoids mutually modulated the adipokines and controlled the energy metabolism (Panahi et al., 2017). Furthermore, combined treatment with piperine and curcumin modulated the body fat in obese caloric restriction mice, thus preventing obesity (Miyazawa et al., 2018). Moreover, piperine has been shown to be a beneficial adjuvant of glimepiride when used in proper dosage for the treatment of diabetes (Veeresham et al., 2012). Research by Chakraborty et al. (2017) showed that piperine (20 mg/kg) in combination with curcumin (50 mg/kg) effectively control the cyclophosphamide-induced cardiotoxicity. In this respect, it is worth mentioning that curcumin alone was not as efficient as when combined with piperine. Moreover, oral piperine and curcumin coadministration has been used to alleviate blood pressure in L-NAME induced hypertension in Wistar rats (Hlavačková et al., 2011).

In ovalbumin-induced chronic asthmatic mice, the combined treatment of curcumin and piperine ameliorated the asthma conditions (Chauhan et al., 2018). Furthermore, piperine enhanced the neuroprotective effect of curcumin in LPS-induced neurochemical and neurobehavioral deficits in mice hippocampus (Jangra et al., 2016). Similarly, piperine and curcumin abrogated the D-galactose-induced lipid and protein oxidation in rat's brain, (Banji, Banji, Dasaroju, & Ch, 2013). Likewise, research by Rinwa and coworkers showed that piperine enhances the bioactivity of curcumin by suppressing apoptotic signaling cascade and neuro-inflammatory responses in depression-induced rats (Rinwa et al., 2013). When piperine was co-administered with curcumin in *Swiss* albino mice, the treatment resulted in significant protection against benzo[a]pyrene-mediated toxicity by lowering lipid peroxidation and protein carbonyl content. Furthermore, improvement in the endogenous liver antioxidant enzymes was also observed (Makhov et al., 2012; Sehgal et al., 2012).

Recent work by Sharma and colleagues indicted that piperine significantly enhances the antioxidant, anti-inflammatory, and neuroprotective effects of quercetin in rats induced with Parkinson's disease via rotenone and iron supplements (Sharma, Raj, & Singh, 2020). Furthermore, Rinwa and Kumar (2017) reported that quercetin in combination with piperine alleviates neuro-inflammation, oxidative stress, and cognitive dysfunction. Similarly, Saraogi et al. (2013) showed that piperine has additive and slight synergistic effect in a combination therapy with phenytoin, providing protection against side effects of this antiepileptic drug. In addition, piperine has also been shown to increase the bioavailability and bioactivity of phyllanthin, thus enhancing the hepatoprotective effects (Sethiya et al., 2015). Research findings also highlighted the combination therapy of resveratrol and piperine as an approach to enhance the biological effects with respect to cerebral blood flow and improved cognitive functions (Wightman et al., 2014).

6 | CONCLUSIONS AND FUTURE DIRECTIONS

In summary, data obtained from this review showed that piperine possesses remarkable broad spectrum of therapeutic activities in addition to pharmacological potentials to treat numerous diseases and ailments. In addition, findings from this review indicate that piperine has diverse physiological effects, as it possesses significant positive effects on various diseases as summarized in the review. Therefore, large number of nutraceutical and therapeutic interventions can be designed, considering the possible mechanisms of this active agent and its derivatives. Furthermore, this natural compound can provide a safer alternative to pharmaceutics to target hepatic, neural, and cancer diseases. However, studies possibly with human subjects are needed to ensure its safety aspects and assess further decomposition products in the body so that it can safely be used in therapeutic regimes. Moreover, the dietary intake from population-based consumption studies along with dietary habits of individuals residing in different regions of the globe should be conducted, and, based on their outcome, the net exposure and necessary dose rates should be estimated. In addition, studies on the effect of different processing conditions at household levels on the activity of piperine are also required as plenty of foodstuffs with high antioxidant contents are consumed, yet people get sick. Such research may open new horizons for insights into establishing processing methods for production of functional foods and nutraceuticals.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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