Clinical Phytoscience

REVIEW Open Access

Phytochemistry and therapeutic potential of black pepper [*Piper nigrum* (L.)] essential oil and piperine: a review

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Abstract

Background: Black pepper [*Piper nigrum* (L.), Family: Piperaceae] is used traditionally for the treatment of various diseases including; cough, cold, dyspnea throat diseases, intermittent fever, dysentery, stomachache, worms and piles. The pharmacological potential of black pepper is due to the presence of metabolites like phenolic compounds, alkaloids, flavonoids, carotenoids, terpenoids, etc. The multipurpose use of black pepper dried seeds has several other beneficial health effects that also received in the light of traditional as well as current medicine perspectives. The review aims to discuss the botany, phytochemical constituents, and pharmacological properties of piperine and black pepper essential oil (BPEO).

Results: Phytochemical analyses have described the main chemical constituents of black pepper, including carbohydrates, proteins, calcium, magnesium, potassium, iron, vitamin C, tannins, flavonoids and carotenoids. The volatile oil content ranges from 0.4 to 7 % in dried berries. The major constituents of BPEO are sabinene, 3-carene, D-limonene, α-pinene, caryophyllene, β-phellandrene, α-phellandrene, α-thujene, and β-bisabolene. Additionally, piperine is the naturally occurring and principal bioactive alkaloid constituent of black pepper owing to its potential therapeutic properties, including cerebral brain functioning and increased nutrient absorption. The BPEO has several biological roles, including antioxidant, anti-inflammatory, anticancer, anti-obesity, antidepressant, antidiabetic, antimicrobial, gastroprotective, and insecticidal activities.

Conclusions: This review examines and presents the appropriate evidence on black pepper and its traditional uses as well as biological activities of BPEO and piperine. Although several previous reports showed diverse biological effects for piperine and bioactive constitutes of BPEO. Thus, minimal investigations were conducted using animal models, and many of these studies also lacked appropriate experimental setting like doses, control details. Hence, future studies are necessary to understand the mechanism of piperine, BPEO, bioactive constituents and their effects upon their use by animal models and humans with the proper experimental procedure which we can facilitate the protection of human health from several diseases.

Keywords: *Piper nigrum*, Botany, Phytochemistry, Essential oil, Piperine, Pharmacological applications

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Background

Black pepper (*Piper nigrum* L.) commonly known as the "King of Spices", belonging to the family Piperaceae, is one of the most popular spices used worldwide and is native to southern India [1]. The name "pepper" originated from the Sanskrit word "*Pipali*", and other Indian vernacular names are Milagu (Tamil), Kari Menasu (Kannada), Kuru Mulagu (Malayalam), Miriyam (Telugu), and Kali Mirch (Hindi). Most of the production of black pepper occurs in India, Malaysia, Indonesia, China, Thailand, Sri Lanka, Vietnam, Brazil and Madagascar [2]. Black pepper is one of the vital spicy ingredients in foods, especially in Asian countries, and it also possesses potential applications in traditional medicine, perfumery, preservatives and insecticides [3].

Plant-based food products are storehouses of several bioactive constituents such as phenolics, flavonoids [4–9], terpenes [10] and sterols [11]. These constituents have been evaluated for their biological and antibacterial effects [12, 13]. In traditional medicines, black pepper has been reported to have a gastrointestinal activity to increase appetite, to antidote cough, cold, dyspnea throat diseases, discontinuous fever, dysentery, stomachache, worms and piles [14] and is used as anti-inflammatory, antipyretic, and to treat epilepsy and snakebite [15–17].

The aroma and pungency of black pepper are mainly attributed to piperine and volatile oils [18]. Piperine is the major bioactive component in black pepper, and its displays various therapeutic benefits including antiplatelet, antihypertensive [19], anticancer, antioxidant [20], analgesic, antidepressants and anti-diarrheal [21]. The alkaloid piperine improves the therapeutic value of several drugs, vaccines and nutrients by enhancing bioavailability through inhibiting numerous digestive enzymes [22]. Likewise, piperine aids in digestion through stimulating pancreatic and intestinal enzymes, and enriches cognitive skills and fertility [22, 23]. Furthermore, piperine is recognized as delivering several therapeutic activities distinct from other chemical components [2].

Black pepper essential oil constitutes approximately 0.4–7 % of the berry dry weight [24] and is beneficial for the management of rheumatism, cold, tiredness, muscular pains and infection. It was also used as a nerve stimulant to enhance blood circulation [24, 25]. Both white pepper and black pepper contained 2–7 % piperine [24, 26]. The volatile oil constituent piperamides and nerolidol exhibited insecticidal activities [27, 28]. β-caryophyllene displayed anaesthetic effects, and piperine was used in perfumes [29]. Black pepper has been used for millennia, including plant breeding activities for the development of superior varieties with improved organoleptic and nutritional properties. It has been used in traditional as well as modern medicine. This review aims to highlight the main phytochemicals and therapeutic effects of *Piper nigrum* (L.) essential oil and piperine related to human health.

Botanical description

Black pepper (*Piper nigrum* L.) belongs to the family Piperaceae. The basic chromosome number x = 13 and 2n = 52 indicates its balanced tetraploid nature. Nevertheless, no species with a diploid number (2 = 26) has been stated from India [30]. According to Ravindran [31] morphological and biosystematics studies, three species *P. wightii, P. trichostchyon* and *P. galeatum* are the putative parents for *P. nigrum*. Black pepper is a perennial climbing vine that grows well in the shade with supporting trees or poles. The glabrous woody climbers grow up to 10 m or more height [32]. Black pepper plant has 10–20 primary adventitious roots developed from the base of the mature stem [32]. The vines are grown dimorphic branching (monopodial, orthotropic branches and sympodial, plagiotropic fruiting branches) pattern. The orthotropic shoot has indeterminate growth, and leaf axils produce lateral fruiting branches. Also, each node of the orthotropic shoot has clinging roots that help the plant climb over the support trees [33]. Leaves are simple, alternate, with 2 to 5 cm long grooved petiole, variable leaf length and breadth, 8–20 cm and 4–12 cm respectively [32]. In India, 2 to 3 years after planting black pepper plants have flowering during south-east monsoon (May – July). The fruiting spikes are varied lengths (3–15 cm). After 10–15 days spike emergence, the first flower appears on the top of the spike and completed nearly 6–10 days. The inflorescence is glabrous; pendulous spike arises opposite to leaves on plagiotropic branches [34]. Wild type flowers are mostly dioecious, but the cultivated type flowers are monoecious. Self-pollination is predominant, and protogyny also encountered in black pepper [35]. The matured fruits are spherical in shape (~ 5 mm diameter) and belong to drupe type. The harvested fruits are sun-dried for further use. A typical photograph of the field view and various botanical features of including such as habitat, spikes, matured and dried berries (seeds) are presented in Fig. 1.

Chemical composition

Proximate, minerals, vitamins and bioactive metabolites

Black pepper is rich in minerals, vitamins and nutrients. The chemical composition of 100 g of black pepper seeds includes carbohydrate 66.5 g, protein 10 g, and fat 10.2 g [36], as well as a relatively high concentration of minerals such as calcium (400 mg), magnesium (235.8-249.8 mg), potassium (1200 mg), phosphorus (160 mg), and the lower concentration of sodium, iron and zinc [36, 37]. These minerals are essential elements for day-to-day activities of humans. Besides, black pepper also has a significant concentration of vitamins such as

Fig. 1 Field view and botanical features of Black pepper (*P. nigrum* L.)

Vitamin C, B1, B2 and B3 (Table 1). Nine accessions of Nigeria grown black pepper had a concentration of tannin ranging from 2.11 to 2.80 mg /100 g [37]. In a recent study on black pepper, Ashokkumar et al. 10 reported flavonoids such as catechin, quercetin and myricetin, and carotenoids, namely lutein and β-carotene was detected in significant concentration (Table 1).

Essential oil, Oleoresin and Piperine

Several researchers evaluated essential oils (EO), oleoresin and piperine in various parts of black pepper (Table 2). The EO yield of black pepper berries and leaves have varied from 1.24 to 5.06 %, and 0.15–0.35 %, respectively [39–41]. However, the oil yield depends on the variety, area and age of the product, parts and methods used (Table 2). Kurian et al. [39] observed variability of volatile oil and oleoresin content in 14 black pepper accessions ranging from 2.7 – 5.1 % and 7.6 – 9.4 %, respectively. These researchers reported that volatile oil content was positively correlated with oleoresin and suggested concurrent improvement of these characters by simple selection programme is the best tool for improvement of quality traits in black pepper. Kurian et al. [39] also reported classical hydro-distillation as a better method of volatile oil estimation compared to other techniques (Table 2). The oleoresin content of black pepper ranged between 4.27 and 12.73 % [38, 42], and the characteristic natural alkaloid of black pepper "piperine" ranged from 2.13 – 5.80 % and 0.12 – 20.86 %, in seeds and leaves correspondingly (Table 2).

The EO profile of black pepper seeds from south India is predominately comprised of β-caryophyllene followed by limonene, sabinene, α-pinene, β-bisabolene, α-copaene α-cadinol, α-thujene, α-humulene; pepper leaves were rich in nerolidol followed by α-pinene and β-caryophyllene [38, 41] (Table 3). Likewise seeds from Bangladesh were contained EO consisting of β-caryophyllene (18.39 %) followed by α-pinene (16.68 %), limonene (16.16 %), β-pinene (13.61 %), δ -3-carene (9.23 %), β-phellandrene (3.16 %), copaene (3.13 %), 1-napthalenol (3.0 %), and β-myrcene (2.89 %) [45]. EO of seeds from Sri Lanka, Malaysia, and Brazil showed some noticeable variations in major metabolites (Table 3). The molecular structures of major essential oil constituents isolated from pepper seeds and leaves were drawn by ChemDraw software and are shown in Fig. 2. The yield of minor EO of black pepper contained β-Elemene (1.74 %), δ-Elemene (0.60 %), α-Cubebene (0.99 %), α-Guaiene (0.36 %), α-Zingiberene (0.74 %), p-Cymene (0.70 %), Bicyclogermacrene (0.31 %), γ-Cadinene (0.65 %), γ-trans-Bisabolene (1.39 %), Hedycaryol (0.37 %), and Germacrene D (0.22 %) [46].

Pharmacological and biological effects of BPEO and piperine

The piperine, BPEO and its active constituents have a number of potential biological activities, including antioxidant, antimicrobial, antitumour, cytotoxicity, and miscellaneous activities that are summarized in Table 4. The potential biological activities of BPEO and piperine were diagrammatically presented in Fig. 3.

Table 1 Nutritional composition of 100 g of black pepper

Chemical composition	Concentration	References
Proximate		
Water (g)	8.0	[36]
Energy (Kcal)	400.0	[36]
Carbohydrate (g)	66.5	[36]
Protein (g)	10.0	[36]
Fat (g)	10.2	[36]
Total Ash (%)	3.43–5.09	[38]
Crude fibre (%)	10.79–18.60	[38]
Minerals		
Calcium (mg)	400.0	[36]
Magnesium (mg)	235.8–249.8	[37]
Phosphorus (mg)	160.0	[36]
Sodium (mg)	10.0	[36]
Potassium (mg)	1200.0	[36]
Iron (mg)	17.0[36]	
Zinc (mg)	1.45–1.72	[37]
Vitamins		
Vitamin C (mg)	27.46–32.53	[37]
Vitamin B1 (mg)	0.74–0.91	[37]
Vitamin B2 (mg)	0.48–0.61	[37]
Vitamin B3 (mg)	0.63–0.78	[37]
Metabolites		
Tannin (mg)	2.11–2.80	[37]
Flavonoids		
Catechin (μg)	410.0	[10]
Myricetin (μg)	56.0	[10]
Quercetin (μg)	13.0	[10]
Carotenoids		
Lutein (μg)	260.0	[10]
β-carotene (μg)	150.0	[10]

Antioxidant effects

Oxidative stress is the main factor for initiation of various degenerative and chronic diseases, including cancer, immune dysfunction, diabetes and Parkinson's [63]. Antioxidants are natural or synthetic constituents that can be used for inhibition of free radical formation by scavenging and suppression of degenerative and chronic diseases [64]. A polyphenolic compound Hydroxytyrosol (HT), has a potent antioxidant effect on hydrogen donation and improved radical stability [65]. Supplementation with HT improves the white adipose tissue (WAT) dysfunction induced by high-fat diet (HDF) fed in mice through the modulation of transcription factors NF-κB, Nrf2, SREBP-1c and PPAR-γ as well as their target genes, involved in inflammation, antioxidant defences and lipogenesis [66, 67]. Vijayakumar et al. [68] noted that piperine has potential protection activity against lipid peroxidation and antioxidant activity in rats fed a high-fat diet which induced oxidative stress to cells. Piperine has greatest antioxidant potential and was utmost effective with minimum inhibitory concentration (MIC) < 325 mg/ml against all assessed gram positive and negative strains [69]. Under *in vitro* conditions, Jeena et al. [52] recorded that essential oil of black pepper scavenged superoxide, and inhibited tissue lipid peroxidation.

Antibacterial and antimicrobial effects

In general, consumers prefer natural and non-toxic products to protect foods from bacteria during storage. Because of the long-term usage of chemical preservatives, a resurgence of food pathogenic bacteria may occur, which can induce severe health problems in humans [70]. The antimicrobial activity of black pepper remains unclear till date. According to Rani et al. [71], piperine had potential antimicrobial as well as antifungal effects against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Aspergillus niger, (A) flavus, Alternaria alternata* and *Fusarium oxysporum*. Phenolic compounds obtained from fresh black pepper seed extracts

Table 2 Yield of volatile oil, oleoresin and piperine from various parts of black pepper

Parts	Volatile oil Extraction method	Volatile oil (%)	Oleoresin (%)	Piperine (%)	References
Seeds	Deep eutectic solvents (DESs) based microwave Hydrodistillation	1.77	-	-	[43]
Seeds	Hydrodistillation	2.66–5.06	7.6–9.4	-	[39]
Seeds	Hydrodistillation	1.60–2.80	4.27–10.74	2.62–5.50	[42]
Seeds	Hydrodistillation	1.60–3.20	5.82–12.73	2.13–4.49	[38]
Seeds	Hydrodistillation	1.24	-	-	[40]
Leaves	Hydrodistillation	0.15–0.35	-	0.12–20.86	[41]
Seeds	Microwave assisted hydrodistillation	1.45	-	-	[40]
Seeds	Supercritical fluid extraction	1.70	10.60	5.80	[44]

Table 3 Composition of major essential oils of *Piper nigrum* from various origins

Origin	Parts	Constituents	Yield (%) and references	
South India	Seeds	β-caryophyllene	9.52–26.95	[38]
		Limonene	15.13–20.78	[38]
		Sabinene	0.00–19.23	[38]
		α-pinene	3.88–6.48	[38]
		β-bisabolene	1.32–7.96	[38]
		α-humulene	1.11–2.44	[38]
		α-copaene	0.20–5.51	[38]
		α-cadinol	0.18–4.89	[38]
		α-thujene	0.60–2.94	[38]
South India	Leaves	Nerolidol	0.14–66.32	[41]
		α-pinene	0.12–20.86	[41]
		β-caryophyllene	2.09–9.65	[41]
Bangladesh	Seeds	β-caryophyllene	18.39	[45]
		α-pinene	16.68	[45]
		Limonene	16.16	[45]
		β-pinene	13.61	[45]
		δ-3-carene	9.23	[45]
		β-phellandrene	3.16	[45]
		Copaene	3.13	[45]
		1-napthalenol	3.00	[45]
		β- myrcene	2.89	[45]
Sri Lanka	Seeds	β-caryophyllene	12.5	[47]
		β-terpenine	19.5	[47]
		Limonene	19.2	[47]
		Sabinene	19.2	[47]
		α-pinene	11.2	[47]
		β-pinene	12.1	[47]
		α β-phellandrene	4.8	[47]
		Myrcene	2.9	[47]
Malaysia	Seeds	Limonene	29.9	[48]
		β-pinene	19.0	[48]
		β-caryophyllene	14.0	[48]
		α-pinene	7.3	[48]
		δ -3-carene	10.6	[48]
		Myrcene	2.6	[48]
		α-phellandrene	2.2	[48]
		Linalool	2.1	[48]
Brazil	Seeds	δ-3-carene	55.43	[49]
		α-pinene	16.25	[49]
		sylvestrene	10.67	[49]
		germacrene D	2.17	[49]
		β-myrcene	1.99	[49]
		Isoterpinolene	1.4	[49]

have the potential to inhibit the growth of *Bacillus, Escherichia coli* and *Staphylococcus aureus*, *S. faecalis and (B) cereus* [72, 73]. Zhang et al. [74] showed that 1.0 μl/ml of BPEO was the effective minimum inhibition concentration against meat-borne *E. coli*, and suggested that black pepper essential oil has potential as a natural antibacterial agent in the meat industry. Similarly, BPEO displayed substantial activity against *E. coli, B. substilis*, and *S. aureus* [75]. Besides, most of the studies focusing on the antimicrobial effects of BPEO have been conducted disc diffusion method [71, 76, 77] though; given its intrinsic limitations, the technique requires to be improved through more relevant MIC assays [78].

Anticancer effects

The BPEO and piperine exert activities against several types of cancer (Table 4). Piperine significantly suppressed the tumour growth of both androgen-dependent and androgen-independent prostate cancer cells [79]. Makhov et al. [80] noted enhanced anticancer activity during co-administration of piperine and docetaxel in human prostate cancer. Additionally, piperine induced DNA damage and apoptosis in tumour cells and was a potential therapeutic agent for the treatment of osteosarcoma [81, 82]. Likewise, piperine reduced lung cancer by stimulation of antioxidative protective enzymes and through reducing lipid peroxidation [83]. Based on the above comments, piperine has potential anticancer activities. However, only a few studies have studied the antitumor potential of piperine and BPEO, and these were conducted in animal models only. Therefore, future studies should be attentive on the bioactivity of BPEO in several clinical investigations with humans.

Cytotoxicity effects

BPEO and piperine have good potential for augmenting the effectiveness of tumour necrosis factor (TNF) related apoptosis in breast cancer cells [84]. Greenshields et al. [85] reported that a combination of piperine and γ-radiation had higher cytotoxicity and effectiveness in stopping the growth of tripe negative cancer cells than radiation alone in immune-deficient mice. Although the safety of piperine and BPEO was showed, the use of cell lines only on *in vitro* assays confines the therapeutically relevance of this outcome.

Insecticidal effects

Black pepper possesses insecticidal activities against European chafer (*Amphimallon majale*, Coleoptera: Scarabaeidae) [27]. Upadhyay and Jaiswal [86], noticed that 0.2 % concentration (v:v) of black pepper essential oil has potential repellent activity against adults of the major wheat grain storage pest *Tribolium castaneum* (Herbst). Naseem and Khan [28], stated that a higher

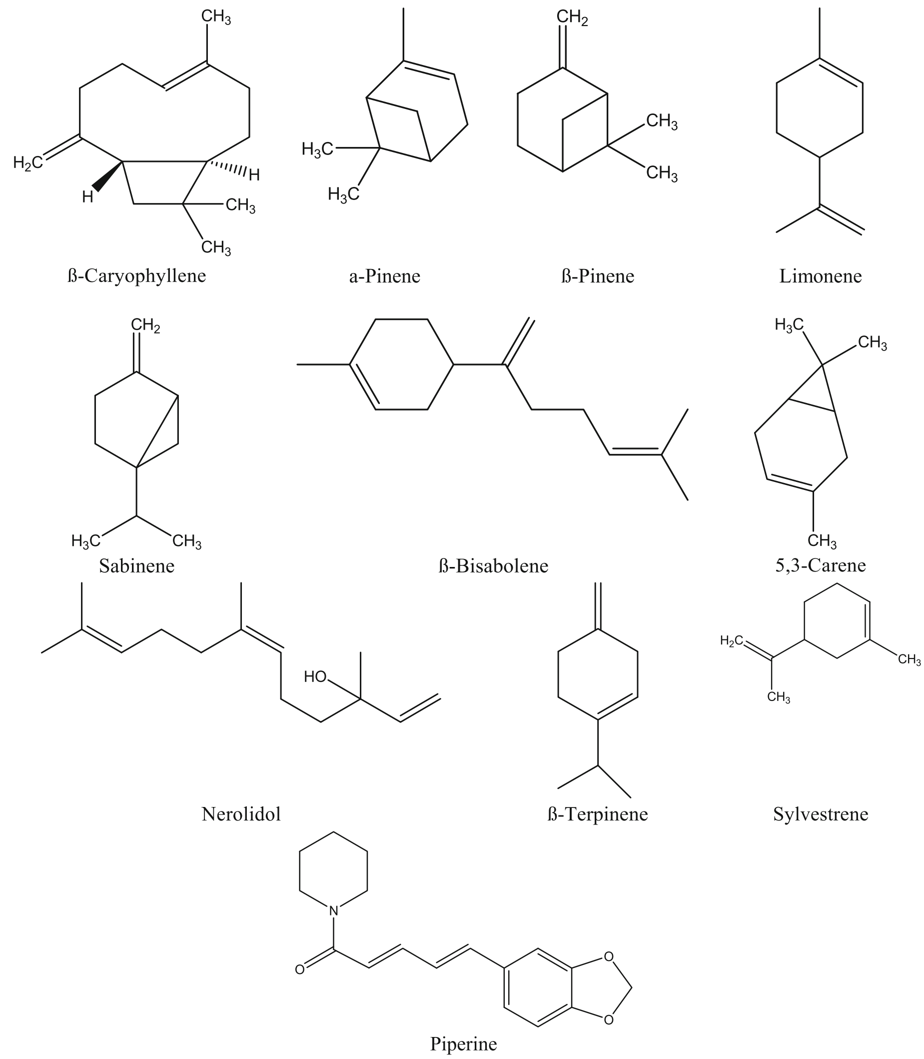

Fig. 2 Molecular structures of piperine and major essential oil constituents from *Piper nigrum* (L.)

concentration of black pepper essential oil leads to maximum repellent effects at maximum exposure duration against *T. castaneum*. Thus far, only two studies have investigated the insecticidal effects of BPEO; therefore, further research needed in this promising application.

Miscellaneous effects

For centuries, black pepper has been used for traditional medicines to cure cuts and wound injuries. Piperine induced bioavailability of the flavonoid linarin in rats by inhibiting the P-glycoprotein, and it helps cellular efflux during intestinal absorption [87]. Hence, piperine is called a natural bio-enhancer [88]. Piperine stimulates a dose-dependent increase in the secretion of gastric acid and interruption of gastrointestinal motility [89]. The oral administration of piperine activates the liver, pancreas and digestive enzymes in the small intestinal mucosa [90]. Furthermore, the addition of piperine in food materials as food flavours may increase the protease, lipase, and pancreatic amylase activities [18].

Conclusions

Based on the reviewed literature, *Piper nigrum* (L.) has many favourable chemical properties and beneficial effects. Besides, this review presents a summary of the data on the chemical composition of black pepper, including minerals, vitamins, carotenoids and flavonoids, and various therapeutic benefits. Up to date existing information, > 80 metabolites have been isolated from *P. nigrum.* Among them, biologically active alkaloid piperine and the main essential oils constituents including β-caryophyllene, limonene, sabinene, α-pinene, β-bisabolene and α-copaene can serve as a new natural source for use in food, aroma, cosmetics and pharmaceutical industries. Piperine also has a broad spectrum of therapeutic potential and potential for improving the

Table 4 Pharmacological activities of *Piper nigrum* extracts, piperine and BPEO

Pharmacological activities	BPEO/ Piperine	*In vitro/ In vivo*	Target/ Model	Control(s)	IC 50/Dosage	Results / Remarks	Reference
Antioxidant	BPEO	*In vitro*	DPPH scavenging	Not reported	EC_{50} : 103.3 μg/ ml	Noteworthy radical activity observed. Though control details are not reported	[50]
Anti-inflammatory	Piperine	*In vitro*	B16F-10 melanoma cells	Not reported	MIC: 2, 5, 10 mg/ μl	Piperine showed dose dependent inhibition against B16F-10 melanoma cell lines. However proper control details not reported	[51]
Anti-inflammatory	BPEO	*In vivo*	Carrageenan induced acute inflammatory Balb/C mice	Positive: Carrageenan	100, 500, 1000 mg/kg body weight	The dose 500 mg/kg body weight was performed significant inhibition (72 %) at 3rd hour compared to control	[52]
Anti-inflammatory	BPEO	*In vivo*	Formalin induced chronic inflammatory Balb/C mice	Positive: Formalin	100, 500, 1000 mg/kg body weight	500 mg/kg body weight BPEO produced 50 % inhibition of paw edema compared to control	[52]
Anti-inflammatory	BPEO	*In vivo*	Dextran induced acute inflammatory Balb/C mice	Positive: Dextran	100, 500, 1000 mg/kg body weight	1000 mg/kg body weight significantly reduced the paw thickness 73.4 % at 3rd hour compared to the control	[52]
Antibacterial activity	BPEO	*In vitro*	*Alcaligenes faecalis, Acinetobacter calcoacetica, Beneckea natriegens, B. subtilis, Brevibacterium linens, Clostridium sporogenes, Citrobacter freundii, E. carotovora, Enterococcus faecalis, E. coli, Micrococcus luteus*	Not reported	Not reported	Highest zone of inhibition (19.7 mm) was obtained against *P. aeruginosa*. However, in this study dosage and control was not reported. It reduces reliability of results	[53]
Anticancer activity	Piperine	*In vivo*	DMBA induced carcinogenesis in Syrian golden hamsters	Postive: DMBA Negative : Distilled water	50 mg / kg, oral administration for 14 weeks	Results showed that piperine totally inhibited the oral carcinoma formation	[20]
Anticancer activity	Piperene	*In vtiro*	MCF-7 cell line	Negative : Distilled water	IC_{50}: 1.21 μM for 24 h exposure	Piperine exhibited significant synergistic effects in combination with paclitaxel on human breast cancer cell line MCF-7	[54]
Anticancer activity	Piperene	*In vtiro*	HER overexpressing breast cancer cell lines (MCF-7 and SKBR-3)	Negative : Distilled water	IC_{50} : 200 μM & 50 μM for MCF-7 and SKBR-3 cell lines respectively, 48 h exposure	Piperine strongly inhibited proliferation and induced apoptosis through caspase-3 activation and PARP cleavage. Also, piperine inhibited HER2 gene expression. This study suggested that piperine may be a potential agent for the prevention and treatment of human breast cancer with HER2 overexpression	[55]
Antiobesity activity	Piperine	*In vivo*	Obesity-induced dyslipidemia in high-fat diet rats	Not reported	40 mg / kg for 3 weeks	Supplementation of piperine with high fat diet significantly reduced body weight and total cholesterol. Though control details not reported	[56]
Antiaging and wrinkling	BPEO	*In vitro*	Human neutrophil elastase	Negative: Distilled water	1 μg/ml	BPEP showed noteworthy elastase inhibitory activity. However, dosage of the experiment is not scientifically accepted	[57]

Table 4 Pharmacological activities of *Piper nigrum* extracts, piperine and BPEO *(Continued)*

Pharmacological activities	BPEO/ Piperine	*In vitro/ In vivo*	Target/ Model	Control(s)	IC 50/Dosage	Results / Remarks	Reference
Antihypertensive activity	Piperine	*In vivo*	Anesthetize induced Sprague-Dawley male rats	Positive: Acetylcholine	1 to 10 mg/kg body weight	Intravenous administration of piperine caused a dose-dependent decrease in mean arterial pressure (MAP) in normotensive anesthetized rats. Also, higher dose (30 mg/kg) of piperine did not cause any further change in MAP. However, this study not reported detailed dosages along with experiment duration.	[19]
Antiasthmatic activity	Piperine	*In vivo*	Asthma induced Balb/c mice	Positive: Ovalbumin + vehicle	4.5 & 2.25 mg/kg, oral administration, five times a week for 8 weeks	Piperine-treated group had suppressed eosinophil infiltration, allergic airway inflammation and airway hyper responsiveness, and these occurred by suppression of the production of interleukin-4, interleukin-5, immunoglobulin E and histamine, than comparing with control group	[58]
Antidepressant & cognitive	Piperine	*In vivo*	Male wistar rats	Positive: Diazepam	5, 10 & 20 mg/kg body weight once daily for 4 weeks	All the treatment showed anti-depression like activity and cognitive enhancing activity	[23]
Antidepressant activity	Piperine	*In vivo*	Corticosterone-induced depression in mice	Negative: Distilled water	10 mg/kg body weight for 24 h.	Significant decrease in sucrose consumption and increase in immobility time in the forced swim test and tail suspension test	[59]
Antidepressant activity	Piperine	*In vivo*	Pilocarpine (350 mg/kg i.p.) induced rats	Positive: Pilocarpine	25 mg/kg, p.o. for 10 days	In comparison with pilocarpine, piperine significantly reduced lipid peroxidase and catalase activity, and increased GSH level, brain-plasma phenytoin and number of viable neurons	[60]
Anticonvulsant activity	Piperine	*In vivo*	Pentylenetetrazole (PTZ)- and picrotoxin (PIC)-induced seizure in mice	Negative: Normal Saline	30, 50 and 70 mg/kg, i.p.	Piperine protected animals from PTZ induced seizures in a dose-dependent manner. PTZ-induced convulsion in piperine treated animals was significantly different compared to saline treated animals	[61]
Insecticidal activity	BPEO	*In vivo*	*Sitophilus zeamais*	Negative: Distilled water	LD_{50}: 26.4 μl/g for 48 h	BPEO showed some insecticide activity (contact toxicity) against *Sitophilus zeamais*	[62]

Note: *BPEO* Black pepper essential oil; *MIC* Minimum inhibition concentration; LC_{50} Lethal concentration; LD_{50} Median lethal dose; IC_{50} Inhibitory concentration; EC_{50} Effective concentration

bioavailability of therapeutic drugs and nutrients. BPEO and piperine have many biological effects such as hepatoprotective, antioxidant, anticancer, antibacterial, anti-inflammatory, antifungal, antimicrobial, antihypertensive, antiasthma, antithyroid, wound healing and insecticidal activities. Black pepper has extensive biological effects and has been utilized in preclinical, clinical and therapeutics trials examining novel and new treatments of diseases. Furthermore, piperine and BPEO have been widely explored for their therapeutic potential (Table 4). However, gaps exist in the previous investigations on *P. nigrum*, and we have given suggestions on a few topics that should have priority for detailed examinations.

First, the essential oil of black pepper loses its flavour quickly upon storing under a normal room temperature. However, limited studies have been accompanied on maintaining the shelf life of BPEO. Hence, future research is required to evaluate the storage quality of

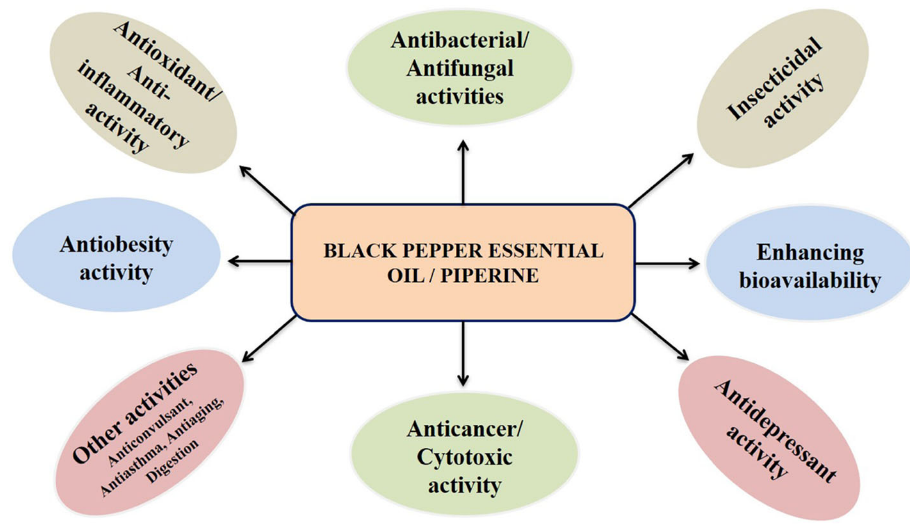

Fig. 3 Diagrammatic representation of black pepper essential oil and piperine potential biological activities

BPEO. Second, insufficient biological and pharmacological investigations have been conducted on piperine and BPEO. A few pharmacological assessments were performed utilizing exceptionally high dosage concentrations, some were inadequate in examination with controls, and others lacked determination of MIC values, perhaps prompting false positive outcomes. Third, even though *P. nigrum* possesses several potential pharmacological effects on antioxidant, antimicrobial, anticancer, and cytotoxic effects, these studies were employed only in cell lines and animal models, scientific studies in humans have rarely been executed. Hence, the future investigation could focus on the pharmacological properties of piperine, BPEO and active constituents in various clinical studies with humans. Fourth, black pepper-based drugs may be industrialized in future. Future research also needs to conduct clinical trials to investigate the excessive consumption of black pepper in humans and animal models. This review supports the expanded use of black pepper in culinary applications. Regular consumption of black pepper could protect humans from various chronic diseases as a nutraceutical as well as functional food.

Abbreviations

BPEO: Black pepper essential oil; EO: Essential oils; TNF: Tumour necrosis factor; MIC: Minimum inhibition concentration; LC_{50}: Lethal concentration; LD_{50}: Median lethal dose; IC_{50}: Inhibitory concentration; EC_{50}: Effective concentration

Acknowledgements

Not applicable.

Authors' contributions

KA and MM conceptualized the manuscript. KA wrote the manuscript. MKD and AP collected and reviewed the literature on the chemical composition and biological activities. TW and MM contributed to the manuscript editing. All authors read and approved the final manuscript.

Funding

This work did not receive any funding from an external source.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 17 June 2020 Accepted: 4 June 2021
Published online: 09 June 2021

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