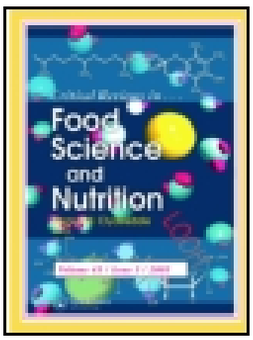

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REVIEW

A systematic review on black pepper *(Piper nigrum* L.): from folk uses to pharmacological applications

Heerasing Takooree[a], Muhammad Z. Aumeeruddy[a], Kannan R.R. Rengasamy[b], Katharigatta N. Venugopala[c], Rajesh Jeewon[a], Gokhan Zengin[d], and Mohamad F. Mahoomodally[a]

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ABSTRACT

Considered as the "King of spices", black pepper (*Piper nigrum* L.) is a widely used spice which adds flavor of its own to dishes, and also enhances the taste of other ingredients. *Piper nigrum* has also been extensively explored for its biological properties and its bioactive phyto-compounds. There is, however, no updated compilation of these available data to provide a complete profile of the medicinal aspects of *P. nigrum*. This study endeavors to systematically review scientific data on the traditional uses, phytochemical composition, and pharmacological properties of *P. nigrum*. Information was obtained using a combination of keywords *via* recognized electronic databases (e.g., Science Direct and Google Scholar). Google search was also used. Books and online materials were also considered, and the literature search was restricted to the English language. The country with the highest number of traditional reports of *P. nigrum* for both human and veterinary medicine was India, mostly for menstrual and ear-nose-throat disorders in human and gastrointestinal disorders in livestock. The seeds and fruits were mostly used, and the preferred mode of preparation was in powdered form, pills or tablets, and paste. *Piper nigrum* and its bioactive compounds were also found to possess important pharmacological properties. Antimicrobial activity was recorded against a wide range of pathogens via inhibition of biofilm, bacterial efflux pumps, bacterial swarming, and swimming motilities. Studies also reported its antioxidant effects against a series of reactive oxygen and nitrogen species including the scavenging of superoxide anion, hydrogen peroxide, nitric oxide, DPPH, ABTS, and reducing effect against ferric and molybdenum (VI). Improvement of antioxidant enzymes *in vivo* has also been reported. *Piper nigrum* also exhibited anticancer effect against a number of cell lines from breast, colon, cervical, and prostate through different mechanisms including cytotoxicity, apoptosis, autophagy, and interference with signaling pathways. Its antidiabetic property has also been confirmed *in vivo* as well as hypolipidemic activity as evidenced by decrease in the level of cholesterol, triglycerides, and low-density lipoprotein and increase in high-density lipoprotein. *Piper nigrum* also has anti-inflammatory, analgesic, anticonvulsant, and neuroprotective effects. The major bioactive compound identified in *P. nigrum* is piperine although other compounds are also present including piperic acid, piperlonguminine, pellitorine, piperolein B, piperamide, piperettine, and (-)-kusunokinin, which also showed biological potency. Most pharmacological studies were conducted *in vitro* ($n = 60$) while only 21 *in vivo* and 1 clinical trial were performed. Hence, more *in vivo* experiments using a pharmacokinetic and pharmacokinetic approach would be beneficial. As a conclusive remark, *P. nigrum* should not only be regarded as "King of spices" but can also be considered as part of the kingdom of medicinal agents, comprising a panoply of bioactive compounds with potential nutraceutical and pharmaceutical applications.

KEYWORDS

Black pepper; piperine; *P. nigrum*; spice; traditional medicine

Introduction

Herbs and spices form an essential part of human nutrition since the dawn of humankind. They have been utilized for thousands of years to increase the flavor, color, and aroma of food, and are also recognized for their preservative characteristics and medicinal properties (Nagalingam and Arumugam 2015). Piper species belong to the Piperaceae family which is considered to be among the most ancient of flowering plants growing in tropical regions, comprising of 13 genera (Scott et al. 2007). This diversified genus *Piper* includes 4,166 scientific plant names of species rank; of these 1,457 are accepted species names, 1,376 synonyms, and 1,333 unassessed (Durant-Archibold, Santana, and Gupta 2018).

Piper nigrum L., most commonly known as pepper, is considered to be the "king of spices" because of its massive

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trade share in the global market (Srinivasan 2007). The name "pepper" originates from the Sanskrit word *pippali*, which means berry (Kumar et al. 2011). *Piper nigrum* is a perennial woody aromatic climber that may grow to a height of 50–60 cm (Bui et al. 2017). White and black peppers are different in their time of harvest and processing techniques. White pepper is obtained by removing the pulp from ripe fruit, while the black pepper is produced by drying unripe fruit until a wrinkled formed; therefore, black pepper contains the pulp. Both white and black pepper has a wide range of applications, like spices, preservatives, insecticides, and also in herbal medicine (Wang et al. 2017).

Geographically, *P. nigrum* is mostly cultivated in hot and moist conditions (Ravindran and Kallupurackal 2012a). The primary areas of the black pepper cultivation are in the Western Ghats of the South Indian Peninsula, subsequently was introduced to other countries in South and Southeast Asia (Hao et al. 2012). Currently, Vietnam is the largest producer in the world, where black pepper is cultivated mainly in the southern region of Vietnam (Hao et al. 2012). In 2016, Vietnam led the world's top pepper producing countries (total production = 140,000 metric tonnes), followed by Indonesia (70,000 metric tonnes), India (48,500 metric tonnes), and Brazil (45,000 metric tonnes) (Ten, 2017). Pepper production in India has gradually decreased over the time since countries like Vietnam and Indonesia have started pepper cultivation (Hussain et al. 2017).

Piper nigrum is mainly used as a culinary item in a wide variety of dishes. In Western cuisine, black pepper is principally used as a seasoning ingredient to enhance food flavor as well as in food preserving (Ravindran and Kallupurackal 2012b). Whole peppercorns may be used in stews and soups or as part of a bouquet garni, together with parsley, thyme, and bay leaf. Lightly crushed peppercorns may be added to creamy sauces or to coat fillet steaks or chicken breasts to add some spiciness to the food. Ground white pepper is used in Thai and Chinese cuisine, in the preparation of salads, cream sauces, and light-colored sauces.

Apart from its culinary uses, the use of *P. nigrum* is well renowned in folk medicine in several countries. The biological profile of this plant is extensively studied by the scientific community, and a wealth of literature has emerged. There is, however, no updated compilation of these available data to provide a complete profile of the medicinal aspects of *P. nigrum*. In this context, this study aimed to systematically review scientific data on the traditional and pharmacological properties of *P. nigrum*

Methodology

Search strategy

Articles published from 1980 to 2018 were used for literature search using two key databases including Science Direct and Google Scholar. Google search was also used. Books and online materials were also considered. The literature search was restricted to only the English language. The scientific name of the plant was identified from The Plant List database (theplantlist.org). The chemical structures of the naturally occurring compounds previously identified in *P. nigrum* were drawn using the ChemDraw Professional v.17. 1 software.

The two following keywords "*Piper nigrum*", "black pepper" were combined with the following terms: "traditional", "medicinal", "ethnomedicinal", "ethnomedical", "ethnoveterinary", "pharmacological", and "phytochemical". The traditional uses of *P. nigrum* were obtained mainly from surveys previously carried out. To obtain a complete profile of the pharmacological properties of *P. nigrum* and not to miss any paper, a number of activities were screened using the following terms: "antioxidant", "antimicrobial", "antibacterial", "antifungal", "antidiabetic", "anticancer", "analgesic", "hypolipidemic" and so on.

Search results

In the search results (see Figure 1), 360 articles related to the search keywords were obtained on Science Direct and 430 articles on Google Scholar up to August 2018. Also, two sources from books were obtained. After the removal of duplicates, 359 articles were recovered from all three sources. When inclusion and exclusion criteria were applied, a total of 181 articles were included, of which 76 were on traditional uses, 24 on phytochemistry and 84 on pharmacological properties of *P. nigrum*. With regards to articles related to pharmacological properties, 37 were related to antimicrobial (*in vitro* = 37, *in vivo* = 0), 17 to antioxidant (*in vitro* = 13, *in vivo* = 4), 11 to anticancer (*in vitro* = 9, *in vivo* = 2), 5 to neuroprotective (*in vitro* = 0, *in vivo* = 5), 3 to anticonvulsant (clinical = 1, *in vivo* = 2) and hypoglycemic (*in vitro* = 1, *in vivo* = 2), and 2 articles on analgesic (*in vitro* = 0, *in vivo* = 2), hypolipidemic (*in vitro* = 0, *in vivo* = 2) and anti-inflammatory (*in vitro* = 0, *in vivo* = 2).

Results and discussion

Traditional uses of P. nigrum

Different parts (flower, seed, fruit, and leaf) of *P. nigrum* have been reported to treat or manage many ailments, as displayed in Table 1. Most reports on the traditional uses of *P. nigrum* have been reported in Asia. The country with the highest number of reports was India ($n = 42$). This may be explained by the fact that India is one of the top producers of black pepper worldwide. Besides, Bangladesh ($n = 6$) also reported some uses of *P. nigrum* in folk medicines. Other countries displayed low number of reports; Pakistan and Mexico ($n = 2$), Cambodia, Thailand, Philippines, Malaysia, Poland, Mauritius, Algeria, and Morocco ($n = 1$). It is to be noted that although black pepper has been previously reported as an ingredient in European cuisine, there was only one reported use in traditional medicine from Poland.

Ethnomedicinal surveys documented so far revealed that the seeds were the most used part of *P. nigrum* ($n = 45$), followed by fruits ($n = 31$) and leaves ($n = 8$). However,

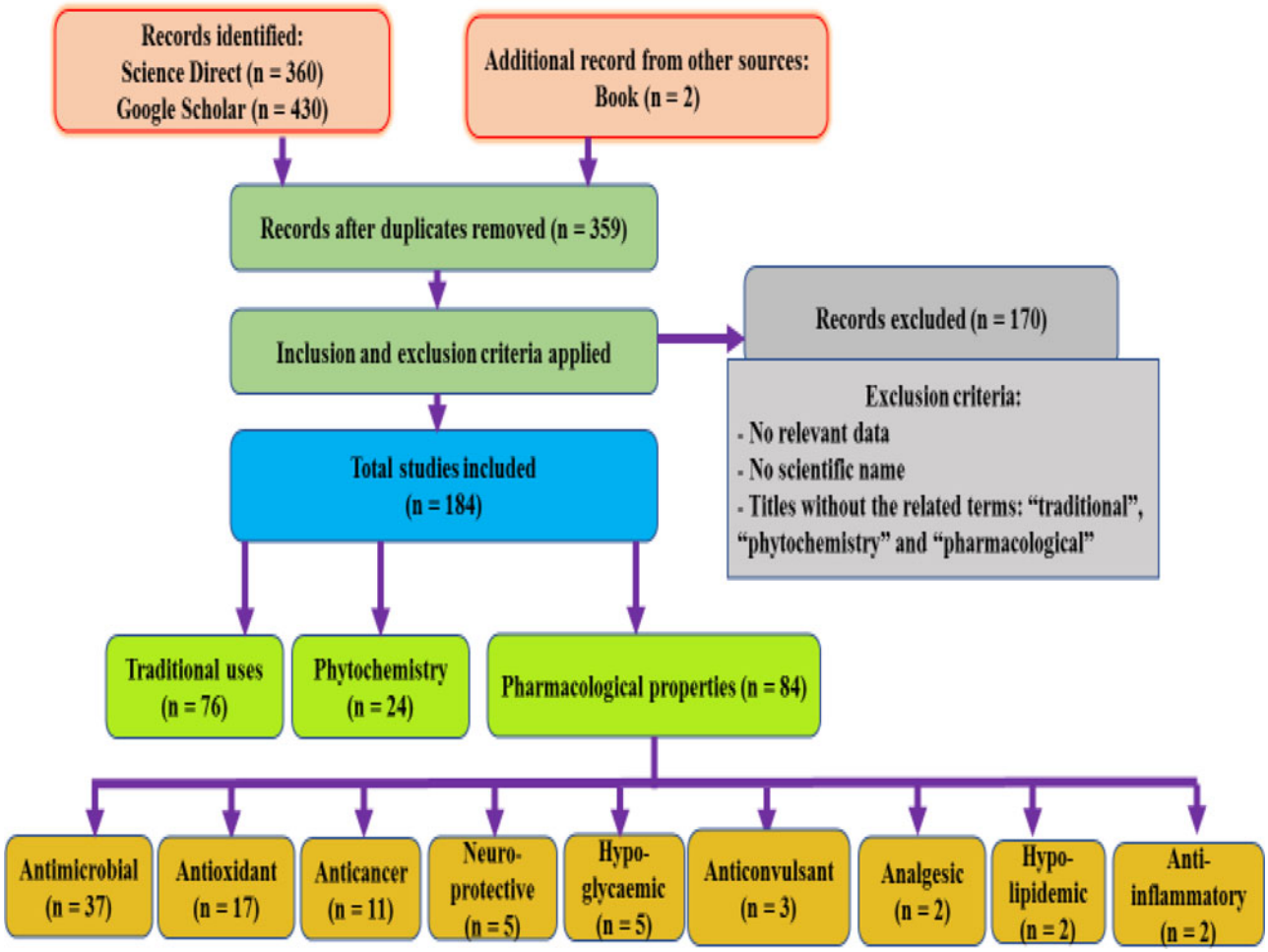

Figure 1. A visual representation of the selection process used in this review.

only two ethnomedicinal surveys reported the traditional use of *P. nigrum* flowers. In addition, diverse methods of preparations were used to target several diseases. The plant parts, mainly seeds and fruits, were ground to powder ($n = 40$) and mixed with other plants either to form pills or tablets ($n = 34$). Other methods of preparations stated were as paste ($n = 23$), crushed ($n = 8$), boiled in milk ($n = 8$), decoction ($n = 6$), and infusion ($n = 4$). Powdered form, pills or tablets, and paste were the most common methods of preparation reported since in these forms, they can be easily administered and stored. Another probable reason is that black pepper is used mainly as a spice in the diet, and therefore, it is mostly taken in its natural form in medicine as well.

Furthermore, among the diseases which *P. nigrum* were reported to treat (see Figure 2), menstrual disorders ($n = 16$) were mostly reported, which include menorrhagia, oligomenorrhea, hypomenorrhea, and dysmenorrhea. The next most reported treatment was for ear-nose-throat (ENT) related problems ($n = 15$), including a cough, sinusitis, throat pain, throat infection, and earache, followed by gastrointestinal disorders ($n = 15$) such as diarrhea and gastric problems. *Piper nigrum* was also used against skin diseases ($n = 10$), such as scabies, pruritus, bed sore, and boils, and also in the treatment of fever ($n = 9$), jaundice ($n = 8$), and snake bite ($n = 6$).

Ethnoveterinary uses of P. nigrum

It is important to highlight that *P. nigrum* was not only reported in the traditional medicine for human treatment but was also used in veterinary medicine to treat a range of ailments (see Table 2). Similar to the traditional human uses of *P. nigrum*, the highest number of ethnoveterinary reports were also from India ($n = 10$). The most reported plant parts of black pepper were seeds ($n = 29$), followed by fruits ($n = 4$), flowers ($n = 1$), and leaves ($n = 1$). The major methods of preparation reported were powder ($n = 16$), paste ($n = 15$), raw ($n = 3$), boiled ($n = 1$), and juice ($n = 1$). On the other hand, three reports did not mention any methods of preparation and stated that they were given orally to the animals.

With regards to the targeted ailments in ethnoveterinary medicine, *P. nigrum* was mostly reported for use against gastrointestinal disorders ($n = 19$), including indigestion, bloating, diarrhea, flatulence, and stomach ache. Other uses outlined were in the treatment of cough and cold ($n = 5$), skin diseases ($n = 3$), loss of appetite ($n = 2$), respiratory diseases ($n = 2$), and infertility ($n = 2$).

Phytochemistry of P. nigrum

Several parts (fruit, seed, and root) of *P. nigrum* have been profiled, and more than 50 compounds have been identified

Table 1. Traditional uses of *P. nigrum*.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
India	Seeds	NI	Indigestion, body ache, bone fracture and post labor ailment	Bhuyan and Baishya 2013
	Leaf Fruit	1 teaspoon of *P. nigrum* leaf juice and five to seven *P. nigrum* fruit powder are made to a mixture.	Hypertension	Sethiya et al. 2018
	Seeds	Decoction	Respiratory system diseases	Venkatachalapathi et al. 2018
	Seed, flower, fruit	Powdered seeds of *P. nigrum* are mixed with butter, and orally consumed. The flower paste of *P. nigrum* is mixed with ghee and is orally given for 4 days.	Snake bite	Upasani et al. 2017
	Fruit	Maceration	Lactation Cough	Chander, Kartick, and Vijayachari 2015
	Fruit	Raw	Sinusitis, Vomiting	Vijayakumar et al. 2015
	NI	Powder	Stomach Problems	
	Seed	Paste	Cuts, Wounds, Fever	
	Fruit	NI	Aphthae, ulcer in intestine, crack foot, cuts, gangrene, gingival wounds, Otorrhoea, snake bite	Bhat, Hegde, and Hegde 2012
	Fruit	300 g of *P. nigrum* powdered fruit and 300 g of fresh flower extract of *Calotropis procera* (Aiton) Dryand are mixed and made to tablets. The tablets are taken 3–4 times per day till recovery.	Epilepsy	Sharma et al. 2013
	Seed	Seed powder mixed with butter.	Snake bite	Upadhyay et al. 2010
	Seed	*P. nigrum* seeds are boiled in milk and water and taken once every day in the early morning consecutively for 4 to 5 days.	Malaria Splenomegaly	
	Leaf	Leaves are crushed and applied topically applied on affected area of the skin.	Skin diseases	
	Leaf	Crushed leaves are mixed with mustard oil or cow milk or crushed with garlic bulbs and mixed with lemon juice.	Ringworm	
	Seed	*Tinospora cordifolia* plant paste and 5 seeds of *P. nigrum* are orally consumed once per day in the morning	Leucorrhoea	
	Fruit	NI	Throat pain Disease resistant Blood circulation Body shining	Francis Xavier, Kannan, and Auxilia 2015
	Fruit	NI	Dandruff, pruritus, scabies, eczema, bed sore, boils	Bhat et al. 2014
	Seed	Seed powder ground with equal amount of betel leaf paste is applied daily.	Eczema	Policepatel and Manikrao 2013
	Seed	A paste is prepared using 10g *Abutilon indicum* roots, 10 g *Clerodendrum indicum* L. roots, 5 g *Cissampelos pareira* roots, 5 g *Azadirachta indica* leaves, 2 g *Andrographis paniculata* whole plant, 3 g fresh bulb of *Curcuma longa*, 15 g seeds of *P. nigrum*, 3 pieces *Zingiber officinale* and 3 pieces *Polygala arvensis* roots are made to pills. Two pills are taken per day; one in the early morning just before breakfast and another at night.	Headache	Dey et al. 2017
	Seed	10 g *Laportea interrupta* roots and 10 g *P. nigrum* seeds are ground to produce a powder. During epilepsy attack, a pinch of this powder is to be inhaled by the patient for the next 4 days.	Epilepsy	

(*continued*)

Table 1. Continued.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
	Seed	50 g *Cissus repanda* stem, 25 g *Leea macrophylla* roots, 10 g *Mucuna pruriens* roots and 10 g *P. nigrum* seeds are ground and made to pills. Pills are taken on empty stomach for one week.	Epilepsy	
	Seed	1 inch of *Dolichos lablab* roots, 1 inch *Achyranthes aspera* roots, 3–4 pieces *Moringa oleifera* dry flower, 7 pieces *P. nigrum* seeds and 1 g *Axis axis* (horn dust) are ground and mixed to a paste. Pills of 1/3 inch diameter are prepared from the paste. One pill is consumed thrice daily for 3 days.	Epilepsy	
	Seed	8–10 pieces of *P. nigrum* seeds are grounded to dust and are mixed with 100 ml of hives fresh honey (from *Apis cerana indica*) and applied inside the nose.	Insomnia	
	Seed	2 g *Axis axis* dried skin, 5 mL *Gallus gallus domesticus* blood, 1 piece *Spilostethus hospes* larva, 2 g *Hemidesmus indicus* roots and 5 *P. nigrum* seeds are mixed together to a paste. Pills, about the sizes of a pea, are made from the paste. A pill is taken for 10 days.	Headache	
	Seed	The leaves together with *Zingiber officinale* rhizome and seeds of *P. nigrum* are decocted and is taken once every day for a period of 5 days.	Reduce swelling	Jagtap, Deokule, and Bhosle2006
	NI	NI	Cardiovascular diseases	Esakkimuthu et al. 2016
	NI	NI	Type 2 Diabetes	
	Fruit	Granulated leaves of *P. nigrum* fruits, *Cynodon dactylon* and *Phyllanthus amarus* are mixed to form an extract which is taken orally.	Jaundice	Patel et al. 2011
	NI	Herbal medicine using *P. nigrum*, *A. vasica* and honey by Kani traditional healers.	Headache, earache, cold	Ayyanar and Ignacimuthu2011
	NI	Herbal medicine using *Elettaria cardamomum*, *A. galanga*, *P. nigrum*, *Zingiber officinale* and sugar by Kani traditional healers.	Headache, asthma	
	NI	Herbal medicine using *Tephrosia purpurea*, *Carmona retusa*, *P. hymenophyllum* and *P. nigrum* by Kani traditional healers.	Gastric problems	
	Fruit	Powder/Oral	Jaundice, Gastric problems, Indigestion	Sureshkumar, Silambarasan, and Ayyanar2017
	Seed	Same proportions of corm of *Amorphophallus paeoniifolius*, roots of *Rawolfia serpentina*, dried rhizome of *Zingiber officinale*, seeds of *P. nigrum* and *P. longum* are made into paste and tablets are prepared and left to dry in the sun. Tablets are orally taken about 2 weeks.	Haemorrhoids	Mallik, Panda, and Padhy 2012
	Seed	The endosperm of *Caesalpinia bonduc* L and seeds of *P. nigrum* L. are crushed to a paste and is consumed together with honey.	Fever	
	Seed	A paste is made from 3 cm long root of *Mimosa pudica* L. with seeds of *P. nigrum* and mixed with curd. It is taken orally in empty stomach for 7 days.	Haemorrhoids	
	NI	A powder is made from dried *Smilax zeylanica* L roots along with *P. longum* and *P. nigrum* and is taken orally twice daily.	Infertility	

(*continued*)

Table 1. Continued.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
	Seed	*Vitex negundo* L. leaves decoction is mixed with powdered seeds of *P. nigrum* and honey and taken orally.	Cough	
	NI	Fresh leaf pastes of *Clitoria ternatea* L. with the paste of *P. nigrum* is applied on affected area.	Swollen legs	Shanmugam, Rajendran, and Suresh 2012
	NI	Decoction of *Tephrosia purpurea* Pers. root is given with the 5 g *P. nigrum* extract for one week.	Urinary disorders	
	NI	Dried leaf powder of *Glossocardia bosvallia* is mixed with *P. nigrum* powder.	Whooping cough	Wagh and Jain 2018
	Seed	Newly grown *Nyctanthes arbor-tristis* L. leaves are ground with *P. nigrum* seeds and made into tablets of 2 g each. One tablet is taken twice daily for 14 days.	Menorrhagia	Bhatia et al. 2015
	Seed	Seeds of *P. nigrum* are ground along with leaves of *Punica granatum* and are mixed with water and the filtrate is taken twice daily.	Leucorrhea	
	Seed	Eight spoons of *Sesamum indicum* seeds and 10 powered seeds of *P. nigrum* and jaggery are boiled in water until it reaches half the initial volume is halved and is taken twice per day for 15 days before the due date of menses.	Oligomenorrhea	
	Seed	Two teaspoons of *Sesamum indicum* seeds are boiled together with *P. nigrum* seeds and jaggery and taken orally twice daily for five days before the onset of period.	Hypomenorrhea	
	NI	A paste is made using the roots of *Tylophora asthmatica, P. nigrum* L., garlic and fruits of *Syzygium cumini* and is orally consumed orally for 2–3 days.	Jaundice	Sharma et al. 2012
	Fruit	*P. nigrum* fruits are ground to powder and are given orally.	Jaundice	
	Fruit	Ground leaves of *Cynodon dactylon, Phyllanthus amarus* are mixed with the fruits of *P. nigrum* and extracted. The extract is administered.	Jaundice	
	NI	The tablets are made from a mixture of *Balanotis roxburghii* seeds, *P. nigrum* and jaggery. The tablet is taken once daily for 3 days.	Jaundice	
	Seed	*P. nigrum* seeds are made to powder and is mixed with ginger and honey. The mixture is orally administered for 3–5 days.	Common cold	Lingaraju, Sudarshana, and Rajashekar 2013
	Leaf and Seed	Decoction of leaves and seeds is taken orally.	Diabetes	
	NI	Powder, decoction or aqueous root extract (20 g in 30 mL water) of *Clerodendrum serratum* (L.) Moon. are mixed with a pinch of powdered *P. nigrum*.	Fever	Patel, Acharya, and Acharya 2014
	Leaf	Powder of leaf and root bark of *Kleinia grandiflora* are mixed with the leaves of *Cardiospermum halicacabum* and leaf juice of *P. nigrum*.	Gastric problems	Ayyanar and Ignacimuthu 2005
	Fruit	Eaten as vegetable	Increases breast milk as well as relieves pain after child birth	Buragohain 2008
	NI	*Pheretima posthuman, Allium sativum* and *P. nigrum* are gound and consumed.	Lactogogue	Chellappandian et al. 2014
	NI	*Gallus gallus domesticus* meat is cooked with *Brassica nigra, Allium cepa, P. nigrum* and *Allium sativum* in the urine of the cow and consumed.	Stomachache	

(*continued*)

Table 1. Continued.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
	Seed	*P. nigrum* seeds are soaked in pig bile, allowed to air dry and made to a powder and consumed orally.	Fever	
	NI	*Gallus gallus domesticus* meat is mixed with *Brassica nigra*, *Allium cepa*, *P. nigrum* and *Allium sativum* and cooked in urine and consumed.	Jaundice	
	NI	Powdered Bezoar of *Bos primigenius taurus* Linnaeus is mixed with *P. longum*, *P. nigrum* and *Allium sativum* and is consumed orally.	Cough, bronchitis	
	Seed	One teaspoon of juice of fresh stem bark of *Bombax ceiba* L, one teaspoon of juice of fresh root of *Asparagus racemosus* Willd., seven dried seed powder of *P. nigrum* L. and a teaspoon of processed sugar taken orally in empty stomach two times daily for 21 days.	Gonorrhoea, impotency, spermatorrhea, sterility, nocturnal emission, leucorrhea, increasing sperm in semen and act as aphrodisiac.	Behera and Misra 2005
	Seed	10 g fresh root of *Elephantopus scaber* L. long with 21 dried *P. nigrum* L. seeds are ground and taken orally with 250 mL of raw cow milk on an empty stomach twice per day.	Spermatorrhea, leucorrhea, ametrorrhagia, menstrual complaints, menorrhagia and dysmenorrhea.	
	Seed	One or two *Mangifera indica* L. kernels along with seven or 21 dried *P. nigrum* L. seeds are ground to powder and orally consumed with one glass of raw cow's milk on an empty stomach, twice every day for 3 weeks.	Dysmenorrhoea, menorrhagia, leucorrhea, metrorrhagia, menstrual complaints and spermatorrhea	
	Seed	20 g of *Pterocarpus marsupium* Roxb. fresh stem bark is boiled in 1 L of water until the volume reaches about one fifth of the initital volume. One cup of this decoction along with seven powdered dried seeds of *P. nigrum* L. is consumed orally on an empty stomach daily for 3 weeks.	Spermaturia, spermatorrhea, leucorrhea, metrorrhagia, amenorrhea, dysmenorrhea, menorrhagia and impotency	
	NI	Leaf paste of *Adhatoda vasica* Nees. is mixed with *P. nigrum* L made into pills taken orally, two to three times daily.	Fever	Mahishi, Srinivasa, and Shivanna 2005
	NI	Roots of *Tylophora asthmatica* with *P. nigrum* L., fruits of *Syzygium cumini* Lam. and garlic are made into a paste and administered orally for 2–3 days.	Jaundice	
	NI	*P. nigrum*, dried ginger and palm sugar are mixed along with water and coffee is prepared.	Cold	Jeeva and Femila 2012
	NI	Omelette is made using powdered *P. nigrum* and salt.	Cold and coughs	
	NI	*P. nigrum* is given along with common salt.	Dental carries (Toothache)	
	NI	NI	Stomach disorders	
	Fruit	Orally consumed in powder	Stomach ache, indigestion	Yabesh, Prabhu, and Vijayakumar 2014
	NI	Herbal medicine prepared by traditional healers using *Vetiveria zizanoides*, honey and *P. nigrum*	Stomach ache	
	NI	Leaf decoction of *Ocimum sanctum* L.with *P. nigrum* and palmgur	Fever	Singh and Chaudhuri 2018
	NI	A mixture of *Cissampelos pareira, P. nigrum* L., *Mimosa pudica* L. and *Hibiscus rosa-sinensis* L. is prepared.	Birth control	Semwal et al. 2014
	Fruit	Oral/Powder	Viral hepatitis, flatulence, indigestion and dermatopathy	Sivasankari, Anandharaj, and Gunasekaran 2014
	Fruit	The fruits of *P. nigrum* L. are crushed and mixed with ghee and the product is orally taken.	Scabies	Saikia et al. 2006
	Seed, Fruit	NI	Indigestion, loss of appetite, waist pain, cough and cold, diarrhea	Rout and Panda 2010

(*continued*)

Table 1. Continued.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
	NI	Fruit powder of *Helicteres isora* L. is boiled with *P. nigrum, allium sativum* rhizome and gingelly oil is applied.	Earache	Kumar, Ayyanar, and Ignacimuthu2007
	Seed	Powdered seeds are orally administered.	Cough, bronchial disorders and as antidote against snake bite	
	NI	Root paste of *Plesmonium margaritiferum* is mixed with *P. nigrum* is taken two times per day.	Dysentery	Sen and Behera2008
	NI	Bark decoction of *Pterospermum xylocurpum* is mixed with *P. nigrum* powder and is taken two times per day.	Infantile diarrhea	
	Fruit	Decoction of leaves of *Trichosanthes dioica* Roxb. and *P. nigrum* fruit powder is taken 3–4 times daily.	Diarrhoea	
	NI	Stem piece of *Cassia auriculata* Linn. is ground with leaves of *Leucas aspera* Spreng., *P. nigrum* Linn. and *Allium sativum* Linn. into paste is taken orally for 3–4 days.	Cold	Rajakumar and Shivanna2010
	Seed	The dried seeds of *P. nigrum* are taken orally.	Throat infection	Ignacimuthu, Ayyanar and Sivaraman2006
	NI	Seed powder of *Annona reticulata* L. is mixed with 3 g of *P. nigrum*.	Spoiling of pregnancy up to 3-4 months duration	Abe and Ohtani2013
	NI	3 g of leaf paste of *Capparis zeylanica* L. is mixed with 2 g of *P. nigrum* paste and applied for slight boiling before bed.	Breast swelling	
	Seed	3 mL of the fresh juice of stem bark of *Crateva nurvala* is mixed with 1 g *P. nigrum* seed powder and is taken by women.	Contraceptive (1st seven days of menstrual cycle)	
	NI	5 g of the stem juice of *Saccharum officinarum* L. with 1 g of *P. nigrum* paste.	Constitutional disorder	
	NI	3 mL of the decocted *Sida acuta* leaf is mixed with 2 g *P. nigrum* paste and 1 mL of lime water and is taken two times per day after food for a week.	Swelling of scrotum	
	NI	About 15 mL of *Vitex negundo* L. decocted root bark together with a paste of 21 *P. nigrum* is taken twice a day after food for seven days.	Typhoid fever	
Bangladesh	Fruit	375 g of leaves and 375 g of stems of *Solanum barbisetum* are mixed with 12 g *P. nigrum* L. fruits, 12 *Cinnamomum tamala* leaves, 2 *P. longum* L. fruits, rock salt, powdered dried bark of *Cinnamomum verum* and 25 g of crystalline sugar is placed in boiling water in an earthen pot. After the decoction has been cooled and the water is filtered through a piece of cloth and the filtrate is orally administered to patients.	Influenza	Rahmatullah et al. 2012
	Seed	Powdered bark of *Diospyros peregrina* L is ground with 2–5 seeds of *P. nigrum* L. and applied to gout affected areas.	Chest pain due to gout	Rahmatullah et al. 2013
	Seed	Leaves of *Eleusine indica* (L.) are macerated with seeds of *P. nigrum* L. and applied to painful areas once daily for 21 days.	Pain in spinal cord	
	Seed	Macerated whole plants of *Sida cordata* are mixed with powdered seeds of *P. nigrum* L. and applied around the sides of the abscess.	Abcess	
	Seed			

(*continued*)

Table 1. Continued.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
		The roots of *Leucas aspera* (Willd.) Link are macerated and the juice obtained is mixed with 10–15 powdered seeds of *P. nigrum* L. and administered orally 3 times daily on an empty stomach.	Severe headache due to fever, dog bite.	
	Seed	Powdered seeds of *P. nigrum* L are taken with two and a half roots of *Solanum virginianum* L.	Chicken pox	
	Seed	Roots of *Rauwolfia serpentina* L. are crushed with seeds of *P. nigrum* L. and rhizomes *Zingiber officinale* and macerated. Honey is added to the mixture to form pills. Three pills are to be taken daily for 3 weeks. The pills serve as prophylaxis from inside	Skin diseases	Islam et al. 2011
	Fruit	Fruits of both *Colocasia nymphaeifolia* Vent. and *P. nigrum* L. are crushed and taken twice for 7 days.	Goiter	
	Fruit	One powdered fruit of *P. nigrum* is mixed with one macerated root of *Achyranthes aspera*. The mixture is taken on an empty stomach for one day.	Menstrual pain	Biswas et al. 2011
	Fruit	Roots of *Abutilon indicum*, roots of *Glycosmis pentaphylla*, roots of *Eleusine indica*, and roots of *Amaranthus spinosus* are mixed and macerated. Sugar and 21 powdered fruits of *P. nigrum* are then added to the macerated mix and of which 42 pills are obtained. One pill is to be taken with 1 cup of water three times per day for 2 weeks.	Prolapse of uterus	
	Fruit	Several *Aristolochia indica* leaves are mixed and macerated with 2–3 fruits of *P. nigrum* and the juice obtained is orally taken immediately.	Snake bite	
	Fruit	20 fruits of *P. nigrum*, one handful of leaves of *Morus indica,* 50 g rhizomes of *Zingiber officinale* and 25–30 drops of oil prepared from seeds of *Brassica campestris* are mixed and macerated. The mixture is then applied to fractured area as a thick paste and covered with a piece of cloth. A fresh mixture is applied and bandaged for a week.	Bone fracture	
	Seed	Roots of *Pergularia daemia* are macerated with 2–3 seeds of *P. nigrum* L. Pills are made from the macerated mix are taken thrice daily	Irregular menstruation	Hasan et al. 2012
	Fruit	2.5 g *P. nigrum* fruits and 3 g *Datura metel* L. root are ground. It is orally administered immediately.	Dog bite	Tumpa, Hossain, and Ishika 2014
	Fruit	*Polygonum hydropiper* leaves are macerated and mixed with 1 powdered *P. nigrum* fruit. From the mixture, pills are prepared. One pill is taken three times per day for 2–3 days.	Menstrual pain	
	NI	2 g of *P. nigrum*, 1 handful leaves of *Polygonum hydropiper.*, 1 nut of *Myristica fragrans*, 1 fruit of *Terminalia chebula*, 3 g *Carum carvi*, 20 g young leaves of *Cynodon dactylon* are macerated. Pills are prepared from the mixture. 1 pill is taken with 1 cup of water thrice daily for 2 weeks.	Ulcer	
	Fruit	1 powdered fruit of *P. nigrum* and the macerated leaves of *Polygonum hydropiper* are mixed. Pills are prepared from the mixture. It is taken three times daily for 2–3 days.	Menstrual pain	
	Fruit		Catarrh with cough	

(*continued*)

Table 1. Continued.

Country	Part of plant used	Mode of preparation/ dosage	Ailments/Medicinal use	References
		12 fruits of *P. nigrum*, 5 g leaves and cord of *Solanum sisymbriifolium*, 12 leaves of *Cinnamomum tamala*, 2 fruits of *P. longum*, 5–6 g bark of *Cinnamomum zeylanicum*, 5–6 g rock salt and 24 g sugar candy are mixed and boiled in 500 mL of water in a clay pot. When it forms 1 cup it is filtered after cooling. The warm solution is taken once a daily for 1 week.		
Cambodia	Seed	Crushed	Liver diseases	Chassagne et al. 2017
Thailand	Fruit	Decoction	Treating numbness	Neamsuvan et al. 2015
Pakistan	Seed	Powder	Fever	Shah and Rahim 2017
	Fruit	Powder	Body pain	
	Seed	Juice of the leaves of *Solanum surattense* along with the seed powder *P. nigrum* is orally taken.	Joint pain	Dey and De 2012
Philippines	Leaf	Decoction or infusion	Toothache	Abe and Ohtani 2013
Malaysia	Fruit	NI	Cough	Mohamad et al. 2011
Mexico	NI	NI	Mouth diseases, gastrointestinal disorders	Sharma et al. 2017
	Leaves	Infusion, Mouthwash	Dental caries, gum disease	Rosas-Pinon et al. 2012
Poland	Leaves	Infusion	Digestive problems	Kujawska and Hilgert 2014
Mauritius	NI	A juice is prepared with 3 leaves of *Mormodica charantia* L. together with *P. nigrum* and is consumed once per week.	Type 2 Diabetes	Mootoosamy and Fawzi 2014
Algeria	Seed	Infusion, powder, cataplasm	Lower blood glucose level	Telli, Esnault, and Ould El Hadj Khelil 2016
Morocco	NI	Dried plants of *Bunium bulbocastanum*, *Capparis spinosa*, *Myristica fragrans*, *Syzygium aromaticum*, *P. nigrum*, *P. longum*, *P. cubeba*, *Rosa centrifolia*, *Illicium verum*, *Asphodelus microcarpus*, *Alpinia officinarum* and *Zingiber officinale* are ground and mixed with food.	General health, gynaecological, musculoskeletal	Teixidor-Toneu et al. 2016

NI: Not indicated.

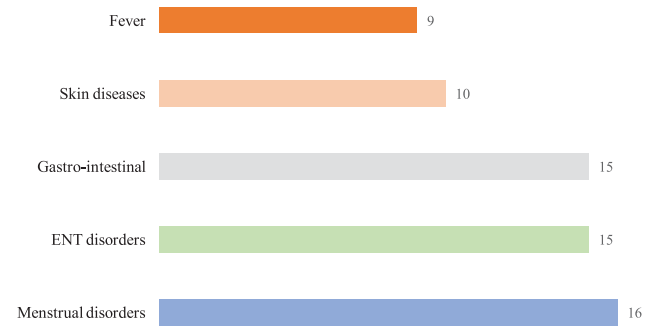

Figure 2. Top 5 most reported disorders using *P. nigrum* as traditional medicine.

anisms of action are displayed in Figure 4. Phytochemical screening of *P. nigrum* fruit extracts (water, methanol, and ethanol) revealed the presence of a range of secondary metabolites, including alkaloids, glycosides, terpenoids, steroids, flavonoids, tannins, and anthraquinones (Nahak and Sahu 2011). The main odorants identified from the fruit of *P. nigrum* were α- and β-pinene, myrcene, α-phellandrene, limonene, linalool, methylpropanal, 2- and 3-methylbutanal, butyric acid and 3-methylbutyric acid (Jagella and Grosch 1999).

The first phytochemical report of *P. nigrum* essential oil was carried out by (Pino et al. 1990), whereby a total of 46 components was detected using gas chromatography-mass spectrometry (GC/MS) including (E)-B-ocimene, 6-guaiene, (Z) (E)-farnesol, 6-cadinol, and guaiol. Another phytochemical analysis conducted by (Kapoor et al. 2009) compared the essential oil, and the ethanol and ethyl acetate oleoresins of *P. nigrum* fruits using Clevenger and Soxhlet apparatus, respectively. GC-MS analysis showed a total of 54 compounds with the major component being β-Caryophyllene (29.9%) together with limonene (13.2%), β-pinene (7.9%), sabinene (5.9%), and some other components in lower amounts. In contrast, Tchoumbougnang et al. (2009) found different levels of compounds in the fruit oil; δ-3-carene (18.5%), limonene (14.7%), β-caryophyllene (12.8%), and sabinene (11.2%) as major components. Additionally, Orav et al. (2004) found that the fruit oil principally contained (E)-β-caryophyllene (1.4–70.4%), eugenol (0.1–41.0%), limonene (2.9–38.4%), β-pinene (0.7–25.6%), 3-carene (1.7–19.0%), sabinene (0–12.2%), and α-pinene (0.3–10.4%). Similarly, caryophyllene (23.98%), limonene (14.36%), and α-terpinene (13.26%) are the main compounds identified in the essential oil, as analyzed by (Jeena et al. 2014). Moreover, Wang et al. (2018) analyzed 23 *P. nigrum* oil samples from various countries including Malaysia, Sri Lanka, Madagascar, Ecuador, India, Vietnam, Indonesia, Brazil, India, and China. The dominant terpenes in all of the oil samples were β-caryophyllene (14.7– 52.5%), 3-carene (0.8–21.1%), limonene (4.4–18.7%), α-pinene (1.5–7.3%), and β-pinene (1.7–9.4%). Also, sabinene was present in many samples (1.0–15.9%) but in trace amount in the Chinese and Malaysian samples (< 0.2%).

On the other hand, in the ethanol and ethyl acetate oleoresins, the key component was found to be piperine (63.9 and 39.0%) along with various other components in smaller quantities. In other phytochemical analyses on *P. nigrum* fruits ethanolic extracts, piperine was also found to be the active major compound (Singh et al. 2013; Zarai et al. 2013). Also, Singh et al. (2004) observed that the acetone extract also showed the presence of piperine (33.53%) as the major component, followed by piperolein B (13.73%), an alkaloid of MW 361 (5.59%) and its isomer (5.49%), piperamide (3.43%), piperettine (2.76%), quineensine (3.23%), hinokinin (1.88%), retrofractamide A (1.57%), and N-trans feruloyltyramine (1.45%). Moreover, Liu et al. (2013) determined the phytochemical profile of the berries of five different genotypes of *P. nigrum* in China, namely: Jianyin-1, Banyin-1, Banyin-2, Banyin-3, and Banyin-4. The piperine content of the five genotypes ranged from 3.12 to 5.78%. Banyin-1 genotype was found to contain higher levels of α-thujene, β-pinene, 3-carene, limonene, and caryophyllene compared to the other tested samples.

Moreover, the petroleum ether extract of *P. nigrum* dried whole fruits was found to contain the compounds: stigmastanol, β-sitosterol, stigmasterol, stigmastanol 3-O-β-D-glucopyranoside, β-sitosterol 3-O-β-D-glucopyranoside, [(2E, 4E)-octadienoyl]-N-isobutylamide, sarmentine, [(2E,4E)- dodecadienoyl]-N-isobutylamide, [(2E,4E)-dodecadienoyl]pyrrolidine, hexadecenoic ethyl ester, octadecanoic acid, pellitorine, hexadecanoylpyrrolidine, [(2E)-octadecanoyl] pyrrolidine, 1-[(2E,4E,12Z)-octadecatrienoyl]-N-isobutylamide, piptaline, 1-[7-(3,4-methylenedioxyphenyl)-(2E,4E)-heptadienoyl]-N-isobutylamide, 1-(3,4-methylenedioxyphenyl)-(1E)-tetradecene (Siddiqui et al. 2004).

Three amides, pipgulzarine, pipzorine, and piptahsine, were also identified in the dried seeds of *P. nigrum* using petroleum ether extraction along with nine known constituents including (2E,4E,8Z)-N-(isobutyl) eicosatrienamide, pellitorine, pipercide, piperine, stigmastanol, stigmasterol, decurrenal, stigmasterol 3-O-β-D-glucopyranoside, and 5,10(15)-cadinen-4-ol (Siddiqui et al. 2003). In addition, the crystalline compound [{(1,5-(1,3)-benzodioxol-5yl)-1-oxo-2,4 pentadienyl}-piperidine] was also isolated from the petroleum ether extract of *P. nigrum* seeds along with fifteen sesquiterpenes (linalool, 4-terpinol, α-terpinol, δ-elemene, α-copane, β-elemene, β-caryophyllene, α-caryophyllene, gurjunene, β-bisabolene, δ-cadinene, elemol, caryophyllene oxide, murrolene, β-eudesmol) (Gupta, Gupta, and Gupta 2013).

Lim et al. (2009) identified the alkaloids piperdine, pelliterine, piperidine, piperine, and pellitorine in *P. nigrum* dried roots from Malaysia. In addition, seven alkaloids, namely N-isobutyl-4-hexanoyl-4-hydroxypyrrolidin-1-one, erythro-1-(1-oxo-4,5-dihydroxy-2E-decaenyl)piperidine, threo-1-(1-oxo-4,5-dihydroxy-2E-decaenyl) piperidine, threo-N-isobutyl-4,5-dihydroxy-2E-octaenamide, 1-(1,6-dioxo-2E,4E-decadienyl) piperidine, 1-[1-oxo-3(3,4-methylenedioxy-5-methoxyphenyl)-2Z-propenyl]piperidine, and 1-[1-oxo-5(3,4-methylenedioxyphenyl)-2Z,4E-pentadienyl] pyrrolidine, were isolated from the roots of *P. nigrum* (Wei et al. 2004).

Table 2. Ethnoveterinary properties of *P. nigrum*.

Country	Part of plant used	Mode of preparation/dosage	Ailments/ Medicinal use	References
India	Seed	Equal quantity of *P. nigrum*, hengu (*Ferula asafetida*), ginger, turmeric and common salt are mixed and orally fed to cattle.	Anthrax, Constipation, Bloating	Usha, Rajasekaran, and Siva 2016
	NI	One handful of the crushed leaves of *Allium sativum*, *Tylophora indica*, *Datura metel*, *Aegle marmelos* and 10–15 *P. nigrum* are mixed with 2 spoons of mustard. Ragi balls along with this paste is orally taken twice a day for 4 days.	Loss of appetite	Naik et al. 2012
	NI	10 *P. nigrum* are mixed with *5* inches of *Tenospora cordifolia* stem with 80 mL of Aloe *barbadensis* is added to 4 betel leaves, 1 *Allium sativum* and *Allium cepa* ground with a cup of water. The mixture is given orally two times daily for 3 days.	Cough	
	NI	10 g *P. nigrum,* 15 leaves of *Adhatoda vasica*, 15 leaves of *Tylophora indica*, 1 handful of *Albizia amera*, 1 or 2 leaves of *Aloe barbadensis*, 1 *Allium sativum* and 100 g cherry are ground to a decoction and is fed twice daily.	Cough	
	Seed	Seeds of *P. nigrum* L., leaves of *Acalypha indica* L. and *Leucas aspera* (Willd.) Link and bulb of *Allium cepa* L. are crushed and given to animals.	Black quarter disease	Seebaluck, Gurib-Fakim, and Mahomoodally 2015
	Seed	Orally given to camels	Snake bite	Sharma and Manhas 2015
	Seed	Equal proportions of seed powder of *P. nigrum*, *F. asafetida*, ginger, turmeric powder and table salt are mixed and fed with rice gruel.	Indigestion	Mallik, Panda, and Padhy 2012
	Seed	A paste is made 10–15 *P. nigrum* seeds, 50 g ginger, 50 g garlic and butter and divided into two equal halves. Half is orally given to the animal and the other half is applied together over.	Cough and cold	
	Flowers	The ground fruit of *Capsicum annuum* is mixed with flowers of *Syzygium aromaticum* and *P. nigrum in* water and given orally.	Skin disease of livestock	Meghvansi et al. 2010
	Fruit	*P. nigrum* fruit, seeds of *Trachyspermum ammi,* rhizome *of Zingiber officinale* and *Ferula asafetida* are mixed and crushed with water and the paste is administered to affected area.	Blot	Phondani, Maikhuri, and Kala 2010
	NI	Powders of *P. nigrum* mixed with water and added to drink.	Poisoning	
	NI	Ground *P. nigrum* is mixed with water and black salt. Mixture is added to feed.	Indigestion	
	NI	*P. nigrum,* seeds of *Trachyspermum ammi*, rhizome of *Curcuma domestica*, leaves of *Trigonella foenum* and *Dendrocalamus strictus* are ground and added to drink.	Pneumonia	
	NI	One teaspoon of root juice of *Clitoria ternatea* Linn. along with a *P. nigrum* Linn. for 20 days.	Infertility	Ghosh 2008
	NI	One teaspoon of root juice of *Mimosa pudica* Linn. along with *P. nigrum* Linn. for 20 days.	Infertility	
	Fruit	5 g of fruit powder of *P. nigrum* Linn. is mixed in a cup of lukewarm water and drunk at night.	Constipation	
	NI	The roots of *Hemidesmus indicus* Linn. are ground with *P. nigrum* and is orally taken.	Stomach ulcers	Rajith and Ramachandran 2010
	Seed	The dried *P. nigrum* seed paste and rock salt are mixed with curd and is fed orally.	Lack of appetite	Jayakumar et al. 2017
	Seed	The seeds of *P. nigrum* are boiled in water and the extract is fed orally.	Bloating	
	Seed	The seed powder of *P. nigrum* is mixed with rock salt and jaggery and fed orally.	Cold	
	Seed	The seed powder of *P. nigrum* is mixed with alcohol and orally fed.	Cold	
	Seed	The seed powder of *P. nigrum* is mixed with rock salt and jaggery and is fed orally.	Constipation	
	Seed	The paste of the seeds is made with rock salt and curd and is orally fed.	Constipation	
	Seed	A paste of *P. nigrum* seeds and seeds of *Cuminum cyminum*, *Carum bulbsocastanum*, *Ferula assa-foetida*, *P. longum*, and *Trachyspermum roxburghianum*, and the rhizome of *Zingiber officinale* in equal proportion are mixed with rock salt and fed orally.	Constipation	
	Seed	The seeds paste of the *P. nigrum, Cuminum cyminum*, *Carum bulbsocastanum*, *Ferula assa-foetida*, *P. longum*, *Trachyspermum roxburghianum*, rhizome of *Zingiber officinale* mixed in equal portion along with rock salt is fed to the animals.	Diarrhoea	

(*continued*)

Table 2. Continued.

Country	Part of plant used	Mode of preparation/dosage	Ailments/ Medicinal use	References
	Seed	Crushed *P. nigrum* seeds are made to a paste with rock salt and curd, and the paste is given orally.	Diarrhoea	
	Seed	The seeds powder is mixed with rock salt and jaggery and is given orally.	Diarrhoea	
	Seed	The seeds paste is mixed with boiled rice and is given orally.	Diarrhoea	
	Seed	A paste is prepared with the seeds of *P. nigrum, Cuminum cyminum*, *Carum bulbsocastanum*, *Ferula assa-foetida*, *P. longum*, *Trachyspermum roxburghianum*, rhizome of *Zingiber officinale*. The paste is mixed in equal amount with rock salt and is given orally.	Ecto-parasitic infection	
	Seed	A paste is made using crushed *P. nigrum* seeds, rock salt and curd and is given orally.	Ecto-parasitic infection	
	Seed	A paste is made with crushed *P. nigrum* seeds, rock salt and curd and is given orally.	Endo-parasitic infection	
	Seed	A paste is prepared using equal amount of crushed seeds of *Cuminum cyminum, Carum bulbsocastanum, Ferula assa-foetida, P. longum, Trachyspermum roxburghianum,* rhizome of *Zingiber officinale* and is mixed with rock salt and is orally fed.	Endo-parasitic infection	
	Seed	Equal amount of seeds of *P. nigrum*, *Cuminum cyminum*, *Carum bulbsocastanum*, *Ferula assa-foetida*, *P. longum*, Trachyspermum roxburghianum and rhizome of *Zingiber officinale* are made to a paste and is mixed in equal amount with rock salt is given orally fed.	Indigestion	
	Seed	Crushed dried *P. nigrum* seeds are made to a paste with rock salt and curd and is given orally.	Indigestion	
	Seed	*P. nigrum* seeds are crushed and is mixed with rock salt and jaggery and is given orally	Indigestion	
	Seed	The seeds paste of the *Cuminum cyminum*, *Carum bulbsocastanum*, *Ferula assa-foetida*, *P. longum*, *Trachyspermum roxburghianum*, rhizome of *Zingiber officinale* mixed in equal portion along with rock salt is given orally.	Flatulence	
	Seed	*P. nigrum* seed powder mixed with rock salt is given along with fodder.	Musth	
	Seed	*P. nigrum* seeds, seeds of *Cuminum cyminum*, *Carum bulbsocastanum*, *Ferula assa-foetida*, *P. longum*, *Trachyspermum roxburghianum*, rhizome of *Zingiber officinale* are made to a paste and are mixed in equal proportion with rock salt and is given orally.	Stomach ache	
Pakistan	Fruit	*P. nigrum* fruit is placed inside the cake of dough and fed to the infected goat.	Skin infection	Aziz et al. 2018
	Seed	50 g of seeds of *P. nigrum* L., *Amomum subulatum* Roxb, *Foeniculum vulgare* Mill and *Cinnamomum* are mixed in jaggery and administered *per os* in 4 equal doses in 4 days.	Genital proloapse	Dilshad et al. 2008
	Fruit	50–100 g of *P. nigrum* fruit is given in a drench ball.	Anthelmintic	Jabbar et al. 2006
Bangladesh	Seed	The leaves of *Tragia involucrata* L. are macerated with seeds of *P. nigrum* L. and fed to cattle	Badla disease in cattle	Rahmatullah et al. 2013
	Seed	The roots of *Physalis micrantha* Link are macerated with two seeds of *P. nigrum* L. and fed to cattle.	Gastrointestinal disorder in cattle	
Ethiopia	Leaves	*P. nigrum* leaves are squeezed to take out fluid and it is drenched to the animals.	Respiratory disease	Assefa and Bahiru 2018

NI: Not indicated.

Pharmacological properties of *P. nigrum*

P. nigrum and its bioactive compounds were also found to possess other important pharmacological properties including antimicrobial, antioxidant, anticancer, analgesic, anticonvulsant, neuroprotective, hypoglycemic, hypolipidemic, and anti-inflammatory activities (see detailed findings in Table 3).

Antimicrobial properties

The emergence and prevalence of drug-resistant pathogenic microorganisms has led to a decline in the efficacy of traditional antimicrobial therapy. Consequently, treatment of infections is becoming progressively more challenging. To address this emerging issue, it is essential that novel therapies be developed to spare existing broad-spectrum antimicrobials including antibiotics (Spaulding et al. 2018).

Antimicrobial efficacy of *P. nigrum* have been reported against a broad range of pathogens (see Table 4). Depending on the tested concentration and different solvents used for *P. nigrum* extraction, the susceptibility of the microorganisms was found to vary among studies. For instance, among several solvent extracts (cold water, hot water, and methanol) of *P. nigrum* fruit, Khan et al. (2013) found that the cold-water extract had the maximum zone of inhibition

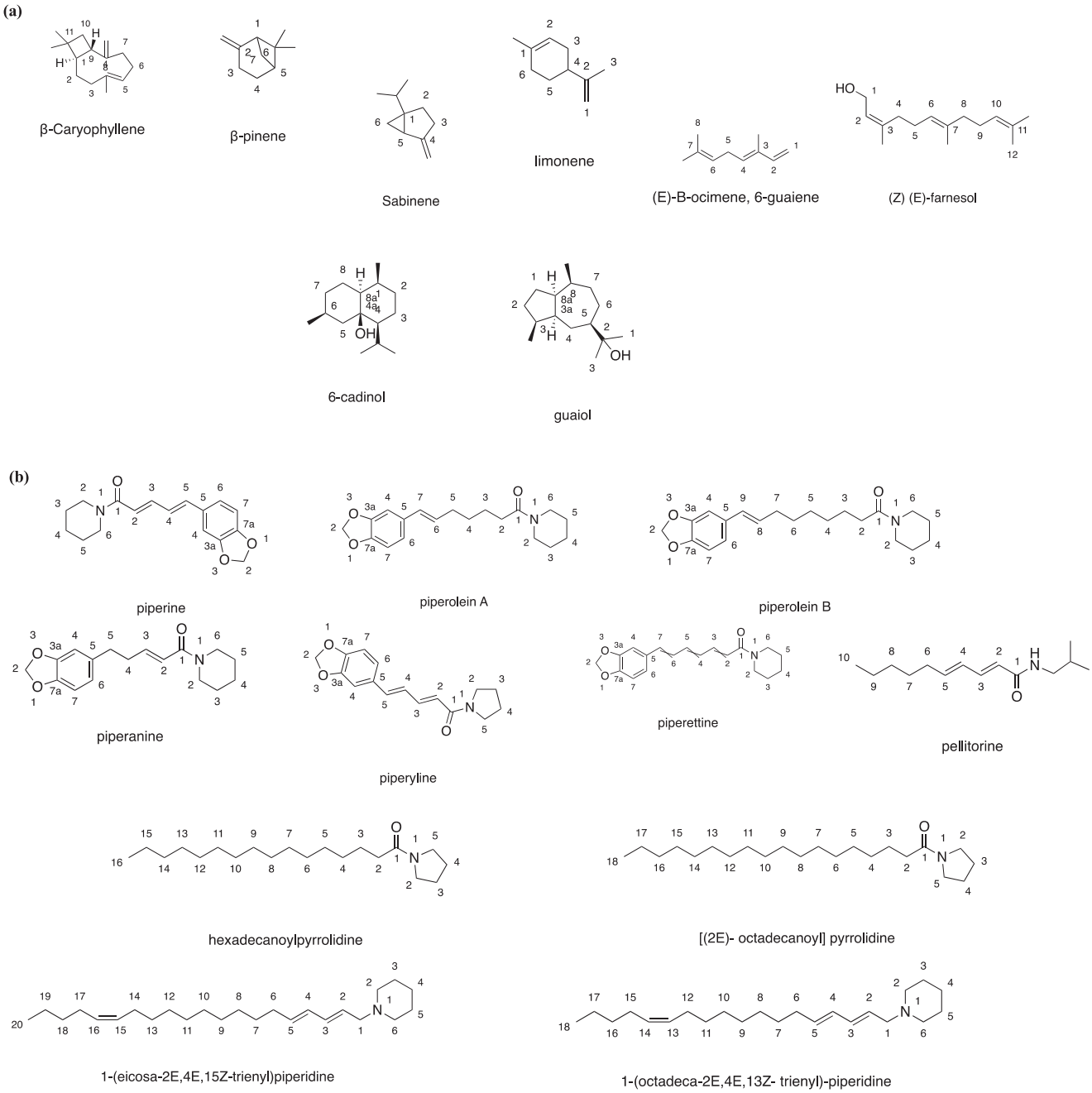

Figure 3. Chemical structures of the compounds identified in *P. nigrum* (seed, fruit and root) (a) Terpene (b) Alkaloid (c) Amide (d) Sterol and fatty acid.

(ZOI) against *E. coli* (ZOI = 23 mm) while the hot water extract showed maximum ZOI against *S. typhi* and *S. aureus* (ZOI = 22 mm). Besides, the methanolic extract showed the highest inhibition against *E. coli*, *S. typhi* and *P. aeruginosa* (ZOI = 21mm), nonetheless, did not affect *S. aureus*. Another study (Karsha and Lakshmi 2010) observed that the acetone extract was more active than the dichloromethane extract against several bacteria among which, *S. aureus* was inhibited to the greatest extent (ZOI = 20 mm). Also, the methanolic extract was found to be effective against several phytopathogenic fungi showing highest inhibition on *Puccinia recondite* (Park et al. 2008).

Furthermore, among different solvent extracts of the seed (hexane, dichloromethane, ethanol, and aqueous), the dichloromethane extract displayed the highest activity against the bacteria *S. aureus*, *E. coli*, *S. typhi,* and *B. subtilis* (Gupta et al. 2014a). Another study by Penecilla and Magno (2011) found that n-Hexane solvent displayed no inhibition against *S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa*. In contrast, the acetone and ethanol extract were able to inhibit *S. aureus* and *B. subtilis*. The aqueous extract was the most effective, inhibiting *S. aureus* (ZOI = 10 mm), *B. subitilis* (ZOI = 9 mm), and *P. aeruginosa* (ZOI = 13 mm). Several solvent leaf extracts have also been tested for its antimicrobial activity (Akthar, Birhanu, and Demisse 2014; Shanmugapriya et al. 2012). Paulkumar et al. (2014) observed that silver nanoparticles from the aqueous extract of the leaf were more effective against both *Citrobacter*

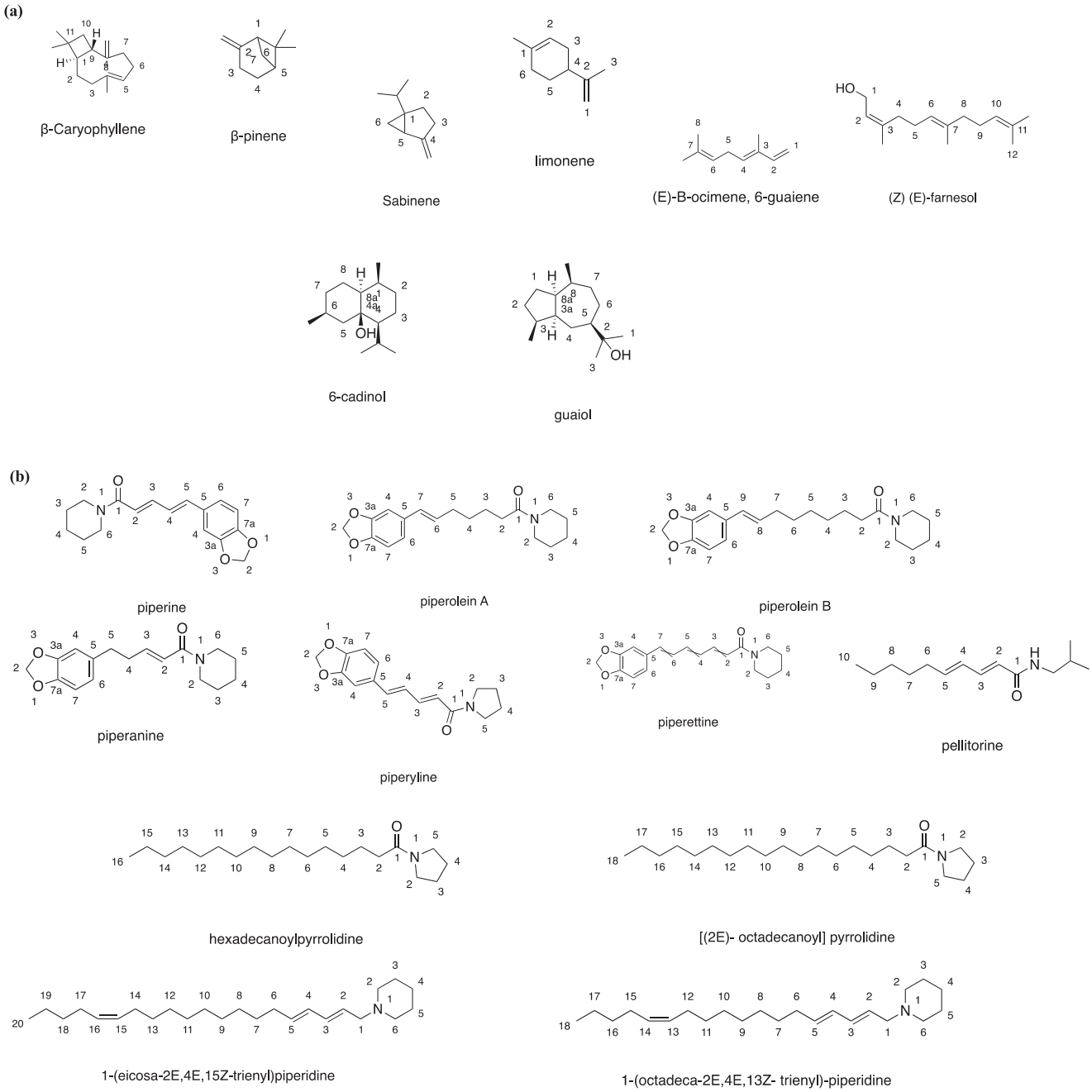

Figure 3. Continued

freundii and *Erwinia cacticida* (ZOI = 8.962 and 9.052 mm, respectively) than the silver nanoparticles synthesized from *P. nigrum* stem (ZOI = 8.894 and 9.012 mm, respectively).

With regards to the bioactive compounds in *P. nigrum*, two phenolic compounds, 3,4-dihydroxyphenyl ethanol glucoside (A) and 3,4-dihydroxy-6-(N-ethylamino) benzamide (B), were found to inhibit the growth of foodborne pathogens including *S. aureus*, *B. cereus*, *E. coli*, and *S. typhimurium* (with the exception of compound A for the latter bacterium). In general, compound A (MIC = 2.25 mmol/L) was more effective than compound B (MIC = 7.6 mmol/L) but less effective than the positive control, 4-methylcatechol (MIC = 2 mmol/L). Moreover, a combination of piperine with ciprofloxacin significantly reduced the MICs and mutation prevention concentration of ciprofloxacin against *S. aureus*, including its methicillin-resistant strain. The presence of piperine resulted in an enhanced accumulation and a decrease in ethidium bromide efflux in the wild-type and mutant (CIP^r-1) strains, thereby suggesting its role in the inhibition of bacterial efflux pumps (Khan et al. 2013). In addition, a study by (Zarai et al. 2013), they found that piperic acid (MIC in the range 78.12–625 µg/mL) showed higher antibacterial activity than piperine (MIC in the range 312.5–625 µg/mL) against many Gram-positive and Gram-negative bacteria.

Biofilm formation is known to play a significant role in the pathogenesis of bacteria. Biofilm development is based on the signal-mediated quorum sensing (QS) system, and

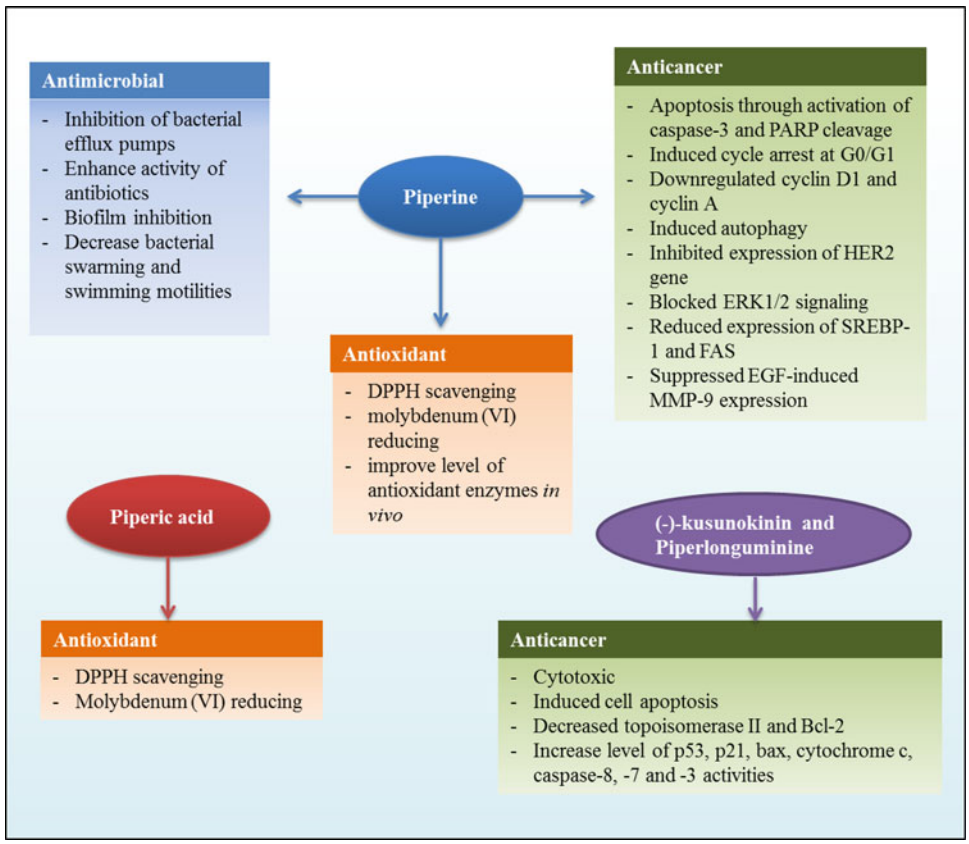

Figure 4. Mechanism of action of mostly studied pharmacological properties of bioactive compounds in *P. nigrum*.

therefore, interference with QS may prevent biofilm formation and further infections. Singh et al. (2016) investigated *P. nigrum* extract for its anti-QS potential in inhibiting the formation of biofilm in *Cronobacter sakazakii* strains. The extract, at a concentration of 100 ppm, caused a 78% reduction in violacein and blue-green color production in both biosensor strains used (*Chromobacterium violaceum* 026 and *Agrobacterium tumefaciens* NTL4 (pZLR4)). The extract also caused 60–72% inhibition of biofilm formation in *C. sakazakii* strains. Also, piperine displayed a minimum biofilm inhibitory concentration (MBIC) of 0.0407 mg/mL against *S. mutans*. At optical density $OD_{492} < 0.5$, the MBIC of both compounds caused significant inhibition of biofilm formation of all the 18 tested strong biofilm-forming isolates (Dwivedi and Singh 2016).

Additionally, Dusane et al. (2014) found that sub-inhibitory concentrations of piperine (0.5–5 µg/mL) decreased bacterial swarming and swimming motilities but increased biofilm formation. At first instance, an increase in biofilm formation seems to be a disadvantage in a therapeutic context, but it should be highlighted that this effect was accompanied by a significant decrease in motility which is known to decrease the spread of infection. In addition, qRTPCR revealed a decrease in the expression of the flagellar gene (fliC) and motility genes (motA and motB) together with an increase in the expression of adhesin genes (fimA, papA, uvrY). More importantly, piperine increased the penetration of both ciprofloxacin and azithromycin into the biofilms of *E. coli* CFT073, and hence enhanced the ability of these antibiotics to disperse pre-established biofilms.

Antioxidant

Several *in vitro* assays based on different mechanism have been performed to assess the antioxidant power of *P. nigrum*. Gulcin (2005) found that the aqueous extract of the seed possesses higher scavenging activity than the ethanol extract against DPPH, superoxide anion, hydrogen peroxide, and total antioxidant activity based on the thiocyanate method, while the latter showed higher ferric reducing power. The variation on antioxidant power of different extracts and fractions of the fruits was also observed by (Nahak and Sahu 2011; Singh et al. 2008). Also, Shanmugapriya et al. (2012) determined the antioxidant power of *P. nigrum* leaf was also assessed using a number of assays. Among three solvent extracts (ethyl acetate, acetone, and aqueous), the ethyl acetate extract showed the highest DPPH, ABTS, and superoxide anion scavenging effects while the acetone extract exhibited the highest inhibition against hydrogen peroxide, nitric oxide, and was most effective in the phosphomolybdenum assay. On the other hand, the aqueous extract was the strongest ferric reducer.

The essential oil of the fruits also showed more potent inhibitory effects in DPPH, FRAP, and lipid peroxidation assays compared to the ethyl acetate and ethanol oleoresin (Kapoor et al. 2009). Bagheri, Abdul Manap, and Solati (2014) evaluated the DPPH scavenging property of the essential of the seed using two different extraction techniques. They found that the essential oil extract obtained from supercritical-CO_2 extraction showed higher activity (EC_{50} = 103.28 µg/mL) than that of hydro-distillation (EC_{50} =

Table 3. Other pharmacological properties of *P. nigrum*.

Activity	Model used	Plant Part	Extract	Assay	Findings	References
Antioxidant	*In vitro*	Seed	Aqueous Ethanol	DPPH scavenging	Aqueous: 55% inhibition at 75 μg/mL Ethanol: 48% inhibition at 75 μg/mL	Gulcin 2005
				Superoxide anion radical scavenging activity	Aqueous: 64.2% inhibition at 75 μg/mL Ethanol: 22.6% inhibition at 75 μg/mL	
				Total antioxidant activity determination (Thiocyanate method)	Aqueous: 95.5% inhibition at 75 μg/mL Ethanol: 93.3% inhibition at 75 μg/mL	
				FRAP	Aqueous: 0.665 inhibition at 75 μg/mL Ethanol: 0.855 inhibition at 75 μg/mL	
				Hydrogen peroxide scavenging	Aqueous: 83% inhibition at 75 μg/mL Ethanol: 63% inhibition at 75 μg/mL	
Antioxidant	*In vitro*	Berries	Phenolic compounds: 3,4-dihydroxyphenyl ethanol glucoside, 3,4-dihydroxy-6-(N-ethylamino) benzamide Phenolic acid glycosides	DPPH scavenging	EC_{50} of 3,4-dihydroxyphenyl ethanol glucoside, 3,4-dihydroxy-6-(N-ethylamino) benzamide and phenolic acid glycosides were found to be 0.076, 0.27 and 0.12 mg/mL, respectively	Chatterjee et al. 2007
Antioxidant	*In vitro*	Fruit	Aqueous Ethanol Methanol	DPPH scavenging	At highest concentration of extract tested (250 μg/mL): Aqueous: 39.92 % inhibition Ethanol: 74.61 % inhibition; IC_{50}= 14.15 μg/mL Methanol: 63.84 % inhibition	Nahak and Sahu 2011
Antioxidant	*In vitro*	Berries	Ethanol extract Compounds: Piperine Piperic acid	DPPH	Ethanol: 65.59% inhibition at 50 μg/mL Piperine: 10.28% inhibition at 50 μg/mL Piperic acid: 29.5% inhibition at 50 μg/mL	Zarai et al. 2013
				Phosphomolybdenum assay	Ethanol: 48.2 μmol/mL α-tocopherol equivalents) at 25 μg/mL Piperine: 58.8 μmol/mL α-tocopherol equivalents at 100 μg/mL Piperic acid: 64.1 μmol/mL α-tocopherol equivalents at 100 μg/mL	
Antioxidant	*In vitro*	Fruit	Essential oil Oleoresins (obtained by extracting with ethanol and ethyl acetate)	DPPH, FRAP, and lipid peroxidation	Inhibitory effect was found in following order: Essential oil > ethyl acetate oleoresin > ethanol oleoresin	Kapoor et al. 2009
Antioxidant	*In vitro*	Fruit	Methanol	DPPH scavenging	IC_{50}= 144.1 μg/mL	Khalaf et al. 2008
Antioxidant	*In vitro*	Seed	Essential oil	DPPH scavenging	Extracts from supercritical-CO_2 and hydrodistillation showed an EC_{50} of 103.28 and 316.27 μg/mL respectively.	Bagheri, Abdul Manap, and Solati 2014
Antioxidant	*In vitro*	Fruit	Three fractions (R1, R2 and R3) obtained from petroleum ether and and ethyl acetate in the ratio of 6:4, 5:5 and 4:6, respectively.	Linoleic acid peroxidation	At 500 μg/mL of fraction used; R1: 10.21% inhibition R2: 58.89% inhibition R3: 60.48% inhibition	Singh et al. 2008
				DPPH scavenging	At 250 μg/mL of fraction used; R1: 12.41% inhibition R2: 61.24 inhibition R3: 61.11 inhibition	
				Nitric oxide radical scavenging activity	At 100 μg/mL of fraction used; R1: 18.22% inhibition R2: 40.23% inhibition R3: 55.68% inhibition	
				Superoxide anion radical scavenging activity	At 100 μg/mL of fraction used; R1: 18.54% inhibition R2: 62.23% inhibition R3: 70.22% inhibition	
				Hydroxyl radical scavenging activity	At 1000 μg/mL of fraction used; R1: 21.87% inhibition R2: 61.04% inhibition R3: 63.56% inhibition	
Antioxidant	*In vitro*	Leaves	Ethyl acetate Acetone Aqueous	DPPH scavenging		Shanmugapriya et al. 2012

(*continued*)

Table 3. Continued.

Activity	Model used	Plant Part	Extract	Assay	Findings	References
					At 100 μg/mL concentration; Ethyl acetate: 84.75% inhibition Acetone: 69.25% inhibition Aqueous: 65.50% inhibition	
				ABTS radical scavenging	At 100 μg/mL concentration; Ethyl acetate: 72.75% inhibition Acetone: 69.25% inhibition Aqueous: 68.96% inhibition	
				Phosphomolybdenum	At 100 μg/mL concentration; Ethyl acetate: 00.76% inhibition Acetone: 00.95% inhibition Aqueous: 00.44% inhibition	
				Hydrogen peroxide scavenging activity	At 100 μg/mL concentration; Ethyl acetate: 10.10% inhibition Acetone: 14.40% inhibition Aqueous: 00.94% inhibition	
				Nitric oxide inhibition	At 100 μg/mL concentration; Ethyl acetate: 34.10% inhibition Acetone: 42.80% inhibition Aqueous: 23.40% inhibition	
				Superoxide inhibition	At 100 μg/mL concentration; Ethyl acetate: 58.50% inhibition Acetone: 25.50% inhibition Aqueous: 18.30% inhibition	
				FRAP	At 100 μg/mL concentration; Ethyl acetate: 1.113 mg BHT equivalent/g inhibition Acetone: 0.852 mg BHT equivalent/g inhibition Aqueous: 1.256 mg BHT equivalent/g inhibition	
Antioxidant	*In vitro*	Peppercorn	50% Acetone 80% methanol	ABTS scavenging	Acetone: 39.8 Trolox equivalent μmol/g Methanol: 23.3 Trolox equivalent μmol/g	Su et al. 2007
				ORAC	Acetone: 395 Trolox equivalent μmol/g Methanol: 363 Trolox equivalent μmol/g	
				FRAP	Acetone: 1.09 disodium ethylenediaminetetraacetate (EDTA) equivalent mg/g Methanol: 0.54 EDTA equivalent mg/g	
				DPPH scavenging	Acetone: ED_{50}= Around 1.20 mg/mL Methanol: ED_{50}= 1.46 mg/mL	
Antioxidant	*In vitro*	NI	Essential oil	ABTS scavenging	IC_{50}= 223.8 mg/mL	Zhang and Xu 2015
				DPPH scavenging	IC_{50}= 1335.8 mg/mL	
Antioxidant	*In vitro*	NI	Compound: N-trans-feruloyltyramine	DPPH scavenging	EC_{50}= 11.82 μg/mL	Tu et al. 2016
Antioxidant	*In vitro*	Fruit	n-hexane Chloroform Methanol Aqueous	DPPH scavenging	Hexane: IC_{50}= 1830.0 μg/mL Chloroform = IC_{50}= 164.9 μg/mL Methanol = IC_{50}= 153.9 μg/mL Aquoeus = IC_{50}= 1025.0 μg/mL	Sruthi and Zachariah 2017
				Phosphomolybdenum method	M AAE: Molar ascorbic acid equivalents/g of extract Hexane: 0.41AAE/g Chloroform: 1.01AAE/g Methanol: 0.73AAE/g Aquoeus: 0.45AAE/g	
				FRAP	M AAE: Molar ascorbic acid equivalents/g of extract Hexane: 0.46 AAE/g Chloroform: 0.55 AAE/g Methanol: 0.52 AAE/g Aqueous: 0.26 AAE/g	
Antioxidant	*In vivo*- Male Wistar rats	Pod	Black pepper powder (0.25 g/kg body weight in water p.o) and piperine (0.02 g/kg body weight in water, p.o)	–	Reduced thiobarbituric acid reactive substances (TBARS) and conjugated dienes (CD) levels Maintained the level of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-	Vijayakumar, Surya, and Nalini 2004

					transferase (GST), and the reduced glutathione (GSH) to near those of control rats	
Antioxidant	*In vivo*-Male Wistar rats	NI	Piperine (40 mg/kg body weight) in 1% carboxymethyl cellulose, p.o	–	Concurrent piperine supplementation along with high fat diet and antithyroid drug administration reduced lipid peroxidation and improved the antioxidant status compared to those rats that did not receive piperine.	Vijayakumar and Nalini2006
Antioxidant	*In vivo*-Male Wistar rasts	Fruit	Methanol	–	Improved amyloid beta (1-42)-induced spatial memory impairment by attenuation of oxidative stress in rat hippocampus.	Hritcu et al. 2014
Antioxidant	*In vivo*-Balb/C mice	Fruit	Essential oil		Treatment by 500 mg/kg bw. of *P. nigrum* oil significantly improved the levels of antioxidant enzymes (catalase, superoxide dismutase, glutathione reductase (GRx) and glutathione) in both the liver and blood samples.	Jeena et al. 2014
Anticancer	*In vitro*	Fruit	Compound: (-)-kusunokinin	MTT assay Breast cancer cell lines (MCF-7, MDA-MB-231 and MDA-MB-468) Colorectal cancer cell line (SW-620)	After 72 h of exposure; MCF-7: IC_{50}=1.18 μg/mL MDA-MB-231: IC_{50}= 91.79 μg/mL MDA-MB-468: IC_{50}= 1.62 μg/mL SW-620: IC_{50}= 2.60 μg/mL	Sriwiriyajan et al. 2017
			Compound: piperlonguminine		After 72 h of exposure; MCF-7: IC_{50}= 1.63 μg/mL MDA-MB-231: IC_{50}= 71.54 μg/mL MDA-MB-468: IC_{50}= 2.19 μg/mL SW-620: IC_{50}= 4.62 μg/mL	
Anticancer	*In vitro*	Root	Chloroform and petroleum ether extract	MTT assay Human myeloid leukemia (HL-60 cell)	After 72 h of exposure: Chloroform : IC_{50} = 9.8 μg/mL Petroleum ether: IC_{50} = 11.2μg/mL	Ee et al. 2009
			Pellitorine	MCF-7 HeLa	IC_{50}= 1.8 μg/mL IC_{50}= 13 μg/mL	
Anticancer	*In vitro*	NI	Compound: Piperine	MTT assay Doxorubicin resistant MCF-7 and A-549	Re-sensitised P-glycoprotein, multidrug resistance protein 1 (MRP1) and breast cancer resistance protein (BCRP) dependent multidrug resistant cancer cells	Li et al. 2011
Anticancer	*In vitro*	NI	Compound: Piperine	MTT assay MCF-7 cell	IC_{50}= 1.21 μM after 24 h exposure	Motiwala and Rangari2015
Anticancer	*In vivo*- male Swiss albino mice	–	Compound: Piperine (50 mg/kg body weight)	–	Suppressed benzo(a)pyrene (B(a)p) induced lung cancer in mice by decreasing the levels of total protein and protein bound carbohydrate components (hexose, hexosamine and sialic acid)	Selvendiran, Prince Vijeya Singh, and Sakthisekaran2006
Anticancer	*In vitro*-	–	Compound: Piperine	MTS assay Human prostate cancer cell lines (LNCaP, PC-3 and DU145)	After 48 h exposure; LNCaP: IC_{50}= 74.4μM DU145: IC_{50}= 226.6μM PC-3: IC_{50}= 111.0μM	Ouyang et al. 2013
Anticancer	*In vitro*	–	Compound : Piperine	MTT assay HER2-overexpressing breast cancer cells (SKBR3 and MCF-7 cell)	After 48 h exposure; SKBR3: IC_{50} = 50 μM MCF-7: IC_{50} = 200 μM	Do et al. 2013
Anticancer	*In vitro*	Fruit	Methanol and dichloromethane	MTT assay Breast cancer MCF-7, MDA-MB-468 and MDA-MB-231 cell lines	After 72 h exposure; Methanol extract: MCF-7: IC_{50}= 20.25μg/mL MDA-MB-468: IC_{50}= 9.04 μg/mL MDA-MB-231: IC_{50}= 22.37 μg/mL Dichloromethane extract: MCF-7: IC_{50}= 23.46μg/mL MDA-MB-468: IC_{50}= 7.94 μg/mL MDA-MB-231: IC_{50}= 38.82 μg/mL	Sriwiriyajan et al. 2014
Anticancer	*In vivo*- C57BL/6 mice	NI	Compound: Piperine	–	Administration of piperine caused a 95.2% reduction in tumor nodule formation,	Pradeep and Kuttan 2002

(*continued*)

Table 3. Continued.

Activity	Model used	Plant Part	Extract	Assay	Findings	References
					reduction in serum sialic acid level and serum gamma glutamyl transpeptidase activity.	
	In vitro			MTT assay B16F-10 melanoma cells	At 100 μg/mL concentration after 48 h, piperine was 100% cytotoxic to B16F-10 cells	
Anticancer	*In vitro*	Fruit	50% ethanol	MTT assay Colorectal cancer cell lines (HT-29, HCT-116, and HCT-15)	After 72 h exposure; HCT-116: IC_{50}= 3.4 μg/mL HCT-15: IC_{50}= 1.9 μg/mL HT-29: IC_{50}= 7.4 μg/mL	Prashant et al. 2017
Anticancer	*In vitro*	Fruit	Piperine free *P. nigrum* extract	MTT assay against various cancer cell lines	MCF-7: IC_{50} = 7.45 μg/mL MDA-MB-231: IC_{50} = 22.67 μg/mL MDA-MB468: IC_{50} = 18.19 μg/mL ZR75-1: IC_{50} = 13.85 μg/mL HT-29: IC_{50} = 27.74 μg/mL SW-620: IC_{50} = 29.56 μg/mL H-358: IC_{50} = 34.69 μg/mL A-549: IC_{50} = 30.77 μg/mL	Sriwiriyajan et al. 2016
Analgesic	*In vivo*- Swiss albino mice	Fruit	Hexane Ethanol Compound: Piperine	Tail immersion method	Reaction time is the time taken by mice to withdraw the tail Maximum activity: Piperine: reaction time after 120 min at a dose of 5 mg/kg = 11.658 s Hexane: reaction time after 60min dose of 10 mg/kg = 8.284 s Ethanol: reaction time after 120 min dose of 15 mg/kg = 9.602 s	Tasleem et al. 2014
				Analgesy-meter	Sensitivity of animals to pain as determined by reaction time Maximum activity: Piperine: reaction time after 60 min at a dose of 15 mg/kg = 9.400 s Hexane: reaction time after 60min dose of 5mg/kg = 13.000 s Ethanol: reaction time after 60 min dose of 10 mg/kg) = 20.900 s	
				Hot plate	Reaction time for paw licking or jumping Maximum activity: Piperine: reaction time after 30 min at a dose of 10 mg/kg = 12.870 s Hexane: reaction time after 120 min dose of 15 mg/kg = 2.738 s Ethanol: reaction time after 60 min dose of 5 mg/kg = 2.486 s	
				Acetic acid induced writhing test	Result expressed as number of writhes counted for 20 min commencing 5 min after injection of acetic acid. Maximum activity: Piperine (dose of 10 mg/kg) = 100.00% protection Hexane (dose of 5 and 10mg/kg) = 99.71% protection Ethanol (dose of 15mg/kg) = 100.00% protection	
Analgesic	*In vivo*- Male mice	NI	Compound: Piperine	Writhing test	At 70mg/kg, caused 89% inhibition of nociception induced by acetic acid	Bukhari et al. 2013
				Tail-flick assay	At 50mg/kg, increased latency of reaction time from 3.7 s (control) to 17.2 s	
Anticonvulsant	*In vivo*- male Wistar Rats	NI	Ethyl alcohol n-Hexane	Pentylenetetrazol (PTZ) induced model Maximal electroshock seizure (MES) induced model	*Piper nigrum* suppressed onset and duration of seizures in both PTZ and MES models.	Belemkar et al. 2013
Anticonvulsant	Clinical-Adult epileptic patients	–	Compound: Piperine	–	Single oral dose of piperine (20 mg) increased the mean plasma concentration	Patnaik et al. 2012

					of diphenyl hydantoin both in the absorption and elimination phases in both 150 and 200 mg dose-phenytoin patients groups.	
Anticonvulsant	*In vivo*- Male mice	NI	Compound: Piperine	Pentylenetetrazol (PTZ)-induced seizures	50mg/kg piperine treatment was most effective than 70 mg/kg in preventing the animals from PTZ-induced seizures	Bukhari et al. 2013
		NI		Picrotoxin-induced seizures	The highest tested dose of piperine (70mg/kg) increased the latency of picrotoxin-induced convulsions to 878.5 s compared to value of control group 358.4 s	
Neuroprotective	*In vivo*- Male C57BL/6 mice	NI	Compound: Piperine	Rotarod and Morris Water Maze (MWM) Test	Attenuated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced deficits in motor coordination and cognitive functioning Also prevented MPTP-induced decrease in the number of tyrosine hydroxylase-positive cells in the substantia nigra. The compound also reduced the number of activated microglia, cytokine IL-1β expression, and oxidative stress following MPTP treatment.	Yang et al. 2015
Neuroprotective	*In vivo*- Male Wistar rats	Fruit	Methanol	Y-maze and radial arm-maze tasks	Ameliorates amyloid beta(1–42)-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus.	Hritcu et al. 2014
Neuroprotective	*In vivo*- Male Wistar rats	Fruit	Methanol	Elevated plus-maze test Forced swimming test	Exhibited anxiolytic- and antidepressant-like effects	Hritcu et al. 2015
Neuroprotective	*In vivo*- Male Wistar rats	NI	Compound: Piperine	Open field test	Piperine treatments reversed partially the decline in locomotor activity of the 6-OHDA (lesioned in the right striatum) group.	Correia et al. 2015
				Rotarod test	Piperine treatments fully inverted the motor deficit of the 6-OHDA group.	
				Apomorphine-induced rotations	Piperine treatments inverted the increased number of apomorphine-induced contralateral rotations observed in the 6-OHDA group.	
Neuroprotective	*In vivo*-Albino rats	Seed	Piperine isolated from ethanol extract	Pilocarpine model	Administration of piperine increased the brain-plasma phenytoin ratio, GSH level, number of viable neurons and decreased lipid peroxidation and catalase activity.	Pany, Abhisek, and Pratap2016
Hypoglycemic	*In vivo*- Male albino rats	Seed	Aquoeus		Treatment of diabetic rats with *P. nigrum* extract for 4 weeks reduced the blood glucose level to 129 mg/100mL compared to diabetic rats (270 mg/100mL)	Kaleem, Sheema, Sarmad, and Bano2005
Hypoglycemic	*In vivo*- rats	Leaf	Ethanol	–	21 days treatment of 100, 200 and 300mg/kg body weight of *P. nigrum* extract reduced blood glucose level in alloxan induced diabetic rats.	Onyesife, Ogugua, and Anaduaka2014
Hypoglycemic	*In vitro*	Seed	Methanol: Water mixture (3:1)	Goat lens aldose reductase inhibitory activity	IC_{50} value = 35.64 µg/mL	Gupta, Singh, and Jaggi2014b
Hypolipidemic	*In vivo*- Male Wistar rats	–	Compound: Piperine	–	Supplementing piperine to the high fat diet rats lowered the levels of plasma total cholesterol, LDL, VLDL tissue HMG CoA	Vijayakumar and Nalini2006

(*continued*)

Table 3. Continued.

Activity	Model used	Plant Part	Extract	Assay	Findings	References
					reductase and raised the levels of LPL and LCAT compared to rats that did not receive piperine.	
Hypolidemic	*In vivo*- Male Wistar rats	NI	Alcohol Compound: Piperine	–	Reduced levels of total cholesterol, free fatty acids, phospholipids and triglycerides in *P. nigrum* extracts (250mg/kg b.w and 500mg/kg b.w) as well as in the piperine (20mg/kg b.w) treated groups. Supplementation with both *Piper nigrum* and piperine extracts increases the plasma HDL cholesterol and reduced the LDL and vLDL cholesterol.	Vijayakumar et al. 2002
Anti-inflammatory	*In vivo*- Swiss albino mice	Fruit	Hexane Ethanol Compound: Piperine	Carrageenan induced paw edema method	Maximum activity: Piperine: Reaction time after 120 min at a dose of 15 mg/kg) = 0.588 s Hexane: Reaction time after 60min dose of 10mg/kg) = 0.470 s Ethanol: Reaction time after 60min dose of 10mg/kg = 0.484 s	Tasleem et al. 2014
Anti-inflammatory	*In vivo*- Balb/C mice (20-25 g)	NI	Essential oil	Carrageenan induced acute inflammatory model	500 mg/kg b.wt. essential oil produced 72 % inhibition at third hour compared to control	Jeena et al. 2014
				Dextran induced acute inflammatory model	1000 mg/kg b.wt. essential oil reduced the paw thickness by 73.4 % at third hour compared to control	
				Formalin induced chronic inflammatory model	500 mg/kg b.wt. essential oil produced 50 % % inhibitions of paw edema compared to control	

Table 4. Antimicrobial properties of *P. nigrum*.

Part used	Extract type/ Isolated compounds	Microorganisms tested	Main findings	References
Fruit	Ethanolic	Gram-positive strains (*B. subtilus, E. faecalis, S. xylosus, S. aureus* and *S. epidermidis*), Gram-negative strains (*E. coli, K. pneumoniae, S. enterica*)	The MIC was <325 mg/mL against all strains tested. The most susceptible bacteria to the ethanol extract *were S. aureus and B. subtilus* with MIC value of 156.25 mg/mL	Zarai et al. 2013
Fruit	Compounds: 3,4-dihydroxyphenyl ethanol glucoside (A), 3,4-dihydroxy-6-(N-ethylamino) benzamide (B)	*S. aureus* ATCC 6538B and *B. cereus* isolated from a food sample, *S. typhimurium*, *E. coli* DH5α	Both the compounds inhibited the growth of all of the four tested bacteria tested except that no inhibition was observed by compound A on S. typhimurium. Compound A (MIC= 2.25 mmol/L) was more effective than compound B (MIC= 7.6 mmol/ L) but less effective than the positive control, 4-methylcatechol (MIC= 2 mmol/L).	Pradhan, Variyar, and Bandekar 1999
Fruit	Ethyl acetate Acetone Methanol	Bacteria: *K. pneumonia* 13883, *B. megaterium* NRS, *P. aeroginosa* ATCC 27859, *S. aureus* 6538 P, *E. coli* ATCC 8739, *E. cloaca* ATCC 13047, *C. xerosis* UC 9165, and *S. faecalis* DC 74) Fungi: *Kluyveromyces marxianus*, *Rhodotorula rubra*	The acetone extract did not show inhibition on any of the microorganisms tested, except for *C. xerosis* (ZOI = 7 mm). The methanol extract displayed no activity against *K. pneumoniae, P. aeruginosa* and *R. rubra*. The ethyl acetate extract exhibited no antimicrobial effect against *P. aeruginosa, S. faecalis* and *R. rubra*.	Keskin and Toroglu 2011
Fruit	Ethanol	Isolated strains of *K. pneumoniae* from urine culture of hospitalized patients suffering from urinary tract infections	MIC= 0.62 mg/mL.	Sepehri et al. 2014
Leaf Fruit	Essential oil	Bacteria: *B. subtilis* (gram positive bacteria), *P. aeruginosa* (gram negative) Fungi: *C. albicans*, *Aspergillus niger, Penicillium spp, Saccharomyces cerevisiae* Dermatophyte: *Trichoderma spp*	Fresh berry oil was most effective against *Bacillus subtilis* (MIC= 1μg/mL) compared to other microorganisms. The dry berry oil and pepper leaf oil were most effective against *Saccharomyces cerevisiae* (MIC= 0.8μg/mL and 2.5/mL, respectively) than other microorganisms.	Sasidharan and Menon 2010
Fruit	Carbon tetrachloride Benzene Chloroform Ethyl acetate Acetone Ethanol Distilled water	Bacteria: *Staphylococcus albus, Salmonella typhi, Pseudomonas aeruginosa, Escherichia coli, Bacillus megaterium* Fungus: *Aspergillus niger*	At a concentration of 40 μg/disc; Carbon tetrachloride extract was effective against all microorganisms (ZOI = 5–9mm) except for *S. typhi*. Benzene extract was most effective against *A. niger* (ZOI= 10–14 mm). Ethyl acetate, acetone and chloroform extracts were effective only against *S. albus, S. typhi, P. aeruginosa* and *A. niger*. (ZOI = 5–9 mm). The ethanolic extract of *P. nigrum* was most effective against *S. typhi* (ZOI = 10–14mm). The aqueous extract of *P. nigrum* was effective only against *E. coli*, *B. megaterium*, *S. albus* and *S. typhi* (MIC = 5–9mm).	Khan and Siddiqui 2007
Fruit	Petroleum ether	*B. subtilis* (MTCC 441), *S. aureus* (MTCC 96), *K. aerogenes* (MTCC 39), *B. sphaericus* (MTCC 511) and *Chromobacterium violaceum* (MTCC 2656)	At the highest concentration tested (100 μg), *P. nigrum* was most effective against *B. subtilis* (ZOI = 12 mm) and *K. aerogenes* (ZOI = 13 mm).	Reddy et al. 2004
Fruit	Aqueous Methanol	Bacteria : *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli* and *Pseudomonas aeruginosa* Fungi: *Aspergillus niger* and *Candida albicans*	All microorganisms were inhibited by both types of extracts at the highest concentration tested of 10 mg/mL (Aqueous: ZOI = 18–25 mm; Methanol: ZOI = −23 mm). *S. aureus* (ZOI = 25 mm) was inhibited to the highest extent by the aqueous extract whereas for the methanolic extract, both *S. aureus* and *E. coli* were the most inhibited (ZOI = 23 mm).	Trivedi et al. 2011
Fruit	Ethanol, Chloroform	Clinical bacterial isolates: *Staphylococcus aureus, Salmonella typhi, Escherichia coli, Proteus mirabilis and Pseudomonas aeruginosa*	At the highest concentration (4 mg/mL) of ethanol extract tested, *E. coli* was mostly inhibited (ZOI = 22mm). The chloroform extract was mostly effective against *E. coli* and *proteus* sp. (ZOI = 18mm)	Ganesh, Suresh, and Aranraj 2014
Fruit	Ethanol	Bacteria: *E. coli* and *S. aureus* Fungi: *A. niger* and *Mucor* species	At concentration of 500μg of extract, all microorganisms were inhibited (ZOI = 3.9–13.0 mm). The extract was most effective against S. aureus (ZOI =13 mm) but was less effective against the two fungal strains. (ZOI = 3.9–4.1 mm).	Reddy and Seetharam 2009

(*continued*)

Table 4. Continued.

Part used	Extract type/ Isolated compounds	Microorganisms tested	Main findings	References
Fruit Seed	Cold water Hot water Methanol	Bacteria: *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi*	The extracts inhibited all the bacteria. Cold water extract had the maximum zone of inhibition against *E. coli* (ZOI = 23mm), hot water extract showed maximum zone of inhibition against *S. typhi* and *S. aureus* (ZOI = 22mm) and the methanolic extract showed maximum zone of inhibition against *E. coli*, *S. typhi* and *P. aeruginosa* (ZOI = 21mm), however the methanolic extract had no effect on *S. aureus*.	Khan et al. 2013
Fruit	Ethanol	*Streptococcus mutans* (MTCC 890, *Enterococcus faecalis* (MTCC 439), *Lactobacillus acidophilus* (MTCC 10307), *Candida albicans* (MTCC 854) and *Candida tropicalis* (MTCC 184).	The ethanolic extract inhibited all the microorganisms (ZOI = 18–25 mm) except *S. mutans*.	Gauniyal, Vir, and Teotia 2014
Fruit	Acetone Dichloromethane	*B. cereus* (NCIM-2016), *S. faecalis* (NCIM-2016), *E. coli* (NCIM-2089), *K. pneumonia* (NCIM-2957), *P. aeruginosa* (NCIM-2200), *S. typhi* (NCIM- 2263)	The acetone extract was more active than the dichloromethane extract and *S. aureus* was inhibited to the highest extent (ZOI = 20 mm).	Karsha and Lakshmi 2010
Fruit	Methanol	Different clinical strains of *Providencia stuartii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *Enterobacter aerogenes* and *Enterobacter cloacae*	The methanolic extract of *P. nigrum* showed some level of inhibition to all microorganisms but was most effective against *P. aeruginosa* PA01 (MIC = 32 μg/mL).	Noumedem et al. 2013
Fruit	Methanol	*P. aeruginosa, Klebsiella pneumoniae, E. coli, Proteus mirabilis* and *Staphylococcus aureus*	The extract was most effective against *Proteus mirabilis* (ZOI= 5.00mm), followed by *E. coli* (ZOI = 4.90 mm) and *Klebsiella pneumoniae* (ZOI = 4.63 mm).	Ghaidaa, Aseel, and Haider 2016
Leaf	Ethanol, diethyl ether, chloroform and water	*S. aureus*, *Bacillus* sp., *E. coli* and *Klebsiella sp.*	The ethanol extract showed greatest activity against all the pathogens, the highest activity noted was against *Bacillus* sp.	Kavitha and Mani 2017
Leaf Stem	Aqueous	*Citrobacter freundii* and *Erwinia cacticida*	Silver nanoparticles from *P. nigrum* leaf were more effective against both *Citrobacter freundii* and *Erwinia cacticida* (ZOI = 8.962 and 9.052 respectively) than the silver nanoparticles synthesized from *P. nigrum* stem (ZOI = 8.894 and 9.012 respectively).	Paulkumar et al. 2014
Leaf	Aqueous Acetone Ethyl acetate	Bacteria: *E. coli*, *B. subtitis, S. aureus, Enterobacter* sp., *Haemophilus* sp. and *Yersinia* sp. Fungi: *Cephalosporium* sp., *A. niger*, *P. notatum* and *C. albicans*.	The ethyl acetate extract was most effective against the bacteria (ZOI = 14–20 mm) but it did not show any antifungal activity. The acetone extract showed moderate inhibition *against C. albicans* (ZOI = 14 mm), *A. niger* (ZOI = 10 mm), *Cephalosporium* sp. (ZOI = 14 mm), and *P. notatum* (ZOI = 18 mm). However, the aqueous extract did not show any significant antimicrobial property.	Shanmugapriya et al. 2012
Leaf	Aqueous Methanol Ethanol Petroleum ether	Bacteria: *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *S. typhimurium* (ATCC 13311) and *P. aeruginosa* (ATCC 27853) Fungi: *Aspergillus spp.* ((JUAS 27031) and *C. albicans* (ATCC 90028)	The methanol extract (ZOI = 11.67–20.00 mm) was found to be the most effective against all the bacteria compared to the ethanol (ZOI = 10.00–14.67 mm), petroleum ether (ZOI = 9.33–11.33 mm) and aqueous (ZOI = 8.00–9.33 mm) extracts. *E. coli* was the microorganism that were most inhibited by all the *P. nigrum* extracts. Among the two fungi tested, *Aspergillus spp.* (ZOI = 11.33–19.67 mm) was inhibited higher than *C. albicans* (ZOI = 8.33–12.67 mm).	Akthar, Birhanu, and Demisse 2014
Leaf	Aqueous Ethanol	*S. mutans, Phorphyromonas gingivalis*	Only the aqueous extract was effective against *S. mutans* (MIC = 125 μg/mL). The ethanolic extract did not show any inhibition against both bacteria.	Rosas-Pinon et al. 2012
Leaf	Aqueous	*E. coli and B. subtilis*	The aqueous extract of *P. nigrum* was only effective against *B. subtilis* (ZOI = 8 mm).	Jain, Bansal, and Bhasin 2010
Seed	Aqueous Ethanol Petroleum ether	*S. aureus* (NCTC 25953), *E. coli* (NCTC 25922), *S. typhi* (NCTC 25936), *P. aeruginosa* (NCTC 27853)	Only *S. aureus* was inhibited by the petroleum ether extract (At 100% concentration: ZOI = 15mm). The ethanolic extract (ZOI =	Gadir, Mohammed, and Bakhiet 2007

(*continued*)

Table 4. Continued.

Part used	Extract type/ Isolated compounds	Microorganisms tested	Main findings	References
			14–18mm) inhibited all bacteria except *S. aureus*. The aqueous extract inhibited only *S. aureus* and *S. typhi*	
Seed	n-Hexane Acetone Ethanol Aqueous	*S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa*	At a concentration of 1000 µg/disc; There was no bacterial inhibition with the n-Hexane solvent. *S. aureus* and *B. subtilis* were the only bacteria inhibited by the acetone (ZOI = 9 mm) and ethanol extract (ZOI = 10–11 mm). The aqueous extract was the most effective as it inhibited *S. aureus* (ZOI = 10 mm), *B. subitilis* (ZOI= 9mm) and *P. aeruginosa* (ZOI = 13mm).	Penecilla and Magno2011
Seed	Hexane Dichloromethane Ethanol Aqueous	*S. aureus* (MTCC 3160), *E. coli* (MTCC 119), *S. typhi* (MTCC 531) and *B. subtilis* (MTCC 121)	All the extracts tested had some level of inhibition. The dichloromethane extract had the highest activity against all the bacteria (ZOI = 10–19mm, MIC = 2–10 mg/mL). The aqueous extract had the lowest activity against all the bacteria (ZOI = 7–9 mm; MIC: >40 mg/mL).	Gupta et al. 2014a
Seed	Hot water Cold water Pepper soup	*E. coli, S. aureus, and C. albican*	The hot water extract had the highest mean ZOI on all the bacteria tested (mean ZOI = 13.775mm). The extracts were most effective against *E. coli* (mean ZOI = 13.548 mm).	Kalunta2017
Seed	Ethanol	Bacteria: *B. subtilis* (ATCC 6633), *S. aureus* (ATCC 25923), *S. epidermidis* (ATCC 12228), *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 10145) Fungi: *Candida albicans* (ATTC 60192), and *A. niger*	The extract was most effective against *P. aeruginosa* (MIC = 5 mg/mL). Among the fungi, *A. niger* was mostly inhibited (ZOI = 15 mm).	Erturk2006
Seed	Essential oil	*A. niger* and *G. candidum*	The extract was more effective against *G. candidum* at 20 ppm and 30 ppm of concentrations tested.	Verma, Chaurasia, and Kumar2011
NI	Aqueous Methanolic Ethanolic	*B. subtilis*, *B. megaterium, B. sphaericus*, *B. polymyxa, S. aureus* (Gram-positive), *and E. coli* (Gram-negative) and eleven molds, *A. luchuensis*, *A. flavus*, *P. oxalicum, R. stolonifer, Scopulariopsis* sp. and *Mucor* sp.) isolated from bakery products and pickles.	The aqueous extracts showed antibacterial activities against all bacterial strains (ZOI = 11—30 mm) except against *B. subtilis.* The methanolic extract, (ZOI = 12–28 mm) was more effective than the ethanolic extract, (ZOI = 15—22 mm). No antifungal activities were observed with any of the extracts.	Pundir and Jain2010
NI	Essential oil	9 Gram-positive and 16 Gram-negative bacteria**	Of all the bacteria tested, only 3 were not inhibited by the volatile oil. *Aeromonas hydrophila* (NCTC 8049) was mostly inhibited (over 90.0 mm).	Dorman and Deans2000
NI	Ethanol	*K. pneumoniae*, *S. aureus*, *M. morgani*, *C. albicans*, *E. coli* and *P. vulgari*	At the highest concentration tested (2000 ppm), the ethanolic extract inhibited all the microorganisms (ZOI = 6–16mm), except *M. morgani*. The extract was most effective against *E.coli* (ZOI = 16mm).	Joe, Jayachitra, and Vijayapriya2009
NI	Alcohol	Bacteria: *Pseudomonas lundensis* and *Bacillus cereus* Fungi: *Aspergillus niger* and *Aspergillus flavus*	At 100% of the extract, all microorganisms were inhibited (ZOI = 10–12mm). The extract was most effective against *B. cereus* (ZOI = 12 mm). However, at lower concentrations tested (25, 50, 75%), not all microorganisms were inhibited.	Hema, Kumaravel, and Elanchezhiyan2009
NI	Aqueous	Clinical isolates of *S. aureus*, *Salmonella* sp., *Bacillus subtilis* and *E. coli*.	The aqueous extract was found to be most effective against *B. subtilis*	Ghori and Ahmad2009
NI	Methanol	*S. aureus P. aeruginosa, E. coli, S. tuphiumirium*	At 50 mg/mL concentration, the methanolic extract inhibited all the bacteria. (ZOI = 9.75–12.25 mm).	ShivaRani and Neeti2013
NI	Aqueous Ethanol Methanol	*S. aureus, B. subtilis, B. cereus, E.coli, S. typhi, P. aeruginosa*	The aqueous extract inhibited only the gram-positive bacteria (ZOI = 12–17 mm). The methanolic extract inhibited all bacteria (ZOI = 11–18 mm) except *B. subtilis*. The	Shete and Chitanand2014

(*continued*)

Table 4. Continued.

Part used	Extract type/ Isolated compounds	Microorganisms tested	Main findings	References
			ethanolic extract was the most effective (ZOI = 16–22 mm).	
NI	Aqueous Ethanol Chloroform Methanol	*E. coli* (MTCC-40), *P. aeruginosa* (MTCC-424), *Salmonella* sp. (MTCC-3215), *Shigella flexneri* (MTCC1457), *S. aureus* (MTCC-3160)	Methanol extract was ineffective against all the bacteria. The aqueous (ZOI= 1-3mm) and ethanolic extract (ZOI = 3–5 mm) showed moderate inhibition on all the bacteria. The chloroform extract also showed inhibitory effects on all the bacteria (ZOI = 1–6 mm) but was most effective against *S. flexneri* (ZOI = 6 mm).	Debnath et al. 2014
NI	Aqueous Methanol Ethanol Acetone Petroleum ether	*E. coli*, *K. pneumoniae*, *Proteus* sp., *P. aeruginosa*, and *B. subtilus*	All extracts inhibited all the bacteria. At 50% v/v, the methanol extract exhibited significant inhibition of all the bacteria (ZOI = 10–14 mm). Petroleum ether extract showed the lowest activity on all the microorganisms (ZOI = 4–6 mm)	Renu, Ekta, and Neha2017
NI	Essential oil	*Propionibacterium acnes* (DMST No. 14916, 14917, 14918, 21823, 21824)	*P. nigrum* oil was ineffective against all of the bacterial strains.	Luangnarumitchai, Lamlertthon, and Tiyaboonchai2007

**Due to the high number of bacteria tested ($n = 25$), the list of bacteria was not added to the table.

316.27 µg/mL). The ABTS scavenging effect of the essential oil (IC_{50}= 223.8 mg/mL) was also determined by (Zhang and Xu 2015).

Phenolic compounds from *P. nigrum* including 3,4-dihydroxyphenyl ethanol glucoside, 3,4-dihydroxy-6-(N-ethylamino) benzamide, and phenolic acid glycosides were found to scavenge DPPH radicals, with EC_{50} values of 0.076, 0.27, and 0.12 mg/mL, respectively (Chatterjee et al. 2007). Another *P. nigrum* compound, N-trans-feruloyltyramine, also showed potent DPPH inhibition (EC_{50} = 11.82 µg/mL) (Tu et al. 2016). Isolated compounds such as piperine and piperic acid also showed higher DPPH and antioxidant activity in the phosphomolybdenum assay compared to the ethanolic extract of the berries. Piperine was more potent DPPH scavenger compared to piperic acid (10.28 and 29.5% inhibition, respectively, at 50 µg/mL) while piperic acid displayed higher molybdenum (VI) reducing activity (64.1 and 58.8 µmol/mL α-tocopherol equivalents at 100 µg/mL, respectively) (Zarai et al. 2013).

In vivo experiments also revealed that *P. nigrum* extracts improved the level of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S- transferase (GST), and the reduced glutathione (GSH) (Vijayakumar, Surya, and Nalini 2004). Also, concurrent piperine (40 mg/kg body weight in 1% carboxymethyl cellulose, p.o) supplementation along with high-fat diet and antithyroid drug administration reduced lipid peroxidation and improved the antioxidant status compared to those rats which did not receive piperine treatment (Vijayakumar and Nalini 2006).

Anticancer

The increasing resistance and associated adverse effects of chemotherapeutic drugs, and the recurrence of cancer have increased the interest in the scientific community to explore for new agents from medicinal plants. Researchers have proved anticancer property of *P. nigrum* and its bioactive compounds against different cancer cell lines. For instance, the chloroform and petroleum ether extract of the root showed the cytotoxic effect against human myeloid leukemia HL-60 cell (IC_{50} = 9.8 and 11.2 µg/mL, respectively after 72 h of exposure) (Ee et al. 2009). The methanol extract of the fruit was more effective than the dichloromethane extract against the breast cancer MCF-7, and MDA-MB-231 cell lines while the latter showed higher cytotoxicity against MDA-MB-468 cell (Sriwiriyajan et al. 2014). The ethanolic extract of the fruit was also found to exhibit the anticancer effect on the three colorectal cancer cell lines (HT-29, HCT-116, and HCT-15) with IC_{50} values of 7.4, 3.4, and 1.9 µg/mL, respectively (Prashant et al. 2017).

Two active compounds isolated from the fruit, (-)-kusunokinin and piperlonguminine, displayed cytotoxic effect against breast and colorectal cancer cells. (-)-kusunokinin showed greater cytotoxicity to MCF-7, MDA-MB-468, and SW-620 (IC_{50} = 1.18, 1.62, and 2.60 µg/mL, respectively), while piperlonguminine was more efficient on MDA-MB-231 (IC_{50} = 71.54 µg/mL). Both compounds displayed lower cytotoxicity against normal breast cell lines with IC_{50} values higher than 11 µg/mL. Besides, the compounds induced cell apoptosis and drove cells towards the G2/M phase. Also, both compounds decreased topoisomerase II and Bcl-2. The increase in the level of p53 further increased p21, bax, cytochrome c, caspase-8, -7 and -3 activities (Sriwiriyajan et al. 2017).

Another compound from the root, pellitorine, was found to be cytotoxic against MCF-7 (IC_{50} = 1.8 µg/mL) and HeLa (IC_{50} = 13 µg/mL) (Ee et al. 2009). The *P. nigrum* compound mostly studied for its anticancer properties is piperine which was found as a potent cytotoxic agent against HER2-overexpressing breast cancer cells (SKBR3 and MCF-7 cell). Piperine strongly inhibited proliferation and caused apoptosis through activation of caspase-3 and PARP cleavage. Moreover, piperine inhibited the expression of HER2 gene at the transcriptional level. Piperine also blocked ERK1/2 signaling and reduced the expression of SREBP-1

and FAS. In addition, piperine actively suppressed EGF-induced MMP-9 expression via the inhibition of AP-1 and NF-jB activation by interfering with ERK1/2, p38 MAPK, and Akt signaling pathways, thereby causing a reduction in migration. Also, piperine pretreatment was found to enhance sensitization to paclitaxel killing in HER2-overexpressing breast cancer cells (Do et al. 2013).

Piperine also showed anticancer property against prostate cancer cell (LNCaP, PC-3 and DU145) (Ouyang et al. 2013). Treatment with piperine resulted in a dose-dependent inhibition of the proliferation of these cell lines. Piperine induced cycle arrest at G0/G1 and downregulated cyclin D1 and cyclin A. The compound also dose-dependently increases the level of p21Cip1 and p27Kip1 in both LNCaP and DU145 but not in PC-3 cells, which was in conformity with the more robust cell cycle arrest observed in the former two cell lines than the latter one. In addition, piperine induced autophagy as proved by an increase in the level of LC3B-II and LC3B puncta formation in LNCaP and PC-3 cells.

Piperine also re-sensitised P-glycoprotein, multidrug resistance protein 1 (MRP1) and breast cancer resistance protein (BCRP) dependent multidrug resistant cancer cells (Li et al. 2011). *In vivo* administration of piperine caused a 95.2% reduction in tumor nodule formation, serum sialic acid level and serum gamma-glutamyl transpeptidase activity in mice. The compound also suppressed benzo(a)pyrene (B(a)p) induced lung cancer in mice by decreasing the levels of total protein and protein-bound carbohydrate components (hexose, hexosamine, and sialic acid) (Selvendiran, Prince Vijeya Singh, and Sakthisekaran 2006).

Anti-inflammatory

Tasleem et al. (2014) evaluated the anti-inflammatory effect of *P. nigrum* and its active compound piperine based on carrageenan-induced paw edema using plethysmometer. Piperine exhibited inhibition of edema at all doses of 5, 10, and 15 mg/kg. The compound showed maximum activity at a dose of 15 mg/kg after 120 min (Reaction time = 0.588 s) but still less than the standard drug diclofenac sodium (Reaction time = 1.330 s after 60 min). In addition, Jeena et al. (2014) observed that, using a carrageenan-induced acute inflammation model, administration of 500 mg/kg b.wt. *P. nigrum* essential oil significantly reduced paw edema by 72% in mice in the third hour when compared to the control group. On the other hand, treatment with 100 mg/kg oil produced 66.1% inhibition in the third hour. Moreover, using a dextran-induced acute inflammation model, the oil, at 100, 500, and 1000 mg/kg bw, dose-dependently reduced the paw thickness by 33.3, 53.3, and 73.4%, respectively, at the third hour when compared to the control group. The essential oil also showed a promising result compared to the standard drug Diclofenac (49.3% inhibition at 10 mg/kg). In the case of chronic inflammation induced by formalin, the *P. nigrum* essential oil caused a 50% inhibition of paw edema at 500 mg/kg while the inhibition exhibited by the standard drug diclofenac at 10 mg/kg was 57.5%.

Analgesic and anticonvulsant

The interest in the exploration for novel and safe pain-alleviating natural agents has stimulated scientists to study *P. nigrum* as a therapeutic pain agent. Tasleem et al. (2014) determined the analgesic activity of hexane and ethanolic extracts of *P. nigrum* and its compound piperine using the tail immersion, analgesy-meter, hot-plate, and acetic acid induced writhing test. In the tail immersion method, piperine showed the maximum analgesic effect after 120 min at a dose of 5 mg/kg (reaction time by mice to withdraw the tail = 11.658 s) while in the analgesy-meter test, the ethanol extract was most effective after 60 min dose of 10 mg/kg (reaction time = 20.900 s). The highest reaction time for paw licking or jumping in the hot plate method was exhibited by piperine (12.870 s after 30 min at a dose of 10 mg/kg). In the writhing test, piperine (dose of 10 mg/kg) and the ethanol extract (dose of 15 mg/kg) completely stopped the number of writhes in mice induced by acetic acid.

Additionally, the anticonvulsant effect of *P. nigrum* was also studied. Belemkar, Kumar, and Pata (2013) observed that the ethyl alcohol and hexane extract of *P. nigrum* suppressed the onset and duration of seizures in Wistar rats using both pentylenetetrazol (PTZ) induced model and maximal electroshock seizure (MES) induced model. In addition, Bukhari et al. (2013) found that 50 mg/kg piperine treatment was most effective than 70 mg/kg in preventing the animals from PTZ-induced seizures. The highest tested dose of piperine (70 mg/kg) increased the latency of picrotoxin-induced convulsions to 878.5 s compared to the value of control group 358.4 s.

Hypoglycemic and hypolipidemic

Treatment of diabetic rats with *P. nigrum* aqueous seed extract for 4 weeks reduced the blood glucose level to 129 mg/100 mL compared to diabetic rats (270 mg/100 mL) (Kaleem, Sheema, Sarmad, and Bano 2005). 100, 200, and 300 mg/kg body weight of the leaf methanolic extract of *P. nigrum* reduced blood glucose level in alloxan induced diabetic rats after 21 days of treatment (Onyesife, Ogugua, and Anaduaka 2014). Aldose reductase is primarily involved in the development of long-term diabetic complications due to increased polyol pathway activity, therefore, its pharmacological inhibition has been recognized as an important strategy in the prevention and attenuation of associated complications particularly retinopathy, neuropathy, and nephropathy. Indeed, the study by Gupta, Singh, and Jaggi 2014b observed that the hydromethanolic extract of the seed inhibited goat lens aldose reductase, with an IC_{50} value of 35.64 µg/mL.

Supplementing piperine to the high fat diet rats lowered the levels of plasma total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), HMG CoA reductase and raised the level of lipoprotein lipase (LPL) and lecithin-cholesterol acyltransferase (LCAT) compared to rats which did not receive piperine (Vijayakumar and Nalini 2006). Vijayakumar et al. (2002) also found reduced level of total cholesterol, free fatty acids, phospholipids, and

triglycerides in *P. nigrum* extracts (250 mg/kg b.w and 500 mg/kg b.w) as well as in the piperine (20 mg/kg b.w) treated groups. Supplementation with both *P. nigrum* and piperine extracts increased the plasma HDL cholesterol and reduced the LDL and VLDL cholesterol.

Neuroprotective

A study by Hritcu et al. (2015) found that the methanolic extract of *P. nigrum* fruit exhibited anxiolytic- and antidepressant-like effects in male Wistar rats. The extract ameliorated amyloid beta (1–42)-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus (Hritcu et al. 2014). The compound piperine was found to attenuate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced deficits in motor coordination and cognitive functioning (Yang et al. 2015). In addition, Correia et al. (2015) observed that piperine reversed partially the decline in locomotor activity, fully inverted the motor deficit, and inverted the increased number of apomorphine-induced contralateral rotations observed in the 6-OHDA (lesioned in the right striatum) group.

Toxicity

Natural plant products have always been considered "safe" for centuries. However, this statement is not always right, especially when considering the dose of the plant product being administered. In this context, *P. nigrum* and/or its active compounds at a specific dose has also been documented to be potentially toxic by both *in vivo* and *in vitro* studies.

Tasleem et al. (2014) found that intraperitoneal administration of 25, 50 and 75 mg/kg of piperine in Swiss albino mice caused irritation and also observed drowsy after 30 min, while paralytic effect on hind limbs were noticed after more than 3hours with no intake of water and feed. More importantly, all six animals receiving 75 mg/kg of piperine died after 24 h, while animals treated with 25 and 50 mg/kg were found dead after 48 h.

The acute toxicity of piperine was also assessed on mice, rats, and hamsters. Single administration i.v., i.p., s.c., i.g. and i.m. to adult male mice displayed LD_{50} values of 15.1, 43, 200, 330 and 400 mg/kg body weight, respectively. Interestingly, in adult female mice. the i.p. the LD_{50} value was increased to 60 mg/kg body weight while in weanling male mice, it was increased to 132 mg/kg body wt. In adult female rats, the i.p. LD_{50} value was 33.5 mg/kg body weight which was lower compared to the i.g. LD_{50} value (514 mg/kg body wt). In addition, most animals receiving a lethal dose of piperine died within 3–17 min due to respiratory paralysis. In the subacute toxicity studies, the rats died within l–3 days (Piyachaturawat, Glinsukon, and Toskulkao 1983).

Chunlaratthanaphorn et al. (2007) found that a single oral administration of the aqueous extract of the *P. nigrum* dried fruits (5,000 mg/kg body weight) to male and female Sprague-Dawley rats did not produce signs of toxicity, behavioral changes, mortality, changes on gross appearance or histopathological changes of internal organs. In addition, the subchronic toxicity was assessed by oral feeding daily at the doses of 300, 600 and 1,200 mg/kg body weight continuously for 90 days. No abnormalities were observed in the test groups as compared to the controls.

Conclusion and future perspectives

From the above review, a disproportion in the amount of reported folk medicinal knowledge on *P. nigrum* was observed in some countries. Since it is a popular spice globally used, further studies should emphasize on conducting surveys on the traditional uses of *P. nigrum* in other regions as well, together with a well-reported method of preparation and dosage taken. Moreover, it was observed that most pharmacological studies were conducted *in vitro* ($n = 60$) while only 21 *in vivo* and 1 clinical trial was performed. Hence, further *in vivo* experiments together with a pharmacokinetic and pharmacokinetic approach would be beneficial. Nonetheless, *in vitro* studies are still required to screen for most potent solvent extracts and fractions, and to understand the mechanism of action such as the enzyme inhibitory pathway through molecular docking. For instance, the observed *in vivo* neuroprotective effects of *P. nigrum* could be further studied *in vitro* with regards to its potential acetylcholinesterase and butyrylcholinesterase inhibition, two key enzymes involved in Alzheimer's and Parkinson disorders. Similarly, research on the inhibitory effect of *P. nigrum* against α-amylase, α-glucosidase, and lipase enzymes could provide information on the mechanism of the *in vivo* hypoglycemic and hypolipidemic action previously observed. Future studies may also explore the interactions of the potent compound piperine with other compounds present in *P. nigrum*, and also in combination with current conventional drugs, in order to observe any synergistic or additive effect, which may ultimately lead to a reduced therapeutic dose with less associated toxicity. To conclude, *P. nigrum* is not only a widely used spice but is also an important medicinal plant which may be considered as potential nutraceutical and pharmaceutical agents.

List of abbreviations

AOA	antioxidant activity
B	W-body weight
CD	conjugated dienes
COX	cyclooxygenase
DPPH- 1	1-Diphenyl-2-picryl-hydrazyl
FC-Folic-Ciocalteu; FOS	
fructo-oligosaccharide	
FPLC	Fast protein liquid chromatography
FRAP	ferric reducing antioxidant power
FW	Fresh Weight; g-gram
GAE	Gallic acid Equivalent
HDL	high-density lipoproteins
HP	hydroperoxide
HPLC	High-performance liquid chromatography
ZOI	Zone of Inhibition
Kg	Kilogram
LDL	low-density lipoproteins
vLDL	very low-density lipoproteins

LOX	lipoxygenase
MDH	malondialdehyde
mg	milligram
MIC	Minimum Inhibition Concentration
mL	mililitre
NOA	National Onion Association
oC	Degrees celcius
PBMCs	Peripheral blood mononuclear cells
SMCS	S-methyl cysteine sulfoxide
SOD	superoxide dismutase
TEAC	Trolox equivalent antioxidant capacity
TLC	Thin layer chromatography
µg	microgram
µl	microliter
LD50	lethal dose to kill 50% population
i.p	intraperitoneal
; i.v	intravenous
s.c-	subcutaneous
; i.g	intragastric
i.m	intramuscular

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