

PIPER LONGUM (PIPPALIMOOL): A SYSTEMATIC REVIEW ON THE TRADITIONAL AND PHARMACOLOGICAL PROPERTIES OF THE PLANT

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Article Received on 19/05/2021

Article Revised on 09/06/2021

Article Accepted on 29/06/2021

ABSTRACT

The universe is gifted with several medicinal herbs. These medicinal herbs are associated with various phytochemical constituents that help in drug development to treat a variety of diseases. One such herbal plant is *Piper longum* Linn. which is also known as pipali or long pepper or pippalimool. This plant is in use since ancient times both as a spice and medicine. *P. longum* carries great potential in the medicinal system and is utilized in different medicinal systems such as Ayurveda, Unani, Chinese and Siddha to cure several ailments and disorders. In Ayurveda, this plant is used as the main ingredient in various formulations and is claimed to treat mainly respiratory and digestive disorders. Despite this, this plant is used to treat nerve disorders such as Parkinson's, Alzheimer's/ dementia, epilepsy, insomnia and others. There are some reported experimental studies that showed the pharmacological activities of *P. longum* such as neuroprotective, anti-inflammatory, analgesic, antibacterial, antidiabetic, antiulcer and many more. In this review article, we have tried to compile all the data available on this plant based upon the folklore, ayurvedic view and modern view along with its reported pharmacological properties.

KEYWORDS: Ayurveda, Rasapanchak, Modern view, Folk view, Pharmacological properties.**INTRODUCTION**

Medicinal plants are known as the 'backbone of the traditional medicinal system. More than 3.3 billion people in developing countries rely on medicinal plants to treat various diseases.^[1] One such plant is *Piper longum* (figure no. 1) which is also known as Javanese, long pepper, pippalimool (the root of *Piper longum* Linn.), Indian or Indonesian long pepper. Pippalimoolam is known as the root of this plant.^[2] *P. longum* was first written by Hippocrates who define this plant as a medicine rather than a spice. The most utilized parts of this plant are mainly fruits and roots. Long pepper was considered one of the major Indian exporters for nearly 2400 years. Theophrastus categorized pepper in two divisions i.e. round one and another one which is long. This plant is mainly utilized as a spice and as a drug in Europe during the medieval period and in the 19th century. It is the source of the drugs Pippali and Pippalimulam. The fruit of *P. longum* has been used as a flavor since ancient times and is used as a preservative in pickles, food items, medicine and traditional drinks.^[3] It is an aromatic climber and is widely distributed in the tropical and subtropical regions of the world. It is mainly used for cooking purposes as a spice. Medicinally, the plant is reported as a good remedy to cure menstrual pain, gonorrhea, sleeping problems, tuberculosis, respiratory tract infections, arthritic conditions and chronic gut-related pain.^[4] In Ayurveda, Unani, Siddha

and the Chinese medicinal system, the roots and fruits of *P. longum* are used to treat fever, asthma, hemorrhoid infection, bronchial stress, abdominal pain, inflammation, jaundice diarrhea and antidote to snake bite. The main active constituent present in the *P. longum* plant is piperine which is reported to have CNS depressant, analgesic, antipyretic, antioxidant,^[5] anti-inflammatory,^[6] and hepatoprotective properties.^[7] In Ayurveda, it comes under panchakola, Shudhashana and is considered a great remedy for dipaniya (stomachic), pachaniya (digestive). From various clinical studies, it was reported that pippali shows significant effects against bronchial asthma in children.^[8] Table no. 1 & 2 represents the vernacular names and taxonomical classification of *P. longum*.

**Figure 1: Piper longum (Pippalimool).**

Table 1: Vernacular names.

Hindi	Pipali, Pipar, Pipal
Kannada	Hippali, Thippali balli
Malayalam	Tippali, Pippali
Marathi	Pimpli
Tamil	Tippili
Telegu	Pippallu, Pippali
Sanskrit	Ushana, Kana, Magadhi, Pippali, Krishnapippali
Bengali	Pipul
English	Long pepper
Gujarati	Lindi pepper
Orissa	Pippalimula
Punjabi	Maghan
Urdu	Filfil Daraz

Table 2: Taxonomical Classification.

Taxonomical Rank	Taxon
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Piperales
Family	<i>Piperaceae</i>
Genus	<i>Piper</i>
Species	<i>longum</i>
Common name	Pippalimool, long pepper

Botanical Description

It is a small, perennial climber, an aromatic shrub that belongs to the *Piperaceae* family. The roots of the plant are woody, wide ovate with cordate leaves. The stem is creeping, jointed and thickened at the nodes.^[9] The leaves are spreading, alternate, without stipules and with blades that varies greatly in size. The lowest leaves are 5-7 cm long and the uppermost leaves are 2-3 cm long. Flowers are cylindrical with solitary spikes. The fruits are small, ovoid that grow in fleshy spikes, blunt, oblong, blackish-green with length 2.5-3.5 cm and 5 mm width. The mature spikes are long, cylindrical, oblong. The berries are red or black with aromatic odor and pungent taste that is collected and dried as the commercial form of pippali. The root radix is known as pippalimula.^[10]

Geographical Distribution

It is a native species of the Indo-Malaya region. It is mainly grown in limestone soil and heavy rainfall areas having high humidity.^[11] The plant is mainly found in the tropical rainforests of Nepal, India, Indonesia, Malaysia, Sri Lanka, Rhio, Philippines and Timor. In India, the plant is distributed from the central Himalayas to Assam, Tamil Nadu, Andhra Pradesh, Madhya Pradesh, Maharashtra, Kerala, Karnataka, lower hills of West Bengal, Khasi hills, Mikir hills and evergreen forests of the Western Ghats from Konkan to Kerala and Nicobar Islands.^[12]

Phytochemical Constituents

The main active constituents present in *P. longum* plant are alkaloids which include piperine, piperlonguminine, piperlongumine and methyl-3,4,5-trimethoxycinnamate.^[13] The fruit part consists of volatile oil (1%), protein, starch, alkaloids, saponins, carbohydrates and amygdalin, a waxy alkaloid N-isobutyldeca-trans-2-trans-4-dienamide, alkaloids piperine, calcium, phosphorus, iron and a terpenoid substance. Lignans and esters such as sesamin,^[14] pulvuatitol, fargesin, Z-12-octadecenoic-glycerol-monoester, tridecyl-dihydro-p-coumarate and eicosanyl-(E)-p-coumarate were also isolated from the fruit part of the plant.^[15] The root part of the plant contains piperlongumine or pipartinine, piperine and dihydrostigmastrolasarinine, pellitorine, refractomide A, brachystine, piperide, piperderidine, piperundecalidine, iperonaline, methyl piperine, tetrahydropiperlongumine,^[16] dehydropiperonaline piperidine, trimethoxy cinnamoyl-piperidine and piperlongumine.^[17,18,19,20,21] The dried spikes of the plant consist of 0.7% essential oil with a spice odor. The essential oil of the plant contains sesquiterpenes, caryophyllene and hydrocarbons. Other chemical constituents present are sesamine, dihydro stigmastrol, piperacide, piperundecalidine, pipernonaline, dieudesmin and sitosterol. The seed part of the plant contains sylvatine and dieudesmin.^[22] The other alkaloids components present are asarinine, pellitorine, refractomide A, brachystine, piperide, piperderidine, piperundecalidine, iperonaline, methyl piperine, tetrahydropiperlongumine, dehydropiperonaline piperidine, trimethoxy cinnamoyl-piperidine and piperlongumine.^[23,24] The essential oil present in the fruit includes caryophyllene (17.8%), pentadecane (17.8%) and bisabolene (11%). Other essential oil constituents present are terpinolene, p-cymene, thujine, zingiberene, p-methoxy acetophenone and duhydrocarveol.^[25] The chemical structures of some major phytochemical constituents are shown in figure no. 2.

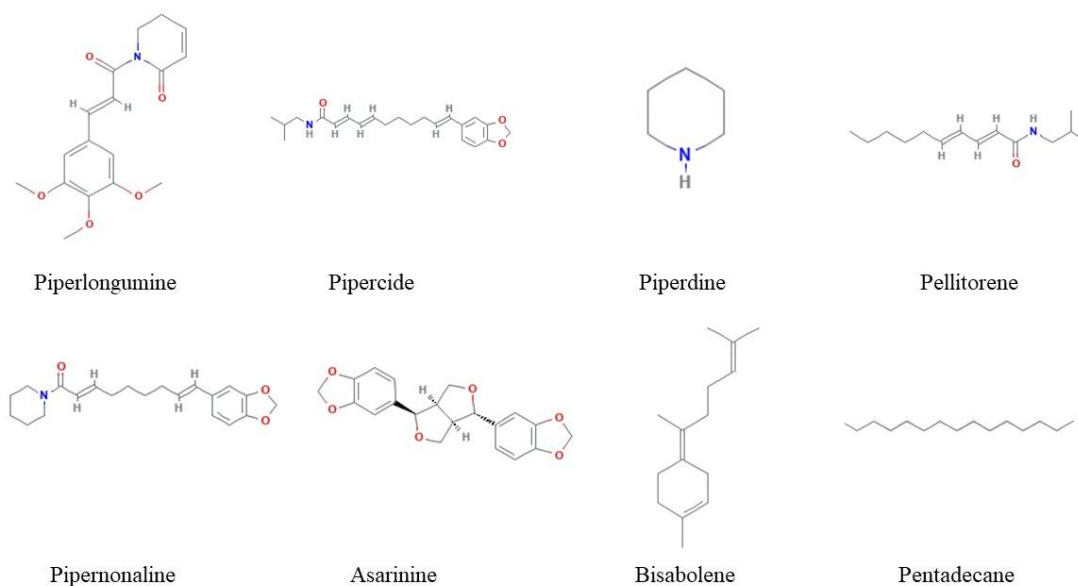


Figure 2: Chemical structures of some major phytochemical constituents of *P. longum* plant.

Traditional and Modern View

a) Ayurvedic view: Pipalimool plant has been used in ayurvedic medicinal system to treat various diseases and disorders.^[26,27] As per ancient scriptures, *P. longum* is used as a bio enhancer that helps in removing endotoxins from the body. It helps in balancing vitiated Kapha and Vata. It is used in India since ancient times. It is considered as one of the significant herb in Ayurveda and is also mentioned in Panchkola, Shadushana, etc. Pippali is used as a significant drug to treat Anaha (constipation) and agnimandya.^[28] In Ayurveda, the plant is mainly used to cure respiratory disorders. The roots of this plant are helpful to cure bronchitis, spleen diseases, stomachaches and tumor. It is used to treat diseases like krimi (parasitic disease), pliha roga (spleen disorders), kshaya (pulmonary tuberculosis), shwasa (dyspnea), urastambha (stiffness of thigh), grahni (dysentery), vatavyadhi (nervous diseases), vishama jvara (intermittent fever), arsha (piles), nidranasha (insomnia) and other disorders.^[29] It is mentioned as Rasayana, Atividha bhesaji, Vatikrita bhesaji and Ksipta bhesaji in arthava veda and is used in the treatment of akshepaka and dhanurvata. Also, this plant is used in various Rasayana formulations such as vardhmana pippali and pippali rasayana. Although, Charaka restricted the excessive use of pippali plants for dietary purposes and not for medicinal usage. Also, this plant is included in Virechana dravya.^[30] In Ayurveda, pipalimool plant is used as a vrishya, medhya, dipan, jvaraghna, kasaghna and cure diseases like kushtha, jvara, udara, gulma,

shvas-kasa, arsha, prameha, pandu, arsha and other disorders.^[31] In Brihatrayi, Charaka represented this plant as dipaniya mahakasaya, kanthaya mahakasaya, kasahara mahakasaya, hikkani-grahan, kanthya mahakasaya and sula prashaman. It is also effective against abdominal tumors, piles, madhumeh, colic indigestion, anemia, cardiac, spleen disorders, Kapha disorders, flatulence, gout, paralysis, rheumatic pain, sciatica and helps in improving digestive fire and immune system of the body.^[32] The fruit of *P. longum* in combination with the powdered seeds of *E. ribes* and borax powder is used as an ayurvedic contraceptive.^[33] *Piper longum* is used in Rasayana therapy which is also helpful in preventing the COVID-19 symptoms.^[34] As per the reported study, *P. longum* plant is used in about 135 ayurvedic formulations.^[35] The rasapanchak (properties) of the plant is shown in table no. 3.

Formulations of *Piper longum*: It is used in various formulations such as pain balm, relief balm, cough syrups, heart and geri/stress care and joint care balm. Some important formulations include Trikatu, Vardhamanas Pippali rasayana, Talisapatradi churna, pippalyedyesava, kanakasava, balacaturbhadraka, shringyadi churna, amrutarishta (amrutarishtam), Guda-pippalyadi choorna, shiva gutika, Abhayaristam, Draksaristam, Chayavanaprasam, Pippalyasavam and Kaishore guggulu, Pancakola Curna, Dasamula taila, Dasam ulastapalaka ghrita, Asvagandhadyarista, Amrtariasta, Ayaskrti, Gudapippali.^[36]

Table 3: Rasapanchak (properties) of *Piper longum*.^[37]

Sanskrit/English	Sanskrit/English
Veerya / Potency	Anushnasheet / Slight cold
Vipak / Metabolic property	Madhur / Sweet
Guna / Physical property	Laghu / light, Tikshna / Sharp, Snigdha / Oily
Rasa / Taste	Katu / Bitter

Actions and Properties

Doshkaram: It alleviates the vitiated Kapha, Piita and Vata dosha and is used to treat the disorders that arise due to misbalance in Kapha, Vata and Pitta.

Sansthanik Karam: The topical application of the plant helps in head evacuation. It is also used as a blood purifier and possesses anthelmintic properties.

Abhyantranadisansthan: It is used as a brain tonic and balances Vata dosha.

Paachansansthan: It is used to cure stomachache, constipation, dysentery, diarrhea, pacify thirst, stimulate the spleen and also act as a mild laxative.

Raktabhansansthan: It is used as a blood purifier.

Shawasansansthan: It is used to stop hiccups and is associated with antitussive and anti-asthmatic properties.

Mutravahansansthan: It acts as a diuretic agent.

Prajanansansthan: It stimulates the uterine muscles and acts as an aphrodisiac agent.

Twacha: It is effective against skin disorders.

Taapkram: It is used as an antipyretic agent.

b) Folk Uses: *Piper longum* is generally used as a spice or flavor in cooking purposes. Traditionally, pipallimool is mainly used to treat respiratory disorders such as bronchitis, asthma and stomach-related disorders such as gynaec problems, indigestion, asthma, tuberculosis.^[38] fever, cough, sinusitis, diarrhea, dysentery and other diseases including insomnia.^[39,40] The fruit of the plant act as an anthelmintic agent and is effective against parasites. It is also used as an expectorant and helps in clearing mucus from lungs and other respiratory parts. The roots and fruit decoction of pipalimool are used to cure chronic bronchitis. The fruit in the roasted form in combination with honey is given twice a day a month to treat rheumatism.^[41] The fruit of the plant in paste form is utilized with a glass of water once a day to cure diabetes.^[42] It is also used against allergic problems. The fruit of the plant in powder form in combination with mishri is taken empty stomach to cure urticarial. Also, it is used to cure cough and cold when taken with honey and tulsi drops.^[43] Also, this plant is used to cure livestock diseases such as horns, buccal cavity, lumbago, acute dysentery, etc.^[44] In the North-western Himalayan region, the root decoction of the plant is used to treat inflammation of joints of cattle.^[45] The unripe fruit of the plant is used as carminative, stimulant and tonic.^[46] The mature spikes of female parts are effective against worms, dyspepsia, amoebiasis and act as an aphrodisiac agent. The plant is also consumed to enhance memory power, helps in regaining health by dispelling diseases and improves appetite. The fruits and roots of *P. longum* are used to cure epilepsy, as cholagogue in obstruction of the bile duct and gall bladder as a sedative in insomnia and as a snuff in coma and drowsiness.^[47] In India, the roots and fruit part of the plant are used as a nullifier or antitoxin against venom and as an antidote to scorpionsting and snake bite.^[48] In the Chinese medicinal system, fruits of *P. longum* are used to treat nausea, headache, acid reflux, stomach and allergic rhinitis.^[49] In Thailand, both mature and immature fruits of the plant are used in

relieving flatulence and post-labor pain.^[50] The external application of the powdered fruit part of the plant helps in curing toothache. The stem decoction of the plant is used to relieve the pain of rheumatoid arthritis and diarrhea.^[51,52]

c) Modern View

There are about 2000 species of genus *Piper* found all over the world out of which 52 species are found in India. One of the important species of this genus is *Piper longum* which is of great medicinal importance both in the traditional and modern medicinal system. The quality and formulation of the drug mainly depend upon the availability of the genuine material. Also, the standardization of the ayurvedic drug or other formulation needs more attention for further therapeutic results and global acceptance. The main parts of *P. longum* used are the fruit and stem in various Ayurveda and modern formulations. Due to the excessive demand and scarcity of the plant, intentional adulteration practice is implemented which alters the quality of the plant. The adulteration practice i.e. both intentional and unintentional reduces the potency of herbal drugs. From the literature study, it was reported that the raw material of species comes in the market always in adulterated or substituted form due to the less availability and high cost of the plant. The collection of the plant parts in a non-scientific way also promotes unintentional adulteration.^[53] As the plant is listed under endangered species, the non-availability of the species results in inter or intraspecies substitution and adulteration. Lack of standardization and effective quality control method is the other causes that are responsible for the adulteration and altered quality of the species.^[54] So, it is necessary to develop an Herbal Authentication System (HAS) which can serve as a regulator and also helps in improving the quality of herbal trade.^[55,56] The other method used is fingerprint profiling which helps in settling the standards and check the adulteration practice (intentional or unintentional).^[57]

Reported Pharmacological and Therapeutic Properties

From various reported studies, it was found that the *Piper longum* plant is associated with various therapeutic and pharmacological properties. Some of the studies are described below.

Antibacterial, Antimicrobial and Anti-amoebic: As per the reported study, the ethyl acetate extract of *P. longum* fruit showed effective antibacterial activity against selected bacteria or microbes using the agar well diffusion method.^[58] In another study, the plant extracts exhibit significant antibacterial activity when tested against different bacterial pathogens such as *Staphylococcus albus*, *Pseudomonas aeruginosa*, *E. coli*, *Bacillus megaterium* and *Salmonella typhi*.^[59] The methanolic extract of the *P. longum* fruit showed significant antimicrobial activity by inhibiting the severity of cecal wall ulceration in mice caused by

Entamoeba histolytica.^[60] The root and fruit extract of the plant showed significant antiamebic activity against amoebiasis almost to the same extent. In another study, ethyl acetate and petroleum ether extract of *P. longum* showed antimicrobial activity against various microorganisms.^[61]

Antidiabetic: The ethanolic extract of *P. longum* plant was demonstrated for the antidiabetic activity in diabetic rats. It was found that the oral administration of the extract restores the blood glucose level which ultimately stimulates the liver activities to maintain the normal homeostasis of blood glucose level.^[62] Another study was conducted on streptozotocin-induced diabetic rats where an aqueous extract of the plant showed significant antidiabetic rat at a dosage of 200 mg/kg b.w. after 6 h of the treatment with the extract.^[63] Another study showed that the oral administration of the dried fruits showed antioxidant, anti-lipid peroxidative and antihyperglycemic activities in diabetic rats when compared with standard reference drug glibenclamide.^[64]

Neuroprotective: The dichloromethane fraction (DF) of *P. longum* and *P. nigrum* was examined for the therapeutic effect of neuron injury after apoplexy using a middle cerebral artery occlusion model in rats. The extract was administered orally in the rat model for 14 days. The model exhibits a significant increase in PSD-95, phosphorylated CaMK II (p-CaMK II), calmodin (CaM) and N-methyl D-aspartate receptor subtype 2B (NR2B).^[65]

Immunomodulatory: The alcoholic extract of *P. longum* was demonstrated to identify the immunomodulatory action of the extract. The rat model was injected with the alcoholic extract of fruit and piperine constituent. A significant increase of the WBC counts and plaque-forming cells contributing antibodies production was observed which ultimately stimulate the hematopoietic system indicating stem cell proliferation and overall immune system.^[66]

Anti-tumor: The piperine and pipartine constituent of the plant was studied for the antitumor activity in the mice model. A significant reduction of tumor weight was observed in pipartine and piperine-treated animals.^[67] In another study, the alcoholic extract of *P. longum* and piperine at the dosage of 10 mg and 1.14 mg restricts the solid tumor development in mice induced with Dalton's lymphoma ascites cells and increases the life span of the mice model. The piperine component showed cytotoxicity in Dalton's lymphoma ascites and Ehrlich ascites carcinoma cells at the dosage of 250 mg/ml.^[68] Another study showed that the piperine constituent inhibits the lung metastasis induced by B16F-10 melanoma cells when studied in C57BL/6 mice, thus showed chemopreventive effects when administered orally.^[69] The oral administration of the ethanolic extract showed a protective effect on the cell surface and maintain the structural integrity of the cell membrane

during DMBA induced hamster buccal pouch carcinogenesis.^[70] The previous studies demonstrated that the piperine constituent exhibits anti-apoptotic, anti-oxidative and restorative ability against cell proliferative mutagenic response.^[71]

Antioxidant: The determination of the antioxidant potential of the extract is based upon the radical scavenging activity of DPPH free radical.^[72] The phenolic compounds and flavonoids exhibit antioxidant activity against free radical-induced oxidative damage. Also, petroleum ether extract and piperine constituents of roots showed a significant reduction in the lipid peroxide level and maintain glutathione content.^[73] In another, *in vitro* study, it was found that the ethanolic extract of Pipali leaves showed the highest radical scavenging activity i.e. 63.84±0.05 and showed less toxicity. Hence the extract showed significant antiviral, hepatoprotective and anticancer activities.^[74]

Antiplatelet: The piperine, pipernonaline, piperlongumine and piperocatalidone constituents of pipali fruit were demonstrated for the antiplatelet activity against washed rabbit platelet aggregation. The inhibition of washed platelet aggregation induced by collagen, platelet-activating factor and arachidonic acid was observed in a dose-dependent manner.^[75]

Antifertility: The antifertility activity of the benzene extract of the *P. longum* plant was studied using a female rat model. It was found that the oral administration of the plant extract in combination with *E. ribes* berries showed 80% inhibition in the pregnancy rate in the female rat model.^[76] The hexane extract of *P. longum* possesses an immobility factor that reduced the sperms motility by disturbing the outer layer of sperm cells.^[77]

Anti-asthmatic: As per the reported study, the *P. longum* fruit extract exhibited bronchorelaxation with 83% inhibiting activity in histamine-induced bronchospasm model in guinea pig at a dosage of 200 mg/kg. It was also reported that the petroleum ether extract exhibited significant antiasthmatic activity against the mice model. The antiallergic activity of the extract was also demonstrated using milk-induced leukocytosis in mice and passive paw anaphylaxis in rats. The extract showed a significant protective effect in histamine-induced bronchospasm in haloperidol-induced catalepsy and passive paw anaphylaxis.^[78]

Anthelmintic: The methanolic, chloroform and n-hexane extract of the *P. longum* fruit showed *in vitro* ovicidal, larvicidal and adulticidal activity against strongyle, ova, larvae and adult amphistomes at the dosage of 1.95 mg/ml respectively. It showed complete larval mortality at the highest concentration of 500 mg/ml within 6 hours and a 50 % mortality rate at the lowest concentration. The chloroform extract exhibited less anthelmintic activity against L3 larvae with IC50 of 12.47 mg/ml.^[79]

Anti-snake venom: *P. longum* ethanolic fruit extract was examined for the anti-snake venom activity against Russell's viper venom in embryonated fertile chicken eggs, rats and mice. The extract showed noticeable inhibition of venom lethal action, venom defibrinogenating action, paw edema, hemorrhagic activity, mast cell degranulation, necrotizing action, catalase activity and creatine kinase assay at a dosage of 250 mg/kg, 500 mg/kg and 750 mg/kg.^[80]

Acaricidal: The acaricidal activity of the aqueous and ethanolic extract of *P. longum* was examined using a three-host ixodid tick, *Hyalomma anatolicum*. The alcoholic extract of the plant showed maximum acaricidal activity with the minimum lethal dosage of 50 (LC50) and lethal concentration 95 (LC95) values respectively.^[81] Another study was conducted in adult engorged females of *Rhipicephalus* (*Boophilus*) *microplus* using an adult immersion test. The extract directly acts on the reproductive physiology of ticks by restricting oviposition with a 36.1-1.89.3% mortality rate.^[82]

Antiulcer: *P. longum* extract was investigated for antiulcer activity. It was found that the administration of the extract to foot shock-induced stress animals protected ulcer severity up to 90% as compared with doxycycline.^[83]

CONCLUSION

As per the literature study, the *P. longum* plant is utilized both as a spice and medicine since ancient times. In Ayurveda medicinal system, there are about 135 ayurvedic formulations where *P. longum* is used as a major ingredient. In the traditional medicinal system, the plant is used to treat numerous diseases such as epilepsy, pleural effusion, spleen disorders, dementia, diarrhea, dysentery, insomnia and many more. There are some reported pharmacological activities of the *P. longum* plant such as antiulcer, anti-inflammatory, anticancer, neuroprotective and others. Still, the plant needs more attention from researchers as the data on the pharmacological properties of this plant is not much explored. This plant claims to treat various diseases as per the literature study but there are no reported pieces of evidence available that showed its effective results. So, the plant needs more experimental and clinical studies to investigate the mechanism of action of the plant extracts in the animal body to prove the significant effects of the plant in treating various diseases.

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