

“Phytochemical Insights and Diverse Pharmacological Activities of *Piper longum*: An Integrative Review”

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Abstract

There are many species of plants in the world, and one notable example is *Piper longum*, which holds significant potential in traditional medicine. This plant is utilized in various medicinal systems, including Ayurveda, Unani, Chinese medicine, and Siddha, for the treatment of different diseases and disorders.

In Ayurvedic medicine, *Piper longum* is an essential ingredient in numerous formulations that claim to address serious conditions, such as Parkinson's disease. Additionally, it is recognized for its use in treating neurological diseases due to its neuroprotective, anti-inflammatory, sedative, analgesic, and antibacterial properties.

In this review article, we aim to compile comprehensive information and pharmacological properties of this important plant, drawing from legends, Ayurvedic perspectives, and modern historical contexts. *Piper longum* Linn. [Piperaceae] plays a vital role in traditional practices like Ayurveda and Unani.

Keywords: *Piper longum*, phytoconstituents, traditional medicine, pharmacology, drug development

Introduction

More than 3.3 billion people in developing countries rely on medicinal plants to treat a variety of ailments.^[1] One significant example is *Piper longum*, which has been considered one of India's most important exports for about 2,400 years. Theophrastus classified peppers into two group round and long. In medieval and 19th-century, this plants primarily served as spices and medicines. *Piper longum* is the basis of medicinal preparations known as Pippali and Pippalimulam. The fruits and roots of *P. longum* have been used since ancient times as food ingredients and flavouring in pickles, various dishes, medicines, and beverages.^[2] The plant is widely used as an expectorant for conditions such as asthma, nausea, and diarrhoea. It is known for its effects on lowering blood sugar, stimulating the spinal cord, and relieving cough. Scientific studies have confirmed that the fruits of *P. longum* possess anti-inflammatory, anti-fertility, and anti-allergic properties, while only the roots have been reported to exhibit contraceptive effects. The Ayurvedic formulation Pippali Vardhmaan Rasayana is regarded as a highly effective treatment for rheumatoid arthritis, chronic fever, and malaria.^[3]

Botanical description

It is a small, perennial, climbing, and aromatic shrub that belongs to the Piperaceae family. The plant has woody roots and broad, oval, heart-shaped leaves. The stems are creeping, jointed, and thickened at the nodes.^[4] The root radix of the plant is known as pippalimula and is recognized for its numerous benefits.^[5] The leaves are numerous and broad, appearing oval

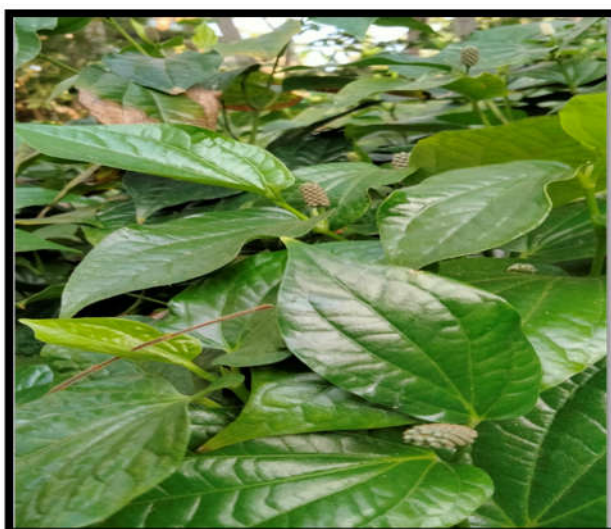


Figure:1 The Piper Longum plant

or heart shaped. The inflorescence consists of cylindrical spikes with stalked flowers, Male flowers are larger and more numerous than female flowers, with the latter measuring up to 2.5 cm long and 4-5 mm wide. Male spikes are greenish- yellow in colour, fleshy, cylindrical, with minute flowers. Female spikes are erect, and yellow, mature female spikes are known as long pepper and are shorter and thicker as compared to male spikes. The fruits are thin, shiny, black, green. When ripe, the fruits emit an aromatic odour and have a bitter taste.^[6]

Geographical description

This plant is a native species of the Indo-Malaya region and is primarily found in limestone soil in areas with heavy rainfall and high humidity.^[7] There are about thirty species of this genus reported in India and approximately seven hundred species worldwide.^[8] The plant thrives in the tropical rainforests of Nepal, India, Indonesia, Malaysia, Sri Lanka, Riau, the Philippines, and Timor. In India, it is distributed from the central Himalayas to Assam, Tamil Nadu, Andhra Pradesh, Madhya Pradesh, Maharashtra, Kerala, Karnataka, the lower hills of West Bengal, the Khasi Hills, Mikir Hills, and throughout the evergreen forests of the Western Ghats, extending from Konkan to Kerala, as well as in the Nicobar Islands.^[9]



Figure:2 Worldwide distribution of Piper longum

Phytochemical constituents

The Piper longum plant contains several primary substances, including alkaloids such as piperine, piperin, piperlongumine, and methyl-3,4,5-trimethoxycinnamate.^[10] The fruits of the plant have approximately 1% volatile oil and are rich in proteins, starch, alkaloids, saponins, carbohydrates, and the waxy alkaloid amygdalin. Additionally, the fruit includes various chemicals such as the alkaloid isobutyldecyl-trans-2-trans-4-dienamide, along with calcium, phosphorus, iron, and terpenoids. From these fruits, one can derive various lignans and esters, including sesame, provalol, fagixin, Z-12-octadecenoic acid monoglyceride, trideacyl dihydro-p-coumaric acid esters, and eicosyl [E]-p-coumarate.^[11,12] The roots of the plant feature several other alkaloids, including piperine, piperate A, short base, piperidine, undecane piperidine, piperonaline, methyl piperine, tetrahydropiperine, and dehydropiperine.^[13] From the dried bark of the plant, approximately 0.7% of an essential oil with a spicy aroma can be extracted. This essential oil comprises sesquiterpenes, caryophyllene, and various hydrocarbons.^[14] Other notable compounds include sesamidine, dihydrostigmasterol, pipercolic acid, piperone, undecanol, dihydrofolate, and sitosterol. The Piper longum plant is also recognized for its antioxidant properties, along with folic acid and dihydrofolic acid. Additional alkaloids found in the plant are asarone, dapoxetine, rapamycin A, and different forms of piperidine.^[15,16] The essential oil further contains terpinene, p-pinene, pinene, zingiberene, p-methoxyacetophenone, and dihydrocarveol.^[18]

Ethnopharmacology

Piper longum Linn., commonly known as Pippali, is a well-regarded medicinal plant. It is a key ingredient in an herbal mixture called "Trikatu," which also includes black pepper and ginger.^[19] Traditionally, pipallimool has been utilized to treat respiratory conditions such as pneumonia and asthma, as well as gynaecological issues, indigestion, infections, fever, cough, sinusitis, diarrhoea, dysentery, and gastrointestinal problems, including insomnia.^[20,21,22] The fruit of this plant possesses anthelmintic properties, making it effective against worms. Additionally, it acts as an expectorant, aiding in the removal of mucus from the lungs and respiratory tract. A decoction made from the roots and fruits of pipalimool is often used to alleviate bronchitis.^[23] It can also serve as an effective remedy for allergies by mixing powdered fruit with mishri [rock sugar] and taking it on an empty stomach can treat itching. The unripe fruits of this plant are known for their carminative, stimulant, and tonic properties,

and they also function as an antidote for bites.^[24,25,26] In traditional Chinese medicine, the fruits of *P. longum* are employed to relieve nausea, headaches, acid reflux, stomach issues, and allergic rhinitis.^[27] In Thailand, both ripe and raw fruits are used to alleviate postpartum gas and pain.^[28]

Ayurvedic formulations of Piper longum

The herb is available in many powerful forms that provide various health benefits including antibacterial, expectorant, heart-healthy, stress-reducing, and immune boosting properties. Notable formulations include Trikatu, Vardhamanas Pippali Rasayana, Talisapatradi Churna, Pippalyedhesava, Kanakasava, Amritarishta and Chyavanaprash. Apart from this, products like Gudapippalyadi Churna, Shiva Gutika, and and Kaishore Guggulu also help in improving health. Each variant provides unique benefits that are important in supporting physical strength and overall health.^[29]

In the Ayurvedic system of medicine, the pipalimool plant is used in the treatment of various diseases and disorders. The herb *P. longum* is used in around 135 Ayurvedic formulas.^[30] It helps in balancing Kapha and Vata. It has been used in India since ancient times. It is considered as one of the important medicines in Ayurveda and is also mentioned in Panchkola, Shadushana, etc. *Piper longum* is an important medicine in the treatment of constipation and impotence.^[31] In Ayurveda, this plant is used only to treat respiratory diseases. The root of this plant helps in the treatment of bronchitis, spleen problems, stomach aches, and tumors. It is used in the treatment of diseases like krimi [parasitic infections], pliha roga [spleen disease], kshaya [tuberculosis], shwasa [difficulty in breathing], urastambha [thigh stiffness], grahni [dysentery], vatavyadhi [nervous system diseases], vishama etc. ^[32] Fever, piles, insomnia, and other diseases. In Arthava Veda, Rasayana is called Atividdha bhesaji, Vatikrita bhesaji, and Ksipta bhesaji and is used to treat akshepaka and dhanurvata. Apart from this, this plant is also used in various Rasayana recipes like vardhmana pippali and pippali rasayana. However, Charaka prohibited excessive consumption of the *Piper longum* plant except for medicinal purposes. This plant is also found in Virechana Dravya.^[33] In Ayurveda, pipalimool plant is used as vrishya, medhya, dipan, jvaraghna, and kasaghna and treats kushtha, jvara, udara, gulma, shvas-kasa, arsha, prameha, pandu, arsha, and other ailments.^[34] It is also effective in the treatment of stomach ache, hemorrhoids, stomach ache, colic

indigestion, anemia, heart disease, spleen disease, Kapha disease, flatulence, gout, paralysis, rheumatism, sciatica, and helps in improving digestion and the immune system.^[35]

Pharmacology and therapeutical uses of Piper longum

Antifungal activity:

The essential oil obtained from the plant *Piper longum* has antibacterial properties. Piperine, a piperidine alkaloid, was isolated from the hexane fraction of the plant *Piper longum* and showed strong bactericidal activity against the species *Puccinia recondite* at concentrations of 0.25 to 0.5 mg/ml. It has also been observed that fruit extracts containing piperine have been tested against phytopathogenic fungi.^[36]

A piperidine alkaloid, piperonaline, was isolated from the hexane fraction of *P. longum* showed a potent fungicidal activity against *P. recondita* with 91% and 80% control values at the concentration of 0.5 and 0.25 mg ml⁻¹, respectively.^[37]

Fungicidal activity of *P. longum* L. fruit-derived materials toward six phytopathogenic fungi, *Pyricularia oryzae*, *Rhizoctonia solani*, *Botrytis cinerea*, *Phytophthora infestans*, *Puccinia recondita*, and *Erysiphe graminis* was evaluated using a whole plant method *in vivo*. This treatment was compared with synthetic fungicides (chlorothalonil, dichlofluanid, and mancozeb) and four commercially available compounds (eugenol, piperine, piperlongumine, and piperettine).^[38]

Antiamoebic activity:

The anti-amoebic effects of crude methanol extract of *Piper longum* fruit, *Piper sarmentosum* root and *Quercus infectoria* nut gall against *Entamoeba histolytica* infecting the caecum of mice were studied. The severity of caecal wall ulceration was reduced in mice which received the plant extract and metronidazole as compared to the control animals.^[39]

The activities of n-hexane, dichloromethane and methanol extracts from five antidiarrheic Thai medicinal plants, *Acacia catechu* (Fabaceae) resin, *Amaranthus spinosus* (Amaranthaceae) whole plant, *Brucea javanica* (Simaroubaceae) seed, *P. longum* (Piperaceae) fruit and *Quercus infectoria* (Fagaceae) nut gall were tested against the *in vitro* growth of fresh

isolates of the intestinal protozoan parasite *Blastocystis hominis*. All extracts showed inhibitory activity with reference to metronidazole.^[40]

The ethanolic extract, hexane fraction, n-butanol soluble fraction exerted in vitro amoebicidal action at 1000 micrograms/mL and the chloroform fraction showed the same at 500 micrograms/mL. The ethanolic extract and piperine, a pure compound, from this plant material cured 90% and 40% of rats with caecal amoebiasis. respectively.^[41]

Antimicrobial activity:

Various extracts of *P. longum* were prepared and evaluated against bacterial pathogens, such as *S. albus*, *S. typhi*, *P. aeruginosa*, *E. coli* and *B. megaterium* and one fungus, *A. niger*. Compared to streptomycin all the extracts exhibited a good antibacterial activity.^[42]

The isolated constituents and n-hexane extract were found to show varying degree of antibacterial activity against all the tested bacteria. However, the aqueous extract did not show antibacterial activity against the tested bacteria.^[43]

Effect on respiratory system:

Isolated piperine showed a central stimulant action in frogs, mice, rats, and dogs along with increased hypnotic response in mice. It antagonized respiratory depression induced by morphine or pentobarbitone in anesthetized dogs.^[44]

A comparative study conducted with piperine and nalorphine, for effects against morphine-induced respiratory depression and analgesia, revealed that both reversed morphine-induced respiratory depression but, unlike nalorphine, piperine did not antagonize morphine induced analgesia in rats.^[45]

Petroleum ether extract of *P. longum* produced respiratory stimulation in smaller dose but higher dose cause convulsion in laboratory animals. This may be due to presence of some medullary stimulant factors in the extract. ^[46,47]

The crude extract of *P. longum* as well as pipartine, one of its alkaloids, suppressed the ciliary movements of the esophagus of the frog, which may be due to the suppression of cough reflex.^[48]

Antidiabetic activity:

The blood glucose level, carbohydrate metabolizing enzymes and the status of lipid peroxidation and antioxidants were assayed using specific colorimetric methods. Oral administration of dried fruits has shown significant anti-hyperglycemic, antilipidperoxidative and antioxidant effects in diabetic rats comparable to that of the standard reference drug glibenclamide.^[49]

Antioxidant activity:

A combination of spices (*Piper nigrum*, *Piper longum* and *Zingiber officinale*), herbs (*Cyperus rotundus* and *Plumbago zeylanica*) and salts make up Amrita Bindu were evaluated for antioxidant activity. The analysis revealed the antioxidant potential of the ingredients in the following order: *Piper nigrum* > *Piper longum* > *Cyperus rotundus* > *Plumbago zeylanica* > *Zingiber officinale*.^[50]

"*P. longum* exhibits promising antioxidant potential against free radical-induced oxidative damage. Petroleum ether extract of the root and piperine from roots of *P. longum* Linn. decrease lipid peroxide levels and maintain luthathione content, demonstrating antioxidant activity."^[51]

Analgesic activity

The aqueous suspension of *P. longum* root powder (200, 400, and 800 mg/kg) was given orally to mice and rat to evaluate it analgesic effects. The delay in reaction time to thermal stimulus was assessed in rats, and the amount of writhing to chemical stimulus was assessed in mice. The effects of the 400 and 800 mg/kg doses of *P. longum* were like that of nonsteroidal anti-inflammatory drugs ($p < 0.001$). Both ibuprofen (40 mg/kg) and *P. longum* (800mg/kg) demonstrated 50% protection against writhing. The delay in reaction time to thermal stimulus was <6% for different doses of *P. longum* as compared with 100% for pentazocine. This indicates that the plant root produces a weak opioid-type but potent nonsteroidal anti-inflammatory drug-type of analgesia.^[52]

Anti-depressant activity:

A bioassay-guided isolation of the ethanol extract from the fruits of *P. longum* yielded a known piperidine alkaloid, piperine having potent antidepressant-like properties which are mediated in part through the inhibition of MAO activity and therefore represent a promising pharmacotherapeutic candidate as an antidepressant agent.^[53]

Hepatoprotective activity

The research conducted by Patel and Shah (2009), the hepatoprotective properties of Piper longum milk extract. Cause the chronic reversible type of liver necrosis, carbon tetrachloride (CCl₄) was administered as a hepatotoxin at a dose of 0.5 ml/kg per orally with olive oil (1:1) three times each week for 21 days. A significant hepatoprotective effect was seen in CCl₄-induced liver damage after treatment with Piper longum milk extract (200 mg/day per orally for 21 days). Piper longum hepatoprotective effects are equivalent to those of the commonly prescribed medication silymarin (25 mg/kg/day per orally for 21 days). The findings of the current investigation showed that Piper longum milk extract significantly hepatoprotective and antioxidant properties.^[54]

Anti-inflammatory activity

The purpose of this study was assessing the anti-inflammatory properties of two Pippali types in albino rats used in acute and sub-acute experimental models of inflammation. Animals that were chosen at random were divided into four groups, six animals in each. Oral administration of 200 mg/kg of the test drug was used, and in both models, the activity was compared with normal anti-inflammatory drug therapy. Between the two distinct test samples analysed, it was discovered that the Badi variation of pippali only inhibited acute phase inflammation, whereas the Chhoti type of pippali lowered both acute and subacute phase inflammation. Therefore, the Chhoti variant of Pippali may be preferred above the Badi variety in terms of medicinal value.^[55]

Neuroprotective activity:

Therapeutic effects of dichloromethane fraction [DF] of *P. longum* on poststroke neuronal damage were studied using a rat middle cerebral artery occlusion model. This extract was administered orally to a mouse model for 14 days. Increases in PSD95, phosphorylated calmodulin kinase II [p-CaMKII], calmodulin [CaM], and N-methyl D-aspartate receptor subtype 2B [NR2B] were observed.^[56]

Anti-asthmatic activity:

According to the published study, *P. longum* fruit extract showed a bronchodilator effect with 83% inhibitory activity at 200 mg/kg dose in the guinea pig histamine-induced bronchospasm model. The petroleum ether extract was reported to show significant anti-asthmatic activity in a mouse model. Antiallergic effects of the extract were also observed in mice with milk-induced leukocytosis and in mice showing passive paw hypersensitivity reaction. This extract has significant protective effects against histamine-induced bronchospasm, haloperidol-induced catalepsy, and passive paw hypersensitivity reactions.^[57]

Antiulcer activity:

The antiulcer activity of *P. longum* extract was investigated. The study found that giving this drug to animals suffering from stress-induced foot drop reduced the severity of pain by up to 90 percent compared to doxycycline.^[58]

Antiplatelet activity:

It has been confirmed that the components piperine, piperine, piperonylamine and piperonylamine found in pepper fruit have anti-platelet aggregation property in rabbits. The study found that single doses of collagen, platelet activating factor and arachidonic acid-induced washed platelet aggregation were inhibited.^[59]

Anthelmintic activity:

Methanol, chloroform and n-hexane extracts of *P. longum* fruits showed in vitro ovicidal, larvicidal, and adulticidal activity against roundworms, eggs, larvae, and adults, respectively, at a dose of 1.95 mg/ml. Total larval mortality occurred within 6h at the highest concentration of 500 mg/ml, while at the lowest concentration, mortality was 50%. Chloroform was shown to reduce anthelmintic activity against L3 larvae with an IC₅₀ of 12.47 mg/mL.^[60]

Anti-snake venom:

The antivenomous activity of the ethanolic fruit extract of *P. longum* against Roselle viper venom in fertilized chicken eggs, mouse, and rat embryos was determined. The extract was found to cause lethal effect, venom defibrinogen effect, paw edema, hemorrhagic activity, mast cell degranulation, necrosis, catalase activity, and muscle weakness at doses of 250 mg/kg, 500 mg/kg, and 750 mg/kg.^[61]

Acaricidal activity:

Acaricidal activities of aqueous and ethanol extracts of *P. longum* were studied using three skin ticks [*Hyalomma anatolicum*]. Alcoholic extract of the plant showed the best acaricidal activity with a minimum lethal dose [LC₅₀] and lethal concentration [LC₉₅] being 50 and 95, respectively.^[62]

Another study was conducted on adult blood-sucking females of microscopic *Rhipicephalus* tick [*Boophilus*] using an adult immersion test. It was determined that the extract directly affected the reproductive physiology of the ticks by inhibiting egg laying, with mortality rates ranging from 36.1% to 1.89%.^[63]

Immunomodulatory:

Alcoholic extracts of *P. longum* have been shown to have immunomodulatory effects and piperine extract was injected into mouse models. A significant increase in the number of white blood cells and plaque-forming cells that aid in antibody production was observed, which

supports the hematopoietic system, promoting stem cell proliferation and general immune function.^[64]

Antifertility activity:

The anti-fertility activity of benzene extract of the *P. longum* plant was investigated using female rat model. The results showed that oral administration of the plant extract together with *Echinochloa crusgalli* fruits prevented pregnancy by 80% in female rat models.^[65]

Anti-tumour activity:

The plant's piperine and piperlongumine components were investigated for their antitumor activity in a mouse model. A decrease in tumor weight was observed in animals treated with piperate and piperine.^[66]

Piperine partially inhibited lung metastasis caused by B16F-10 melanoma cells when examined in C57BL/6 mice, thus exhibiting a chemopreventive effect when taken orally.^[67]

Oral administration of the ethanol extract was shown to protect cells during DMBA-induced carcinogenesis in the hamster cheek pouch and to preserve the integrity of the cell membrane.^[68]

Toxicological Considerations

Toxicological data are scarce, though available studies suggest that *P. longum* is safe within therapeutic ranges. Excessive consumption may produce gastric irritation or hepatotoxic effects^[69]

Clinical Evidence

Human data are limited. Formulations containing *P. longum* have been trialed for asthma and metabolic conditions, showing modest improvements. However, these studies lacked rigorous design, sample size, and long-term evaluation^[70].

Discussion

The therapeutic relevance of *P. longum* is strongly supported by its chemical diversity, particularly alkaloids such as piperine and piperlongumine. Preclinical evidence confirms multiple pharmacological properties consistent with traditional uses. However, translation to clinical settings is hindered by inadequate standardization, poor bioavailability of active molecules, and limited mechanistic studies.

Future work should prioritize:

- Establishing standardized extracts with defined chemical markers.
- Conducting pharmacokinetic and bioavailability studies.
- Applying systems biology and molecular pharmacology tools to clarify mechanisms.
- Designing well-controlled randomized clinical trials.

Conclusion

The Piper longum plant has been used as a spice and medicine since ancient times. In the Ayurvedic medical system, there are approximately 135 species of this plant, which are traditionally employed to treat various diseases. However, despite numerous studies conducted on this plant, there is currently no convincing evidence to support its effectiveness in treating these conditions with different individual part. More experiments and clinical studies on animals are necessary to determine whether the plant can effectively treat various diseases.

References:

1. "Davidson-Hunt I. Ecological ethnobotany: stumbling toward new practices and paradigms." ("Ethnobotanical study of medicinal plants used in Arjan – Parishan ...") MASA J., 2000; 16(1): 1-3.
2. "Subramaniam K, Subramanian SK, Bhargav S, Parameswari R, Praveena R, Ravikumar R, Yuvaraj E, Kumar VM." ("A Validated Stability-Indicating RP-HPLC Method for Quantification of ...") "Review on potential antiviral and immunomodulatory properties of Piper Longum." ("Review on potential antiviral and

- immunomodulatory properties of Piper ...) In IOP Conference Series: Materials Science and Engineering Apr 1 (Vol. 1145, No. 1, p. 012099). IOP Publishing, 2021.
3. "Anand A, Rao CS (2000) A rapid in vitro propagation protocol for Piper barberi Gamble, a critically endangered plant." ("Sustained Shoot Multiplication and Method for Overcoming In Vitro ...") In Vitro Cell Dev Biol 36:61–64.
 4. Manoj P, Soniya EV, Banerjee NS, Ravichandran P. Recent studies on well-known spice, Piper longum Linn, 2004; 3(4): 222-227.
 5. Williamson EM. Major herbs of Ayurveda. Churchill Livingstone, 2002; 24
 6. "Ghosal S, Prasad BN, Lakshmi V (1996) Antiamoebic activity of Piper longum fruits against Entamoeba histolytica in in vitro and in vivo." ("Direct shoot regeneration from nodal, internodal and ... - Springer") J Ethnopharmacology 50:167–170
 7. "Ghosal S, Prasad BN, Lakshmi V (1996) Antiamoebic activity of Piper longum fruits against Entamoeba histolytica in in vitro and in vivo." ("Direct shoot regeneration from nodal, internodal and ... - Springer") J Ethnopharmacol 50:167–170
 8. Satyavati GV, Raina MK, Sharma M. Medicinal plants of India. Indian Council of Medical Research, 1987.
 9. Gomez KA, Gomez AA (1984) Statistical procedures for agricultural research. Willey, New York
 10. Viswanathan TV. Medicinal and aromatic plants in: KL Chadha, and R. Gupta (Eds.), Advances in Horticulture, 1995; 373-383
 11. Chatterjee A, Dutta CP. The structure of piperlongumine, a new alkaloid isolated from the roots of Piper longum. Sci Cult, 1963; 29: 568-70.
 12. Atal CK. Occurrence of sesamin in Piper longum Linn. Indian J Chem, 1966; 4: 252
 13. Tabuneng W, Bando H, Amiya T. Studies on the constituents of the crude drug "Piperis Longi Fructus." On the alkaloids of fruits of Piper longum L. Chemical and pharmaceutical bulletin, 1983 Oct 25; 31(10): 3562-5.
 14. Madhusudhan P, Vandana KL. Tetrahydropiperine, the first natural aryl pentanamide from Piper longum. Biochemical systematics and ecology, 2001 May; 29(5): 537-8.
 15. Dutta CP, Banerjee N, Roy DN. STUDIES ON GENUS PIPER. 3. LIGNANS IN SEEDS OF PIPER-LONGUM. Phytochemistry, 1975 Jan 1; 14(9): 2090-1
 16. . Das B, Kashinatham A, Madhusudhan P. Long chain esters and alkamides from Piper longum. ("piperine from pepper - Erowid") Bollettino chimico-farmaceutico, 1998; 137(8): 319-20.

17. Nigam SS, Radhakrishnan C. Chemical examination of the essential oil derived from the berries of piper longum. Bulletin of the National Institute of science of India, 1968; 37: 18
18. Handa K, Sharma M, Nigum M. Essential oil of Piper longum. Properties of the components and isolation of two monocyclic sesquiterpenes, *Perfum. Kosmet*, 1963; 44: 233.
19. Mujumdar AM, Dhuley JN, Deshmukh VK, Raman PH, Naik SR (1990) Anti-inflammatory activity of piperine. *J Med Sci Biol* 43:95–100.
20. Chhattisgarh, India. *Global Journal of Research on Medicinal Plants & Indigenous Medicine*, 2013 Jul 1; 2(7): 525.
21. Das SK, Satapathy MK, Bisoi SS, Mohanty RC. Biodiversity of RIE campus: Plants with medicinal value. *Journal of Pharmacognosy and Phytochemistry*, 2019; 8(1): 2717-25.
22. Balasubramani SP, Venkatasubramanian P, Kukkupuni SK, Patwardhan B. Plant-based Rasayana drugs from Ayurveda. *Chinese journal of integrative medicine*, 2011 Feb; 17(2): 88-94
23. "Agarwal K, Varma R. Ethnobotanical study of antilithic plants of Bhopal district." ("Kanchnar (bauhinia Variegata) As A Medicinal Herb: A Systematic Review.") *Journal of ethnopharmacology*, 2015 Nov 4; 174: 17-24.
24. Pandey AK, Tripathi NN. Aromatic plants of gorakhpur division: Their antimycotic properties and medicinal value. *Extraction*, 2011 Mar; 7(2): 026.
25. Sumy Oommen, Ved DK and Krishnan R, *Tropical Indian Medicinal Plants, propagation methods*, 2000; 268-269
26. Neelam and Krishnaswamy Kamala Nutritive value of Pepper, In: *Pepper market review*, National Institute of Nutrition, Hyderabad, 2001; 1-5.
27. . Bezerra DP, Castro FO, Alves AP, Pessoa C, Moraes MO, Silveira ER, Lima MA, Elmiro FJ, Costa-Lotufo LV. In vivo growth-inhibition of Sarcoma 180 by piplartine and piperine, two alkaloid amides from Piper. *Brazilian journal of medical and biological research*, 2006 Jun; 39(6): 801-7.
28. "Chahal J, Ohlyan R, Kandale A, Walia A, Puri S. Introduction, phytochemistry, traditional uses and biological activity of genus Piper: A review." ("Introduction, Phytochemistry, traditional uses and biological activity ...") *International Journal of Current Pharmaceutical Review and Research*, 2011; 2(2): 130-44.

29. . Sivarajan VV, Balachandran I. Ayurvedic drugs and their plant sources. Oxford and IBH publishing, 1994; 374-376.
30. Kamboj, V.P. Herbal medicine. Current Sci., 2000; 78(1): 35-39.
31. Charaka. Charaka Samhita (Ayurved dipika commentary by Chakarapanidutta). Yadavji Trikamji, editor. 1 st ed. Varanasi: Chaukhamba Surbharati Prakashan, 2008; 246.
32. J Krutika, K Nishteswar, Goyale M, Ladani S. Pharmacognostic evaluation of Pippali mula (root of piper longum linn.) WSR to micrometric and isolation techniques, 2014; 3(6): 162-170
33. Vaidya BG, Adarsh N. Chaukhambha Bharati Academy. Varanasi, Vasadi Varga, 2005; 229.
34. Singh B, Upadhyaya SD. A review of Pippali (Piper longum Linn.) wsr of Rasayan effect. Journal of Pharmaceutical and Biological Sciences, 2015; 3(1): 9.
35. Manoj P, Soniya EV, Banerjee NS, Ravichandran P. Recent studies on well-known spice, Piper longum Linn, 2004; 3(4): 222-27.
36. "Koul IB, Kapil A (1993) Evaluation of liver protective potential of Piperine, an active principle of black pepper and long pepper." ("© 2018 JETIR December 2018, Volume 5, Issue 12 Piper longum ...") Planta Med 59:413–417.
37. Lee S, Park B, Kim M, Choi W, Kim H, Cho K, Lee S and Hoi-Seon Fungicidal activity of piperlongonine, a piperidine alkaloid derived from fruits of long pepper, Piper longum, against phytopathogenic fungi, Lee, Crop Prot, 20(6), 2001, 523-528.
38. Lee SE, Park BS, Kim MK, Choi WS, Kim HT, Cho KW, et al. Fungicidal activity of piperlongonine, a piperidine alkaloid derived from long pepper, Piper longum L., against phytopathogenic fungi Crop Protection 2001;20:523-8.
39. Sawangjaroen N, Sawangjaroen K and Poonpanang P, Antiamoebic effects of Piper longum fruit, Piper sarmentosum root and Quercus infectoria nut gall on caecal amoebiasis in mice, J Ethnopharmacol, 91(2-3), 2004, 357-360.
40. Sawangjaroen N and Sawangjaroen K, The effects of extracts from anti-diarrheic Thai medicinal plants on the in vitro growth of the intestinal protozoa parasite: Blastocystis hominis, J Ethnopharmacol, 98(1-2), 2005, 67-72.
41. Ghoshal S, Prasad BN, Lakshmi V, Antiamoebic activity of Piper longum fruits against Entamoeba histolytica in vitro and in vivo, J Ethnopharmacol, 50 (3), 1996, 167-170.
42. Khan M and Siddiqui M, Antimicrobial activity of fruits of Piper longum, Nat prod Rad, 6, 2007, 111-113.

43. . Lokhande PD, Gawai KR, Kodam KM, Kuchekar BS, Chabukswar AR and Jagdale SC, Anti-bacterial activity of some alkaloids, *Pharmacol Toxicol*, 2 (6), 2007, 574-579.
44. Singh N, Kulshresta VK, Shrivastava RK, Kohli RP, Analeptic activity of some alkaloids, *J Res Indian Med*, 8(1), 1973,1-3.
45. Dhanukar SA, Karandikar SM, Desai SM, Efficacy of Piper longum in childhood asthma. *Indian Drugs*, 21,1984, 384-386.
46. Kulshresta VK, Singh N, Shrivastava RK, Kohli RP, A study of central stimulant effect of Piper longum, *Indian J Pharmacol*, 1(2), 1969,8-10.
47. Kulshresta VK, Singh N, Shrivastava RK, Kohli RP, Rastogi SK, A study of central stimulant activity of Piper longum, *J Res Indian Med*, 6(1), 1971,17-19.
48. "Banga SS, Garg LC, Atal CK, Effect of pipartine and Crude extracts of Piper longum on ciliary movements, *Indian J Pharm*, 26, 1964, 139-141." ("CHEMISTRY AND PHARMACOLOGY OF PIPER LONGUM L.-A REVIEW ... - 1Library")
49. Manoharan S, Silvan S, Vasudevan K and Balakrishnan S, Antihyperglycemic and antilipidperoxidative effects of Piper longum., *Dried Fruits in Alloxan Induced Diabetic Rat*, *J Biol Sci*, 7(1), 2007, 161-168.
50. Natarajan KS, Narasimhan M, Shanmugasundaram KR, and Shanmugasundaram ER, Antioxidant activity of a salt-spice-herbal mixture against free radical induction, *J Ethnopharmacol*, 105(1-2), 2006,76-83.
51. Natarajan KS, Narasimhan M, Shanmugasundaram KR, Shanmugasundaram ER. Antioxidant activity of a salt/spice/herbal mixture against free radical induction. *J Ethnopharmacol* 2006; 105:76-83.
52. Vedhanayaki G, Shastri GV, Kuruvilla A, Analgesic activity of Piper longum Linn. Root, *Indian J Exp Biol*, 41(6), 2003, 649- 651.
53. Seon AL, Seong SH, Xiang HH, Ji SH, Gab JO, Kyong SL, Myung KL, Bang YH and Jai SR, Piperine from the Fruits of Piper longum with inhibitory effect on monoamine oxidase and antidepressant-like activity, *Chem Pharm Bull*, 53(7), 2005,832-835.
54. Patel JA And Shah US. Hepatoprotective Activity of Piper LongumTraditional Milk Extract on Carbon Tetrachloride Induced Liver Toxicity in Wistar Rats. *BoletínLatinoamericano y del Caribe de PlantasMedicinales y Aromáticas*. 2009; 8(2): 121-129.
55. ""Kumari M, Ashok BK, Ravishankar B, Pandya TN, Acharya R. Anti-inflammatory activity of two varieties of Pippali (Piper longum Linn.)."" ("37+ Best Herbs for Lung Health and Clearing Mucus (2025)") ("37+ Best Herbs for Lung Health and

- Clearing Mucus (2025)”) (“37+ Best Herbs for Lung Health and Clearing Mucus (2025)”) (“37+ Best Herbs for Lung Health and Clearing Mucus (2025)”) (“37+ Best Herbs for Lung Health and Clearing Mucus (2025)”) An International Quarterly Journal of Research in Ayurveda. 2012; 33(2): 307-310.
56. "Kumar S, Kamboj J, Sharma S. Overview for various aspects of the health benefits of *Piper longum* linn." (“TPI 2017; 6(12): 15-17 P, Vijitha Vijayan, Athulya CM and Ittoop J Ancheril”) (“TPI 2017; 6(12): 15-17 P, Vijitha Vijayan, Athulya CM and Ittoop J Ancheril”) fruit. Journal of acupuncture and meridian studies, 2011 Jun 1; 4(2): 134-40
57. Kaushik D, Rani R, Kaushik P, Sacher D, Yadav J. In vivo and in vitro antiasthmatic studies of plant *Piper longum* Linn." (“Phytotherapeutics in Inflammatory Lung Diseases | SpringerLink”) (“AYU (An International Quarterly Journal of Research in Ayurveda) - LWW”) Int J Pharmacol, 2012 Apr 1; 8(3): 192-7
58. Yadav V, Chatterjee SS, Majeed M, Kumar V. Long lasting preventive effects of piperlongumine and a *Piper longum* extract against stress triggered pathologies in mice. Journal of intercultural ethnopharmacology, 2015 Oct; 4(4): 277.
59. Iwashita M, Saito M, Yamaguchi Y, Takagaki R, Nakahata N. Inhibitory effect of ethanol extract of *Piper longum* L. on rabbit platelet aggregation through antagonizing thromboxane A₂ receptor. (“Piperine Inhibits the Activities of Platelet Cytosolic Phospholipase A”) (“Anti-inflammatory and antiarthritic effects of piperine in human ...”) Phytomedicine, 2007; 14: 853–5.
60. Koorse KG, Samraj S, John P, Narayanan PM, Devi SS, Usha PT, Sunilkumar S, Gleeja VL. "Anthelmintic activity of fruit extract and fractions of *Piper longum* L. In vitro." (“Anthelmintic Activity of Fruit Extract and Fractions of”) (“Anthelmintic Activity of Fruit Extract and Fractions of”) Pharmacognosy Journal, 2018; 10(2): 333-340.
61. Shenoy PA, Nipate SS, Sonpetkar JM, Salvi NC, Waghmare AB, Chaudhari PD. Anti-snake venom activities of ethanolic extract of fruits of *Piper longum* L. (Piperaceae) against Russell's viper venom: characterization of piperine as active principle. Journal of Ethnopharmacology, 2013 May 20; 147(2): 373-82.
62. Singh NK, Saini SP, Singh H, Sharma SK, Rath SS. In vitro assessment of the acaricidal activity of *Piper longum*, *Piper nigrum*, and *Zingiber officinale* extracts against *Hyalomma anatolicum* ticks. (“In vitro assessment of the acaricidal activity of *Piper longum*, *Piper* ...”) (“In vitro assessment of the acaricidal activity of *Piper longum*, *Piper* ...”) Experimental and Applied Acarology, 2017 Mar 1; 71(3): 303-17.

63. "Godara R, Verma MK, Katoch R, Yadav A, Dutt P, Satti NK, Katoch M. In vitro acaricidal activity of *Piper nigrum* and *Piper longum* fruit extracts and their active components against *Rhipicephalus (Boophilus) microplus* ticks." ("Exploring the Potential of Plant Extracts as Novel Bioacaricides - Springer") ("Larvicidal activity of the black pepper, - SpringerOpen") *Experimental and Applied Acarology*, 2018 Jul; 75(3): 333-43.
64. Bezerra DP, Pessoa C, Moraes MO, Alencar NM, Mesquita RO, Lima MW, Alves AP, Pessoa OD, Chaves JH, Silveira ER, Costa-Lotufo LV. In vivo growth inhibition of sarcoma 180 by piperlonguminine, an alkaloid amide from the *Piper* species. *Journal of Applied toxicology*, 2008 Jul; 28(5): 599-607.
65. Lakshmi V, Kumar R, Agarwal SK, Dhar JD. Antifertility activity of *Piper longum* Linn. ("Antifertility effects of the fruits of *Piper longum* in female rats ...") ("Antifertility effects of the fruits of *Piper longum* in female rats ...") in female rats. *Natural Product Research*, 2006 Mar 1; 20(3): 235-9.
66. Anuradha V, Srinivas PV, Madhusudana Rao J. Isolation, and synthesis of isodihydropiperlonguminine. *Natural product research*, 2004 Jun 1; 18(3): 247-51.
67. "Selvendiran K, Sakthisekaran D. Chemopreventive effect of piperine on modulating lipid peroxidation and membrane bound enzymes in benzo (a) pyrene induced lung carcinogenesis." ("Chemopreventive effect of piperine on mitochondrial TCA ... - Springer") ("In vitro anticancer activity of ethanolic extracts of *Piper nigrum* ...") *Biomedicine & pharmacotherapy*, 2004 May 1; 58(4): 264-7.
68. Manoharan S, Kavitha K, Balakrishnan S, Rajalingam K. *Clerodendron inerme* protects cellular integrity during 7, 12-dimethylbenz [A]- anthracene induced hamster buccal pouch carcinogenesis. *African Journal of Traditional, Complementary and Alternative Medicines*, 2008 Oct 17; 5(2): 213-22.
69. OECD. Guidelines for testing of chemicals: Acute oral toxicity. OECD; 2001.
70. Sharma A, et al. Clinical evaluation of *Piper longum*-containing formulation in asthma. *Phytother Res*. 2016;30:1087–93.