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A Review on *Piper Longum*

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Abstract

Piper longum L. (Piperaceae) commonly known as "long pepper" is a well-known medicinal plant in ayurveda. Different parts of this plant, such as root, seed, fruit, whole plant etc. are used traditionally in various ailments. Extract of Piper longum fruits have been shown to possess various activities like Bioavailability enhancer, immunomodulatory effect, anti-asthamatic and hepatoprotective activity. In the present review an attempt has been made to explore different aspects of Piper longum.

Keywords

Piper longum, long pepper, Pippali, Piperine, Piperaceae

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INTRODUCTION

Plants have been the source of medicines since thousands of years. Species of the genus *Piper* are among the important medicinal plants used in various systems of medicine. *Piper longum* L. (Piperaceae), commonly known as "long pepper", is widely distributed in the tropical and subtropical regions of the world, throughout the Indian subcontinent, Sri Lanka, Middle Eastern countries and the Americas. It is said that the Roman emperors valued it even more highly than black pepper due to its high commercial and economical importance.[1]

SYNONYMS:

Piper sarmentosum
Piper latifolium
Chavica roxburghii
Chavica [2]

VERNACULAR NAMES:

English: Long pepper
Hindi: Pippali
Sanskrit: Pipali
Marathi: Pippali
Tamil: Tippili
Malayalam: Tippali
Telugu: Pippallu
Kannada: Kandan Lippili
Konkani: Pipli
Urdu: Pipul
Gujrathi: Pipari
Sanskrit: Pippali, Magadhi.[3]

AYURVEDIC PROPERTIES:

Rasa: Katu (pungent)
Guna: Laghu (light), snigdha (unctuous), tikshna (sharp)
Veerya: Anushnashita (slight cold)
Vipaka: Madhur (sweet)
Dosha: Pacifies kapha and vata[3]

TAXONIMICAL CLASSIFICATION

Kingdom:*Plantae*
Subkingdom:*Tracheobionta*
Superdivision:*Spermatophyta*
Division:*Magnoliophyta*
Class:*Magnoliopsida*
Subclass:*Magnoliidae*
Order:*Piperales*
Family:*Piperaceae*
Genus:*Piper L.*
Species:*Piper longum L.*[4]

HABIT AND HABITAT

The native of plant is considered to be South Asia and is found both wild as well as cultivated, throughout the hotter parts of India from central to the north-eastern Himalayas. The herb also grows wild in Malaysia, Singapore, Bhutan, Myanmar and elsewhere.[5]

STANDARDISATION

Parameters	Results
Total Ash	4.31 % w/w
Water soluble ash	4.78 % w/w
Acid insoluble ash	0.41% w/w
Water Soluble Extractive	25.88 % w/w
Methanol Soluble Extractive	12.35% w/w
Acetone Soluble Extractive	4.15 % w/w
Chloroform Soluble Extractive	5.02 % w/w
LOD	2.85 % w/w[6]

PHARMACOGNOSTICAL CHARACTERISTICS:

Macroscopy: Fruit very small, ovoid, completely sunken embedded in solid fleshy spike, 2.5 - 4.0 cm long. Colour of fruit is light green to olive green when immature, after ripening colour changed to shining blackish green with aromatic odour and pungent taste producing numbness on tongue.[7]

PHYTOCHEMICAL DETAILS

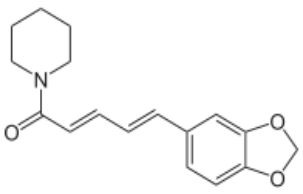
Piper longum contains resin, volatile oil, starch, gum,fatty oil, Lignans and a large number of alkaloids and related compounds, the most abundant of which are Piperine, piperlongumine, piplartine. Piperine has been shown to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics i.e by increasing permeability.[7, 8]

Piper longum as one of the major ingredients was tested in combination with other drugs. The study reported that increased their bio availability either by promoting

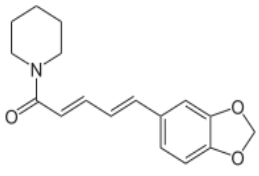
rapid absorption from the gastrointestinal tract or by protecting the drug from Icing metabolized during its first pass through the liver after being absorbed or by combination of both mechanisms.[8,9]

Alkaloids and amides

The fruit of P. longum contains a large number of alkaloids and related compounds, the most abundant of which is piperine, together with methyl piperine, iperonaline, piperettine, asarinine, pellitorine, piperundecalidine, piperlongumine, piperlonguminine, refractomide A, pregumidiene, brachystamide, brachystamide-A, brachystine, pipercide, piperderidine, longamide and tetrahydropiperine, terahydro piperlongumine, dehydropipernonaline piperidine, piperine, terahydropiperlongumine and trimethoxy cinnamoyl-piperidine and piperlongumine have been found in the root of P. Longum.[7,8,9,14]



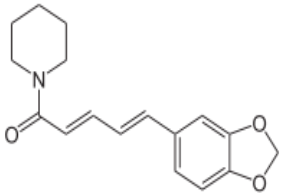
Piperine



piperlongumine

Lignans

Sesamin, Pulvuatilol, Fargesin and others have been isolated from the fruit of P. Longum.[10]



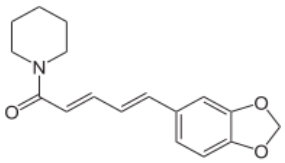
Sesamin

Esters

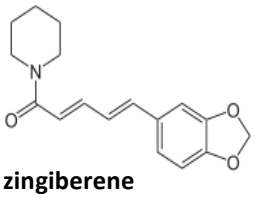
The fruit of P. longum contains tridecyl-dihydro-p-coumaarate, eicosanyl-(E)-p-coumarate and Z-12 octandecenoic –glycerol-monoester.[9,11]

Volatile oil

The essential oil of the fruit P. longum is a complex mixture, the three major components of which are (excluding the volatile piperine) caryophyllene and pentadecane (both about 17.8%) and bisaboline [13,14]



β-caryophyllene



zingiberene

(11%). Others include thujine, terpinoline, zingiberine, p-cymene, p-methoxy acetophenone and dihydrocarveol. Long pepper contains less essential oil than its relatives (about 1%), which consists of sesquiterpene hydrocarbons and ethers (bisabolene, β-caryophyllene, β-caryophyllene oxide, each 10 to 20%; α-zingiberene, 5%), and saturated aliphatic hydrocarbons such as 18% pentadecane, 7% tridecane, 6% heptadecane.[10]

MEDICINAL AND PHARMACOLOGICAL ACTIVITIES:

Piper longum (Piperaceae) are used in Indian traditional medicine and used as a spice globally. Piperine (C17H19NO3), the alkaloid is responsible for the pungency of P. longum L. Piperine can be obtained from the oleoresin in the peppercorns. Piperine makes up about 5-7% of the peppercorns. It exhibits a wide variety of biological effects.[15]

Bioavailability Enhancer:

Simultaneous administration of piperine (20 mg p.o.) on plasma concentration of carbamazepine (300mg or 500mg) twice daily in epileptic patients.Piperine significantly increased the mean plasma concentrations of carbamazepine in both dose groups.There was a significant increase in AUC (0-12hr) ($p < 0.001$), average C (ss) ($p < 0.001$), t (1\2el) ($p < 0.05$) and a decrease in K (el) ($p < 0.05$), in both the dose groups,whereas changes in K (a) and t(1\2a) were not significant.C max ($p < 0.01$) and t (max) ($p < 0.01$) were increased only in the 500 mg dose group.[15]

Antidepressant:

When Piperine is administered to Wister male rats, at various doses ranging from 5, 10 and 20 mg/kg/day, body weight, (p.o.) for 4 weeks and the neuropharmacological activity (elevated plus maze, spontaneous locomotors behaviour, forced swimming test, cognitive function) was determined after single, 1, 2, 3 and 4 weeks of treatment. The results showed that piperine during entire dosage range possessed anti-depression like activity and cognitive enhancing effect during entire treatment duration with significance ($P<0.001$).[15, 16]

Antifungal activity:

The essential oil of the fruits showed fungicidal activity of P. longum L. The fruit-derived materials were tested towards six phytopathogenic fungi, Pyricularia oryzae, Rhizoctonia solani, Botrytis cineria, Phytophthora infestans, Puccinia recondita, and Erysiphe graminis using a whole plant in vivo method. A piperidine alkaloid, pipernonaline, 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 .[17]

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.The activities of n-hexane, dichloromethane and methanol extracts from five anti-diarrheic 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. Both the root and fruit of P. longum possess antiamoebic activity approximately to the same extent. 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.[17, 18]

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. 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. [18]

Antiasthmatic activity:

Asthma induced in Balb/c mice by ovalbumin sensitization. Piperine (4.5 and 2.25 mg/kg) was orally administered 5 times a week for 8 weeks and it was found that piperine-treated groups had suppressed eosinophil infiltration, allergic airway inflammation and airway hyperresponsiveness, and these occurred by suppression of the production of interleukin-4, interleukin-5, immunoglobulin E and histamine.[21]

Effect on cardiovascular system:

Intravenous administration of piperine caused a dose-dependent (1 to 10 mg/kg) decrease in mean arterial pressure in normotensive anesthetized rats; the next higher dose (30 mg/kg) did not cause any further change in mean arterial pressure. Piperine, in vitro study on rabbit heart causes a partial inhibition of force, rate of contraction and coronary flow. In rabbit aortic ring, piperine inhibited high K+ (80 mM) precontractions and partially inhibited phenylephrine, due to Ca2+ channel blockade. In Ca2+-free medium, piperine (1 to 30 microM) exhibited vasoconstrictor effect.[19, 20]

Antithyroid activity

When piperine (40mg/kg) was simultaneously administered with carbimazole (10 mg) for 10 days significant reduction in plasma lipids and lipoproteins levels occured, except for high density lipoprotein, which was significantly elevated. Piperine supplementation also improved the plasma levels of apo A-I, T3, T4, testosterone, and I and significantly reduced apo B, TSH, and insulin to near normal.[22]

Antidiabetic activity:

The antihyperglycemic and anti-lipidperoxidative effects of ethanolic extract of Piper longum dried fruits in alloxan-induced diabetic rats were studied. 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, anti-lipidperoxidative and antioxidant effects in diabetic rats comparable to that of the standard reference drug glibenclamide with significance of ($P<0.001$).[15]

Hypochoesterolaemic activity:

Methyl piperine significantly inhibited the elevation of total serum cholesterol, and the total cholesterol to HDL-cholesterol ratio, in rats fed with a high cholesterol diet. The unsaponificable fraction of the oil of P. longum also significantly decreased total serum cholesterol and hepatic cholesterol in hypercholesterolaemic mice.[18]

Antioxidant activity:

A combination of spices (Piper nigrum, Piper longum and Zingiber officinale), herbs (Cyperus rotundus and Plumbago zeylanica) and salts make up Amrita Bind were tested for anti-oxidant activity. The analysis revealed the antioxidant potential of the ingredients in the following order: Piper nigrum > Piper longum > Cyperus rotundus > Plumbago zeylanca >Zingiber officinale.[21]

The protective effect of piperine on DNA damage and activities of detoxifying enzyme such as glutathione transferase, quinone reductase and UDP-glucuronosyl transferase in lung cancer bearing animals induced by Benzo (a) pyrene. They observed that supplementation of piperine (50 mg/kg, b.wt) enhanced the activities of detoxification enzymes and reduced DNA damage as determined by single cell electrophoresis.[21]

Anti-inflammatory activity:
Piperine at 2.5, 5 and 10 µg/ml concentration inhibited the collagen matrix invasion of B16F-10 melanoma cells in a dose-dependent manner. It also significantly reduced the pro-inflammatory cytokines (such as IL-1β, IL-6, TNF-α, GM-CSF).[22]

Immunomodulatory activity:
The immunoregulatory potential of P. longum and piperinic acid, one of its active constituents, in Balb/C mice (in vivo) and human PBMCs (in vitro) models showed a dose dependent decrease of lymphocytes (CD4+ and CD8+ T cells) and cytokine levels in sensitized Balb/C mice with a marked inhibition 72. Alcoholic extract of the fruits of P. longum and its component piperine was studied for their immunomodulatory and antitumor activity. Alcoholic extract of the fruits and piperine were found to be cytotoxic. An aqueous extract of P. longum fruit powder showed 100% giardicidal activity. P. longum was found to offer protection against externally induced stress. A famous Ayurvedic preparation containing long pepper in pippli rasyana was tested in mice infected with Giardia lamblia and found to produce significant activation of macrophages, as shown by an increased MMI and phagocytic activity.[24]

Anti-cancer activity:
The chemoprotective effect of piperine (50 mg/kg, b.wt, p.o, alternate days) against 7, 12 dimethylbenz[a]anthracene (0.5% in liquid paraffin, three times a week for 14 weeks) induced buccal pouch carcinoma of Syrian golden hamsters. They observed that piperine completely prevented the formation of oral carcinoma, probably due to its antilipidperoxidative and antioxidant potential as well as its modulating effect on the carcinogen detoxification process.Another study investigated the influence of piperine on chromosomes in rat bone marrow. piperine administered to Wister male rats at dose of 100, 400 and 800 mg/kg, b wt,(p.o.) for 24 hrs then challenged with cyclophosphamide at a dose of 50 mg/kg, b wt, (i.p.). They demonstrated that piperine at a dose of 100 mg/kg, gave a statistically significant ($P<0.005$) reduction in chromosomal aberrations.[23,24]

Antiulcer activity:
The water decoction of ginger making up one of the constituents of Mahakasyaya drugs along with water decoction of P. longum and colloidal solution of Ferula asafoetida has been reported to protect against CRS-, ASP- and PL- induced gastric ulcers in rats. Piperine, an alkaloid of long peppers, inhibited gastric emptying (GE) of solids/liquids in rats and gastrointestinal transit (GT) in mice in a dose and time dependent manner. GE inhibitory activity of piperine is independent of gastric acid and pepsin secretion.[24]

Fertility Enhancer
The effect of piperine on fertilization of egg in female hamsters from day 1st through day 4th of the oestrous cycle at dose of 50 and 100 mg/kg (b. wt, p.o). They observed that there was enhancement of fertilization, 85.4±4.1 and 82.8 ±4.8 at doses of 50 and 100mg/kg, respectively at 9 hr after artificial inseminated. However, examination of the embryos retrieved 48 hr after artificial insemination revealed no difference in the stage of embryonic development.[21]

Hepatoprotective activity:
The fruit extract improved the regeneration process by restricting fibrosis, but offered no protection against acute damage or against cirrhotic changes in rodents. Treatment with the ethanol extract of P. Longum at doses of 2.5-10 mg/kg (p.o.) inhibits liver fibrosis induced by carbon tetrachloride (CCl4). Piperine exerted a significant protection against tert-butyl hydroperoxide and carbon tetrachloride hepatotoxicity by reducing both in vitro and in vivo lipid peroxidation, enzymatic leakage of GPT and AP, and by preventing the depletion of GSH and total thiols in the intoxicated mice. Piperine showed lower hepato-protective potency than silymarin.[22]

Insecticidal and acaricidal activity:
The essential oil of the fruits showed insecticidal and insect-repellent activity. Toxicities of two piperidine alkaloids, pipernonaline and piperoctadecalidine, isolated
from P. longum were determined against five species of arthropod pests. Both of the alkaloids showed insecticidal activity.[19]

Toxicity
Immunotoxicity occurs if piperine administration (1.12,2.25, and 4.5 mg/kg, p.o) for 5 consecutively. At 2.25 and 4.5 mg/kg caused a significant reduction in total leukocyte counts, increase in the percentage of neutrophils and suppressed the mitogenic response of B-lymphocyte to lippoploysaccharide. Treatment with highest dose, however results in significant decreased in the weight of the spleen, thymus and mesenteric lymph nodes.

TABLE 1: Work so far done on Piper longum

S. No	ACTIVITY	PART	EXTRACT	ANIMAL	MODEL	DOSE	P VALUE	REFERENCES & YEAR
1	Mosquito larvicidal activity	Fruit	Methanol extract	Mosquitoes	-	5.0 mg/L	P = 0.05	Yang et al,(2002)[25]
2	Antimicrobial activity	Fruits	Ethanol,Methanol,Aqueous extract	Staphylococcus album, Salmonella typhi, Pseudomonas aeruginosa,E.coli,& Bacillus megaterium	Disc diffussion method	40 µg	-	Khan M et al,(2007)[26]
3	Cardioprotective effect	Fruits	Methanolic extract	Male Wistar Albino rats	Isoproterenol induced myocardial infarction.	250 mg/kg and 500 mg/kg	P<0.05	Chauhan et al,(2010)[27]
4	Antithrombogenic activity	Fruits	Alcoholic extract	Male white rabbits and male ICR mice	Pulmonary thrombosis test.	100, 50 & 10 mg/kg	P<0.05	Lee S.E et al,(2010)[28]
5	Antioxidant, Antimicrobial & Anti tumor	Fruits	Hexane: Water, Ethyl acetate: Water, Methanol: Water	E coli, Bacillus subtilis & Staphylococcos aureus	Total Phenolic Content, DPPH radical Scavenging Capacity, ABTS Cation Decolorisation Capacity, Cytotoxicity analysis by MTT Assay	200µg/mL, 400µg/mL and 800µg/mL	P<0.05	Beena Joy et al,(2010)[29]
6	Antibacterial activity	Roots	Methanolic extract	Klebsiella pneumoniae, Pseudomonas aeruginosa and Staphylococcus aureus	Bacterial Susceptibility Testing	25, 50, 100µg/100µL	-	Raja Naika et al, (2010)[30].
7	Anti rheumatoid activity	Fruits	Aqueous extract	Male albino rats	adjuvant-induced arthritis	200 and 400 mg/kg p. O	P<0.01	Yende et al, (2010)[31]
8	CNS depressant and Analgesic activities	Leaves	Methanolic extract	Young Long-Evans rats	Locomotor activity, exploratory behavior,	100 and 200 mg/kg B. W	P<0.01	Mamun et al, (2011)[32]

					acetic acid-induced writhing model and formalin test			
9	Anthelmintic activity	Leaves	Alcoholic extract	Earth worms (Pheretima posthuma)	-	4mg/ml	P<0.05	Devi et al., (2011)[33]
10	Anti-hyperglycemic and Antioxidant	Fruits	Ethanolic extract	Adult male Wistar albino rats	Streptozotocin-nicotinamide induced	200 and 400 mg/kg bw p.o	P<0.01	Suresh Kumar et al, (2011)[34]
11	Antimicrobial activity	Fruits	Aqueous and Methanolic extract	Staphylococcus aureus, Bacillus subtilis, E. coli, Pseudomonas aeruginosa	Agar cup plate method	5 mg/ml, 7 mg/ml and 10 mg/ml	-	Trivedi M N et al, (2011)[35]
12	Cognitive enhancing activity	Fruits	Ethanolic extract	Male Wistar albino rats	Elevated plus maze and Passive avoidance task methods	1, 2, 3, 4 & 5mg/kg. B. W	P<0.05	Madhavi et al, (2012)[36]
13	Antiasthmatic activity	Fruits	Alcoholic extraction	Guinea Pig,Wistar rats and Albino mice	Histamine induced bronchospasm,Milk induced leukocytosis,Haloperidol induced catalepsy, passive paw anaphylaxis	50,100,200 mg/kg B. W	P<0.001	Kauskih et al, (2012)[37]
14	Anti-tussive activity	Churana	Aqueous Maceration	Guinea Pig	acetic acid induced cough	100,200,300,400,500 mg/kg B. W	P< 0.05	Sonvale et al, (2012)[38]
15	Antimycobacterial	Fruits	Ethanolic extract	M. tuberculosis H37Rv strains	Resazurin Microplate Assay	1, 10 and 100 µg/ml	-	Deepthi Swapna P Ret al, (2012)[39]
16	Antidiabetic and Antihyperlipidemic activity	Roots	Aqueous extract	Male Wistar albino rats	Streptozocin incuded method	100,200,300,400,500 mg/kg B. W	P < 0.01	Nabi et al, (2013)[40]

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