

THERAPEUTIC POTENTIAL OF PIPER LONGUM LINN: A CRITICAL ANALYSIS OF PHYTOCHEMISTRY AND PHARMACOLOGY

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ABSTRACT

Medicinal plants have shown tremendous potential for the development of the new drug molecules for various serious diseases. Many plant derived products have found to play an important role in various disease conditions. Piper longum Linn. is a native of the Indo-Malaya region, belongs to family Piperaceae. Piper longum Linn. (Piperaceae) has been used as a therapeutic agent in the treatment of various pathological conditions. The tribal population uses the plant for cardiovascular activities, anti-inflammatory activity and as a spice. Alkaloids, Lignans and volatile oil are reported in this plant. Extract of Piper longum fruits have been shown to possess various activities like Bio-availability enhancer, immunomodulatory effect, antiasthmatic and hepatoprotective activity. In the present review an attempt has been made to explore different aspects of Piper longum.

KEYWORDS: Piper longum, Piperaceae, Piperine.

INTRODUCTION

Medicinal plants have shown tremendous potential for the development of the new drug molecules for various serious diseases. Many plant derived products have found to play an important role in various disease conditions. Although, modern medicines are available, herbal medicines have often retained popularity for historical and cultural reasons. Since the usage of these herbal medicines has increased, the issues regarding their safety, quality, and efficacy in industrialized and developing countries are cropped up.^[1] Piper longum Linn. (Piperaceae) has been used as a therapeutic agent in the treatment of various pathological

conditions.^[2] Drug consists of dried fruiting spikes of *Piper longum* Linn.; *P. Latifolium* hunter., *Chavica roxburghii*., Fam. Piperaceae. It is an aromatic, slender, perennial climber plant. Occurrence and distribution Long pepper is a native of the Indo-Malaya region. It is found growing wild in the tropical rainforests of India, Nepal, Indonesia, Malaysia, Sri Lanka, Timor and Philippines. Indian Long pepper is mostly derived from the wild plants but is also occurs in hotter parts of India, from central Himalayas to Assam, Khasi and Mikir hills, lower hills of West Bengal and evergreen forests of Western Ghats from Konkan to Kerala, also recorded from car Nicobar Islands.^[3]

Other Names

Bengali:- Pipul,

English:- Long pepper,

Gujarati:- Lindi Pepper,

Hindi:- Pippal, pippar,

Kan.: - Hippali, Modi,

DESCRIPTION OF THE PLANT

Piper longum Linn is a slender, climbing, under shrub, creeping and rooting below. The young shoots are downy; the leaves are 5-9 cm long, 5 cm wide, ovate, cordate with broad rounded lobes at the base, sub- acute, entire, glabrous. The plant bears unisexual flowers in solitary, erect spikes during or just after the rainy season. The male spikes are larger, slender and are 2.5 to 7.5 cm long, while the female spikes are 1.25 to about 2 cm long when in flower, growing to about 3 cm when in fruit.^[5] The berries are ovoid, yellowish orange, sunk in thick rachis about 0.25 cm in diameter.^[6]



Figure 1: Piper longum Shrub.



Figure 2: Fruit Spike of Piper longum.

PHARMACOGNOSTICAL CHARACTERISTICS

The root in transection shows thick walled parenchyma, simple or compound starch grains, lignified and striated stone cells, resinous cells in the cortex, perivascular fibers in phloem, and radial strips of xylem which meet at the center. Pith is absent. The stem has a secretory cavity in the center. The cortex shows starch grains as well as resinous and some stone cells. The phloem is capped by perivascular fibers and xylem is arranged in V-shaped groups.^[7] The fruits are three layered pericarp. Endocarp is wavy in outline, which is a distinguishing character. Fruitlet of *P. longum* is a thick-walled with heavy brown contents in the outermost layer, mesocarp with thickened cells, endocarp and seed coat fused to form a deep zone with hyaline content in the outer layers, and orange-red pigment.^[8]

WILD SPECIES AND VARIETIES

The Indian long pepper appears to be derived from two or three species, including the one which is imported from Malaysia and Indonesia. It is a product of either *P. longum* or *P. pepuloides*, while the java long pepper is from *P. officinarum* DC. (Syn. *Chavica officinarum* Miguel). The long pepper of English commerce is chiefly the produce of the java variety. In different agro-climatic regions of the country, a number of geographical races exist. The Assam, West Bengal and Nepal races are the most popular among them. The west Bengal type is the Gol Thippali (round ball type). The Maharashtra type is Pipal Nonsori. The races found in Assam are Asali (true) and Suvali (female in Assamese). Under the All India Co-ordinated Research project on Medicinal and Aromatic Plants, a selection from 'Cheemathippali', which bears female type spikes possessing the highest spike weight and total yield has FYM or compost. In order to avoid water stagnation in the pits and beds, channels are made to drain excess rain water.^[9]

ETHNOPHARMACOLOGY

The unripe fruit is sweetish, cooling and useful in biliousness. The ripe fruit is sweet, pungent, a stomachic, aphrodisiac, alternative, laxative, antidiarrhoeic, antidysentric, is useful in vata and kapha, asthma, bronchitis, abdominal complaints, fevers, leucoderma, urinary discharges, tumours, piles, diseases of the spleen, pains, inflammation, leprosy, insomnia, jaundice, hiccoughs, tubercular glands and reduces biliousness (in the Ayurvedic system of medicine). The roots and fruits are used in palsy, gout and lumbago. The root has a bitter, hot and sharp taste. It is used as a carminative, a tonic to the liver, stomachic, emmenagogue, abortifacient, aphrodisiac, haematinic, diuretic, digestive, and as a general tonic, useful in inflammation of the liver, pains in the joints, lumbago, snakebite, scorpion-sting and night-blindness (in the Unani System of medicine). Extract of the plant *Piper longum* Linn is used as a folk medicine in India and China. Roots of the plant are reported for the treatment of heart diseases in ancient literature of East Asia. In the Travancore region, an infusion of the root is prescribed after parturition, to help in the expulsion of the placenta. It appears to partake, in a minor degree, of the stimulant properties of the fruit. As an alternative tonic, long pepper is recommended for use in a rather peculiar manner. An infusion of three long pepper is to be taken with honey on the first day, then for ten successive days. The dose is to be increased by 3 peppers every day, so that on the tenth day the patient will take thirty at one dose. Then the dose is gradually reduced by 3 daily, and finally the medicine is to be stopped. Thus administered, it is said to act as a valuable alternative tonic in paraplegia, chronic cough, enlargement of the spleen and other abdominal viscera. Long pepper is used in the composition of several snuffs; boiled with ginger, mustard oil, butter-milk and curds it forms a liniment, used in case of paralysis. In the Konkan region, the roasted fruits are beaten up with honey and given to treat rheumatism; they are also given powdered with black pepper and rock salts (2 parts of long pepper and 1 of salt) in half tola doses. The dried immature fruit and the root in the form of decoction are extensively used in acute and chronic bronchitis attended with cough and found to give gradual relief in all cases.^[9]

PHYTOCHEMISTRY

The fruits gave positive tests for the presence of volatile oil, starch, protein and alkaloids, saponins, carbohydrates, and amygdalin but no tannins.^[10] Major chemical constituents are alkaloids piperine, piperlongumine, piperlonguminine and also methyl-3, 4, 5 - trimethoxycinnamate.^[11] The spikes of this plant contain the alkaloids piperine (4-5 %) and piplatin, and two new alkaloids one of which is designated as alkaloid A and which is closely

related to pellitorine; and three more new alkaloids- piperolactum A, piperolactum B and piporadione.^[12] The roots contain the alkaloids, piper longuminine (0.2-0.25%) and piper longumine (0.02%) besides piperine. Further purification of piper longumine has yielded six known alkaloids-cepharadione B, cepharadione A, cepharanone B, aristolactum A 11, norcepharadione B and 2 hydroxy 1 methoxy 4 H dibenzoquinoline- 4,5 (6 H) dione); lignins, viz., pluriatilol, fargosin, sesamine, asarinine, guineensine and pipericide.^[13] Besides, the dried spikes on steam distillation, yield 0.7% essential oil with a spicy odour resembling that of pepper and ginger oil. The plant contains essential oil consisting of long chain hydrocarbons, mono- and sesquiterpenes, caryophyllene being the main product. Other constituents are piperine, pipartine, pipernonaline, piperundecalidine, pipericide, sesamine, dieudesmin, β -sitosterol and dihydrostigmasterol. Four aristolactams (cepharanone B, aristolactum AII, piperlactam A apiperlactum B) and five 4,5-dioxoaporphines (cepharadione A, cepharadione B, norcepharadione B, piperadione (2- hydroxyl-methoxy-6-methyl-4H-dibenzo (de,g) quinoline-4,5-(6H)-dione), its 6 demethyl derivative and amino acids, dehydropipernonaline from the fruit and tetrahydropiperine from the plant have been isolated.^[14,15] Sesamine, a lignin, dihydrostigmasterol and two melting unstable compounds, one of which appeared to be isobutylamide of an unsaturated acid, n-isobutyl-deca-trans-4-dieneamide, essential oil of consisting of n-hexadecane, n- heptadecane, n-octadecane, n-nonadecane, n-cicosane, n-henocosane, α - thujene, terpinolene, zingiberine, p-cymene, p-methoxyacetophenone, dehydrocarveol and two monocyclic sesquiterpenes. The prescence of L-tyrosine, L-cysteine hydrochloride, DL- serine and L- aspartic acid as free amino acids also has been reported in the fruits.^[16] The seeds contain syvatine, dieudesmin.^[17] In addition to palmitic, hexadecenoic, stearic, linoleic, oleic, linolenic, higher saturated acids, arachidic and behenic acids are also reported.^[18]

MEDICINAL & PHARMACOLOGICAL ACTIVITIES

Immunomodulatory activity

Tests such as haemagglutination titre (HA), macrophage migration index (MMI) and phagocytic indeJ (PI) in mice have demonstrated the immunostimulatory action of Piper longum fruits to be both specific and non-specific. The effect was more prominent at lower doses (225 mg/kg) and was marginally reduced when the dose was increased," In another study, it was found to offer protection against externally induced stress,' A famous Ayurvedic preparation containing long pepper, Pippali Rasayana, was tested in mice infected with

Giardia lamblia and found to produce significant activation of macro phages, as shown by an increased MMI and phagocytic activity.^[19]

Stimulant effects

Isolated piperine showed a central stimulant action in frogs, mice, rats and dogs and increased the hypnotic response in mice. It antagonised respiratory depression induced by morphine or pentobarbitone in anaesthetised dogs and a petroleum ether extract of the fruits antagonised morphine-induced respiratory depression in mice. A comparative study conducted with piperine and nalorphine, for effects against morphine-induced respiratory depression and analgesia, found that both reversed respiratory depression but, unlike nalorphine, piperine did not antagonise morphine-induced analgesia in rats.^[19]

Antiasthmatic activity

Studies have been carried out to validate the traditional claims of Ayurveda for antiasthmatic activity of *Piper longum*. An extract of the fruits in milk reduced passive cutaneous anaphylaxis in rats and protected guinea pigs against antigen-induced bronchospasm.^[20]

Bio-availability enhancement

Piperine has been shown to enhance the bio-availability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics, due to its easy partitioning and increasing permeability. The effect of 'Trikatu', a compound Ayurvedic preparation containing *Piper longum* as one of the major ingredients, was tested in combination with other drugs. The study reported that 'Trikatu' increased their bio-availability either by promoting rapid absorption from the gastrointestinal tract or by protecting the drug from being metabolised during its first passage through the liver after being absorbed, or by combination of both mechanisms.^[21]

Hepatoprotective activity

Piperine was evaluated and found to exert significant protection against tertiary butyl hydroperoxide and carbon tetrachloride-induced hepatotoxicity, by reducing both in vitro and in vivo lipid peroxidation. A fruit extract was assessed in rodents for its hepatoprotective action against CCL₄-induced acute, chronic and reversible damage and chronic irreversible damage, using morphological, biochemical and histopathological assessment parameters. The extract improves the regeneration process by restricting fibrosis, but offered no protection against acute damage or against cirrhotic changes.^[19]

Hypocholesterolaemic 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 unsaponifiable fraction of the oil of *Piper longum* also significantly decreased total serum cholesterol and hepatic cholesterol in hypercholesterolaemic mice.^[19]

Antiinflammatory activity

A marked antiinflammatory activity of a decoction of *P. longum* fruits has been reported using carrageenan-induced rat oedema.^[22]

Antiamoebic activity

The fruits were tested for their efficacy against *Entamoeba histolytica* in vitro and experimental caecal amoebiasis in vivo. Both the ethanolic extract and isolated piperine produced an improvement of 90% and 40% respectively, in rats with caecal amoebiasis.^[23]

Antibacterial activity

The essential oil of *P. longum* showed antibacterial action against a number of bacterial strains^[32,33] although a 50% ethanolic extract of the fruits did not show any effect.^{3'} Piperlonguminine was found to have potent activity against *Bacillus subtilis* while piperine was more effective against *Staphylococcus aureus*.^[24] Furthermore, antitubercular activity of *P. longum* is reported.^[25,26] Recently, it has found to play a role as a cardioprotective agent in Isoprenaline and Coronary artery ligation induced MI.^[27]

SAFETY PROFILE

Since it is so widely used in cooking and traditional medicine, it is generally assumed to be safe in moderate doses. However, as the fruits are reported to have contraceptive activity in experimental models, its use during pregnancy and lactation should be avoided. Piperine may interfere with enzymatic drug biotransformations, resulting in the inhibition of hepatic arylhydrocarbon hydroxylase (AHH) and UDP -glucuronyl transferase, and alter the pharmacokinetic parameters of barbiturates and phenytoin. A single oral dose of 3 g/kg body weight in experimental animals, and chronic toxicity studies with 100 mg/kg body weight for 90 days, revealed no untoward effects. Studies of isolated constituents in mice gave LD50 values for piperine, piperlongumine and piperlonguminine as 56.2, 110.1 and 115.3 mg/kg body weight respectively. In the evaluation of antifertility activity, long pepper at a dose of 1

g/kg body weight was found to be an effective contraceptive agent without toxic or teratogenic effects.^[29]

CONCLUSION

In the present review we have made an attempt to congregate the botanical, phytochemical, nutritional, ethnopharmacological, pharmacological and toxicological information on *Piper longum*, a medicinal herb used in the Indian system of medicine. Survey of literature revealed the presence of alkaloids, lignans, volatile oil and esters in different parts of this plant. Research on alkaloid has gained a special attention in recent times as several of them have shown promising activities like immunosuppressant, antiasthmatic, stimulant effect, hepatoprotective, Hypocholesterolaemic activity, anti-inflammatory, antiameobic and antibacterial etc. Investigating the new sources of natural products to isolate more potent alkaloids and structurally modifying the known compounds to retain activity is still the best possible way to develop safe and effective cardioprotective agent drugs of this class. The ethnopharmacological approach used in the search for new compounds from such plants appears to be helpful compared to the random screening approach. However, a promising approach is needed to use these agents as templates for designing new derivatives with improved properties. This review will definitely help for the researchers as well as practitioners, dealing with this plant, to know its nature proper usage. The extract and purified fractions of *Piper longum* were strong plant growth inhibitors, therefore could be considered as potent, effective and environmentally safe agricultural pesticides.

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