PHYTOCHEMISTRY AND PHARMACOLOGY OF *P*IPER *L*ONGUM – A SYSTEMATIC REVIEW

Dhanalakshmi D.*, Umamaheswari S., Balaji D., Santhanalakshmi R. and Kavimani S.

Mother Theresa Post Graduate and Research Institute of Health Sciences
(Govt of Puducherry Institution) Indira Nagar, Gorimedu, Puducherry- 605006, India.

ABSTRACT

*Piper longum* Linn. Piperaceae, Long pepper is a highly beneficial plant, used since from immemorial times. This spices *Piper longum* is belonging to South Asian origin. Usually long pepper is mixed with honey, and used as a tonic for cold and fever. Long pepper contains alkaloids, amides, Lignans, Esters, volatile oils etc., *Piper longum* traditionally have been used for the treatment of various disorders like cancer, diabetes, obesity, hyperlipidemia, asthma, fungal infection, arthritis, pain,ameobiasis, ulcer, depression, inflammation etc. It also exhibits antioxidant activity and inhibits aggregation of platelets. The phytoconstituents present in it with their pharmacological potential will be discussed in this review article.

KEYWORDS: *Piper longum*, antioxidant, phytoconstituents, pharmacological profile.

INTRODUCTION

*Piper longum* Linn.(family: piperaceae) is a flowering plant in the piper family. *Piper longum* commonly known as indian long pepper, it is widely used as a spice and flavouring agent in preparation of various foods and herbal formulations.[1,2] it is native to indo- Malaya region. It is now largely cultivated in India, Nepal, Indonesia, Malaysia, Sri-lanka, Timor and Philippines.[3] In India, it is mainly cultivated in central Himalayas to Assam, Khasi and Mikir hills, lower hills of west Bengal and evergreen forests of Western Ghats from Konkan to Kerala and also from Car Nicobar Islands.in various pathological conditions *Piper longum* has been used as a therapeutic agent. The fruit and root of species *Piper longum* are used as anti-irritant, analgesic, anti-asthma and bronchitis. Apart from its root and stem whole plants
are used for the treatment of variety of diseases traditionally. The medicinal properties attribute to *Piper longum* are extensive.\[^4\]

**Medicinal uses**

The root and stem part of the *Piper longum*, has been used for various ayurvedic and unani system:\[^5\] the fruits are used as a stomachic, liver tonic, emmenagogue, aboartifacient, fruit is sweet, pungent, aphrodiasic, a stomachic, laxative, alternative, anti diarrhoeial, anti-dysenteric, asthma, bronchitis, abdominal complaints, fever, leucoderma, urinary discharges, tumours, diseases of the spleen, pains, inflammation, leprosy, insomnia, jaundice, hiccoughs and Tubercular glands (in the Ayurveda system of medicine). Roots of the *Piper longum* are used for the treatment of heart diseases in ancient literature of East Asia. In the region of Travancore, an infusion of the root is used for parturition, to help in the expulsion of the placenta. It appears to part take, in a minor degree of the stimulant properties of the fruit and also used as an alternative tonic in paraplegia, chronic cough, enlargement of the spleen and other abdominal viscera. Long pepper has been used in various compositions of drugs, boiled with ginger, mustard oil, butter milk and curds. It forms a liniment, used in case of paralysis. The roasted fruits are beaten up with honey and given to treat rheumatism in konkan region. The decoction of dried immature fruit and root are used in the form of decoction in the treatment of acute and chronic bronchitis.\[^6\]

**Description**

*Piper longum* is a perennial long, slender, climber with woody roots, creeping and jointed stem with fleshy fruits embedded in the spikes. Branchlets were in the form of erect, glaborous with swellen nodes. Leaves arrangement is alternate, ovate shaped, apex acute to acuminate with entire margins\[^7\]. The morphological character of both male and female plants were similar till the formation of spikes\[^8\]. Male spikes greenish- yellow, cylindrical, fleshy with minute flowers, female spikes, erect, yellow. The female spikes are shorter and thicker when compared with male spikes\[^9\]. The fruit spikes which are cylindrical, oblong, berries red, or black when ripe, globose with aromatic odour and pungent taste\[^10,11,12\].

digestive, aphrodiasic, haematinic, diuretic, digesrive and as ageneral tonic, useful in inflammation of the liver lumbago, snake bite, pain in the joints, scorpion – sting and night blindness (in the unani system of medicine). The unripe fruit is useful in bibousness. The ripe
Division: Magnoliophyta  
Class: Magnoliopsida  
Order: Piperales  
Family: Piperaceae  
Genus: Piper  
Species: longum  
Botanical name: *Piper longum*

**Other names:**  
Sanskrit - Pippali, Magadhi, Kana, Usana, etc; English- Indian long pepper, Long pepper  
Hindi- Pipal, Pipli, ; Gujarati- Lindipipal, Pipli ; Marathi- Pimpi ; Bengali- Pipul, Pipli ;  
Sindhi- Tippali ; Malyalam- Pimipli,Tippali,Magadhi,Lada,Mulagu, ; Punjabi- Maghs- pipal,  
Pipal, Filfillardas, Drafilfil. ; Telagu- Pippallu, pipili, Pippali katte. ; Tamil- Pippili, Tippili,  
Kundan, tippili, Sirulumal, Pippallu. ; Kannada- Tipili, Hipli, yippali ; Arabian- Dra-filfil. ;  
Oriya- Baihehi, Krykola, Mogodha, Pippoli. ; Persi- Filfilidray, Pipal, Filfil-i-daras. ; Santhal-  
Ralli ; Urdu- Pipul.

**Chemical constituents**

*Piper longum* contain piperine as the major and active constituent, The piperine content is 3-5% (on dry weight basis) in *Piper longum*. The fruits gave positive result for presence of starch, protein and alkaloids, volatile oils, saponins, carbohydrates, and amygdalin and negative result for tannins.

**Alkaloids and amides**

The fruit of *Piper longum* contains a more number of alkaloids and related compounds, the most abundant of which is piperine, followed by methyl piperine, pipernonaline, pipertonine, asaridine, pellitorine, piperundecalidene, piperlongumine, piperlonguminine, retrofractamide A, perumidiene, brachystamidene-B, a dimer of desmethoxypiplartine, N-isobutyl decadienamide, brachyamide-A, brachystine, pipericine, piperdidine, longamide, dehydropipernonaline piperidine, and tetrahydro piperine. Piperine, piperlongumine, tetrahydropiperlongumine, trimethoxy cinnamoyl-piperidine, and piperlonguminine have been found in the root. Newly identified chemical constituents are 1-(3,4-methylenedioxyphenyl)1E-tetradecene, 3-(3,4-methylenedioxyphenyl)propenal, piperoic acid, 3,4-di-hydroxy- biabola-1, 10-diene, eudesm-4(15)-ene-1beta, 6-alpha-diol, 7-epi-
eudesm-4(15)-ene-1beta, 6beta-diol, guineesine, and 2E,4E-dienamide, (2E, 4E, 8E) - Nisobutylhenicosa-2,4,8-trienamide.\textsuperscript{[18,19]}

**Lignans**
The main lignans isolated from the fruit of *Piper longum* are sesamin, pulviatilol, and fargesin.\textsuperscript{[20,21,22,23]}

**Esters**
The fruit of *P. longum* contains tridecyl-dihydro-pcoumaarate, eicosanyl-(E)-p-coumarate and Z-12octandecenoic – glycerol-monoester.\textsuperscript{[20,21,22,24]}

**Volatile oil**
The essential oil of the fruit *Piper longum* is a complex mixture and the three major components of which are (excluding the volatile piperine) caryophyllene and pentadecane (both about 17.8%) and bisaboline (11%). Others include thuinline, terpinoline, zingiberine, pcyemene, p-methoxy acetophenone and dihydrocarveol.\textsuperscript{[20,21,22,24,25,26]} The volatile constituents and microbiological studies on *Kaempheria galanga*, *Hibiscus abelmoschus*, and *Piper longum* revealed presence of over 15 components which were further identified by GC-MS of the volatile oil of *Piper longum*. The variations in the piperine content with maturity were also monitored. The *P. longum* and *H. abelmoschus* seed oil had only antibacterial activities. By using a systematic bioassay guided fractionation method pipataline, pellitorine, sesamin, brachystamide B and guineensine active principles were isolated. A reversedphase high-performance liquid chromatography method was developed to quantify these active principles in the plant material.\textsuperscript{[27]} In the chromatogram of *P. longum* fruits, retrofractamides B and D, and N-isobutyl-2E, 4Octadecadienamide can be detected. The HPLC chromatogram of *P. longum* showed a homogeneous distribution of numerous peaks, with piperine and pellitorine as the predominant compounds.\textsuperscript{[28]} A simple and convenient HPTLC method was developed for standardization of the plant material using the two major constituents, pellitorine and dihydropiperlonguminine, as markers at 260 nm.\textsuperscript{[29]} The hexane extract of dried fruits of *Piper longum* on fractionation afforded a new alkamide, isodihydropiperlonguminine and two phenyl propanoic acid derivatives. The structures of these compounds were established based on spectroscopic evidence and synthesis.\textsuperscript{[30]} Thymoquinol and 6-Hydroxydopamine were also identified in *Piper longum*.\textsuperscript{[31]}
Organic acids
The major organic acids present are palmitic acid and tetrahydropiperic acid.\textsuperscript{18,19}

Anti-apoptosis and antioxidant
The hexane: ethanol (2:8) extract of \textit{Piper longum} shows anti-apoptosis and antioxidant activity through TUNEL ASSAY and Radical scavenger activity (DPPH Assay). The fruit extracts on GM-induced hair cell loss in basal, middle and apical regions in a neonatal cochlea cultures. The study accomplished that the fruit extract of \textit{Piper longum} shows anti-apoptosis and antioxidant activity.\textsuperscript{32} The petroleum ether extract of the fruit decrease lipid peroxide levels and maintain glutathione content, demonstrates antioxidant activity.\textsuperscript{33}

Analgesic activity
The aqueous extract of \textit{Piper longum} root powder (200, 400, and 800/kg) was given orally to mice and rat to study its analgesic effects. In rat the delay in reaction time to thermal stimulant was assessed. In mice the amount of writhing to chemical stimulus was assessed. The effect of the 400 and 800mg/kg doses of fruit were similar to that of NSAID drugs (p<0.0001). Both ibuprofen (40mg/kg) and piper longum (800mg/kg) demonstrated 50% protection against writhing. The delay in reaction time to thermal stimulus was <6% for different doses of fruit as compared with 100% for pentazocaine. The result shows that the plant and root extract of piper longum produces a weak-opioid-type but potent non-steroidal anti-inflammatory drug type of Analgesic.\textsuperscript{34}

Anti-inflammatory and anti-arthritis activity
The fruit extract of \textit{Piper longum} were reported to possess anti-inflammatory activity in carrageenan rat paw edema.\textsuperscript{35,36} And the piper extract and piperine possess inhibitory activities on prostaglandin and leukotrienes Cox-1 inhibitory effect and thus exhibit anti-inflammatory activity.\textsuperscript{37} On the other hand the aqueous extract of \textit{piper longum} shows anti-arthritis effect on CFA (Complete Freuds Adjuvant) induced arthritis in rats.\textsuperscript{38}

Immunomodulatory activity
The immunomodulatory potential of \textit{Piper longum} fruit extract have been evaluated by haemagglutination titre (HA), macrophage migration index (MMI), and phagocytic index (PI) in mice. A familiar ayurvedic preparation containing long pepper, pippali Rasayana, 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.\textsuperscript{39}
Anti-cancer and Anti-tumor activity
The alcoholic extract of *Piper longum* (10mg/dose/animal) and piperine (1.14mg/dose/animal) inhibits solid tumor development in mice induced with Daltons lymphoma ascites cells and increases the life span of mice. Piperine also shows cytotoxic towards Doltons lymphoma ascites and Ehrlichascites carcinoma cells at 250mg/ml.\[^{40,41}\]

Piplartine and piperine are the major constituents of *piper longum* was shown to produce anti-tumor effect on sarcoma 180 tumors transplanted in mice, it shows reduction of tumor weight in piplartine and piperine treated animals.\[^{42}\]

Anti-asthmatic activity
The ethanolic extract of *Piper longum* in milk reduced passive cutaneous anaphylaxis in rats and protected gunia pigs against antigen-induced bronchospasm.\[^{43,44}\]

Anti-diabetic activity
The aqueous extract of *Piper longum* shows anti-hyperglycemic and anti-lipidperoxidative in sterptozotocin induced diabetic rat.\[^{45}\]

Oral administration of dried fruits of *Piper longum* has shown significant anti-hyperglycemic, anti-hyperlipidemic effects in diabetic rats compared to that of the standard reference during glibenclamide.\[^{46}\]

Hypocholestrolaemic activity
Piper analogue isolated from *Piper longum* significantly inhibited the elevation of total serum cholesterol, and the total serum cholesterol to HDL-cholesterol ratio in rats fed with a high cholesterol diet.\[^{47}\]

The unsaponicable fraction of the oil of *Piper longum* also significantly decreased total serum cholesterol and hepatic cholesterol in hypercholesterolaemic mice.\[^{48}\]

Hepatoprotective activity
The plant extract of *Piper longum* was studied in rodents for its hepatoprotective action against carbontertrachloride induced acute, chronic reversible and irreversible damage using morphological, biochemical and histopathologic parameters. The main piperine was found to protect against tertiary butyl hydroperoxide induced and carbontetrachloride induced hepatotoxicity by reducing lipid peroxidation by *invitro* and *invivo* methods.\[^{49,50}\]

Anti-obesity activity
Pharmacological inhibition of acyl CoA diaylglycerol acyltransferase has emerged as a potential therapy for the management of obesity. Compounds containing piperidine groups
are considered potential acyl COA diacylglycerol acyltransferase inhibitors. This supports its traditional use as an anti-oedematogenic remedy.\textsuperscript{[51]}

**Larvicidal activity**

Ethanolic extracts of *Piper longum* were evaluated for efficacy against early fourth instar larvae of *Aedes aegypti* mosquito using a larvicidal bioassay.\textsuperscript{[52,53]}

**Anti-microbial activity**

The various solvent extract of *Piper longum* was tested for its anti-bacterial and anti-fungal activity against a variety of pathogenic bacteria and fungi respectively.\textsuperscript{[54]} The fruit extract of *Piper longum* shown to possess anti-microbial activity against certain antibiotic resistant specific bacteria, this supports its traditional use as an anti-microbial remedy.\textsuperscript{[55,56]}

**Antidepressant activity**

A bioassay guided isolation of the Ethanolic extract from the fruit yielded a piperine alkaloid and piperine having potent antidepressant like activity, which are mediated in part through the inhibition of MAO activity.\textsuperscript{[57]} Treatment with piperine (6.25-25mM) for 72h reversed the (corticosterone)induced reduction of BDNF mRNA expression in cultured hippocampal neurons.\textsuperscript{[58]} Therefore the fruits of *Piper longum* represent a promising pharmacotherapeutic agent against depression.\textsuperscript{[59]}

**Anti-amoebic activity**

The methanolic extract of *Piper longum* fruit were tested for their efficacy against Entamoeba histolytica in vitro and against experimental cecal amebiasis in vivo.\textsuperscript{[60]} The ethanolic extract and constituents piperine of *Piper longum*, a pure compound, cured 90% and 40% of rats with caecal amoebiasis respectively.\textsuperscript{[61,62]}

**Adulticidal activity**

The dose dependent adulticidal effect of ethanolic extract of ethanolic extract of fruits was observed against Stegomyiaegypti, a main vector of dengue and dengue hemorrhagic fever. The various extracts of *Piper longum* were demonstrated impressive adulticidal activity when tested on female mosquitoesley topical application.\textsuperscript{[63]}

**Coronary vasodilation**

The amide dehydropiperonaline analogue isolated from the fruit of *Piper longum* has demonstrated the ability to induce coronary vasodilation.\textsuperscript{[64]}
Anti-fertility activity

The studies elucidated that the hexane fraction of *Piper longum* has potent anti-implantation activity accompanied by the mortality of animals. The root extracts of *Piper longum* were used along with Embelica ribes seeds shown 100% anti fertility activity in female albino rats. On the other hand *Piper longum* potentiates the contraceptive activity of other plant products, the feasibility of such a combination needs to be investigated further for the development of a contraceptive for the female as reported in Ayurveda Garbhhanivarana Aushadham used for both female and male without interfering with the activity of ovarian hormones on uterus.

Anti-stress activity

The aqueous extract of *Piper longum* was evaluated for anti-stress activity in stress rat models. With this result stress induced memory loss aqueous extract of *Piper longum* decreased the latent period indication extract-produced nootropic activity.

Protective myocardial activity

Piperaldehyde one of the main active constituent of *Piper longum*, shows significant DPPH scavenging activity and exert protective effect and exert protective effect in the myocardial narcotic rats. Therefore it can be concluded that the extract and piperaldehyde are useful in exerting protective activity against myocardial ischemia is treated animals.

Radioprotective activity

The ethanolic extract of *Piper longum* shown radioprotective activity in swiss mice.the fruit extract attenuated the elevated levels of glutathione pyruvate transferase, alkaline phosphatase and lipid peroxidation in the liver and serum of radiation treated animals. And also restored glutathione production to offer radio-protection.

Anti-fungal activity

The essential oil isolated from the fruits of *Piper longum* showed fungicidal activity 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 *Piper recondita* with 91% and 80% control values at the concentration of 0.5 and 0.25 mg ml⁻¹, respectively.
Antiplatelet activity
The inhibitory effects of the four acid amides piperine, pipernonaline, piperoctadecalidine, and piperlongumine, isolated from the fruits of *Piper longum* Linn. were evaluated on washed rabbit platelet aggregation. These four tested acid amides dose-dependently inhibited washed platelet aggregation induced by collagen, arachidonic acid, and platelet-activating factor, but not that induced by thrombin.\(^{[76]}\)

Melanin-inhibiting activity
Piperlonguminine one of the constituent of *Piper longum* which inhibits melanin production in melanoma B16 cells stimulated with alpha-melanocyte-stimulating hormone, 3-isobutyl1-methylxanthine, or protoporphyrin IX, where the compound exhibited stronger depigmenting efficacy. This effect was attributed to the inhibitory action of piperlonguminine on alpha-melanocyte stimulating hormone signaling through cAMP to the cAMP-responsive element binding protein, which in turn regulates the expression of the microphthalmia associated transcription factor, a key activator of tyrosinase expression. By this way the enzyme is inhibited internally, thereby suppressing the production of melanin.\(^{[77]}\)

Anti-snake venom activity
The ethanolic extract of *Piper longum* Linn.(piperaceae) and piperine showed the anti-snake venom activities against Russell's viper venom in embryoated fertile chicken eggs, mice and rats by using various models. They found that administration of *P. longum* extract (PLE) and piperine significantly (p<0.01) inhibited venom induced lethality, haemorrhage, necrosis, defibrinogenation and inflammatory paw edema in mice in a dose dependent manner. PLE possesses good anti-snake venom properties and piperine is one of the compounds responsible for the effective venom neutralizing ability of the plant.\(^{[78]}\)

Bioavailability enhancers
Piperine the main active constituent of *Piper longum* shown to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics due to its easy partitioning and increase in permeability of other drugs such as vasicine, indomethacin, diclofenac sodium etc.\(^{[79-81]}\) Piperine also has been reported to enhance the oral bioavailability of phenytoin in humans.\(^{[82-84]}\)

Classic Ayurvedic Preparations:\(^{[85]}\)
Pippalyasavam
Vardhamana pippali
Causasti pippali Pippali
khanda Sitopaladi churna
Guda pippali

**Antiulcer activity**
The antiulcer activity was demonstrated by water decocion of ginger making up one of the constituents of Mahakasyaya drugs along with water decocion of *P. longum* and colloidal solution of *Ferula asafoetida* has been reported to protect against CRS-, ASP- and PL-induced gastric ulcers in rats.\(^86\) 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.\(^87\)

**Insecticidal and acaricidal activity**
The essential oil of the *piper longum* showed insecticidal and insect-repellant activity.\(^88\) *Cinnamomum zeylanicum* 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.\(^89\)

**Safety profile of piper longum**
Since, it is widely used in cooking and traditional medicine, it is generally assumed to be safe in moderate doses. As the fruits are reported to have contraceptive activity in experimental models therefore its use during pregnancy and lactation should be avoided. Long pepper at a dose of 1gm/kg body weight was found to be an effective contraceptive agent without toxic or teratogenic effects.\(^90\) Acute and chronic oral toxicity studies on the ethanolic extracts of common spices bark and *P.longum* fruits were carried out in mice showed no significant acute or chronic mortality compared to the control during this study.\(^91\) The ethanolic extract of *piper longum* showed radio protective property and reduced the elevated levels of glutathione pyruvate transaminase (GPT), alkaline phosphatase (ALP), and lipid peroxidation (LPO) in liver and serum of radiation treated mice. The extract administration also increased the reduced glutathione (GSH) production to offer the radioprotection.\(^92\) Piperine may interfere with enzymatic drug biotrasformations resulting in the inhibition of hepatic aryl hydrocarbon hydroxylase (AHH) and UDP-glucuronyltransferase and altered the pharmacokinetic parameters of barbiturates and phenytoin.\(^91,93,94\)
CONCLUSION

_Piper longum_ (long pepper) have been explored phytochemically and pharmacologically by various researcher for their potential. Since, it has been reported for various useful pharmacological activities, taking this along with food as spice may be useful to prevent the development of most of the above mentioned disorders. Moreover it is economically cheap and easily available.

REFERENCE

15. www.google.com
38. Yende SR, Sannapuri VD, Vyawahare NS et al. (2010). Antirheumatoid activity of aqueous extract of piper longum on freunds adjuvant-induced arthritis in rats. IJPSR. 1(9): 129-133


91. Shah AH, Al-Shareef AH, Ageel AM and Qureshi S, Toxicity studies in mice of common spices, Cinnamomum zeylanicum bark and Piper longum, Plant Foods Human Nut, 1998; 52(3); 231-239.

