



Ethenobotanical and Recent Phytopharmacological Research of Piper longum Linn: a Review

Shazad Yaqub¹, Mohd Aftab*¹, Mohd Asif¹, Aisha Siddiqui¹, Sheikh Haneef Mohd²

1. Dept. Of Ilmul Advai, f/o Medicince jamia hamdard university ,(New Delhi)-110062

2. Dept. Of Moilijat, f/o Medicince jamia hamdard university ,(New Delhi)-110062

ABSTRACT

Herbal medicine is currently in demand not only in developing countries but also in developed countries because of their easy availability, low cost and minimum side effects. Long time traditional use of most of the herbs for therapeutic purposes provides a data regarding their safe clinical usage. *Piper longum* linn is one among such herbs mentioned in various Unani pharmacopeia's and is indicated for various ailments of human body. It belongs to family *piperacea*. In Unani system of medicine it is commonly known as *Filfil daraz* and from last hundreds of years the drug *piper longum* linn been accepted to be as good therapeutic agent particularly for cough, spasmodic pain, inflammation and flatulence. on the other hand recent Bioavailability enhancing and antioxidant property has increased its importance for further clinical research . In the present review it has been tried to give a comprehensive data regarding its ethenobotanical particularly of Unani background and phytopharmacological profile of the drug so that to provide a bird eye view presentation of its historical and modern research aspect.

Key words: Herbal medicine, Filfil daraz, *piper longum* linn, phytopharmacology

*Corresponding Author Email: maahmad@jamiyahamdard.ac.in

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INTRODUCTION

Herbal medicine has its origin from the vast experience and struggling practice of the great physicians and philosophers. In the current era of synthetic drug practice herbal drug treatment is still a preferable treatment and the reason of its aliveness and progression is its low cost, easy availability, lesser side effects and having better compatibility with the human body. Recent instrumental advancement had thrown a miraculous light on the phytochemistry of the plant and their related pharmacological action on various pathologies of human body. *Piper longum* Linn commonly known as Indian pipli in Indian system of medicine and popularly named as filfil daraz in unani system of medicine was considered a mostly in spice category and first time Hippocrates discussed the herb as midicament¹. *Piper longum* belongs to the family *piperaces* of kingdom *plantea*. The drug is used in unani system of medicine from hundreds of years with a successful clinical outcome. The drug has vast pharmacological action profile in its credit like Expectorant, Antispasmodic, Antiinflammatory, Carminative, Diuretic, Thermogenic, Vermifuge, Emmanagogue, Laxative, Digestive, Abortifacient.² Because of the properties like Laxative, Digestive, Anti-inflammatory and Carminative the drug has been kept as principal constituent of number of unani compound formulations like Jawarish bisbasa, Javarish atraj, Javarish jalin which are known for their best therapeutic effects in various Gastrointestinal diseases.³ Recent antioxidant, anticancer and antihyperlipidemic properties have increased the importance of the herb for further clinical research.



Figure 1: Images of Piper longum Linn

TAXONOMICAL CLASSIFICATION

Kingdom	-Plantea
Subkingdom	-Tracheobionta/VascularPlant
Super Division	-Spermatophta (Seed Plant)
Division	-Magnoliophyta (Flower Plant)

Class	-Manoliospsida Dictyledons
Order	-Piperales
Family	-Piperacea
Gender	-Piper
Species	-P. Longum Linn ⁴
Botanical name	- <i>Piper longum</i> linn ⁴

Vernicular Names

Sanskrit: *Pippali, Trikankana, Tikshnatandula, Maghadhi*. English: Dried Catkins, Long Piper
Hindi: *Pimpli, Papal, Pipli*. Bengali: *Pipli, Pepul* Gujrat: *Pipli, Papal, Pipara* Maharashtra:
Pimpli, Pipli, Mothi. Arab: *Darfilfil, Filfil Darz, Filfilae Moya*. Persion: *Maghz Papal, Filfildray,*
Papal, Pipli Telgu: *Pippali-Katti, Filfildray, Papal, Pipli* Tamil *Pipili, Tippilli, Tippali*. Punjab:
Papal, Darfilfil. Bombay: *Zipli* Malaysia: *Lada, Mula-Gu* Burma: *Peikehin* Santal: *Ralli*
Nepal: *Pipla-Mol*^{5,6,7}

Distribution

Piper longum is slender aromatic climber with perennial woody roots and is found all over India especially in the hotter parts from, khasi and mikir hills of Bengal, central parts of Himalayas to Assam and evergreen forests of western ghats from konkan to Travancore. It has also been recorded from carnicolbar islands.^{5,6,7}

Morphology:

Stems of *piper longum* is creeping and giving rise to jointed young shoots, leaves are downy and of 5-9cm length, 3-5cm width and alternate, ovate and cordate with broad rounded lobes, spiker cylindrical pedunculate. Fruits are ovoid in shape, yellowish orange in colour and sunken in fleshy spikes.^{5,6,7}

Chemical Composition:

Fruits of *Piper longum* has shown the presence of the alkaloid piperine and piplartine and piper longumine. Piperine constituents of 4 to 5 %.^{5,7} Lignans like fargesin, Sesamin, pulvuatilol, and others have been isolated from the fruit of *P. Longum*^{8,9,10,11} and esters like eicosanyl-(E)-p-coumarate, tridecyl-dihydro-pcoumaarate, and Z-12- octandecenoic –glycerol-monoester has been found in the fruit¹². The three major components essential oils of fruit has been isolated which are bisabolone (11%). and caryophyllene and pentadecane (both about 17.8%) and Others include terpinoline, thujine, zingiberine, p-methoxy acetophenone, pcymene, and dihydrocarveol Root of *Piper Longum* contains the chemicals like methyl piperine, iperonaline, piperettine, asarinine, pellitorine, piperundecalidine, iperlongumine, longamide piperlongumine,

refractomide-A, brachystine, piperide, piperderidine, brachystamide, brachystamide pregumidiene, , and tetrahydropiperine, dehydropiperonaline piperidine, terahydro piperlongumine, piperine, trimethoxy cinnamoyl-piperidine terahydro piperlongumine and piperlongumine^{13,14}

Mizaj (Temperament):

Hot¹ and dry² and according to some physician like Hakeem Kabiruddin temperament “Hot” is of second degree^{15,16,17}

Unani Pharmacological Action

Munaffis-e-Balgum (Expectorant), Daf-e-Tashanuj (Antispasmodic), Daf-e-Iltihaab (Anti inflammatory), Carminative,^{5,6,18,19,20} Mudir-e-Bol (Diuretic), Musakhin (Thermogenic) Qatil-e-Dedaan (Vermifuge), Mudir-e-Haiz (Emmanogogue), Mulayyan (Laxative), Hazim (Digestive), MUSAQIT-e-HAMAL (Abortifacient) ,Adaptogenic,^{21,22} Antiemoebic, Muqawwi-e-Jigar (Hepatoprotective), Coronary vasodilation, Maney Hamal (Anti fertility), Muhazzil (Hypolipidaemic), Muhallil (Resolvent), Muharik-e-Bah (Sexual stimulant), Muharik-e-Bah (Sexual stimulant) Mushtahi (Appitizer), Maney-Qai (Antiemetic), Maney-Qai (Antiemetic), Muteeb Dahan (Aromatic), Musaffi-e-Dam (Blood purifier)^{23,24}

Therapeutic uses (unani)

Saul (Cough), Muzmin waram-e-shoib (Chronic bronchitis), ziq-un-nafas (Asthma), Sara (Epilepsy), Falj (Paralysis), Fawaq (Hiccup), Bahatus-Saut (Hoarseness of voice), Hudar (Rheumatism). Zoaf-e-Ishtiha (anorexia), piles (Bawaseer), Dard-e-Maidah (Stomach pain), Sulaat (Tumors), Shab-Kori (Night blindness), Mar aur Aqrab Gazeedgi (Snake and Scorpion Bites), Ishaal wa Zaheer (Diarrhoea and dysentery), Nafkhe-Shikam (flatulence), Sue-e-Hazam (Indigestion)^{25,26,27,28,23,17,16}

Muzir asrat (adverse effects)

Some unani physician has mentioned mild head ache by using the drug especially in hot and dry temperament patients^{16,22,29}

Musleh (corrective)

Sandal Safaid (*Santalum album* linn) Samag-e-Arabi (*Acacia Arabica* Linn.) Gulab (*Rosa Damascus Mill.*) Zarshak (*Berberis vulgaris* DC.) are known to have corrective property for piper nigrum^{30,23,22,29,18}

Badal (Substitute)

The drugs indicated in case of unavailability of the *piper nigrum* linn are Filfil safaid (*Piper nigrum* Linn.) Zanjabeel (*Zingiber officinalis* Linn.) Zarnbad (*Curcuma zedoaria* Rose)^{30,23,22,29,18}

Miqdar-e-Khurak (Dosage)

4-10 mashah (one masha = 1 gm) and according to the some unani physician the dose given is 1-2 masha^{30,31}.

Pharmacological studies

Antifertility effect

The study was done by using female rates as an experimental animals in which crude extract of *piper longum* linn, its different fractions and fractionalised pure compounds in different groups were studied for antifertility effect . It was found that crude extract of piper longum fruit and its hexane fraction exhibited 100 and 86 % efficacy respectively. Were as butanol soluble and butanol insoluble and chloroform fraction were found ineffective.³²

Antiulcer activity

The water extract of *Piper longum* was found to have significant gastric ulcer protective properties when rats were given 50mg/kg orally 60 mintues prior to subjecting them to ulreogenic activities including cold restrained stress, aspirin (200mg/kg, 4hrs) and 4 hr pylorus ligation did not develop gastric ulcer.³³

Antihyperlipidaemic activity

Studies confirm that compounds piperine, piperlonguminine, pipernonaline isolated from of the fruit of *Piper Longum* were the found to have significant antihyperlipidaemic activity when comparable to those of simvastatin.³⁴

Anti-inflammatory activity

Study showed that the *Piper longum* chloroform extract expressed the anti-inflammatory activity by inhibiting adhesions of neutrophils to endothelial monolayer by blocking the TNF-alpha-induced expression of CAMs i.e. ICAM-1, VCAM-1 and E-selectin through inhibition of NF-kappa B in endothelial cells. At the same time the extract exhibited antioxidant activity which further contributes to the anti-inflammatory activity. A component of the oil of *P. longum* is piperine which expressed its anti-inflammatory activity through inhibition of LPS-induced endotoxin shock via inhibition of 1 IFN production³⁵

Anti-platelet aggregation activity

In a preliminary study on the anti-platelet aggregation activity of *P. longum* was done and it was found that the ethanol extract contain factor the inhibit platelet aggregation as a non-

competitive thromboxane A receptor antagonist. Also an subsequently isolated compound piperlongumine was also proved to be a thromboxane A(2) receptor antagonist . In one more study it was founded that three other acidamides (piperine, piperonaline and piperoctadecalidine) also has similar effects but not as strong as piperlongumine. Park B S et al further used piperlongumine as the lead compound to synthesize seven other derivatives with anti-platelet aggregation activities ³⁶

Analgesic activity

Study done by Vedhanayaki et al reported some analgesic activity in the root extracts of *P. longum*. Their studies indicated that the root has weak opoid but potent NSAID type of analgesic activity³⁷

MAO Inhibitor and Antidepressant activity

Lee SA et al studied the MAO and Anti-depressant activity of *Piper longum* extracts. They isolated three compounds piperine, methylpiperine and guineensine which showed activity against MAO and also anti-depressant activity³⁸

Anti-melanogenesis activity

In the study the identified Piperlonguminine was found to possess an inhibitory effect on alpha-melanocyte stimulating hormone-induced melanogenesis. This effect is by an inhibitory effect on alpha-MSH-induced tyrosinase synthesis. This effect was through inhibiting the alpha-MSH-induced signalling through cAMP to the cAMP responsive element binding protein that in turn regulates the expression of the microphthalmia-associated transcription factor which is a key activator of the tyrosinase promoter. However, it was further found that it did not suppressed tyrosinase activity nor has a direct depigmenting effect on melanin³⁹

Antioxidant activity

Piperin antioxidant activity was studied and it was found that it could lower the TNF-alpha levels in lipopolysaccharide and concanavalin-A stimulated animals. It also reduced the nitrite level in Concanavalin-A and Lipopolysaccharide treated animals. In other study by Wakade et al it was found that the anti-oxidative activity could reduce the cardiotoxicity effects of Adriamycin. A study conducted by Thomas et al found that the ethanol extract of *Piper longum* could reduce the oxidative stress induced by monosodium glutamate.⁴⁰

Cytotoxic activity

Piperine also expressed cytotoxic activity in many different cell lines. It was found to be toxic to Dalton's lymphoma ascites and Ehrlich ascites carcinoma cells. Apart from affecting the cell viability, piperine showed chemopreventive activity. Selvendiran et al showed that piperine

enhanced the detoxification enzyme system and reduced DNA damage. Thus it played a role in the prevention of carcinogenesis. Again Selvendiran et al showed that the chemopreventive effect can also be attributed to its ability to increase the activities of mitochondrial enzymes suggesting its role in mitochondrial energy production. In another study, Selvendiran et al found that the chemopreventive activity could also be through modulation of protein bound carbohydrate levels as they are one of the markers of tumorigenesis. Pradeep et al reported its ability to inhibit lung metastasis induced by B16F-10 melanoma cells in mice. Another anticancer activity of piperine is its ability to inhibit angiogenesis as observed by Sunila et al. This is attributed to its regulation of pro-inflammatory cytokines and growth factors⁴¹

Radioprotective activity

The ethanol extract of *Piper longum* showed radio protective activity as evidenced by the following changes seen in animal treated with the extract prior to irradiation. (I). The white blood cell count was 2783.3 cells/mm³ after 3 days as compared to 1900 cells/mm in untreated animals. (II). The extract enhanced the number of bone marrow cells and alpha-estrerase positive cells. (III). The extract reduced the elevated levels of glutathione pyruvate transferase, alkaline phosphatase and lipid peroxidation and increased the reduced glutathione production⁴²

Antigiardiasis

Giardiocidal study on various individual extracts of *P. longum* was done and it was found that the aqueous and ethanol extracts have 100% giardiocidal activity. The extracts also showed demonstrable immune-stimulatory activity both specific and non-specific.⁴³

Immunomodulatory and Antitumor Activity

Alcoholic extract of the fruits of the plant *Piper longum* and its component piperine was studied for their immunomodulatory and antitumor activity. Alcoholic extract of the fruits was 100% toxic at a concentration of 500 microg/ml to Dalton's lymphoma ascites (DLA) cells and 250 microg/ml to Ehrlich ascites carcinoma (EAC) cells. Piperine was found to be cytotoxic towards DLA and EAC cells at a concentration of 250 microg/ml. Alcoholic extract and piperine was also found to produce cytotoxicity towards L929 cells in culture at a concentration of 100 and 50 microg/ml, respectively.⁴⁴

Hepatoprotective

The results from the present study demonstrated a significant hepatoprotective and antioxidant activity of *Piper longum* milk extract. the study was designed to investigate the hepatoprotective activity of *Piper longum* milk extract. Carbon tetrachloride (CCl₄) was used as a hepatotoxin at a dose of 0.5 ml/kg p.o. with olive oil (1:1) thrice a week for 21 days to produce the chronic

reversible type of liver necrosis. Following treatment with *Piper longum* milk extract (200 mg/day p.o. for 21 days), a significant hepatoprotective effect was observed in CCl₄ induced hepatic damage as evident from decreased level of serum enzymes, total bilirubin and direct bilirubin. The hepatoprotective effect of *Piper longum* is comparable to the standard drug silymarin (25 mg/kg/day p.o. for 21 days).⁴⁵

Chronotropic and Inotropic Effects

In the present study four major fractions namely F, G, H and I was isolated from piper longum extract and the activity of the fractions was studied on isolated frog heart. Fraction F has produced negative inotropic and negative chronotropic effect on isolated frog heart at 200 µg mL⁻¹. Fraction F shows maximum antagonistic activity on beta-receptors by decreasing **heart rate** and force of contraction. Actions of Adrenaline are blocked by fraction F and in the presence of propranolol, it shows continuous decrease in **heart rate** and force of contraction. In the present study, it was observed that fraction F shows antagonistic activity on beta adreno-receptors.⁴⁶

Enhancing proliferation of mesenchmal stem MSC proliferation

In this study Mesenchymal stem cells were dissociated from rat bone marrow and marked by Brdu, and the expression of CD44, CD54 and double label of Brdu and CD44. The growth of rat mesenchymal stem cell under volatile oil and aqueous soluble part of Piper longum was observed by means of cell viability measurement (MTT) and morphological observation and Brdu, PCNA immunohistochemical methods. And it was found that Volatile oil of Piper longum promote the cell viability of MSC and the number of Brdu, PCNA positive cell in dose-dependant and There was significant difference in comparison with control groups, C = C(50.66%), -OH(27.02%) and other functional groups in volatile oil of Piper longum were determined by GC-MS, but the aqueous soluble part of Piper longum could not promote the proliferation of MSC.⁴⁷

VEGF effect

The antiangiogenic activity of Piper longum was studied using in vivo as well as in vitro models. In vivo, antiangiogenic activity was studied using B16F-10 melanoma cell-induced capillary formation in C57BL/6 mice. Intraperitoneal administration of the extract (10 mg/dose/animal) significantly inhibited (50.6%) the number of tumor-directed capillaries induced by injecting B16F-10 melanoma cells on the ventral side of C57BL/6 mice. The cytokine profile in the serum of these animals showed a drastically increased level of proinflammatory cytokines such as IL-1beta, IL-6, TNF-alpha, GM-CSF and the direct endothelial cell proliferating agent, VEGF.

Administration of the methanolic extract of *P. longum* could differentially regulate the level of these cytokines. The level of IL-2 and tissue inhibitor of metalloprotease-1 (TIMP-1) was increased significantly when the angiogenesis-induced animals were treated with the extract. The extract of *P. longum* at non-toxic concentrations (10 microg/ml, 5 microg/ml, 1 microg/ml) inhibited the VEGF-induced vessel sprouting in rat aortic ring assay. Moreover, *P. longum* was able to inhibit the VEGF-induced proliferation, cell migration and capillary-like tube formation of primary cultured human endothelial cells. Hence, the observed antiangiogenic activity of the plant *P. longum* is related to the regulation of these cytokines and growth factors in angiogenesis-induced animals.⁴⁸

Antimicrobial Effect

Piper nigrum and *piper longum* together were evaluated against bacterial pathogen such as salmonella typhi, e coli, pseudomonas aeruginosa, staphylococcus albus and on fungus *Aspergillus niger* and compared to streptomycin. Study shows that ethanolic extract among different extracts has more activity against the all bacteria and fungus antimicrobial activity of piper fruit.⁴⁹

Neuroprotective

In the study an experimental glioma model was developed in rats using C6 glioma cells and the effect of PI *Piper longum* Linn. (PI). Was evaluated in the brain tissue of experimental group of rats. From the study, the glioma induced animals showed an increased level of lipid peroxides (LPO), tissue marker enzymes lactate dehydrogenase (LDH), creatine kinase (CK), 5'nucleotidase (5'ND) and acetylcholine esterase (AChE). But PI treatment (20 mg/kg body weight) significantly attenuated these alterations thereby showing potent anticancer effect in glioma induced rats. In addition, the anticarcinogenic effect of *Piper longum* Linn. (PI). PI was confirmed by microscopic analysis and the restoration of increased lipids and protein bound carbohydrates (PBCs) in the brain tissue of glioma induced rats. Hence our results implicate a major role for PI in preventing the cancer development in the experimental glioma model.⁵⁰

Antitussive

The present study is on anti-tussive activity of the macerated extract of *piper longum* churna (powder) by comparison to other marketed preparation as well as reference standard Codeine phosphate using the acetic acid induced cough models in guinea pigs. The standard drug codeine phosphate brought about a reduction of bouts of cough from $15.62 \pm$ to 1.0 ± 0.11 (93.60% inhibition), which was significant compared ($P < 0.01$). The percentage inhibition of bouts of cough for in-house formulation (92.15%) was very significant compared to standard as well as

other marketed preparation .Thus the present study justifies the traditional claims of piper longum Churna In The Treatment Of Cough.⁵¹

Anti Diabetic

The present study was undertaken to evaluate the antihyperglycemic and antihyperlipidemic effects of *Piper longum* root aqueous extract (PlrAqe) in streptozotocin (STZ) induced diabetic rats. Diabetes was induced in male Wister albino rats by intraperitoneal administration of STZ (50 mg/kg.b.w). Fasting blood glucose (FBG) levels were measured by glucose-oxidase & peroxidase reactive strips. Serum biochemical parameters such as glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol were estimated. The activities of liver and kidney functional markers were measured. The statistical analysis of results was carried out using Student t-test and one-way analysis (ANOVA) followed by DMRT. During the short term study the aqueous extract at a dosage of 200 mg/kg.b.w was found to possess significant antidiabetic activity after 6 h of the treatment. The administration of aqueous extract at the same dose for 30 days in STZ induced diabetic rats resulted in a significant decrease in FBG levels with the corrections of diabetic dyslipidemia compared to untreated diabetic rats. There was a significant decrease in the activities of liver and renal functional markers in diabetic treated rats compared to untreated diabetic rats indicating the protective role of the aqueous extract against liver and kidney damage and its non-toxic property⁵²

CNS Depressant

Present study reports CNS depressant and analgesic activities of methanol extract obtained from the leaves of *Piper longum* L (MEPL). CNS depressant activity was evaluated by using open field and hole cross tests at doses of 250 and 500 mg/kg body weigh. In Hole cross test test animals were treated with methanol extract at two doses (250 mg/kg & 500 mg/kg) showed dose dependent reduction in the locomotor activity and at higher dose, it was comparable with that of standard drug diazepam. Open field test was carried out to determine the depressive action of the test drugs on CNS in rats 12. In the test, the extract showed a noticeable decrease in locomotion in the test animals from the second observation period to last study period at both dose levels (250 and 500 mg/kg body weight). The effect observed was increasing with time and a noticeable result was found at 120min of test sample administration.⁵³

Antioxidant activity

Antioxidant activities were evaluated by using In-vitro antioxidant assay models like hosphomolybdenum and reducing power assay. Anti-bacterial activity was evaluated using

streptomycin as a standard against E.coli ATCC (LB M1655) to find MIC value of crude extract. The ethanolic extract showed maximum anti-bacterial activity. The percentage of antioxidant activity by phospho-molybdenum assay was in the order acetone>ethanol> water> petroleum ether. The results obtained in this study showed that the fruits of Piper longum have antioxidative and anti-bacterial properties which provide a basis for the traditional use of the plant. The maximum values of both antioxidative and anti-bacterial activity and was found to be 300 µg/mL (acetone extract) and 200 µg/mL (ethanol extract) respectively.⁵⁴

Bioavailability enhancer

A study on trikatu , a compound ayurvedic formulation in which piper longum i s a main ingredient with other drugs shows that the trikuta increases the bioavailability of these drug ether by promoting rapid absorption from gastrointestinal tract or by protecting the drug from its pass mechanism of liver⁵⁵

Anti asthmatics activity

Studies have shown *piper longum* fruit extract in milk reduced passive cutaneous anaphylaxis in rat and decreases the antigen induced spasm in guinea pigs.⁵⁵

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