

Therapeutic potential of *Piper longum* L. for disease management - a review

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ABSTRACT

Medicinal plants have been used as traditional treatment for numerous human diseases from time immemorial in many parts of the world and herbs are considered as the heart of Indian traditional system of medicine. In today's world of modern medicine where increased resistance of bacteria or virus to antibiotics, adverse effects associated with use of antibiotics and their expensiveness are of a great concern, there is a urge for development of prevention and treatment options that are natural, safe, effective and economical. The search for alternative products continues and natural phytochemicals isolated from plants used as traditional medicines are considered as good alternatives. Plants and their extracts have been used as herbal remedies from many years ago for various health related problems. With the advent of new and innovative transformation technologies like Recombinant DNA technology, metabolomics, proteomics etc opened up new avenues to extend the use of plants for biopharmaceuticals. One such plant is *Piper longum* (commonly called as Pippali (fruit) or Piplamul (root) in hindi) which is highly valued for its medicinal benefits. Pharmacological profile shows that the plant exhibits anti-diabetic and anti-hyperlipidemic, hepatoprotective, neuroprotective, cardioprotective, anti-bacterial, aphrodisiac, relieves respiratory disorders and can be also used as digestive agent. Therefore, the purpose of this review is to present some recent examples from the literature of studies that have served to validate the traditional use of *Piper longum* with specific biological activity.

Keywords: *Piper longum*, piperine, hepatoprotective, anti-cancerous, anti-bacterial, anti-diabetic, neuroprotective.

INTRODUCTION

Plants play a major role in the discovery of new therapeutic agents. They have received a lot of attention during these days for the isolation of biologically active substances for the cure of diseases. Plant based medicinal compounds is long established to be used as traditional treatment for innumerable human diseases from time immemorial in many parts of the world. It is still the primary source of medicine in rural areas of the developing countries [1]. About 80% of the population in developing countries use traditional medicines for their health related problems [2]. Biologically active compounds derived from medicinal plants have been the basis for the development of new chemical leads for the pharmaceutical industry. Evidences shows that out of the 500 000 plant species occurring worldwide, only 1% has been phytochemically investigated, which shows that the medicinal plants has a great potential

for discovering novel bioactive compounds [3]. The urge for plant based herbal compounds as an alternative prevention and treatment method comes from increasing number of health issues as well as the increased resistance gained by pathogenic bacteria to currently used chemotherapeutics, infections in immune-compromised individuals and financial concerns in developing countries [4,5].

Many plant-derived compounds have been used as drugs, either in their original or semi-synthetic form. *Piper longum* or Pipali which was mostly used for household cooking purposes as a spice and as seasoning now is a component of medicine as attested by several studies. It is reported as good remedy for treating gonorrhea, menstrual pain, tuberculosis, sleeping problems, respiratory tract infections, chronic gut-related pain and arthritic conditions [6]. Since a long time *P. longum* has been used to possess immunomodulatory and antitumor activity [7].

Pharmacological and clinical studies have revealed that piperine, a compound isolated from *P. longum* act as CNS depressant, antipyretic, analgesic, anti-inflammatory [8], antioxidant [9], and possess hepatoprotective activities [10]. In addition piperine has also shown to enhance the bioavailability of several drugs, for example sulfadiazine, tetracycline, streptomycin, rifampicin, pyrazinamide, ionized, thambutol, and phenytoin [11]. Considering its significant effect on the bioavailability enhancing capability of drugs, it has potential to be used as an adjuvant with therapeutic drugs in chronic ailments, to reduce the effective dose of the drug intake thus reducing the subsequent adverse effects [12-15].

Plant profile

Piper longum plant is deciduous slender aromatic climber with perennial woody roots or a perennial creeping shrub that belongs to the family Piperaceae.



Piper longum plant

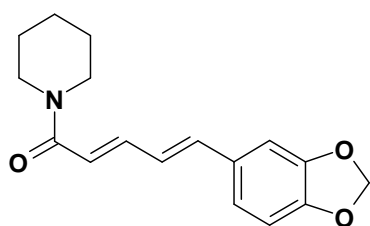


Piper longum seeds

Chemical profile

Long pepper contains aromatic oil, piperine, alkaloids, sesamin and pipalestrol. The roots of this plant contain piperin, pippalartin, piperleguminin, sterols and glycosides, piperlongumine or pipartine and dihydrostigmasterol [21].

The fruits contain 1% volatile oil, resin, alkaloids piperine and piperlonguminine, a waxy alkaloid N-isobutyldeca-trans-2-trans-4-dienamide and a terpenoid substance. The pungency of the fruits is mainly due to the piperidine alkaloid piperine. The fruits also contain calcium, 1230; phosphorous, 190; and iron, 62.1mg/100g [16].



Chemical structure of piperine

Branchlets:

Erect, glabrous with swollen nodes, roots clasping at nodes which help it to attach to the host trees. Leaves arrangement is alternate, shape ovate, apex acute to acuminate with entire margin [16].

Fruits:

Spikes which are long cylindrical, oblong, berries red or black when ripe, globose with aromatic odour and pungent taste [17,18,19]. Plants are monoecious in nature where male and female flowers are borne on different plants. *P. longum* is a native of Indo-Malaya region. It is found growing wild in the tropical rain forests of India, Nepal, Indonesia, Malaysia, Sri Lanka, Timor and Philippines. Indian Long Pepper is mostly derived from the wild plants but 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 and Nicobar Islands [20].

Pharmacological profile- Why the plant may be called as wonder drug?

This plant has gained attention for its therapeutic value in last few years. The ripe fruit of *P. longum* has been widely used as popular medicine to treat a number of diseases some of which are listed below.

Anti-tumor activity

Bezerra *et al.* [22] studied the effect of piperine and pipartine on Sarcoma 180 tumors transplanted in mice where they observed significant reduction of tumor weight in pipartine- and piperine-treated animals. According to Sunila and Kuttan [23], the antitumor activity of piperine is related to its immunomodulatory properties, which involve the activation of cellular and humoral immune responses. The anti-tumor properties of piperine marks it as a potential candidate for future cancer therapy

Anti-diabetic activity

Nabi *et al.* [24] elucidated the anti-hyperglycemic and anti-hyperlipidemic effects of *Piper longum* root aqueous extract (PlrAqe) in streptozotocin (STZ) induced diabetic rats. Their studies envisages that the plant extract is capable of managing hyperglycemia and

complications of diabetes in STZ induced diabetic rats making this plant as one of the potential sources for the isolation of new oral antihypoglycemic agents.

Cardioprotective

Chauhan *et al.* [25] observed the cardioprotective effect of methanolic extract of *P. longum* (MePI) in a rat model having acute myocardial infarction, induced by Isoproterenol. The MePI extract used was in crude form and likely to contain compounds such as alkaloids and amides, lignans, esters and volatile oil. They propounded that MePI significantly prevents the damage induced by Isoproterenol on histopathological and biochemical changes in rat model of myocardial infarction.

Hepatoprotective activity

Gurumurthy *et al.* [10] experimented with aqueous extract of fruits of *P. longum* and piperine were chosen to study their hepatoprotective potential on administration with normal doses of anti-tubercular drugs. *P. longum* and piperine on administration with the anti TB drugs lowered the rate of lipid peroxidation and also increased the reduced glutathione levels and thus exhibits hepatoprotective effect.

Anti-apoptosis and antioxidant

Yadav *et al.* [26] illustrated the anti-apoptosis and antioxidant activity of *P. longum* through TUNEL ASSAY and Radical scavenger activity (DPPH ASSAY). They evaluated the effect of hexane:ethanol (2:8) *P. longum* extract on GM-induced hair cell loss in basal, middle and apical regions in a neonatal cochlea cultures. An anti-apoptosis effect and potent radical scavenger activity of subfraction PL extract protects from GM-induced hair cell loss at basal, middle and apical regions in neonatal cochlea cultures.

Anti-snake venom activity

Shenoy *et al.* [27] propounded the anti-snake venom activities of ethanolic extract of fruits of *Piper longum* L. (Piperaceae) and piperine against Russell's viper venom in embryonated 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.

Anti-stress activity

Srikanth and Venkatesh [28] evaluated the anti-stress activity of aqueous extract of *P. longum* in stress rat models. With this evidence stress-induced memory loss was found to be reversed by aqueous extract of *P. longum*. Treatment with *P. longum* decreased the latent period indicating extract-produced nootropic activity.

Anti-microbial

Abbas Ali *et al.* [29] tested the antibacterial and antifungal activity of various solvent extract of *P. longum* against a variety of pathogenic bacteria and fungi respectively. According to Singh and Rai [30], *P. longum* can be promising source of antimicrobial agents where it could be used against certain antibiotic resistant specific bacteria, besides their use as traditional spice.

Anti-inflammatory and Anti-arthritis activity

According to Stohr *et al.* [31] *Piper* extracts and piperine possess inhibitory activities on prostaglandin and leukotrienes COX-1 inhibitory effect and thus exhibit anti-inflammatory activity. On the other hand Yende *et al.*, [32] studied anti-arthritis effect of *P. longum* in CFA (Complete Freund's adjuvant) induced arthritis in rats where they illustrated that the aqueous extract of *P. longum* has the capability to significantly reduce the swelling of the paws which may be attributed to the immunomodulatory activity exhibited by piperine [23].

Protective myocardial activity

Studies conducted by Mishra in 2010 [33], elucidated Piper aldehyde is one of the important constituent of *P. longum* L which was isolated from the fruits of the *P. longum* by extracting it with methanol as solvent. Studies conducted revealed that the alcoholic extract and piper aldehyde shows significant DPPH scavenging activity and exert protective effect in the myocardial narcotic rats. They activity protected myocardium from the harmful effects of lipid per oxidation and even maintained the glutathione levels to normal. Hence it can be concluded that the alcoholic extract as well as piper aldehyde are useful in exerting protective activity in case of myocardial ischemia is treated animals.

Anti-fertility activity

Studies conducted by Lakhmi *et al.* [34] elucidated that the hexane fraction of *P. longum* has potent anti-implantation activity accompanied by the mortality of animals. *P. longum* roots when used along with *Embelia ribes* seeds showed 100% anti-fertility activity in female albino rats as also mentioned by Garg in 1981 [35]. It is believed that *P. longum* probably 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 Garbhanivarana Aushadham used for both female and male [36] without interfering with the activity of ovarian hormones on uterus [37].

Other medicinal applications

Therapeutic agent for Alzheimer disease

Studies conducted by Jeon *et al.* [38] revealed that a mix of piperlonguminine and dihydropiperlonguminine can considerably control the expression of APP (Amyloid Precursor Protein). When the production of this protein is controlled it is helpful for patients with Alzheimer's disease.

Respiratory disorders

For centuries this spice is used as a medicine to cure diseases related to the lungs and respiratory system. An extract of the fruits in milk reduced passive cutaneous anaphylaxis in rats and protected guinea pigs against antigen-induced bronchospasm [39, 40].

Bioavailability enhancement

Bioavailability is the rate and extent to which a therapeutically active substance enters systemic circulation and becomes available at the required site of action. Intravenous drugs attain maximum bioavailability, while oral administration yields a reduced percentage due to incomplete drug absorption and first-pass metabolism [41]. Piperine was found 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 [42,43,44]. Mechanism worked out behind the logic was piperine might be inducing alterations in membrane dynamics and permeation characteristics, along with induction in the synthesis of proteins associated with cytoskeletal function, resulting in an increase in the small intestine absorptive surface, thus assisting efficient permeation through the epithelial barrier [45, 46].

CONCLUSION

Every antibiotic has a certain life span regarding its efficacy and their prolonged usage is may be harmful in one or the other way. Therefore scientists are relying more on natural products synthesised from medicinal plants to serve as alternate source of medicine for combating and alleviating various disorders in human beings and that too without any or much less negative effect on a lower price. *P. longum* whose ethnobotanical importance has been realised long back, now is one of the active ingredients of modern medicines as evidences by cited studies with its wider application against various diseases.

From the points discussed above we can conclude that plant derived herbal extracts are an effective alternative for disease management therefore may be considered as one of the potential sources for isolation of new therapeutic agents with relatively less or no side effects as compared to other therapeutic agents.

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