



**Review Article**

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## Review on Anti-tumor activity, Immunomodulatory and neuromodulatory properties of *Piper longum* Linn

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### ABSTRACT

In ancient times, people were very keen on using natural plant products as a potential drug for its hepatoprotective, respiratory protective neuroprotective, and cardio-protective activities. However, in today's advanced world of medicine use of ayurvedic medicine is replaced by allopathic medicine and antibiotic-resistant bacteria, untreatable viruses, and other great concerns have been aroused. Now there is an emerging need for alternatives that are typically safe, natural, and cost-effective. In this context, this review aimed to offer essential data focusing on the traditional use, phytochemistry, and pharmacological profile of *Piper longum* thereby identifying research gaps and future opportunities for investigation on this plant. In the current review, we discussed the medicinal effects of *Piper longum* on the different sections of the human body. The finding showed that it is rich in many phytochemicals mainly piperine and piperlongumine. And this particular herb's therapeutic potential can be utilized as the primary medicine for curing diseases related to the respiratory, immune, digestive, and cardiovascular systems. Additionally, the therapeutic potential of this herb can be utilized to suppress the growth of cancerous cells. In most of the studies conducted in different in-vitro and in-vivo models, the above-mentioned herb was found nontoxic and suited for the treatment of various diseases. Further, due to its low economical cost and easy availability, it is considered a suitable medicinal herb. Moreover, plant-based therapy can be used as an excellent.

**Keywords:** *Piper longum*, Antitumor, Immunomodulatory, Cardioprotective, Antilarvacidal.

### INTRODUCTION

Our diverse planet is enriched with a hefty number of therapeutic plants that are used to augment the immunity of human beings. In India, numerous medicinal plants are nurturing due to favorable climatic conditions and seasons. However, therapeutically only a few medicinal plants and their phytochemical extract are evaluated so far. Natural components have seen a wide range of suitability for the anticipation and treatment of diseases throughout history. In developing countries, approximately 80% population is dependent on the use of traditional medicines for their health-related problems [1]. The *Piper longum* Linn is also called Indian Long Pepper (Pippali) because of its geographical distribution. It is a flowering plant present in the family Piperaceae cultivated for its fruit production and used as a spice in Indian food [2]. Medically, *Piper longum*'s (*P. longum*) fruit and its main phytochemical component piperine was potentially exhibited for Immunomodulatory and antitumor activity. According to Ayurveda's book Dhanvantari Nighantu, it has several Sanskrit synonyms that express its characteristics such as Sana – pungent, Capala – quickly acting, Magadhi – geographical location *P. longum* is used in various ayurvedic preparations such as 'Trikatu' [3]. It is an element of numerous ayurvedic medicine as stated in the ancient ayurvedic texts like Charaka Samhita [4], Susruta Samhita [5], (Vagbhata's Astanga hrdayam [6]. Being a component of ayurvedic medicines it is used to cure diseases like leprosy, tuberculosis, cardiac, spleen disorders, and chronic-fever. The *P. longum*'s fruit and root are commonly used portions for medicinal purposes however, other parts such as leaf and stem are also used, but information regarding their use is scarce [7]. This plant is inexpensive, readily available, and effective for many diseases. It has medicinal properties due to its antioxidant, anti-inflammatory, hepatoprotective, immunomodulatory, anti-microbial, anti-hyperlipidemic, antidepressant, and cardioprotective action [2,8,9,10]. Some other therapeutic characteristics of this herb are analgesic and diuretic action and its role in lessening muscle tension and mitigation of anxiety [11]. The goal of this article is to highlight the therapeutic potential of *P. longum* plant and create interest among researchers to study this plant. In this review, we comprehensively mentioned the effect of *P. longum* and its active ingredients on the different body systems of humans.

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## Phytochemical constituents of medicinal plants

Globally medicinal plants are contributing to health services and playing an important role as the source of medicine [12]. The medicinal properties of the plants exist in their chemical components or phytochemicals. Plants are rich with several compounds such as alkaloids, tannins, and phenolic compounds [13]. In the case of *P. longum*, a total of 159 phytochemicals grouped into 26 different classes were identified by using computational biology [14]. Some important classes of chemicals are alkaloids, flavonoids, phenols, gums, and saponins recognized by standard chemical tests. Among all phytochemicals, alkaloids are the most prevalent chemicals as reported by qualitative and quantitative analyses of *P. longum* by UHPLC-DAD-MS [15]. Mainly fruit and roots are used for medicinal purposes however few studies also showed the use of stem and leaves. Dried ripe fruit is rich with medicinal phytochemicals such as volatile oil, resin, alkaloids such as piperine, piperlonguminine, and so on. Piperine alkaloid is responsible for its characteristic pungent taste. Another important medicinal part is the root; chemically it is also rich in piperine, piperlongumine, and dihydro stigmasterol [16]. Piperine being a constituent of both root and fruit is the most abundant alkaloid [17]. It has the potential to maintain redox homeostasis and suppresses tumor development and angiogenesis [18]. Another plentiful phytochemical is a phenolic compound that has antioxidant properties [19]. The antioxidant property of this plant could be utilized for the preparation of antioxidant-based medicine for the treatment of diseases that occurred due to oxidative stress such as atherosclerosis, stroke, diabetes, Alzheimer's disease, and cancer [20].

## Effect of *P. longum* on various body systems in the human

### Immune System

The immune system protects the host through various layers of defense and response. Among them, inflammation is the paramount reaction to infection which involves the pathogenesis of numerous inflammatory diseases. So, the main preventive mechanism of any drug depends on its anti-inflammatory action. Inflammation is a complex process interconnected by a web of various adhesion molecules, cytokines, and signaling pathways. Further, anti-inflammatory effects can be exerted at the transcriptional level by inhibiting the expression of genes involved in the production of inflammatory cytokines and cell molecules [21,22]. Like Hexane and chloroform extraction of this herb suppress the inflammation by indirectly inhibiting expression of TNF-alpha induced ICAM-1 mRNA in human umbilical vein endothelial cells and also hampered the adhesion of neutrophils to cells [23]. In a similar study, [24], observed the inhibitory action of piper extract and piperine against the prostaglandin and leukotriene inflammatory molecules. Moreover, dried fruit oil also shows beneficial effects in the treatment of rat edema [25]. Another mechanism that helps in the progression of the disease is the production of reactive oxygen species [26]. In this situation, the herb's antioxidant property could be utilized to suppress the progression of the disease. Regarding this, piperine's antioxidant action is already established in the *in-vitro* system. It acts as a dominant superoxide scavenger inhibiting lipid peroxidation up to 52%, which proved piperine's antioxidant activity against free radicals. However, it shows dose-dependent action, at low concentration, it acts as a hydroxyl radical scavenger, but at higher concentrations, it leads to the generation of hydroxyl radicals [27]. In a recent study, a subnetwork

of immune pathways regulated by *P. longum* has been designed. It was discovered that 106 phytochemicals out of 159 regulate the 19 human immune pathways *via* 131 proteins [14]. The anti-inflammatory effect of this herb in the *in vivo* rat cerebral ischemia model is also established. The concluding result shows that the dichloromethane fraction of the herb downregulates the expression of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  and accelerates the superoxide dismutase activity [28]. It also inhibits cell-mediated immunity by decreasing thymus and cell signaling molecule NF-Kb at the transcriptional level. Piperlongumine also acts as an immunosuppressant by inhibiting human T cells. This effect is exerted by increasing the level of ROS and decreasing glutathione manifest the cell-dependent mechanism of action of piperlongumine [29].

### Respiratory System

*P. longum* fruit acts as a potent booster for the respiratory systems and shows a revitalizing effect on the lungs. The decoction of immature fruit and root has been successfully used for chronic bronchitis, cold, and cough [30]. Previously reported *in vivo* study shows that piperine inhibits eosinophil infiltration and airway hyperresponsiveness in ovalbumin-induced asthma mice model by quashing the immune system [31]. Likewise, a clinical study also revealed the effectiveness of this plant in the treatment of bronchial asthma in children [32]. Further effects of petroleum ether and an alcoholic decoction of the fruit of *P. longum* in the guinea pig ileum-culture (*in vitro* model) and bronchospasm-induced guinea pig (*in vivo* model) have been studied. The result shows that this decoction inhibits the histamine-induced contraction and also improves bronchospasm condition by decreasing induced WBCs number [33]. Fruit extract's role in reducing passive cutaneous anaphylaxis in rats and guinea pigs against antigen-induced bronchospasm is also reported [34]. Similarly, piperlongumine is also helpful in the treatment of chronic obstructive pulmonary disease induced by cigarette smoking in mice. It reduces lung inflammation, decreases the expression of NF-KB and neutrophil elastase [35].

### Nervous System

Numerous studies show the influential effect of this herb as a neuromodulator in improving brain function and in the treatment of some neurological illnesses such as Parkinson's and Alzheimer's disease. The earlier study established the anti-depression like the action of this herb in the animal model [36]. This is further supported by an *in-vitro* study in which the treatment of methanolic extract of the fruit improves memory performance and repaired the memory [37]. Similarly, the aqueous extract of this herb reverses the stress-induced memory loss in the rat model [38]. Thus the *P. longum* fruit can be used as a pharmacotherapeutic candidate against depression. In a recent study, [14], evaluated the effect of *P. longum* phytochemicals on human proteomics by the computational method and found 434 target proteins in the nervous system involves in the signaling transmission and developmental pathway. Additionally, its neuromodulatory action for the treatment of nervous system diseases and mental disorders was tested using the PC-PT-DA network. Results show that 384 protein targets, out of these 215 are FDA-approved protein targets for neurological diseases as listed in Drugbank [40]. The use of a mixture of piperlongumine and dihydro piperlongumine alters the expression of the amyloid precursor protein, which is helpful for Alzheimer's patients [41]. Likewise, piperine and piperlongumine alkaloids also showed neuroprotective effects in Parkinson's mice model by increasing

glutathione levels and decreasing lipid peroxidation [42]. Moreover, ethanol extraction of fruit is rich with piperidine and piperine alkaloids, which inhibits the monoamine oxidase [43]. Another hurdle in the treatment of brain disease is the blood-brain barrier (BBB) which obstructs the drug entry into the brain [44]. Concerning this brain permeability potential of major pharmaceutical ingredients such as piperine, piperlongumine and pellitorine were evaluated by HPLC-LTQ-Orbitrap MS. Results conclude that piperine could enter the brain through the BBB that further makes it, a potential drug for neurological illness [45]. Piperlongumine improves the cognitive function in a murine model in a dose-dependent manner by deacetylase the sirtuin gene and decreasing amyloid precursor protein [46].

#### Digestive System

This herb has the potential to improve the digestive system by improving liver condition, inhibiting the growth of harmful microorganisms, and improving digestion. It also controls metabolic diseases such as diabetes. *In vivo* results show that *P. longum* aqueous extract improves the condition of streptozotocin-induced diabetic rats with anti-hyperglycemic and anti-hyperlipidemic activity [47]. Additionally, the ethanolic extract of herb and pure piperine compound shows up to 90% inhibitory activity against *Entamoeba histolytica* in the rat [48]. Its piperine extract has a hepatoprotective function, improves the carbon tetrachloride-induced hepatotoxicity in the *in vivo* model, and also reduces lipid peroxidation in both *in vitro* and *in vivo* conditions [49]. The most important phytochemical piperine was found to protect against tertiary butyl hydroperoxide and carbon tetrachloride-induced hepatotoxicity by reducing lipid peroxidation by *in vitro* and *in vivo* methods [50]. Piperine suppresses the gastric mucosa damage in a dose-dependent manner by inhibiting gastric juice and gastric acidity [51]. In another study, *P. longum* fruit extract shows hepatoprotective activity in metal-induced mice model indicted by alternation in serum enzymes. Verma and coworkers [52], used the plant's fruit extract in a hyperlipidemic model of rats and, found a decrease in cholesterol, phospholipid, and triglyceride level. Its beneficial effects are not only limited to fruit but its leaf extract also protects the liver against carbon tetrachloride toxicity in rats [53]. In a previous study, piperine's beneficial effect was also observed in the pancreas of the mice where piperine administration improved pancreatic weight (PW) to body weight (BW) ratio and increased digestive enzyme production [54]. Piperine also involves in the absorption of nutrients by forming complexes with xenobiotics and nutrients that aid them to cross plasma membranes [55]. Likewise, it also modulates intestinal membrane permeability by changing epithelial cell dynamics [56].

#### Reproductive System

So far only a few studies have been conducted to evaluate the effect of *P. longum* on the reproductive system. A previous study showed that *P. longum* has anti-fertility action as its roots extract along with the *Emelia ribes* seeds produced the anti-fertile female rat [57]. Further, it also has the anti-implantation activity as observed during animal studies by Lakshmi and co-workers [58]. On the positive side, this herb's root extract could help in birth complications by expulsing the placenta [59]. Though the mechanism of action is not clear, it is believed that it interferes with female hormones.

#### Cardiovascular System

This herb prevents cardiovascular damage by acting as an antioxidant drug. The antioxidant effect of methanolic extract of fruit was established in the Wistar rat model where adriamycin-induced cardiotoxicity was reduced with the pretreatment of *P. longum* extract [60]. In another related study, the treatment of isoproterenol-damaged rats by methanolic extract of herb decreases the chance of myocardial infarction [61]. Not only methanolic extract but piper aldehyde extract of fruit also has antioxidant potential, protects from lipid peroxidation, and maintains glutathione level to normal in the myocardial necrotic suffering rat [62].

#### Anti-tumor

Uncontrolled growth of the cells forms the tumor, which progresses through angiogenesis and invades the nearby organs subsequently leading to the formation of cancer. In the progression of cancer, numerous genes and signaling molecules are involved such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hypoxia-inducible factors, platelet-derived growth factors, angiopoietin-1 and 2, and matrix metalloproteinases [63]. Therefore, suppression of angiogenesis at the early stage can prevent the formation of cancer [64]. The preceding study demonstrated that the most active chemical compound piperine inhibits tumor growth and metastasis by diminishing PMA-induced COX-2 expression at the transcriptional level in the *in-vitro* and *in-vivo* model of breast cancer. Significantly, it also reduced the COX-2 promoter-driven luciferase activity by obstructing nuclear factor- $\kappa$ B (NF- $\kappa$ B) and activator protein-1 (AP-1) mediating signaling in a dose-dependent manner [65]. A recent study showed that piper longumine compounds hamper the activity of Glutathione S-transferase pi 1 (GSTP1) by its antioxidant property. GSTP1 is one of the overexpressing proteins in cancerous cells and helps in the proliferation of cells however it is suppressed by reactive olefins containing the active compound of piperine which blocks the active site of cancer cells [66]. This is supported by piperine's anti-cancerous action in sarcoma tumor transplanted mice along with piperlongumine amide compounds. Both these compounds activate the cellular and humoral immune response and significantly reduce the tumor weight in mice [67]. Likewise, alcoholic extract of *P. longum* fruit and pure piperine was used which increased the life span of mice suffering from solid tumors through modulation of the immune system [68]. Also, *in vitro* studies have shown the role of piperine in relieving oxidative stress by quenching free radicals and reactive oxygen species. This is contradicted by a previous study in intestinal cancer cells in which piperlongumine increased the production of ROS leading to oxidative stress and nuclear fragmentation which ultimately cause cell death [69]. From this study, the variable effect of *P. longum*'s extract on cancer cells was established. For a long time, *P. longum* has been used to possess immunomodulatory and antitumor activity [70].

#### Antimicrobial and larvicidal activity

The antimicrobial effect of extract of *P. longum*'s different portion is reported in the *in vitro* conditions. However, their efficacy against bacterial class varies such as root extract is more effective against *Staphylococcus aureus* (*S. aureus*) while both stem and leaf extract showed mild to moderate antimicrobial activity against all

tested bacteria such as gram-negative klebsiella species and others *Shigella boydii*, *S. aureus*, *Sorana lutea*. whereas among all phytochemicals' ethyl extract was more effective [71]. Similarly, pure piperine and piperlongumine extract were tested and found highly effective against *S. aureus* and *Bacillus subtilis* [72]. In another study, *P. longum* leaves were used against various bacterial species in a dose-dependent manner and found significantly effective against *S. aureus* and *Salmonella typhi*. All these investigations established the antimicrobial activity of different portions of the herb against numerous bacteria [73]. However, further specific studies are needed to better evaluate the potential effectiveness of the crude extracts as the

antimicrobial agent. *P. longum* has not only antimicrobial properties but also larvicidal and ovicidal properties. Its leaf larvicidal effect was observed against larvae of diseases causing mosquitoes. The result showed significant mortality in *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus*. The aqueous extract of *P. longum* (PLWE) showed the highest larval mortality on 24 h post-treatment and it also shows Ovicidal activity after 48 h post-treatment. It was causing larval death by altering the midgut epithelium. Although a detailed study is required to establish the mechanism of action of larvicidal activity of plant extract [74].

**Table 1:** In-vivo studies for components, models and various outcomes of *Piper. Longum L.*

S.No.	Compound	Model	Outcome	Reference
1.	Piperine & piperlongumine	Sarcoma tumor transplanted mice	Reduction of tumor weight	Bezerra <i>et al.</i> , 2006
2.	root aqueous extract	Streptozotocin induced diabetic rats	Anti-hyperglycemic & anti-hyperlipidemic effect	Nabi <i>et al.</i> , 2013
3.	Methanolic extract of root	Rat (damage induced by isoproterenol)	Prevent myocardial infarction	Chauhan <i>et al.</i> , 2010
4.	Alkaloids extract	MPTP-induced mouse model	Increased ROS decrease lipid peroxidation	
5.	Methanol extract of fruit	Adrimycin induced cardiotoxicity mice model	Reduced cardiotoxicity by antioxidant activity	Wakade <i>et al.</i> , 2008
6.	Piperlongumine	Stress triggered mice	Induce stress resistance	Yadav <i>et al.</i> , 2015
7.	Alcoholic extract of fruit	Mice with tumors	Inhibit growth of solid tumor and induced life-span of mice	Sunila and kuttan 2005
8.	Leaf extract	Rat with liver fibrosis	Hepatoprotective	Young <i>et al.</i> , 2007
9.	Piperlongumine from fruit	Xenograft mouse model	Inhibit tumor growth and decreased PCNA and Ki-67 gene expression	Wang <i>et al.</i> , 2015

**Table 2:** In-vitro studies for components, models and various outcomes of *Piper longum L.*

S. No.	Compound	Model	Outcome	Reference
1.	Hexane-ethanol extract	Neonatal cochlea culture	AntiApoptotic effect on cells	Yadav <i>et al.</i> , 2014
2.	Hexane -ethanol and chloroform extract	Human Umbilical vein endothelial cells (HUVEC)	Decreased TNF-alpha induced ICAM-expression	Kumar <i>et al.</i> , 2018
3.	Piperlongumine	Pancreatic cell line	Inhibition of proliferation of cells and expression of c-myc, vegf, survivin and cyclin D1	Wang <i>et al.</i> , 2016
4.	PIPERINE	HUVEC	Inhibit angiogenesis	
5.	Decoction of fruit	Guinea pig ileum culture	Inhibit histamine induced contraction	Kaushik <i>et al.</i> , 2012
6.	Piperine	Murine macrophages cells	Downregulation of NF-kappa B and AP-1 signaling pathway	Kim <i>et al.</i> , 2012

## CONCLUSION

*Artavakshaya* (oligo-hypomenorrhoea) is a clinical condition Indian heritage Ayurveda is the treasure of medical science consisting of several hidden gifts of nature. One of its gifts is *P. longum* used in numerous ayurvedic formulations. Though, the multi-targeting potential of this herb and the underlying mechanism of its cellular-level action are still unexplored. In the present review, we reviewed the medicinal effects of *P. longum* on different systems of the body. This review will open a new avenue for the researchers and provide insights to look upon the unseen therapeutic potential of this herb. Plant-based therapy is marketed due to its low cost and easy availability.

Furthermore, the plant appears to be nontoxic, in most of the studies. Therefore, in summary, we conclude that this plant is safe and

effective for use in various diseases. These outcomes suggest that *Piper longum* extracts or its phytochemical element can be used as a dietary supplement for the prevention of many diseases.

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### Conflict of Interest

None declared.

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