REVIEW ARTICLE

Pharmacological Properties and Therapeutic Applications of *Piper longum*

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Publication history: Received on 2nd Mar 2025; Revised on 15th March 2025; Accepted on 16th March 2025

Article DOI: 10.69613/4mr0fh52

Abstract: *Piper longum*, commonly known as long pepper, holds significant importance in traditional medicine systems across Asia. The plant contains various bioactive compounds including piperine, pipermundine, sylvatine, and piperlongumine, which is responsible for its pharmacological activities. Recent studies reveal its potent anti-inflammatory effects through modulation of cytokine production, prostaglandin synthesis inhibition, and NF-κB signaling pathway regulation. It also exhibits antioxidant properties by free radical scavenging and improvement of endogenous enzymatic defenses, contributing to neuroprotection and cardiovascular health. Its antimicrobial attributes demonstrate efficacy against various bacterial and fungal pathogens, while hepatoprotective and antidiabetic effects occur through regulation of hepatic detoxification pathways, insulin sensitivity, and lipid metabolism. Moreover, piperlongumine exhibits selective anticancer properties by inducing oxidative stress specifically in cancer cells while sparing healthy cells. The plant also functions as a bioenhancer, improving therapeutic efficacy and drug absorption. Modern analytical techniques have identified over 275 lignans, including novel compounds with unique structural scaffolds. The plant's constituents show promise in treating various conditions including arthritis, inflammatory bowel disease, and neurological disorders. The aim of this review is to present the current literature available on the uses and therapeutic applications of *Piper longum*.

Keywords: *Piper longum*; Piperine; Anti-inflammatory; Bioenhancer; Traditional medicine.

1. Introduction

Piper longum L. (Piperaceae), an important medicinal plant extensively used in Ayurvedic and traditional Chinese medicine systems, has garnered significant scientific attention for its therapeutic potential [1]. The plant, particularly its dried fruit spikes, contains diverse bioactive compounds that contribute to its pharmacological properties [2]. Native to the Indo-Malaya region, *P. longum* grows predominantly in limestone-rich soils with high humidity and has adapted to various geographical locations including India, Nepal, Indonesia, Malaysia, and Sri Lanka [3]. The plant's historical significance spans centuries, with documented medicinal applications in ancient texts for treating respiratory ailments, digestive disorders, and inflammatory conditions [4]. Modern scientific investigations have validated many of these traditional uses, identifying key bioactive constituents such as piperine, piperlongumine, and various lignans that exhibit therapeutic effects [5]. *P. longum* belongs to the family Piperaceae, order Piperales, and class Magnoliopsida. The species represents one of the economically significant members of the genus Piper, which comprises over 2000 species worldwide [6]. The fruit spikes, the primary medicinal part, exhibit variations in size, with the large variety measuring 2-5 cm in length and 0.4-0.5 cm in diameter, while the small variety ranges from 1.0-1.9 cm in length and 0.2-0.3 cm in diameter. The spikes possess a characteristic aromatic odor and display a hot, sweet taste profile [7].

Figure 1. Leaves and fruit spikes of *Piper longum*

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2. Phytochemical Composition

2.1. Major Chemical Constituents

Gas chromatography-mass spectrometry (GC-MS) analyses provides composition of both leaf and fruit volatiles, identifying and quantifying 53 distinct compounds. In the leaf tissue, the predominant compounds include e-nerolidol, comprising 19.56% of the total volatile composition, contributing to the plant's aromatic properties and potential therapeutic effects. β-pinene represents 17.07% of volatile constituents, known for its antimicrobial and anti-inflammatory properties. α-pinene constitutes 6.8% of the volatile fraction, recognized for its potential therapeutic applications.

Table 1. Major Chemical Constituents of *Piper longum* L.

Class of Compounds	Major Components	Plant Part	Percentage (%)
Alkaloids	Piperine	Fruit	3-5
	Piperlongumine	Fruit	0.2-0.4
	Piperidine	Root	0.1-0.3
Essential Oils	β-caryophyllene	Fruit	8.20
	Germacrene-D	Fruit	23.38
	e-nerolidol	Leaf	19.56
	β-pinene	Leaf	17.07
Lignans	Sesamin	Fruit	0.4-0.7
	Pluviatilol	Root	0.2-0.4
Fatty acids	Palmitic acid	Fruit	1.2-2.1
	Linoleic acid	Fruit	0.8-1.5

The fruit contains germacrene-D as the primary component at 23.38%, known for its antimicrobial and insecticidal properties. 8-heptadecene represents 8.95% of the volatile fraction, while β-caryophyllene accounts for 8.20%, recognized for its anti-inflammatory and analgesic properties. These differences in chemical composition between plant parts suggest tissue-specific biosynthetic pathways and potentially distinct therapeutic applications [8].

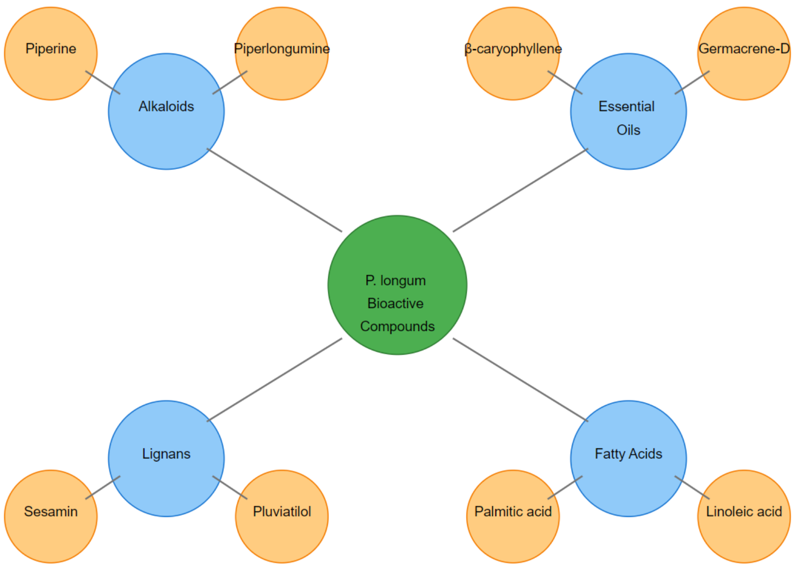

Figure 2. Major bioactive compounds in *P. longum*

2.2. Lignans

P. longum contains an extensive array of at least 275 identified lignans, representing one of the most diverse lignan profiles known in medicinal plants. These compounds can be categorized into several distinct structural classes. Conventional lignans are characterized by traditional 8,8'-linked structures, formed through oxidative coupling of phenylpropanoid units, and demonstrate various biological activities. Neolignans are characterized by unique coupling patterns, show structural diversity in carbon-carbon bonds, and exhibit distinct pharmacological properties.

Oxyneolignans contain additional oxygen functionalities, display enhanced polarity and bioavailability, and contribute to antioxidant properties. Norlignans feature modified carbon frameworks, demonstrate unique structural characteristics, and show specialized biological activities. Secolignans contain cleaved structural elements, present modified ring systems, and exhibit distinct pharmacological profiles. Polyneolignans possess complex structures with multiple neolignan units, show advanced structural organization, and demonstrate enhanced biological activities. [9]

3. Pharmacological activities

3.1. Antioxidant activity

Piper longum shows substantial antioxidant activity, particularly through its fruit volatile compounds. Analysis using multiple assay systems have revealed the plant's robust free radical scavenging activity. The antioxidant capacity, systematically evaluated through both DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assays, demonstrates significantly higher activity in fruit extracts compared to leaf extracts. This differential activity suggests tissue-specific accumulation of antioxidant compounds and potentially distinct therapeutic applications [10].

Table 2. Pharmacological Activities of Different Extracts of *P. longum*

Extract Type	Biological Activity	Test Model	Effective Concentration
Ethanol Extract	Antimicrobial	*In vitro*	250-500 μg/mL
	Antioxidant	DPPH assay	IC50: 52.4 μg/mL
	Anti-inflammatory	Carrageenan-induced edema	200-400 mg/kg
Aqueous Extract	Immunomodulatory	*In vivo*	100-200 mg/kg
	Hepatoprotective	CCl4-induced toxicity	300-500 mg/kg
Essential Oil	Larvicidal	Aedes aegypti	LC50: 65.8 ppm
Methanol Extract	Anticancer	MCF-7 cell line	IC50: 35.5 μg/mL
	Antidiabetic	STZ-induced diabetes	250-500 mg/kg

3.2. Anti-inflammatory and Antinociceptive Effects

P. longum exhibits significant anti-inflammatory activity through multiple sophisticated mechanisms. Detailed studies utilizing dimethylbenzene-induced ear vasodilatation and acetic acid-induced capillary permeability models have demonstrated the extract's remarkable ability to reduce inflammatory responses. The essential oil components play crucial roles in these anti-inflammatory properties, with β-Selinene (7.38%), aromadendrene (5.30%), and β-elemene (5.22%) being key contributors. These compounds work synergistically to modulate inflammatory pathways and reduce inflammation markers.

The plant also shows significant peripheral antinociceptive effects, particularly evident in inflammatory pain models. These effects are attributed to the complex interaction between various bioactive compounds present in the plant, suggesting multiple mechanisms of action in pain modulation [11, 12].

3.3. Antimicrobial Activities

3.3.1. Antibacterial Properties

P. longum exhibits impressive broad-spectrum antibacterial activity, with particularly noteworthy effectiveness against clinically significant pathogens such as Klebsiella pneumoniae and Acinetobacter baumannii. The fruit volatiles consistently demonstrate enhanced antimicrobial properties compared to leaf extracts, suggesting concentrated accumulation of antimicrobial compounds in the fruit tissue. This differential activity provides important insights for therapeutic applications and extract standardization [13].

3.3.2. Antifungal Effects

Recent studies have revealed significant antifungal activity against both non-MDR (Multi-Drug Resistant) and multidrug-resistant fungal isolates. This broad-spectrum antifungal activity suggests promising potential applications in treating resistant fungal infections, particularly in clinical settings where conventional antifungal agents may prove ineffective [14].

3.4. Anticancer Properties

Piperlongumine, a principal alkaloid isolated from *P. longum*, demonstrates remarkable anticancer effects, particularly in breast cancer treatment. The compound exhibits sophisticated mechanisms of action, working synergistically with conventional chemotherapeutic agents such as doxorubicin, thereby enhancing treatment efficacy. Studies have revealed that piperlongumine selectively induces oxidative stress in cancer cells while demonstrating minimal effects on normal cells, suggesting a favorable therapeutic window for clinical applications [15, 16].

3.5. Neuroprotective Effects

The alkaloid constituents of *P. longum* demonstrate significant neuroprotective properties through multiple mechanisms. Advanced metabolomic studies have identified various bioactive metabolites related to Δα, β-dihydropiperlonguminine, piperine, piperanine, and piperlonguminine. These compounds contribute to neuroprotection through various pathways, including antioxidant effects, neurotransmitter modulation, and cellular protection mechanisms [17].

3.6. Antiplatelet Activity

Four specific acidamides isolated from *P. longum* fruits have demonstrated significant antiplatelet properties. These compounds - piperine, pipernonaline, piperoctadecalidine, and piperlonguminine - exhibit dose-dependent inhibitory effects on platelet aggregation. Their activity is particularly notable against various platelet activation stimuli, including collagen, arachidonic acid, and platelet-activating factor. This multi-target approach to platelet aggregation inhibition suggests potential therapeutic applications in cardiovascular health [18].

3.7. Bioenhancement

Piperine can act as highly effective bioenhancer, significantly improving both the bioavailability and therapeutic efficacy of various pharmaceutical compounds. The bioenhancement properties operate through several key mechanisms including thermogenic and bioenergetic effects that enhance drug absorption, modification of membrane dynamics to facilitate better drug permeation, inhibition of drug-metabolizing enzymes, particularly in the liver, enhancement of blood supply to the gastrointestinal tract, and reduction of first-pass metabolism of co-administered drugs [19].

These properties have profound implications for drug development and delivery systems, offering potential solutions to bioavailability challenges in pharmaceutical formulations. The ability to enhance drug absorption and effectiveness could lead to reduced dosage requirements, potentially minimizing side effects while maintaining therapeutic efficacy. This characteristic is particularly valuable in the development of new drug delivery systems and the optimization of existing therapeutic regimens [20].

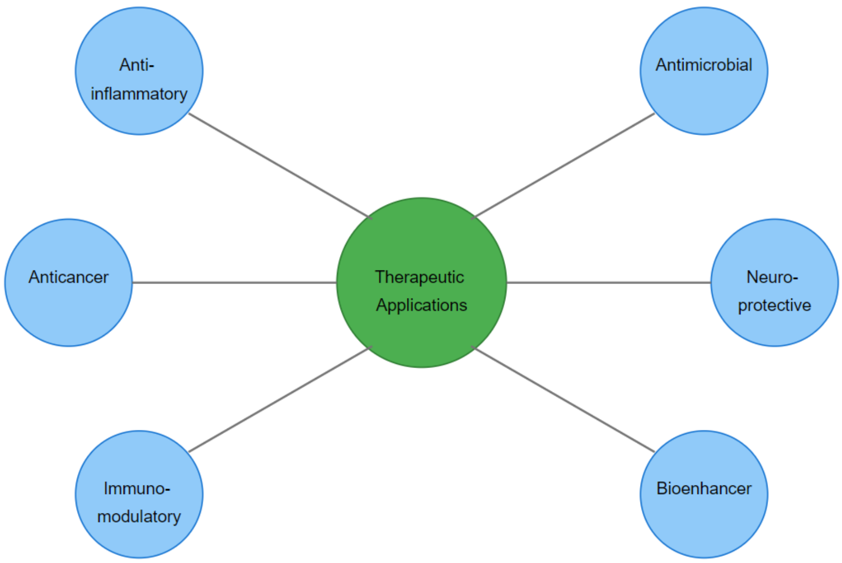

Figure 3. Therapeutic applications of *P. longum*

4. Molecular Mechanisms and Genomic Studies

4.1. Transcriptome Analysis

Recent advanced de novo transcriptome profiling has revealed unprecedented insights into the molecular complexity of *Piper longum*. The identification of 173,381 high-quality transcripts represents a significant breakthrough in understanding the plant's genetic architecture. These transcripts provide crucial information about pathways involved in secondary metabolite production, offering a comprehensive view of the plant's biosynthetic capabilities.

The discovery of 8,041 simple sequence repeats (SSRs) provides valuable molecular markers for genetic studies and breeding programs. The identification of 21,235 transcription factors distributed across 65 families has shown the networks controlling metabolite synthesis [21].

4.2. Biosynthetic Pathways

Detailed molecular analysis has uncovered 14 expressed genes encoding enzymes that play essential roles in the biosynthesis of tropane, piperidine, and pyridine alkaloids. These findings provide a mechanistic understanding of alkaloid production in *P. longum*. High-performance liquid chromatography studies have revealed differential piperine concentrations across various plant tissues, with the highest concentrations found in spikes, followed by roots and leaves. This tissue-specific distribution pattern suggests specialized biosynthetic compartmentalization and transport mechanisms [22].

5. Therapeutic Applications

5.1. Traditional Medicine

5.1.1. Ayurveda

In Ayurveda, *Piper longum* is extensively utilized for treating various respiratory disorders, with particular emphasis on asthma and bronchial conditions. The plant's application extends to managing gastrointestinal disorders, where it is valued for its digestive and absorption-enhancing properties. Its use in treating fever and inflammatory conditions demonstrates the traditional recognition of its anti-inflammatory and immunomodulatory properties [23].

5.1.2. Chinese Medicine

In Chinese medicine, *P. longum* is used for treating neurological conditions. Its application in treating insomnia and headaches reflects traditional understanding of its neuromodulatory properties. The plant's use in addressing digestive disorders and allergic conditions suggests recognition of its diverse therapeutic potential [24].

5.2. Modern Medicine

5.2.1. Respiratory diseases

Contemporary research has provided scientific validation for the traditional use of *P. longum* in respiratory conditions. Studies have shown significant bronchodilatory effects and potent anti-inflammatory properties specifically targeting airway inflammation. These findings provide mechanistic support for its traditional applications while suggesting new therapeutic possibilities [25].

5.2.2. Metabolic Disorders

Recent studies have illuminated the plant's potential in managing complex metabolic disorders. Research demonstrates significant effects in diabetes management through regulation of glucose metabolism and enhancement of insulin sensitivity. These findings suggest broader applications in metabolic syndrome and related disorders [26].

Table 3. Traditional Uses and Modern Scientific Evidence of *P. longum*

Traditional Use	Modern Scientific Evidence	Mechanism of Action
Respiratory disorders	Bronchodilation and anti-inflammatory effects	Inhibition of inflammatory mediators
Digestive ailments	Improved gastric motility and secretion	Enhanced digestive enzyme activity
Pain management	Analgesic and anti-inflammatory activity	COX-2 inhibition
Immunomodulation	Enhanced immune response	Increased lymphocyte proliferation
Liver disorders	Hepatoprotective effects	Antioxidant activity
Antimicrobial	Broad-spectrum antimicrobial activity	Cell wall disruption
Bioenhancer	Improved drug bioavailability	P-glycoprotein inhibition

6. Safety

6.1. Acute and Chronic Toxicity

Safety evaluations have indicated generally favorable toxicity profiles for *P. longum* extracts. While these findings support the traditional safety record, the need for standardized dosing guidelines has become apparent. Current research emphasizes the importance of controlled clinical trials to establish precise safety parameters and optimal therapeutic dosing ranges [27].

6.2. Drug Interactions

The potent bioenhancing properties of piperine, while therapeutically valuable, necessitate careful consideration in clinical settings. These properties can significantly affect drug metabolism and bioavailability of co-administered medications. This interaction potential requires careful monitoring and potential dose adjustments when used in combination with other therapeutic agents [28].

7. Quality Control

The variability in chemical composition due to geographical location, cultivation conditions, and extraction methods necessitates development of standardized protocols for consistent therapeutic outcomes [29]. Different analytical techniques reveal varying concentrations of active compounds, highlighting the need for unified quality control parameters [30]. Modern analytical techniques including HPLC, GC-MS, and NMR spectroscopy enable accurate identification and quantification of bioactive compounds. Recent development of HPLC methods for piperine and its derivatives provides reliable quality control measures [31]. Microscopic and macroscopic characteristics, along with chemical fingerprinting, serve as essential parameters for authentication of *P. longum* materials. These measures help prevent adulteration and ensure therapeutic efficacy [32].

8. Conclusion

P. longum represents a valuable medicinal plant with various pharmacological properties validated through scientific research. Its bioactive constituents show significant therapeutic effects across various pathological conditions, from inflammatory disorders to cancer. The plant's unique bio-enhancing properties offer promising applications in drug development and delivery systems. The identification of novel compounds and elucidation of molecular mechanisms help in expanding our knowledge of its therapeutic applications. Modern analytical techniques have enabled better understanding of its chemical composition and biological activities. However, standardization of extraction methods, quality control parameters, and clinical validation remain crucial areas requiring attention.

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