

From Ancient Spice to Advanced Science: Therapeutic, Nutraceutical and Nanotechnological Insights into the Fruits of *Piper Longum* Linn for Modern Drug Development

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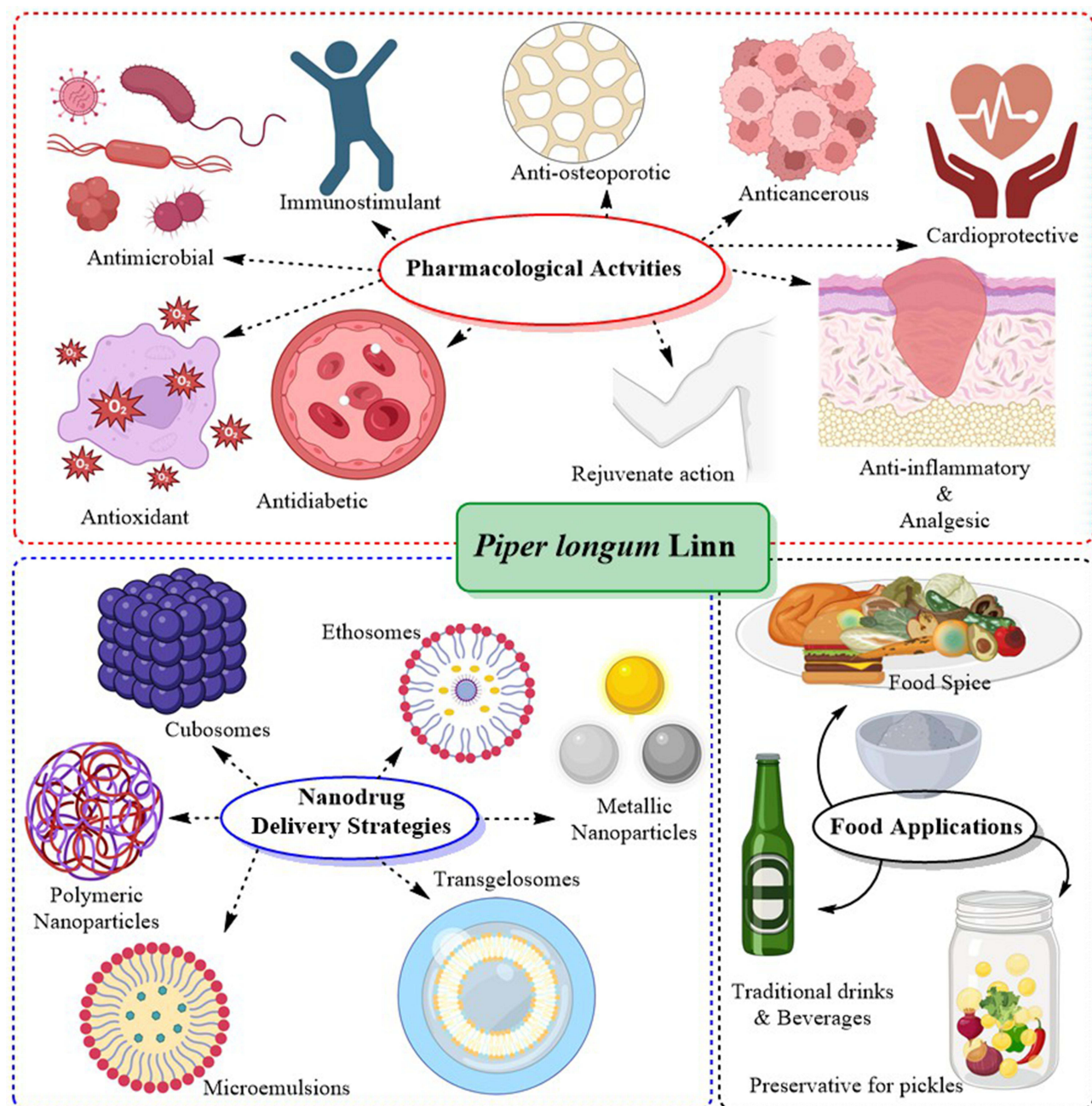
Abstract: *Piper longum* Linn (*P. longum*), a historically revered culinary spice and medicinal herb, has transitioned from its traditional roots in Ayurveda, Siddha, and Unani medicine to modern biomedical and technological applications. This review provides a comprehensive overview of its phytochemistry, therapeutic potential, and translational relevance in drug development. Rich in bioactive compounds such as piperine, piperlongumine, and piperlonguminine, *P. longum* exhibits significant antimicrobial, antioxidant, anti-inflammatory, cardioprotective, antidiabetic, and anticancer activities. Emerging studies also highlight its role as a bioenhancer, functional food ingredient, and sustainable source for nutraceuticals. Furthermore, advances in nanotechnology including liposomes, cubosomes, and transgelosomes, have enhanced its solubility, bioavailability, and targeted pharmacological efficacy. Industrial applications span nutraceuticals, phytopharmaceuticals, and green nanotechnology, underscoring its potential for commercialization. Clinical and preclinical studies validate its efficacy and safety within therapeutic ranges. By bridging ancient knowledge with modern innovations, this review highlights *P. longum* as a versatile candidate for integrative medicine and novel drug delivery strategies.

Keywords: *Piper longum* Linn, phytochemistry, therapeutics, nutraceuticals, nanotechnology, drug delivery, industrial applications

Introduction

P. longum is commonly known as long pepper or Pippali has played a pivotal role in traditional medicine systems for centuries, especially in Ayurveda, Siddha, and Unani practices, where it is recognized as a Rasayana herb known for its rejuvenating and immunomodulatory properties.¹ Historically valued for both its medicinal efficacy and its role in trade, *P. longum* was a sought-after commodity in ancient Greece, Rome, and throughout Southeast Asia.^{2,3} In contemporary times, the plant has regained prominence due to its multifaceted pharmacological activities and industrial potential. Despite its wide range of reported pharmacological effects, the commercial exploitation of *P. longum* remains limited. Major barriers include variability in phytochemical composition, lack of large-scale clinical validation, and regulatory hurdles related to standardization and approval of herbal formulations.⁴ *P. longum* is widely used in culinary practices, particularly in pickles, spice blends, traditional beverages, and as a flavoring agent in food items where a subtle pungency is desirable.⁵ In foods, *P. longum* is incorporated as a flavoring agent when a delicate amount of hotness is required⁶ and

Graphical Abstract



also incorporates the preservative features into the food.⁷ A key bioactive compound, piperine, is not only used for seasoning but also as a food supplement, enhancing both flavor and appetite.^{8,9}

Unlike earlier reviews that focused primarily on traditional formulations or isolated bioactivities, this review presents an integrated evaluation of *P. longum*'s translational relevance, particularly in the realms of integrative medicine, green nanotechnology, and nutraceutical innovation. Its diverse chemical composition, including alkaloids, amides, and lignans, contributes to its broad-spectrum pharmacological activities, such as antimicrobial, cardioprotective, anticancer, and antidiabetic effects.^{10,11} In

addition, advancements in nanoformulation technologies, including liposomes, cubosomes, and transgelosomes, have significantly enhanced the bioavailability and therapeutic efficacy of *P. longum*'s phytoconstituents.^{12,13}

This review offers a comprehensive perspective on the underexplored potential of *P. longum*, encompassing its phytochemical composition, therapeutic efficacy, industrial applications, and commercial promise. By bridging its ancient use as a spice and remedy with modern scientific innovation, this work underscores its emerging role in therapeutics, nutraceuticals, and nanotechnological innovations for modern drug development. Given the increasing global burden of chronic diseases, the limitations of current synthetic drugs, and the rising demand for safe, effective, and sustainable natural alternatives, a focused evaluation of *P. longum* is both timely and necessary. This review highlights its potential as a multifunctional candidate in integrative medicine and advanced drug delivery, thereby meeting urgent healthcare and industrial needs in the current scenario. Importantly, emerging evidence reveals that *P. longum* exerts multifaceted pharmacological actions through the modulation of oxidative stress and inflammatory signaling networks. Its principal alkaloids, piperine and piperlongumine, orchestrate redox homeostasis by enhancing endogenous antioxidant defenses while concurrently attenuating pro-inflammatory pathways involving nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), mitogen-activated protein kinases (MAPKs), and NLR family pyrin domain containing 3 (NLRP3) inflammasome activation. Beyond these mechanistic effects, piperine also serves as a potent bioenhancer that regulates cytochrome P450 enzymes and efflux transporters, thereby amplifying the bioavailability and pharmacodynamic efficacy of co-administered therapeutics. These molecular insights, along with the emerging nanotechnological and translational applications of *P. longum*, are comprehensively elaborated in the following sections of this review.

Historical Importance and Medicinal Heritage of *Piper Longum* Linn

P. longum has held a revered place in medicinal and culinary traditions since antiquity. Its earliest documented use appears in ancient Ayurvedic texts, where it was prominently featured for treating respiratory, digestive, and inflammatory conditions. Known as Pippali in Sanskrit, it was classified as a Rasayana herb for its rejuvenating and immunity-boosting effects and was frequently incorporated into classical Ayurvedic formulations.¹

Several cultivars of *P. longum* have been developed for specific properties. For example, Pippali Madhur is valued for its inherent sweetness, while Pippali Suvarna is cultivated for its high-quality essential oil content, making both varieties desirable for commercial and residential use.¹⁴ Beyond India, *P. longum* was also embraced in early Greek medicine, where Hippocrates and his contemporaries acknowledged its efficacy in respiratory ailments. By 400 BCE, it had become a widely traded and prized spice in the Indian Ocean trade network. During the Roman era, its value surged to the extent that it was used as currency, reportedly worth twice as much as black pepper due to its more intense flavor profile. However, its popularity declined in Europe around the 12th century with the increased availability of black pepper (*Piper nigrum*), which was easier to cultivate and more cost-effective. The introduction of chili peppers from the Americas in the late 15th century further contributed to its diminished culinary use, as these alternatives offered comparable pungency with greater ease of cultivation.²

Despite this decline, *P. longum* has remained a staple in Indian traditional medicine and continues to be used in select regional cuisines and niche markets. Its enduring legacy as both a therapeutic agent and a trade commodity highlights its significant historical role and suggests strong potential for revival in clinical and industrial contexts.³

Morphological and Anatomical Insights of *Piper Longum* Linn for Quality Control and Commercial Use

Understanding the morphological and anatomical features of *P. longum* is essential not only for its taxonomic classification but also for its authentication, cultivation, and industrial standardization as a high-value medicinal and nutraceutical resource. *P. longum* is a slender, perennial, dioecious climbing or trailing herb, thriving in tropical and subtropical climates. Its stem is terete, angular, and distinctly grooved, with clearly demarcated nodes and internodes, features that facilitate identification during vegetative growth. The plant exhibits heterophylly: the lower leaves are ovate-cordate with elongated petioles, whereas the upper leaves are narrow, elliptic-lanceolate, sessile, and smaller in size, ranging from 2.5 to 10 cm in length and 1 to 6 cm in width.^{15,16}

The reproductive structures show sexual dimorphism. Male inflorescences are slender, elongated yellow spikes, while the female inflorescences are shorter (up to 2.5 cm), thicker (4–5 mm in diameter), and cylindrical. The fruiting spike is fleshy and greenish to reddish-brown when mature, measuring approximately 1.8–2.5 cm in length and 0.6–0.75 cm in diameter. The roots are long, cylindrical, and reddish-brown, exuding a pungent aroma and spicy, acrid flavor attributes often exploited in traditional medicine and spice blends.¹⁷

Anatomically, transverse sections of *P. longum*'s roots and stems display typical dicotyledonous features. The structure includes a double-layered epidermis, a parenchymatous cortex rich in starch grains, and a robust exodermis. The vascular system exhibits hexagonal xylem rays and well-differentiated protoxylem and metaxylem elements enclosing a central pith. These features are vital for microscopic identification and pharmacognostic authentication, particularly for raw drugs subjected to grinding and processing.^{15,18} With increasing interest in the large-scale cultivation and commercialization of *P. longum*, such detailed morphological and anatomical characterization provides a critical foundation for ensuring authenticity, purity, and batch-to-batch consistency, ultimately supporting the development of standardized therapeutic and nutraceutical formulations.

Bridging Traditional and Modern Medicine: The Therapeutic Scope of *Piper Longum* Linn

Over the past few decades, there has been a significant global increase in chronic inflammatory, metabolic, and immune-mediated disorders, especially in industrialized nations. This trend is largely attributed to environmental and lifestyle factors, including increased exposure to airborne allergens, pollutants, processed foods, and synthetic chemicals found in medications and personal care products.¹⁹ Conventional treatments, though effective in acute care, often result in adverse effects, drug resistance, or diminished efficacy over long-term use, prompting a shift toward safer, natural alternatives with established historical usage.

In this context, *P. longum*, a prominent botanical in Ayurvedic, Siddha, and Unani medical systems, has attracted renewed scientific interest. Traditionally regarded as a Rasayana (rejuvenator), *P. longum* has been prescribed for ailments ranging from respiratory and gastrointestinal disorders to metabolic imbalances and general immune support.^{1,20} It is a key component in more than 100 classical Ayurvedic formulations, such as Trikatu and Chyawanprash, demonstrating its long-standing role in systemic healing and disease prevention.¹⁶ Phytochemical studies have identified a diverse array of bioactive compounds in *P. longum*, including alkaloids (piperine, piperlongumine, and piperlonguminine), essential oils (eg, β -caryophyllene and bisabolene), and amide alkaloids with demonstrated pharmacological effects such as immunomodulation, anti-inflammation, and antioxidant activity.^{10,11} These constituents synergistically contribute to the plant's adaptogenic and therapeutic profile, as different traditional healing systems are demonstrated in Figure 1.

Emerging scientific data now support the integration of *P. longum* into contemporary healthcare models. In a clinical study by Kataria et al,²¹ patients with mild-to-moderate COVID-19 were treated with a combination of *P. longum* and *Tinospora cordifolia* alongside standard care. Compared to the control group, the combination therapy significantly reduced hospital stay duration and improved post-discharge quality of life, underscoring its potential in immune support and recovery acceleration. Similarly, *P. longum* has shown promise in regenerative and musculoskeletal medicine. Sanap et al²² demonstrated that *P. longum* fruit extract significantly enhanced osteogenic differentiation in human Wharton's Jelly Mesenchymal Stem Cells (WJMSCs). The extract promoted cell proliferation, increased calcium mineralization, and upregulated markers such as alkaline phosphatase (ALP) and osteocalcin, indicating its potential application in bone regeneration and osteoporosis management (Figure 2). The adaptogenic properties of *P. longum* are further supported by evidence of its modulation of the hypothalamic-pituitary-adrenal (HPA) axis, reduction in oxidative stress, and enhancement of mitochondrial function.²³ These actions contribute to resilience against physical and mental fatigue, supporting their role in stress-related and neurodegenerative disorders.

Collectively, these findings bridge ancient wisdom with contemporary scientific validation, positioning *P. longum* as a promising natural adjunct in integrative medicine. Future directions should prioritize dose standardization, pharmacokinetic optimization (eg, nanoformulations), and large-scale clinical validation to establish its efficacy in evidence-based practice.

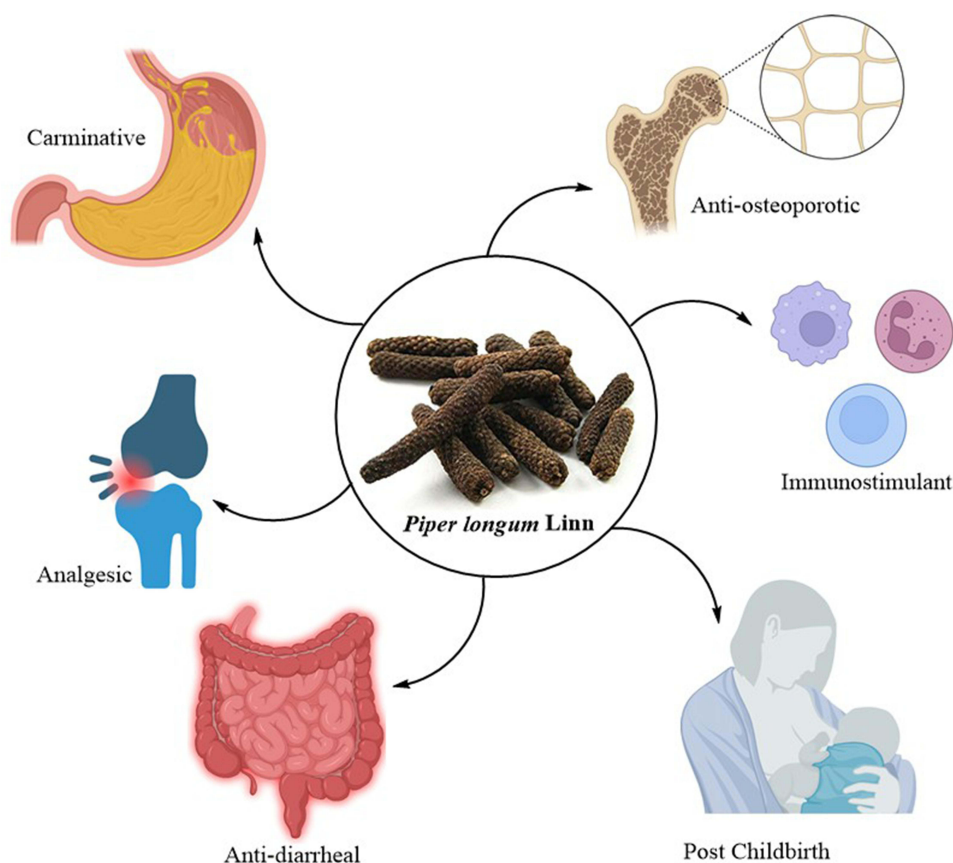


Figure 1 Overview of Ailments Addressed by *Piper longum* Linn in Traditional Healing Systems.

Pharmacological Properties of *Piper Longum* Linn

Antimicrobial Potential of *Piper Longum* Linn

Recent research underscores the promising antimicrobial potential of *P. longum*, driven by its bioactive constituents and innovative applications in nanotechnology. Anandan et al²⁴ demonstrated that a *P. longum*-based polyherbal formulation exhibited potent antibacterial activity against common oral pathogens, including *Staphylococcus aureus*, *Streptococcus mutans*, and *Candida albicans*, while showing negligible cytotoxicity in vitro. However, the formulation was ineffective against *Enterococcus faecalis*, suggesting selective antimicrobial activity. Additionally, the formulation possessed notable antioxidant and anti-inflammatory effects, positioning it as a valuable adjunct in oral health therapeutics.

In a comparative microbiological evaluation, Naika R et al²⁵ reported that isolates derived from *P. longum* showed robust antibacterial activity against Gram-positive organisms, with moderate efficacy against Gram-negative bacteria. Ciprofloxacin is a standard drug for antimicrobial activity, and researchers assessed the comparative antimicrobial activity of piperlongumine against this drug. For *K. pneumoniae*, the zone of inhibition for piperlongumine was 24.00 ± 0.12 mm at 100 μ g, which was very close to that of ciprofloxacin (24.20 ± 0.12 mm). The study stated that piperlongumine was more effective in controlling the growth of *K. pneumoniae* at 100 μ g concentrations when compared to the standard antibiotic ciprofloxacin, and its zone of inhibition was almost equal to that of the standard antibiotic ciprofloxacin. Moreover, for *P. aeruginosa* and *S. aureus*, piperlongumine showed a significant zone of inhibition around 20.00 ± 0.12 mm and 16.47 ± 0.18 mm, respectively. However, the antimicrobial effect of piperlongumine against *S. aureus* was moderate and less than the value observed for ciprofloxacin 21.87 ± 0.47 mm.²⁵ Its activity was comparable to ciprofloxacin, indicating its potential as a lead scaffold for the development of novel antibacterial agents. Furthermore, the significant antimicrobial activity is exhibited by *P. longum*'s isolated compounds in contrast to crude extract.²⁶

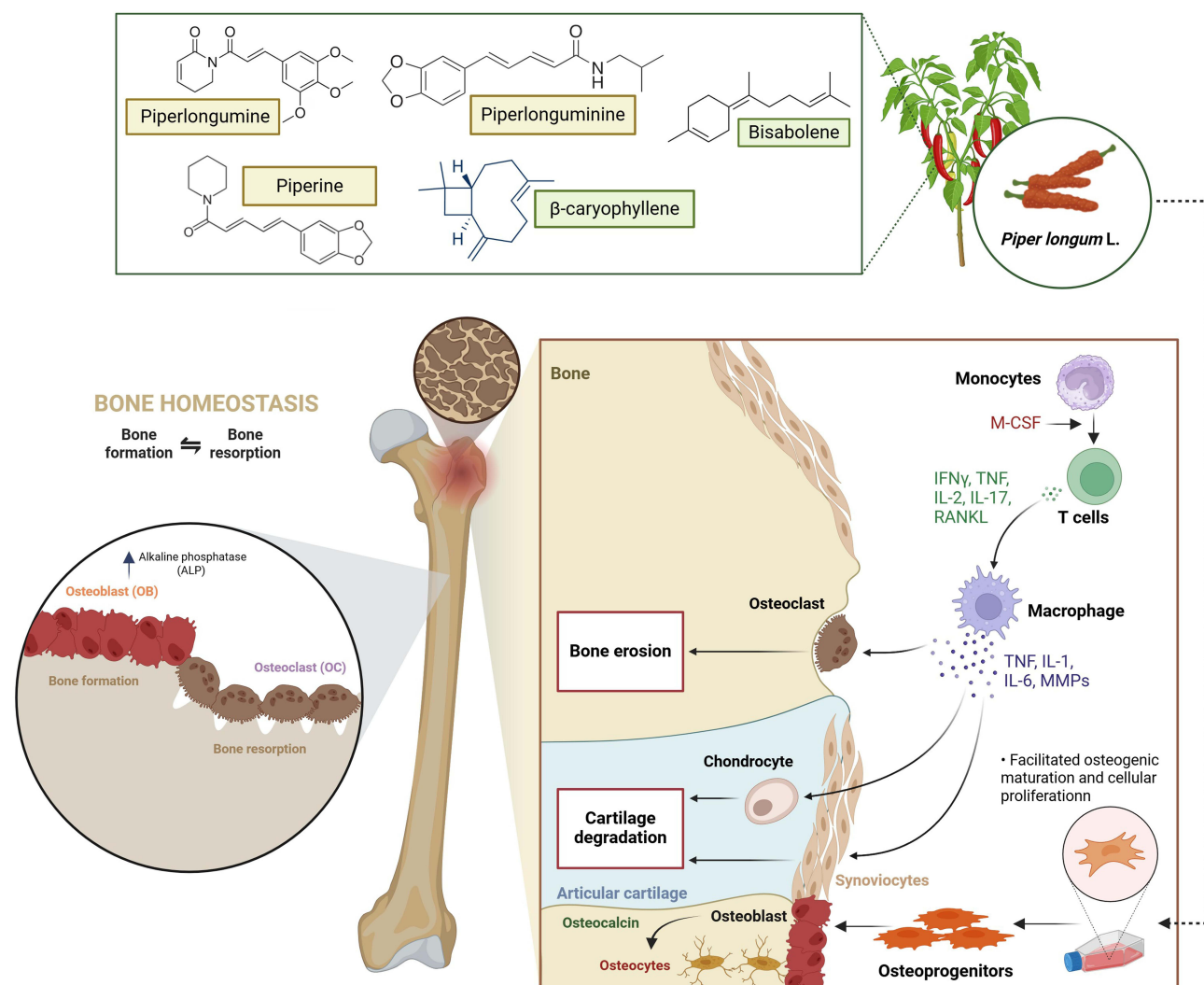


Figure 2 Mechanism of *Piper longum* Linn in bone homeostasis. The bioactive compounds interact with various signaling pathways involved in bone formation and resorption. Monocytes are activated and differentiate into macrophages and osteoclasts (OC), which mediate bone erosion during stimulation. The osteoclast activation is regulated by pro-inflammatory cytokines (TNF- α , IL-1, IL-6, IFN- γ) and the RANKL-RANK signaling axis, which also modulates osteoblast (OB) activity and osteogenesis. Additionally, chondrocytes, synoviocytes, and cartilage degradation are involved in the inflammatory process. The compounds presented are able to modulate these cellular processes, enhancing osteogenic differentiation and supporting bone homeostasis.

Abbreviations: M-CSF, Macrophage colony-stimulating factor; T cells, T lymphocytes; TNF- α , Tumor necrosis factor-alpha; IL-1, Interleukin-1; IL-6, Interleukin-6; IFN- γ , Interferon gamma; IL-17, Interleukin-17; RANKL, Receptor activator of nuclear factor kappa-B ligand; OB, Osteoblast; OC, Osteoclast; ALP, Alkaline phosphatase; MMPs, Matrix metalloproteinases.

Another evidence highlights the role of *P. longum* as a modulator rather than a replacement for commercially available antibiotics. Nanoliposomes were fabricated and co-loaded with gentamicin and piperine, and their activity was assessed against methicillin-resistant *S. aureus* (MRSA).²⁷ Usually, the MIC of gentamicin and piperine is 32 $\mu\text{g/mL}$ and 100 $\mu\text{g/mL}$ against MRSA. While the liposomal combination reduced the MIC of gentamicin around 32-fold, reflecting the remarkable potential of *P. longum* constituents as an adjunct therapy to deal with microbial infections.

Advances in green nanotechnology have expanded the application of *P. longum* in antimicrobial formulations. Faiz et al²⁸ synthesized gold nanoparticles using *P. longum* and *Eucalyptus globulus* extracts, which exhibited enhanced antibacterial activity, particularly against *Candida albicans*, with moderate efficacy against *S. mutans*, *S. aureus*, and *E. faecalis*. These nanoparticles were benchmarked against standard amoxicillin (500 mg), highlighting their biomedical relevance and possible utility in antimicrobial coating technologies and drug delivery systems.

Mechanistically, the antimicrobial effects of *P. longum* constituents, especially piperine and piperlongumine, are attributed to their ability to disrupt microbial cell membranes, inhibit nucleic acid synthesis, and alter microbial redox

homeostasis. These compounds induce oxidative stress in pathogens, interfere with membrane integrity, and inhibit DNA gyrase and topoisomerase enzymes, thereby hindering replication and survival. Moreover, their immunomodulatory effects further support host defense by reducing local inflammation and oxidative damage. Overall, the spectrum-specific action of *P. longum* with greater efficacy against Gram-positive bacteria, due to their simpler membrane structure, offers a strategic advantage for targeted therapy. Additionally, combining *P. longum*-derived phytochemicals with conventional antibiotics may reduce the risk of resistance development and potentiate treatment efficacy against multidrug-resistant pathogens.

In the modern era, the microbial resistance is still a public health problem against commercially available antibiotics. Mgbeahuru et al in 2019 performed a study to analyze the constituent of *P. longum* as an alternative or adjunct therapy for dealing with microbial infections effectively.²⁹ It was assessed that both piperine and piperlongumine showed a strong synergistic response with rifampicin against *S. aureus*, and piperine also worked synergistically with tetracycline. Overall, it was summarized that the *P. longum* constituents have a promising potential to enhance the therapeutic utility of certain antibiotics.²⁹ Although the extract or phytochemicals alone often require higher doses to inhibit microbial growth, the ability to reduce antibiotic concentration when used in combination is pharmacologically relevant.

Anti-Inflammatory Potential of *Piper Longum* Linn

P. longum is increasingly recognized as a potent natural anti-inflammatory agent, with recent studies shedding light on its underlying molecular mechanisms. Traditionally used in Ayurveda for respiratory and arthritic conditions, modern research now validates its role in modulating key inflammatory pathways. A landmark study by Tran et al³⁰ identified a novel alkaloid, piperlongumine A, along with ten previously known amides from *P. longum* leaves. In lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, piperlongumine A exhibited strong anti-inflammatory activity by significantly inhibiting nitric oxide (NO) production ($IC_{50} \approx 0.9 \mu M$), interleukin-6 (IL-6) secretion, and the expression of pro-inflammatory enzymes iNOS and COX-2. Molecular docking further confirmed high binding affinity to inflammation-related targets (binding energy -7.09 kcal/mol), suggesting its strong pharmacodynamic potential (Figure 3).

Complementing this, Uyen Thù Phan et al³¹ performed LC-HRMS profiling of *P. longum* fruit methanolic extract (PLE), identifying 66 bioactive constituents spanning alkaloids, flavonoids, and terpenoids. At concentrations of 10–100 $\mu g/mL$, PLE markedly reduced LPS-induced production of NO, IL-6, and TNF- α ($IC_{50} \approx 28 \mu g/mL$), and inhibited MAPK pathway activation (notably p38 and JNK). Simultaneously, PLE upregulated the antioxidant enzyme HO-1, indicating a dual anti-inflammatory and antioxidative mode of action.

Qian Wan et al³² expanded on this by isolating 16 amide alkaloids—including nine novel structures—from *P. longum* roots. These compounds showed superior anti-inflammatory activity (IC_{50} range: 1.9–40 μM) compared to the standard anti-inflammatory drug indomethacin ($IC_{50} \approx 53 \mu M$). Interestingly, some dimeric amides also enhanced the efficacy of chemotherapeutics in cervical cancer models, suggesting a synergistic potential for inflammation-associated malignancies. Further validation came from network pharmacology and integrated in vitro/in vivo studies,³³ where piperine, piperlongumine, and piperlonguminine were identified as key inhibitors of osteoarthritis (OA)-associated inflammatory markers such as NO, IL-1 β , IL-6, IL-17A, MMPs, and PTGS2. Oral administration of *P. longum* extract in rat OA models significantly reduced joint degradation and pain, highlighting its disease-modifying effects.

Crucially, piperlongumine has been shown to inhibit the NLRP3 inflammasome, a central regulator of inflammation in autoimmune and degenerative diseases. This mechanism further strengthens its candidacy as a multi-target anti-inflammatory agent.³⁴

These converging lines of evidence underscore *P. longum*'s evolution from a traditional anti-inflammatory herb to a scientifically validated therapeutic candidate. Its ability to target multiple inflammatory pathways—including MAPK, NF- κB , and NLRP3—positions it as a promising lead for drug development in chronic inflammatory and immune-related disorders.

Cardioprotective Potential of *Piper Longum* Linn

Cardiovascular diseases (CVDs), particularly heart failure, continue to represent a global health burden, driven by sedentary lifestyles, poor diets, stress, and metabolic disorders. These issues are especially pronounced in industrialized

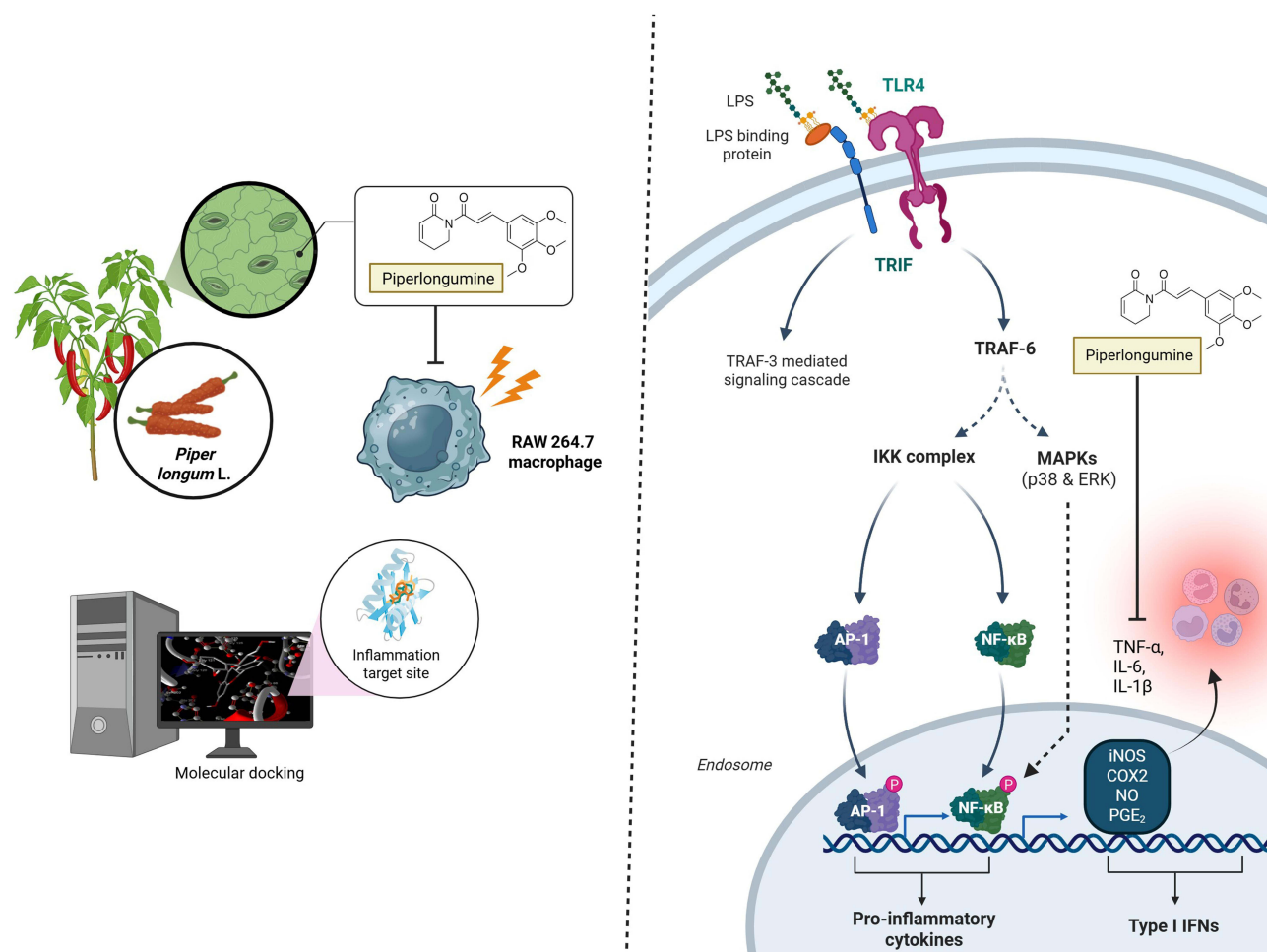


Figure 3 Schematic illustration of anti-inflammatory mechanism of piperlongumine. Upon LPS binding to TLR4, the TRIF pathway is activated, leading to TRAF-6 and the IKK complex. This triggers MAPKs (p38 and ERK), which activate the transcription factors AP-1 and NF- κ B, inducing the production of pro-inflammatory cytokines and enzymes. Piperlongumine is proposed to modulate this signaling cascade, reducing inflammation.

Abbreviations: LPS, Lipopolysaccharide; TLR4, Toll-like receptor 4; TRIF, TIR domain-containing adapter inducing interferon; TRAF-6, TNF receptor-associated factor 6; IKK complex, I κ B kinase complex; MAPKs, Mitogen-activated protein kinases; AP-1, Activator protein 1; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; TNF- α , Tumor necrosis factor-alpha; IL-6, Interleukin-6; IL-1 β , Interleukin-1 β ; iNOS, Inducible nitric oxide synthase; COX-2, Cyclooxygenase-2; NO, Nitric oxide; PGE₂, Prostaglandin E₂; ERK, Extracellular signal-regulated kinase.

nations and among the aging population. While conventional pharmacotherapies primarily address symptomatic relief or disease progression, they often neglect the potential of natural agents with intrinsic cardioprotective effects. In this context, *P. longum* has gained increasing scientific attention due to its ability to modulate key pathways implicated in cardiac dysfunction. Recent studies have highlighted the cardioprotective role of *P. longum* through multiple mechanisms, notably its antioxidant activity, mitochondrial stabilization, and anti-inflammatory effects. Mitochondrial dysfunction and oxidative stress are critical factors in myocardial injury and heart failure. In this regard, Kazuo et al³⁵ proposed that *P. longum* phytoconstituents regulate mitochondrial dynamics and reduce reactive oxygen species (ROS) accumulation, thereby safeguarding cardiac tissue integrity and function.

Preclinical studies substantiate these claims, Sharma et al^{36,37} demonstrated that pretreatment with a methanolic extract of *P. longum* in Wistar rats significantly mitigated adriamycin-induced cardiotoxicity. The protective effect was evidenced by improved cardiac histopathology, normalized levels of serum biomarkers (LDH, CK-MB), and restored antioxidant enzyme activities. Similarly, in another study,³⁸ a researcher reported that a crude methanolic extract of *P. longum* fruit conferred protection against isoproterenol-induced acute myocardial infarction in rats. The treatment reduced myocardial necrosis, lipid peroxidation, and improved endogenous antioxidant status. More recently, It was justified in the study³⁹ that the piperlongumine and piperlonguminine are active alkaloids exerting vasorelaxant and anti-inflammatory actions through

nitric oxide modulation and NF- κ B pathway suppression. These molecular effects directly contribute to the preservation of vascular endothelial function and inhibition of inflammatory cytokine release in cardiac tissues.

Moreover, phytosome- and nanoparticle-based delivery systems of *P. longum* extracts have been developed to improve its bioavailability and pharmacodynamic effects. Kumar et al¹¹ and Mitra et al⁴⁰ emphasize that such formulations not only enhance tissue penetration but also provide prolonged cardioprotection with reduced systemic toxicity. Collectively, these findings highlight *P. longum* as a promising cardioprotective agent with multifaceted therapeutic actions ranging from oxidative stress mitigation and mitochondrial regulation to anti-inflammatory signaling. Further clinical trials are warranted to validate its efficacy and safety in human cardiac pathologies and to enable its integration into evidence-based integrative cardiology.

Antidiabetic Potential of *Piper Longum* Linn

Diabetes mellitus remains one of the most pressing global health challenges, with rising prevalence driven by sedentary lifestyles, poor diet, and genetic predisposition. While synthetic antidiabetic agents are available, their long-term use often leads to undesirable side effects and limited efficacy in preventing disease progression. As such, plant-derived alternatives with multi-target actions and minimal toxicity are gaining importance in complementary diabetes management strategies. *P. longum*, traditionally used in Ayurvedic medicine for metabolic disorders, has shown promising antidiabetic activity through diverse phytochemical mechanisms. A study by Thapa et al⁴¹ explored the therapeutic potential of dichloromethane (DCM) extracts from *P. longum* roots, revealing significant antidiabetic and antibacterial activity. The researchers also suggested that in vitro-grown callus cultures could serve as a sustainable source for producing pharmacologically active compounds while conserving wild populations. This innovative approach aligns with the increasing demand for sustainable herbal medicine production.

Surya et al⁴² demonstrated that a polyherbal formulation comprising *P. longum* fruits and *Stevia rebaudiana* leaves significantly reduced blood glucose levels in diabetic models, indicating synergistic effects. The combination was found to outperform monotherapies, highlighting *P. longum*'s potential as an effective adjunct in managing hyperglycemia and associated metabolic imbalances. In a detailed phytochemical investigation, Shrestha et al⁴³ conducted GC-MS analysis of *P. longum* fruit extract and identified 33 bioactive compounds, including 5,6-dihydroergosterol, β -sitosterol, and piperine. Molecular docking studies revealed that these compounds exhibited high binding affinities with critical carbohydrate-metabolizing enzymes— α -amylase and α -glucosidase—surpassing standard antidiabetic agents. Additionally, ADMET profiling predicted favorable pharmacokinetic attributes and low toxicity, supporting their candidacy as drug-like molecules.

Furthermore, Thakuria et al⁴⁴ reported that core bioactive constituents of *P. longum*—including piperine, piperlongumine, piperlonguminine, and retrofractamide A—showed potent inhibitory interactions with dipeptidyl peptidase-4 (DPP-4) and protein tyrosine phosphatase 1B (PTP1B), enzymes known to impair insulin signaling and glucose metabolism. These interactions suggest a potential mechanism for improving insulin sensitivity and glycemic control. Collectively, these findings emphasize *P. longum*'s role as a multi-target antidiabetic agent acting through enzyme inhibition, antioxidant activity, and possibly pancreatic β -cell protection. While preclinical studies are promising, rigorous clinical trials are essential to validate efficacy, safety, and dosage optimization for its inclusion in mainstream antidiabetic therapy.

Anticancer Properties of *Piper Longum* Linn

Cancer remains one of the leading causes of mortality worldwide, necessitating the continuous search for effective and less toxic therapeutic agents. In this context, *P. longum*, a medicinal plant with a rich history in traditional medicine, has emerged as a potential source of bioactive compounds with anticancer properties. Among its constituents, piperine and piperlongumine have been extensively investigated for their ability to modulate cellular signaling pathways associated with tumorigenesis, apoptosis, and drug resistance. Piperine, a major alkaloid found in *P. longum* and *Piper nigrum*, is renowned for its diverse biological activities, including antibacterial, antioxidant, anti-inflammatory, and anticancer effects. It also acts as a potent bioenhancer, increasing the bioavailability of co-administered drugs by inhibiting drug-metabolizing enzymes and efflux transporters.⁴⁵ These properties make it a valuable candidate in adjunct cancer therapy to potentiate the effects of chemotherapeutics and reduce required dosages.

Several studies have elucidated the mechanisms by which *P. longum* constituents exert anticancer effects. Guo et al⁴⁶ reviewed the traditional use of *P. longum* in cancer treatment and reported that its extracts possess tumor-inhibitory properties across multiple cancer types, including lung, breast, colon, and leukemia. Piperlongumine, a key amide alkaloid isolated from *P. longum*, has shown remarkable anticancer potential by selectively inducing reactive oxygen species (ROS) accumulation in cancer cells, leading to mitochondrial dysfunction and apoptosis without harming normal cells. A pivotal study by Kung et al⁴⁷ demonstrated that piperlongumine effectively inhibited the proliferation of aggressive thyroid cancer cells (including anaplastic, papillary, and follicular types). It achieved this by suppressing the Akt signaling pathway, inducing G2/M cell cycle arrest, and promoting mitochondria-mediated apoptosis. Similarly, in breast cancer models, piperlongumine was found to trigger ROS generation, apoptosis, and autophagy, while sensitizing tumors to standard chemotherapeutic agents. These synergistic effects position piperlongumine as a promising lead compound for combination therapy aimed at overcoming drug resistance.

Despite these promising outcomes, the clinical utility of *P. longum* compounds is often constrained by their poor aqueous solubility and limited systemic bioavailability. To overcome these challenges, recent advances in nanotechnology have facilitated the development of nano-drug delivery systems (NDDS) such as nanoparticles, liposomes, cubosomes, and transgelosomes. These carriers enhance solubility, stability, targeted delivery, and controlled release of the bioactives. A study by Wang et al⁴⁸ demonstrated that nanoformulated *P. longum* extract significantly improved anticancer efficacy and reduced off-target toxicity, validating the potential of NDDS in improving therapeutic indices. Collectively, these findings affirm *P. longum* as a potent anti-tumor agent capable of modulating critical cancer-related pathways. Its minimal toxicity to healthy cells, in conjunction with its synergistic effects when used alongside conventional therapies, supports its further development as a novel complementary strategy in oncology. However, clinical trials and advanced pharmacokinetic studies are essential to translate these promising results into standardized, effective therapies.

Antioxidant Activity of *Piper Longum* Linn

Oxidative stress, a condition resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is a major contributing factor in the pathogenesis of chronic diseases, including cardiovascular disorders, neurodegeneration, diabetes, and cancer. Natural antioxidants derived from medicinal plants have garnered significant attention as safer and more effective alternatives to synthetic antioxidants. Among these, *P. longum* stands out for its robust antioxidant profile and therapeutic versatility. As a member of the Piperaceae family, *P. longum* contains a rich repertoire of bioactive compounds—particularly piperine, piperlongumine, and various lignans and flavonoids—that exert potent free radical-scavenging effects. Jobi et al⁴⁹ reported that oral administration of *P. longum* and its active component piperine not only enhanced the antioxidant status of experimental models but also promoted the secretion of bile acids and stimulated pancreatic and intestinal enzyme activity. These effects contribute to improved metabolic homeostasis and gastrointestinal health. In addition to its traditional applications, *P. longum* has been shown to combat lipid peroxidation, reduce oxidative DNA damage, and restore endogenous antioxidant enzyme levels, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This positions the plant as a multi-functional antioxidant capable of counteracting oxidative damage at cellular and systemic levels.

Research by Carsono et al⁵⁰ has further advanced our understanding of *P. longum*'s antioxidant capacity through structure-activity relationship (SAR) studies and synthetic modifications. These studies led to the development of analogues with improved radical-scavenging activity and reduced IC₅₀ values, paving the way for drug design strategies based on *P. longum* scaffolds. Comparative studies across Piper species have also demonstrated similar benefits. For instance, Agbor et al⁵¹ examined the antioxidant and anti-atherosclerotic potential of *Piper guineense*, *Piper nigrum*, and *Piper umbellatum* in hamsters fed a high-cholesterol diet. Supplementation with these Piper species significantly attenuated oxidative stress markers, preserved the erythrocyte antioxidant defense system, and lowered elevated plasma lipid levels. These results affirm the genus-wide potential of Piper species, including *P. longum*, in oxidative stress-related disease prevention. In summary, *P. longum* exhibits significant antioxidant properties through both direct free radical scavenging and the upregulation of endogenous defense mechanisms. These attributes underscore its value in preventing and managing oxidative stress-associated disorders and support its further development into nutraceutical and therapeutic formulations.

Comprehensive Mechanistic Insights into the Pharmacological Actions of *Piper Longum* Linn: Molecular Targets and Therapeutic Pathways

Emerging preclinical investigations have unveiled the broad-spectrum pharmacological activities of *P. longum*, attributed to its rich phytochemical profile comprising piperine, piperlongumine, piperlonguminine, pipernonaline, and other bioactive constituents. These compounds act through diverse molecular pathways, demonstrating anti-inflammatory, antihypertensive, antispasmodic, and contraceptive effects. The mechanisms of action involve modulation of neurotransmitter receptors, enzyme inhibition, calcium signaling, cytokine suppression, and redox homeostasis.

Antispasmodic Mechanism via Neurotransmitter Receptor Antagonism

A study by Tiwari et al⁵² investigated the smooth muscle relaxant effects of a polyherbal formulation comprising *P. longum*, *Piper nigrum*, *Terminalia bellerica*, and *Zingiber officinale*. The formulation showed dose-dependent inhibition of 5-hydroxytryptamine (5-HT)-induced contractions in isolated rat ileum, indicating antagonism at 5-HT receptors. This spasmolytic activity was further attributed to the modulation of intracellular calcium levels, suggesting the potential use of *P. longum*-based formulations in managing gastrointestinal and uterine spasms.

Anti-Inflammatory and Cartilage-Protective Action Through Cytokine Suppression and Targeted Signaling

In a recent osteoarthritis (OA) model, Jo et al³³ employed network pharmacology and molecular docking to delineate the interaction of *P. longum* alkaloids with inflammation-related targets. Piperine, piperlongumine, and piperlonguminine were found to inhibit key pro-inflammatory mediators, including IL-6, TNF- α , and matrix metalloproteinases (MMPs). In vitro validation confirmed reduced expression of COX-2 and iNOS, indicating suppression of the NF- κ B and MAPK signaling pathways. These findings suggest that *P. longum* may serve as a disease-modifying agent in inflammatory and degenerative joint diseases.

Antihypertensive Effect via Vascular Modulation and Bioactive Alkaloid Action

The antihypertensive potential of *P. longum* has been linked to its vasorelaxant and blood pressure-lowering properties. The alcoholic fruit extract, rich in piperine, piperlongumine, piperlonguminine, and pipernonaline, exhibited significant hypotensive effects in preclinical models. Bodiwala et al⁵³ developed a validated HPTLC method for quantifying these bioactives, providing a standardized tool for quality control in future therapeutic applications. These effects are believed to involve endothelial nitric oxide release, calcium channel inhibition, and angiotensin-converting enzyme (ACE) modulation.

Contraceptive Mechanism via Sperm Immobilization and Membrane Disruption

An intriguing application of *P. longum* is in male contraception. Sarwar et al⁵⁴ demonstrated that hexane extracts of *P. longum* caused immediate and complete immobilization of spermatozoa within 20 seconds. The extract significantly compromised sperm viability and integrity, with observable damage to the plasma membrane, indicating its spermicidal activity. While the precise molecular targets remain to be elucidated, this suggests a membrane-disruptive mechanism, potentially involving lipid peroxidation or calcium influx interference.

Collectively, these studies reinforce the therapeutic versatility of *P. longum*, mediated by multifaceted molecular mechanisms including receptor antagonism (5-HT and cytokine receptors), enzyme inhibition (COX, ACE), modulation of intracellular calcium, and cell membrane disruption. These insights underscore the value of *P. longum* as a promising source of lead compounds for the development of novel therapeutics in the domains of inflammation, cardiovascular regulation, smooth muscle disorders, and contraception.

Phytochemistry of *Piper Longum* Linn

P. longum is a chemically rich medicinal plant with a diverse spectrum of phytoconstituents contributing to its broad pharmacological profile. Both fruits and roots harbor a wide array of bioactive compounds (as mentioned in Figure 4),

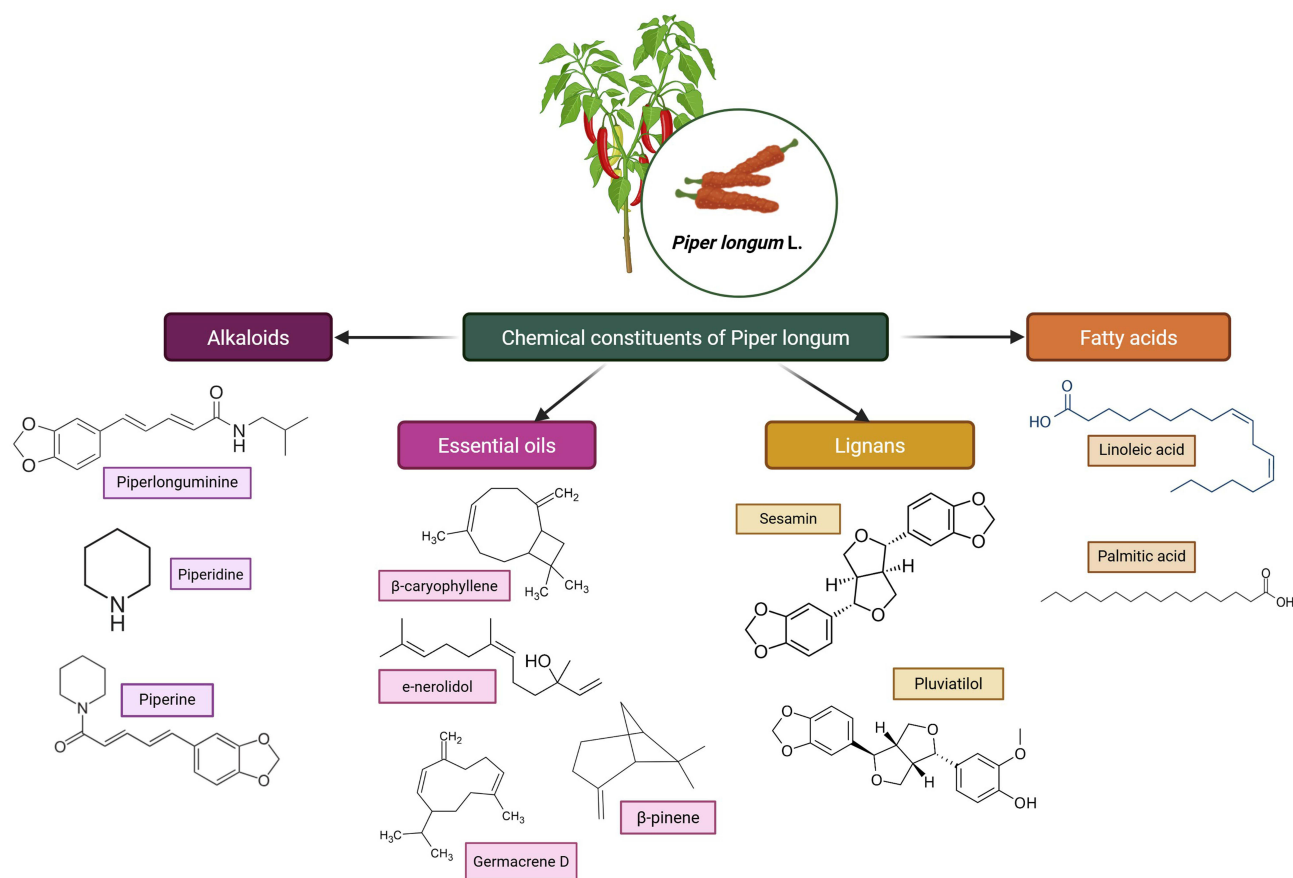


Figure 4 Key Phytochemical Constituents of *Piper longum* Linn.

including alkaloids, amides, lignans, esters, volatile oils, and other secondary metabolites, many of which possess well-documented anti-inflammatory, antioxidant, antimicrobial, and anticancer properties.¹⁰

Primary Bioactive: Piperine

Piperine is the most abundant and pharmacologically significant alkaloid in *P. longum*, comprising approximately 3–5% of the fruit's dry weight.¹⁷ It imparts the characteristic pungency and exhibits notable bioenhancer properties by inhibiting drug-metabolizing enzymes such as CYP3A4 and P-glycoprotein, thereby enhancing the oral bioavailability of co-administered drugs and phytochemicals.⁵⁵

Amide Alkaloids and Related Compounds

Besides piperine, *P. longum* fruits are particularly rich in structurally diverse amide alkaloids. Recent phytochemical profiling has identified key compounds including piperlongumine, piperlonguminine, pipernonaline, pellitorine, methylpiperine, brachystamides, refractamide A, and piperettine.^{11,56} These compounds are credited with a wide range of biological activities, such as ROS modulation, apoptosis induction, and antimicrobial effects, supporting their roles in cancer prevention and infectious disease management.⁴⁷ The roots of *P. longum* also contain a unique alkaloid profile, including tetrahydropiperlongumine, dehydropipernonaline, and trimethoxy-cinnamoyl-piperidine. These root-derived compounds contribute neuro-protective, anti-inflammatory, and antioxidant activities, expanding the plant's systemic therapeutic value.^{10,18}

Lignans and Esters

Notable lignans such as sesamin, pulvuatilol, and fargesin have been isolated from *P. longum* fruits. These phenylpropanoid derivatives are recognized for their antioxidant, hepatoprotective, and anti-inflammatory effects, often acting via

modulation of oxidative stress pathways.⁵⁶ Additionally, lipid-soluble esters like tridecyl-dihydro-p-coumarate and eicosanyl-(E)-p-coumarate have demonstrated lipid-modulating and anti-inflammatory properties, highlighting their potential in metabolic disorder interventions.⁵⁷

Volatile Oils and Terpenoids

Though present in small amounts (~1%), *P. longum*'s volatile oil fraction contains a chemically diverse mixture of bioactive terpenes and aliphatic hydrocarbons. Major constituents include β -caryophyllene, bisabolene, pentadecane, zingiberene, and α -zingiberene.⁵⁸ These compounds contribute to the plant's characteristic aroma and are known for their mild antispasmodic, antimicrobial, and gastroprotective actions. β -caryophyllene, for instance, is a known CB2 receptor agonist with established anti-inflammatory and analgesic effects.

Toxicological Effects of *Piper Longum* Linn

P. longum is extensively utilized in Ayurvedic medicine and Indian culinary practices for its therapeutic and flavor-enhancing properties. While traditionally regarded as safe, caution is advised when consumed in excessive quantities. Toxicological evaluations have provided valuable insights into its safety profile. A study conducted by Pathak et al⁵⁹ on Wistar rats demonstrated that administration of *P. longum* at five times the recommended therapeutic dose resulted in no mortality, while threefold doses showed no significant signs of toxicity, affirming its safety within prescribed limits. In addition to its therapeutic applications, *P. longum* has shown potential in eco-friendly pest management. An ethanol extract of *P. longum* leaves exhibited potent insecticidal activity against *Tribolium castaneum*, a common pest in stored grain products. Among the tested fractions, F5, F10, and F13 demonstrated the highest efficacy, with LD₅₀ values of 17.6 mg/L, 26.6 mg/L, and 10.0 mg/L, respectively. These active fractions were rich in bioactive fatty acids, indicating the plant's potential as a source of natural, biodegradable insecticides.⁶⁰

A comparative toxicological study involving ethanolic extracts of *Cinnamomum zeylanicum* and *P. longum* revealed no significant acute or chronic toxicity in mouse models. Interestingly, *C. zeylanicum* was associated with reduced liver weight and decreased hemoglobin levels, whereas *P. longum* administration resulted in an increase in lung and spleen weights. Notably, both extracts enhanced reproductive organ weights and sperm parameters without inducing spermatotoxicity, suggesting potential reproductive health benefits alongside a favorable safety profile.⁶¹ Furthermore, recent chemotypic analyses revealed significant intraspecific variation in the piperine content of *P. longum* accessions. Among the studied chemotypes, PL9 (fruit) yielded the highest piperine concentration. Antioxidant assays indicated moderate free radical-scavenging activity, and genotoxicity tests confirmed the absence of DNA damage or harmful genetic effects. A validated High-Performance Thin-Layer Chromatography (HPTLC) method was developed to assist in chemotype selection for pharmaceutical and commercial exploitation.⁷ Collectively, these findings support the safe use of *P. longum* at therapeutic doses, while also highlighting its biopesticidal, reproductive, and antioxidant potentials. Continued toxicological assessments and clinical validations will be essential for its broader integration into modern therapeutics and sustainable agriculture.

Pharmacokinetics and Pharmacodynamics of *Piper Longum* Linn

Advancements in drug development increasingly demand the exploration of novel therapeutic strategies, particularly those that can enhance the pharmacokinetics and pharmacodynamics (PK/PD) of both synthetic and natural compounds. *P. longum*, known for its bioactive constituent piperine, has shown considerable promise in this area due to its ability to influence drug absorption, metabolism, and efficacy.⁵⁵ However, the pharmacokinetic properties of *P. longum* also raise important considerations regarding herb-drug interactions. A notable example involves Trikatu, a classical Ayurvedic formulation composed of equal parts of *P. longum*, *Piper nigrum*, and *Zingiber officinale*. In a study by Lala et al,⁶² Trikatu was shown to significantly reduce the anti-inflammatory effect and bioavailability of diclofenac sodium, a widely used nonsteroidal anti-inflammatory drug (NSAID). This suggests that Trikatu may interfere with the pharmacokinetics of certain conventional drugs, potentially altering therapeutic outcomes and necessitating caution in co-administration.

Further insights into *P. longum*'s pharmacokinetic profile were provided by Xu et al,⁶³ who developed a UFLC-ESI-MS/MS-based analytical method to simultaneously quantify major alkaloids - piperine (PPR), piperlongumine (PPL), and

pellitorine (PLTR) in plasma samples from a Parkinson's disease (PD) rat model. The pharmacokinetic analysis revealed that while most PK parameters were comparable between PD and sham-operated rats, mean residence times (MRTs) of these alkaloids were significantly altered in the PD group, indicating possible disease-mediated effects on drug metabolism and clearance. Moreover, a recent study by Christianty et al⁶⁴ emphasized the pharmacodynamic impact of piperine-rich Piperaceae extracts when co-administered with conventional drugs such as diclofenac sodium, alprazolam, and dexamethasone. The results demonstrated enhanced analgesic, anxiolytic, and anti-inflammatory responses, suggesting that piperine not only influences drug bioavailability (a pharmacokinetic effect) but may also synergistically amplify pharmacodynamic responses through mechanisms such as receptor modulation or enzyme inhibition. These findings collectively underscore the dual role of *P. longum* in modulating both PK and PD parameters of drugs, either beneficially by enhancing efficacy or adversely through unintended interactions. Therefore, while *P. longum* holds significant potential in integrative medicine, careful dose standardization, pharmacovigilance, and clinical evaluation are essential to harness its benefits while minimizing risks in polypharmacy settings.

Clinical Validation of *Piper Longum* Linn: Translating Ethnopharmacology Into Evidence-Based Medicine

Emerging clinical and translational research has begun to validate the traditional claims surrounding *P. longum* (Pippali), reinforcing its potential as a therapeutic agent in modern medicine. Preliminary investigations have highlighted its broad-spectrum antibacterial activity. A study by Sarma et al⁶⁵ demonstrated that extracts of *P. longum* and *Terminalia chebula* (Haritaki) exhibited significant inhibitory effects against both Gram-positive and Gram-negative human pathogens. These findings support the use of these herbs as natural antibacterial agents, offering promising alternatives to conventional antimicrobials and encouraging further research into phytochemical-based anti-infective therapies.

In the context of genotoxicity and chemotherapy-related toxicity, Yadav et al¹ reported that *P. longum* extract exerted genoprotective effects, notably reducing cytogenotoxicity associated with cyclophosphamide, a commonly used chemotherapeutic agent. The study showed that *P. longum* attenuated oxidative stress, hepatotoxicity, neurotoxicity, oxidative DNA damage, and DNA double-strand breaks, suggesting its potential as an adjunct therapy to reduce the adverse effects of chemotherapy and safeguard genomic integrity in cancer patients.

Further evidence of *P. longum*'s anticancer potential was reported by Varadharajan et al,⁶⁶ who used network pharmacology and molecular docking approaches to assess the activity of phytochemicals isolated from the plant's roots and fruits against targets associated with lung cancer. The study identified key bioactive compounds capable of interacting with cancer-related molecular pathways, thereby supporting *P. longum*'s candidacy as a lead source for future anticancer drug development. Another mechanistic study by³¹ analyzed the chemical profile and anti-inflammatory activity of *P. longum* extract (PLE) using LC-HRMS, Griess reagent testing, and ELISA. The extract was found to suppress nitric oxide (NO) production, enhance heme oxygenase-1 (HO-1) protein expression, and reduce IL-6 and TNF- α secretion by modulating the MAPK signaling pathway. Additionally, both mRNA and protein expressions of iNOS and COX-2 were downregulated. A total of 66 compounds were identified, including alkaloids, flavonoids, terpenoids, phenolics, lactones, and organic acids, reinforcing the plant's diverse pharmacological properties.

Toxicological validation of *P. longum* was also explored through an acute and subacute toxicity study by,⁶⁷ using Wistar rats to assess the safety of hydroethanolic extract of dried fruits (HEPL). The oral LD₅₀ was determined to be greater than 2000 mg/kg, indicating a high safety margin. No mortality or significant changes in body weight, hematological parameters, or biochemical markers were observed in the subacute toxicity phase, confirming the safety of HEPL for both short- and long-term oral use. Collectively, these clinical and preclinical studies not only substantiate *P. longum*'s therapeutic versatility, ranging from antibacterial and anti-inflammatory actions to genoprotection and cancer modulation, but also highlight its favorable safety profile, supporting its continued development in clinical applications and integrative healthcare settings.

Industrial Applications of *Piper Longum* Linn

While *P. longum* has been traditionally prized in culinary and medicinal contexts, recent scientific advancements have uncovered its vast potential across multiple industrial sectors, including phytopharmaceuticals, green nanotechnology,

functional foods, and environmental remediation. These developments are supported by the plant's rich reservoir of bioactive compounds, such as piperine and piperlongumine, as well as its sustainable cultivation and adaptability to diverse agro-climatic conditions.

Phytopharmaceuticals and Functional Ingredients

The pharmaceutical and nutraceutical industries have increasingly incorporated *P. longum* as a key ingredient in functional formulations due to its antioxidant, anti-obesity, anti-inflammatory, and bioenhancing properties. Its principal bioactive compound, piperine, enhances the bioavailability of various drugs by modulating drug-metabolizing enzymes and transporters.¹⁷ This has made *P. longum* an attractive co-component in herbal and synthetic drug formulations, especially in integrative medicine. Moreover, a study by Gaur et al⁶⁸ highlighted the industrial relevance of *P. longum* roots by isolating six bioactive pseudoalkaloids, including pellitorine, from agricultural waste. Pellitorine demonstrated potent pancreatic lipase inhibitory activity ($IC_{50} = 3.35 \mu\text{g/mL}$), suggesting its role as a potential phytopharmaceutical for obesity management. Molecular docking further supported its binding affinity with key enzymes, offering pathways for anti-obesity drug development.

Biogenic Nanoparticle Synthesis and Environmental Applications

In green chemistry and nanotechnology, *P. longum* has emerged as an effective biogenic agent for synthesizing metal nanoparticles. Plant extracts contain reducing agents and stabilizing phytochemicals capable of forming metal oxide nanoparticles in an eco-friendly manner. Asha et al⁶⁹ successfully synthesized zinc oxide (ZnO) nanoparticles using *P. longum* extract as a bio-capping agent. These ZnO nanoparticles demonstrated high photocatalytic efficiency in degrading industrial dyes like Malachite Green (96%), Methyl Blue (69%), and Methyl Orange (48%) under UV light, indicating their utility in wastewater treatment and environmental detoxification. Similarly, silver nanoparticles synthesized using *P. longum* fruit extract have shown enhanced antibacterial, antioxidant, and anticancer properties compared to the crude extract, supporting their potential in biomedical and packaging industries.⁷⁰

Microbial Fermentation and Sustainable Bioactive Production

A groundbreaking study by Verma et al⁷¹ reported the isolation of piperine from an endophytic fungus (*Periconia* sp.) associated with *P. longum*. This was the first evidence of piperine biosynthesis outside of the plant, suggesting the feasibility of microbial fermentation as a sustainable and scalable production method for high-value bioactive compounds. Such innovations could reduce reliance on plant biomass and encourage the development of biotechnological platforms for natural product manufacturing.

Functional Foods and Nutraceuticals

Owing to its pungent flavor, aromatic profile, and antioxidant activity, *P. longum* is increasingly used as a natural additive in functional foods. It serves dual roles, acting as a flavoring agent and a health-promoting component. The demand for “clean-label” ingredients has boosted the use of *P. longum* in dietary supplements, metabolic health formulations, and digestive aids.⁷² In particular, piperine has been shown to synergistically enhance the absorption of curcumin and resveratrol, contributing to its inclusion in polyherbal blends and nutraceutical capsules.

Agro-Industrial and Veterinary Applications

Preliminary studies also suggest insecticidal and growth-promoting properties of *P. longum*, making it relevant to agro-industrial applications. Ethanol extracts of *P. longum* have demonstrated larvicidal activity against *Tribolium castaneum*, a common grain pest, positioning the plant as a candidate for natural pesticide development.⁶⁰ Furthermore, its use in ethno-veterinary medicine and livestock feed additives is being explored due to its immunomodulatory and anti-parasitic potential.

Overall, the industrial potential of *P. longum* extends far beyond its historical medicinal uses. Its versatility, ranging from pharmaceutical adjuvants and anti-obesity agents to green catalysts and biopesticides, places it at the intersection of traditional knowledge and emerging biotechnologies. Harnessing this potential through sustainable cultivation,

bioresource valorization, and industrial innovation could unlock new commercial pathways while preserving its ethno-pharmacological legacy.

Analytical Standardization and Quality Control of *Piper Longum* Linn: Ensuring Safety, Efficacy, and Regulatory Compliance

Quality assurance plays a pivotal role in determining both the market value and therapeutic efficacy of spices such as *P. longum*. As a high-value commodity, particularly in Indian exports, spices are subject to strict chemical and physical quality criteria. However, due to their premium status and widespread demand, spices are often vulnerable to adulteration, which can compromise their safety, efficacy, and economic worth. Ensuring the purity and standardization of *P. longum* is therefore essential for both domestic use and international trade.

In response to this need, various analytical techniques have been developed to authenticate and quantify the bioactive constituents of *P. longum*. Rajopadhye et al⁷³ established a validated HPTLC method for the simultaneous detection of piperine and piperlongumine in the methanolic root extract of *P. longum* and a commercial Ayurvedic formulation, Mahasudarshan Churna®. The method demonstrated excellent linearity, precision, accuracy, and recovery, in accordance with International Council for Harmonisation (ICH) guidelines. Importantly, Accelerated Solvent Extraction (ASE) was used to obtain well-resolved peaks, providing a cost-effective, reproducible, and efficient approach for routine quality assessment of herbal raw materials and finished products.

Building upon these advancements, Bodiwala et al⁵³ developed another sensitive HPTLC method specifically for quantifying piperine, piperlongumine, and piperlonguminine in the alcoholic extract of *P. longum* fruits. This method adhered strictly to ICH Q2(R1) standards, ensuring analytical parameters such as specificity, accuracy, precision, linearity, and robustness were thoroughly validated. The reliability of this method makes it particularly well-suited for quality control, standardization, and formulation development, ensuring consistency in bioactive content across production batches. These validated analytical techniques serve as critical tools in maintaining the integrity, safety, and therapeutic reliability of *P. longum*-based products. Standardized quality control protocols not only help preserve the phytochemical fingerprint of the herb but also support its regulatory approval and commercialization in the global phytopharmaceutical market.

Adulteration Challenges in Medicinal Spices: Safeguarding the Authenticity of *Piper Longum* Linn

Adulteration in spices remains a critical concern in the global food supply chain, posing serious implications for consumer health, product integrity, and market credibility. Driven largely by economic incentives, the adulteration of spices often involves the intentional substitution, dilution, or addition of low-cost materials, including inferior plant parts, synthetic fillers, and artificial dyes, to increase product volume and maximize profit margins. Spices, being high-value commodities, are particularly vulnerable to such malpractices. One of the most commonly adulterated spices is saffron, which commands a premium price due to its labor-intensive cultivation and limited geographical production. Adulterants commonly found in saffron include safflower petals, marigold petals, synthetic coloring agents, gelatin, moisture, sugar syrup, salt, and starch, all of which compromise the purity and therapeutic efficacy of the product.⁷⁴

Similarly, ground cinnamon is often adulterated with sugar, powdered nuts, rhizome starches, and synthetic colorants, followed by the addition of cinnamaldehyde aroma to mimic its natural scent and taste. Such practices not only deceive consumers but also interfere with the organoleptic and pharmacological qualities of the spice. Furthermore, spices such as turmeric and ground chillies are frequently adulterated with cheap dyes, cereal flour, tapioca starch, and even toxic substances like lead chromate, which is particularly concerning due to its carcinogenic and nephrotoxic properties. The use of such hazardous additives introduces significant health risks, especially with long-term consumption, including heavy metal toxicity, gastrointestinal disorders, and allergic reactions. These adulteration practices highlight the urgent need for robust quality control systems, authentication techniques, and regulatory enforcement to ensure consumer safety. Modern analytical tools such as HPTLC, LC-MS, and DNA barcoding can aid in the detection and prevention of

adulteration, thereby preserving the authenticity, safety, and medicinal value of spices in the food and pharmaceutical industries.

Stability Profiling of *Piper Longum* Linn: Ensuring Shelf-Life, Bioactivity, and Pharmaceutical Reliability

The stability of natural products, including medicinal herbs such as *P. longum*, is a crucial parameter influencing their safety, efficacy, and shelf life. Unlike synthetic pharmaceuticals, which typically contain a single active ingredient, natural products are composed of complex mixtures of phytochemicals, making their stability studies considerably more challenging. Physical and chemical processes such as hydrolysis, oxidation, isomerization, and polymerization can significantly affect the chemical integrity, potency, and therapeutic value of the plant-derived material over time. Stability testing of herbal products involves periodic monitoring of quality parameters under defined environmental conditions (temperature, humidity, light exposure) to ensure the consistency and reliability of the formulation. Key strategies for evaluating stability include the use of marker molecules, metabolic fingerprinting, and advanced chromatographic techniques such as HPTLC and LC-MS. These tools help in detecting chemical degradation, loss of bioactivity, and the formation of potentially harmful by-products.⁷⁵

A significant contribution to the understanding of *P. longum*'s stability came from the study by Aodah et al,⁷⁶ which focused on the thermal degradation kinetics of piperlongumine, a major bioactive constituent of the plant. The study demonstrated that piperlongumine degrades according to first-order kinetics, with maximum stability observed at pH 4, where the T90 (time required for 10% degradation) was recorded at 17 weeks at 25°C. The calculated activation energy for degradation ranged between 88–95 kJ/mol, indicating moderate thermal sensitivity. Interestingly, variations in ionic strength and buffer species had minimal effect on degradation at pH 3 and 5, suggesting that pH is a dominant factor influencing compound stability.

The research also identified 3,4,5-trimethoxycinnamic acid as the major degradation product, formed primarily through imide hydrolysis in ethanolic alkaline conditions, along with the formation of piperlongumic acid. These findings provide important insights into the degradation pathways of piperlongumine and highlight the necessity of maintaining optimal pH and storage conditions to preserve its therapeutic value. Overall, while stability evaluation in herbal products is inherently complex, such studies are essential for ensuring the quality control, regulatory compliance, and clinical reliability of natural formulations. Future research should focus on developing standardized protocols for long-term stability testing of plant-based compounds, particularly under various formulation and packaging conditions.

Global Market Landscape of *Piper Longum* Linn: Trends, Trade Dynamics, and Industrial Potential

P. longum holds a prominent position in the global spice and herbal medicine markets due to its wide-ranging ethnomedicinal, Ayurvedic, and pharmacological applications. Among the producing nations, India is the leading global producer and exporter, accounting for approximately 65% of the global export market. In 2021, India's manufacturing output surpassed 460,000 metric tons, with peak harvesting occurring between April and June.¹⁶ The increasing domestic and international demand for Pippali has been driven by its recognized therapeutic potential and its use in functional foods, nutraceuticals, and Ayurvedic formulations. A substantial portion of *P. longum* traded in India is wild-harvested from forested regions, particularly in the states of Assam, Karnataka, Maharashtra, and Kerala, as illustrated in Figure 5, on the political map of India. These regions serve as critical supply zones for raw material collection and initial processing before the spice enters the supply chain.

According to Volza's Global Export Data, between March 2023 and February 2024, a total of 182 export shipments of *P. longum* were recorded worldwide. These were facilitated by 65 exporters and 93 buyers, reflecting a 29% increase compared to the previous 12-month period. Notably, 24 shipments were made in February 2024 alone, indicating a 14% sequential growth from January 2024 and a 14% year-over-year increase compared to February 2023. These figures suggest growing momentum in the international trade of *P. longum*, driven by rising interest in herbal therapeutics and natural remedies.⁷⁷

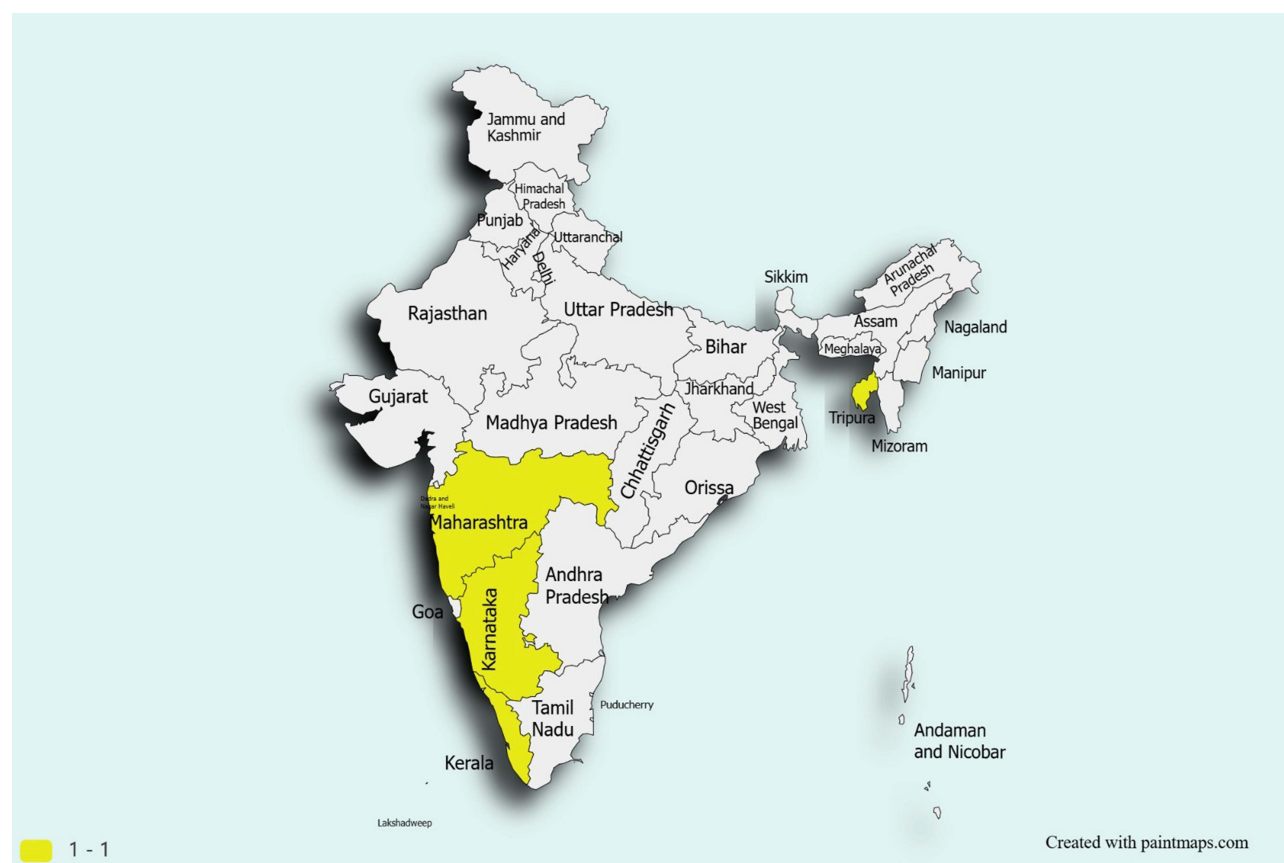


Figure 5 Map of India showing the major states where *Piper longum* Linn is cultivated and collected for commercial use (Karnataka, Maharashtra, and Kerala).

The United States, the Netherlands, and Sri Lanka emerged as the top global importers of *P. longum*, signaling its rising popularity across both Western and South Asian markets. Meanwhile, the top three global exporters of *P. longum* are India, Indonesia, and Pakistan. India continues to dominate export activity with remarkable 1,434 shipments, followed by Indonesia with 33 shipments and Pakistan with 23 shipments.⁷⁷

In addition to these leading exporters, several countries—including Sri Lanka, Nepal, Bangladesh, and Thailand cultivate *P. longum* primarily for domestic use and traditional medicine. Although detailed export statistics from these nations are limited, their role in the regional herbal medicine landscape remains significant. India also serves as a key exporter to a range of countries, including Sri Lanka, Bangladesh, Japan, and France, demonstrating the spice's diversified international market reach. These export relationships are visualized in Figure 6, highlighting India's role as a central node in the global *P. longum* trade network. The expanding market presence of *P. longum* underscores its value not only as a traditional medicinal herb but also as a high-potential commodity in the global phytopharmaceutical, spice, and nutraceutical industries. Ensuring sustainable harvesting, quality assurance, and regulatory compliance will be vital to maintaining India's leadership and meeting future global demand.

Commercial Potential of *Piper Longum* Linn Nanocarriers for Improved Therapeutic Efficacy

Plant extracts and herbal medicines, such as *P. longum*, play a vital role in delivering diverse pharmacological effects.⁷⁸ One of the major benefits of phytoconstituents is their reduced toxicity and adverse effects, in contrast to other active pharmaceutical ingredients.⁷⁹ However, the effectiveness and therapeutic response of these ingredients can be compromised due to their reduced solubility and bioavailability issues.⁸⁰ So, to conquer these drawbacks is a herculean task. Therefore, numerous nanoformulations⁸¹ like nanoemulsions, liposomes, polymeric nanoparticles, solid lipid nanoparticles, phytosomes, nano-gels¹³ nanostructured lipid carriers and cubosomes⁸² have been developed in order to enhance the

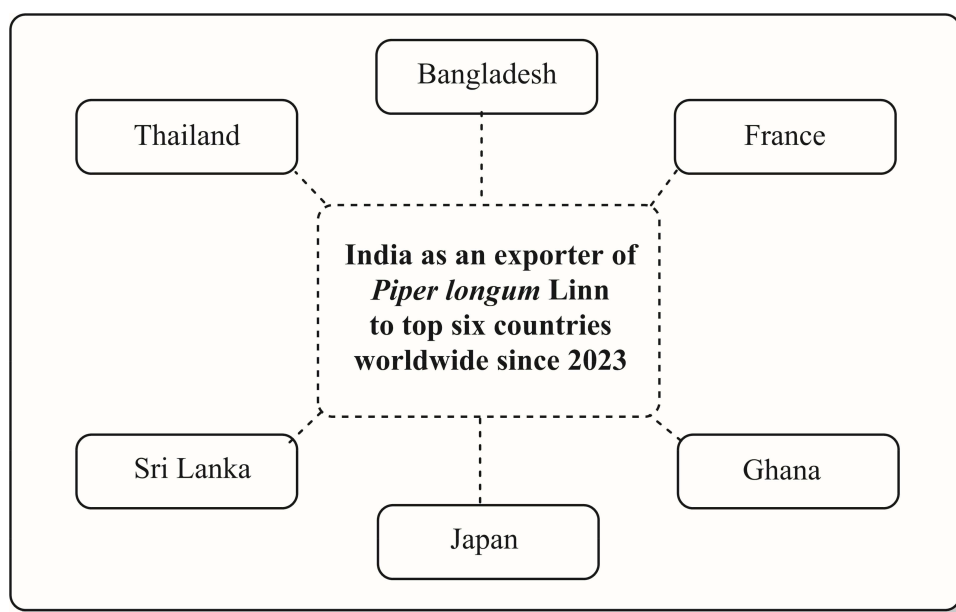


Figure 6 Representing the top six countries importing *Piper longum* Linn from India since 2023.

solubility, bioavailability, stability and pharmacological activity of plant-based products.⁸³ In the same manner, novel nano drug delivery strategies can be utilized for *P. longum* for the sake of its improved bioavailability and therapeutic response,¹² as illustrated in Figure 7. It is essential to generate pharmacokinetic and toxicological data in humans to confirm the bioavailability and safety of its active constituents.

A. M. Akotkar et al conducted a study,¹² in which researchers extracted piperine from *P. longum* through maceration and passed it through sieve 60. Subsequently, piperine nanoparticles were formulated using the solvent evaporation technique, employing 0.2% polyvinyl alcohol as the polymer and dichloromethane as the organic solvent.⁸⁴ The in vitro release profile indicated the enhanced release of piperine from nanoparticles. Among the six formulations, F3, containing the highest polymer concentration, demonstrated the greatest drug release from the nanoparticles. In the results, it was summarized that the nanoparticle can be employed to enhance the efficacy of piperine.

In 2010, a patent was filed regarding the preparation of topical microemulsions⁸⁵, so as to treat the rheumatic irregularities, ie, gout, arthritis and fibromyalgia. Essential oils from different herbs, also from *P. longum*, were acquired and accordingly, the topical microemulsions were designed. Subsequently, novel herbal formulations were found to be effective in managing rheumatoid-associated disorders. It was found that the designed formulations provided improved percutaneous absorption and enhanced bioavailability along with reduced fluctuation in absorption. In another study, silver nanoparticles (AgNPs) were designed via a bio-green method and loaded with *P. longum* fruit extract (PL).⁸⁶ As a result, the designed *P. longum* fruit extract-loaded silver nanoparticles (PLAgNPs) were 46 nm in size and characterized via scanning electron microscopy and dynamic light scattering. Moreover, FTIR was performed to verify the presence of phytoconstituents in the designed formulation. The results indicated that PLAGNPs exhibited superior antimicrobial activity compared to the *P. longum* fruit extract. Moreover, antioxidant activity was also increased in the designed formulation along with an enhanced anti-cancerous response. It can be summarized that the employment of nano-drug delivery strategies for the delivery of herbal constituent, ie, *P. longum*, is appropriate to enhance the therapeutic efficacy and patient compliance. Another study revealed that the preparation of *P. longum* -loaded silver nanoparticles provided better antioxidant, radical-scavenging, anti-cancerous and larvicidal activities as compared to the given crude drug. This discovery offered a novel perspective on utilizing phytoconstituent-loaded nano-drug delivery systems to enhance therapeutic efficacy, as demonstrated in an in vivo study involving a mosquito vector model.⁷⁰

Debadatta Mohapatra et al⁸⁷ performed a study to overcome melanoma, a severe form of skin cancer. In this study, they designed the *P. longum* -loaded nanovesicular transgelosome (transferosome into hydrogels), which demonstrates better permeation into the skin. It was concluded that the nanovesicular transgelosome showed improved ex-vivo skin

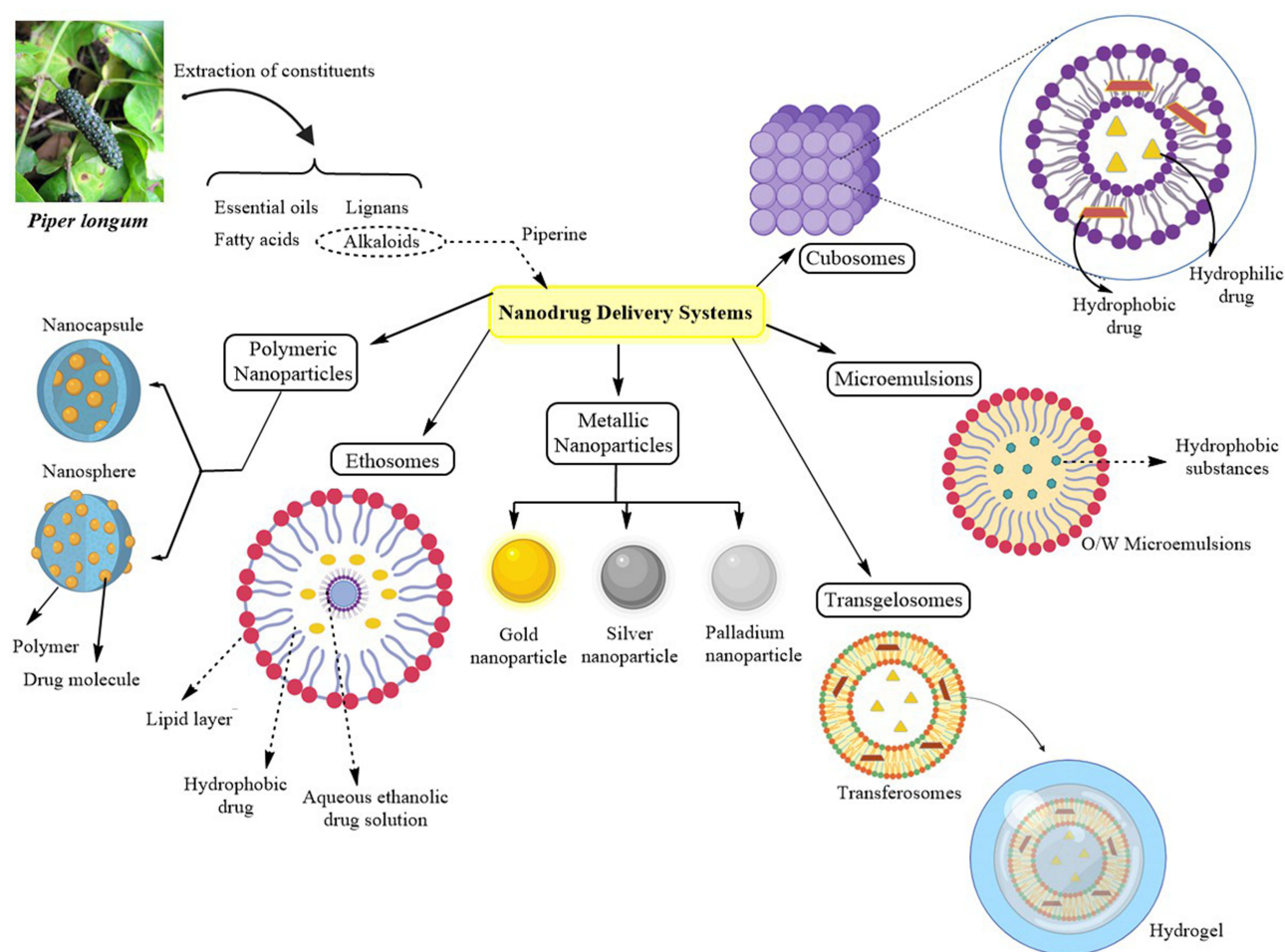


Figure 7 Diagrammatic illustration of various nano-drug delivery systems employed for *Piper longum* Linn extract; polymeric nanoparticles, ethosomes, metallic nanoparticles, transgelosomes, microemulsions and cubosomes.

permeation as compared to plain *P. longum* fruit extract gel. Collectively, the evidence supports nano drug delivery as a promising strategy for the effective administration of *P. longum*. Pravin Kumar et al⁸⁸ conducted a study to treat atopic dermatitis via lipid nanoparticles, ie, ethosomes of piperine-loaded cream. The designed formulation was characterized and evaluated for physicochemical features, likely drug retention in skin, along with its ex-vivo permeation via female BALB/c mice. The therapeutic potential of ethosome-loaded cream is much better than the conventional one due to its enhanced permeation and improved skin retention behavior. Moreover, the designed formulation was considered more suitable for atopic dermatitis treatment and improved patient compliance.

A study was performed by Yosra SR Elnaggar et al⁸⁹ to overcome the drastic effects of Alzheimer's disease via piperine-loaded tween-modified monoolein cubosomes for targeted oral drug delivery. A total of 42 male Wistar rats were utilized in the study, with Alzheimer's-type dementia experimentally induced to model neurodegeneration. After that, in vivo evaluation revealed that the piperine-loaded cubosomes prominently increased the cognitive functions and also restored them to the normal level. Furthermore, cubosomes showed much more effective anti-apoptotic and anti-inflammatory behavior. As a result, it might be summarized that the orally administered piperine-loaded cubosomes are a promising approach to deliver *P. longum* extract with improved oral bioavailability.

As compared to conventional treatment, nanotechnology and novel nano-based drug delivery systems are considered new and quite different. Therefore, the regulation of nano-based therapies remains complex and uncertain. So, it is necessary to regulate this sort of treatment with respect to ethical concerns. Research on ethical, social and environmental aspects of nano-based technology is a genuine field of inquiry in Western countries.⁹⁰

Conclusion and Future Perspectives

P. longum is a versatile medicinal plant with diverse phytochemistry and broad therapeutic promise. It demonstrates activities ranging from antimicrobial, antioxidant, anti-inflammatory, cardioprotective, and anticancer effects to roles in metabolic regulation. However, reported pharmacological effects are sometimes inconsistent due to variability in bioactive content, limited clinical validation, and safety considerations that remain unresolved. In addition to its traditional uses, its growing applications in nutraceuticals and nanotechnology-based drug delivery present new opportunities to overcome the limitations of conventional therapies. Although much potential remains underexplored, future research focusing on safety, pharmacokinetics, and clinical validation will be crucial to translate this plant from traditional heritage to modern pharmaceutical and nutraceutical innovations.

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Disclosure

The authors report no conflicts of interest associated with the publication.

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