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A Comprehensive Review: Phytochemistry, Pharmacology, Uses and Nanotechnological Approaches of Piper longum L.

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Abstract: *Piper longum L., commonly referred to as long pepper or pippali, is a plant belonging to the Piperaceae family and has been widely used in Ayurvedic and other traditional medical systems for a long time. The various reported biological properties of this plant have led to extensive research into its phytochemical makeup, pharmacological effects, potential as a bioavailability enhancer, and applications in new drug delivery systems. This review provides an overview of the botanical features and traditional uses of P. longum, the main phytochemical groups identified, the proposed mechanisms at the cellular level, preclinical findings related to specific conditions, combination strategies, methods of extraction, computational techniques, nanotechnology-based formulations, and safety aspects. Piperine and piperlongumine are two of the most commonly studied compounds in the literature, although the level of evidence supporting them varies depending on the compound and its application. Many of the findings related to anti-inflammatory, metabolic, respiratory, neuroprotective, antimicrobial, and anticancer properties are primarily based on laboratory or animal studies and should not be taken as proof of clinical effectiveness. Piperine may also affect the way other medicines are absorbed or metabolized through its influence on drug-metabolizing enzymes and transporters, which can offer new formulation opportunities but also pose interaction risks. The use of nano-enabled delivery systems may help overcome issues related to solubility and exposure, but their actual benefits need to be evaluated through systematic assessment of formulation performance, safety, and clinical results. Before many of the proposed uses can be considered for routine medical applications, there is a need for better-characterized extracts, reliable analytical methods, thorough toxicology studies, and well-structured human clinical trials. [1,11,14,15].*

Keywords: Piper longum; pippali; piperine; piperlongumine; phytochemistry; pharmacology; bioavailability; nanotechnology; drug delivery

I. INTRODUCTION

Piper longum L., often known as long pepper or pippali, is an aromatic plant that has been used in traditional Indian medicine. In Ayurveda, it is connected with the concept of rasayana and is included in Trikatu, a traditional formulation that combines P. longum, Piper nigrum, and Zingiber officialities traditional uses of this plant have sparked modern research aimed at understanding its chemical components and potential medicinal properties. It is important to note that traditional use, experimental findings, and clinical benefits represent different levels of evidence and should be considered separately. [5,6,7,8,11,14,15]

Research has investigated effects related to anti-inflammatory, antioxidant, gastrointestinal, metabolic, neuroprotective, antimicrobial, and anticancer properties. Another area of interest is Piperine's ability to influence the absorption or

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metabolism of certain compounds taken alongside it. This review organizes the topics covered in the source material and highlights limitations that need to be addressed before submitting the work for publication. [11,14,15,18]

However, there is no mention of a reproducible database search strategy, specific search dates, eligibility criteria, or a formal risk-of-bias evaluation. As such, the paper cannot be classified as a systematic review. Before submitting the manuscript, the authors should verify each reference against the original publication and include a documented literature search method if the target journal requires it. [14,15]

II. BOTANICAL DESCRIPTION AND DISTRIBUTION

A member of the Piperaceae family contains piper longum. The genus Piper comprises many species that are predominantly found in tropical and subtropical areas. P. longum is a perennial climbing plant with jointed stems, an aromatic root system, and alternate leaves that are typically ovate or cordate. Its fruiting structures are compact, cylindrical spikes that contain many small fruits. The roots and fruiting spikes are often considered important for medicinal use. [3,4,11,14,15]

The source document describes the plant as native to warm and humid regions of India, including the Himalayan foothills, the Western Ghats, and parts of eastern India. It mentions cultivation conditions like humidity, rainfall, rich organic soil, and partial shade. Before publication, the geographic distribution and cultivation claims should be cross-checked with a botanical or floristic reference. [4,11,14]

III. TRADITIONAL AND HISTORICAL CONTEXT

Long pepper has a long history of use in South Asian traditional medicine and is featured in classical Ayurvedic texts such as the Caraka Samhita, Sushruta Samhita, and Ashtanga Hridaya. In the traditional formulation Tsikata, it is combined with black pepper (P. nigrum) and ginger (Z. officinale). These traditional uses provide historical background for research into digestive and respiratory applications, but they do not independently confirm effectiveness under today's clinical standards. [5,6,7,8,11,14,15]

The source also discusses the historical trade of long pepper in the Mediterranean and Europe, and its later decline in commercial use compared to black pepper and chili peppers. These historical details should be verified using dedicated historical sources and are only acceptable if they are supported by traceable references.[15]

IV. PHYTOCHEMISTRY

The chemical composition of P. longum varies depending on the part of the plant, its geographic origin, growing conditions, the solvent used, and the analytical method applied. In this method the use of GC–MS, HPTLC and HPLC. [10,11,14,15]

4.1. Alkaloids and amides

Piperine is a major pungent amide found in Piper species and is often studied for its influence on the absorption and metabolism of other substances. Research indicates that piperine can affect drug-metabolizing enzymes and transporters, including CYP3A4 and P-glycoprotein. The extent and clinical significance of these effects depend on the compound, dose, and the research setting.[18]

Piperlongumine, also known as Piplartine, is another amide that has been examined for its biological activity, particularly in experimental cancer models. Proposed mechanisms involve changes in cellular redox balance and oxidative stress signaling. While piperlongumine and related amides are mentioned in the literature, their pharmacological roles and evidence base are not consistently established. [14,15,17]

4.2. Lignans and volatile constituents

The source lists lignan-related compounds like Sesamin and Farge sin, along with volatile components such as caryophyllene, limonene, and pinene.

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The abundance of volatile compounds may vary between different plant parts, such as roots, stems, leaves, and fruits. In these the biological activity of plant parts and analytical evidence are generally obtained. [10,11,14]

Reported constituent	Plant material noted in source	Reported or proposed activity
Piperine	Fruit/fruiting spike	Potential enhancement of bioavailability; effects on CYP3A4/P-glycoprotein; digestive effects studied
Piperlongumine	Root material	Redox-related and pro-apoptotic effects studied in experimental cancer models
Piperlongumine	Roots and stems	Neuroactive or antinociceptive effects proposed; further evidence is needed
Sesamin	Leaves/fruits (as listed in source)	Antioxidant and lipid-metabolism effects reported in broader literature; plant-part attribution needs verification
Caryophyllene	Volatile oil	Antimicrobial activity investigated; specific evidence should be cited

V. PHARMACOLOGICAL ACTIVITIES AND PROPOSED MECHANISMS

The reported activities of P. longum and its components have been covering a range of biological systems. Because chemical compositions of the extracts might vary and many of the studies are preclinical experiments, the results should be regarded as experimental or potential effects unless they are well-documented clinical findings. [11,14,15]

5.1. Anticancer-related activity

Piperlongumine has been studied in experimental cancer models for its impact on oxidative stress and pathways that lead to cell death. The source document suggests that interfering with antioxidant defenses, including pathways related to glutathione S-transferase, may increase levels of reactive oxygen species in certain cancer cells. This could contribute to changes in mitochondria, activation of caspases, altered expression of Bcl-2, and cell-cycle arrest. However, these mechanisms alone are not enough to establish selective anticancer effects in humans. Any claims about protecting normal cells, reducing metastasis, or improving the effectiveness of chemotherapy need careful evaluation and direct supporting evidence. [14,15,17]

5.2. Anti-inflammatory and immunomodulatory activity

Extracts and components of P. longum have been studied for their effects on inflammatory signaling, including pathways involving NF-κB, cytokines such as IL-1β and IL-6, tumor necrosis factor, cyclooxygenase-2, and inducible nitric oxide synthase. These findings are mostly based on mechanistic or preclinical studies. Clinical claims related to conditions like rheumatoid arthritis or gout should not be made without proper human evidence. [11,14,15]

5.3. Gastrointestinal and metabolic effects

The source describes effects of piperine on digestive secretions and reports antidiabetic or metabolic properties of root extracts. These observations need to be linked to specific experimental models, formulations, doses, and outcomes. The current material does not provide sufficient detail at the study level to assess the consistency, magnitude, or clinical significance of these effects. [11,14,15,18]

5.4. Respiratory effects

Traditional use and experimental research have considered P. longum for treating cough and other respiratory issues. The source refers to conditions like asthma and chronic bronchitis, including possible effects on bronchial symptoms and release of mediators. However, the clinical trials supporting these claims are not clearly identified in the provided references. Therefore, these claims need to be verified and should not be presented as proven treatment options. [11,14,15]

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5.5. Gastroprotection and intestinal infections

Preclinical studies mentioned in the source suggest that certain fractions of P. longum might influence gastric secretion, mucosal protection, or outcomes related to ulcers. These claims require specific study citations and should be clearly differentiated from established treatments for ulcers or intestinal infections. [11,14,15]

6.6. Neuroprotective and antimicrobial effects

Animal studies have examined potential effects on oxidative stress, learning, and memory. Laboratory studies have also assessed the antimicrobial activity of extracts or volatile components. While these findings could support further research, they do not prove the prevention or treatment of human neurodegenerative diseases or infections. [2,10,11,14,15]

VI. EXTRACTION AND ANALYTICAL METHODS

The source lists various materials used in the extraction and analysis process, including long pepper material, piperine, ethanol, acetone, hexane, deionized water, and acetonitrile. Methods mentioned include ultrasound-assisted extraction, Soxhlet extraction, batch solvent extraction, and chromatographic analysis. Rathod and Rathod (2014) are cited for their work on the ultrasound-assisted extraction of piperine.[1]

Extraction time and temperature, ultrasound power if applicable, filtration and concentration procedures, extraction yield, analytical standards, instrument settings, validation parameters, and the number of replicates. These details are not present in the supplied manuscript and should not be fabricated.[1]

VII. BIOAVAILABILITY ENHANCEMENT AND COMBINATION STRATEGIES

Piperine is being studied as a potential enhancer of drug bioavailability. These effects may increase the exposure of some co-administered compounds, but the outcome is drug-specific and could also lead to increased risk of adverse effects or clinically significant interactions. Products containing piperine should not be assumed to improve the safety or effectiveness of other medications.[18]

Combination or platform described in source	Rationale proposed in source	Evidence qualification Curcumin with piperine
Rifampicin/other antitubercular medicines	Potential increase in curcumin exposure	The suggested rise of up to 2,000% needs to be checked against the specific primary study, dose, and formulation before it can be used
Piperlongumine with anticancer drugs	Potential experimental effects on resistance or sensitization	Improved treatment time or results cannot be assumed without clinical proof; the risk of interaction should be examined
Chitosan or other polymer-based carriers	Protection and controlled release of selected constituents	Each preparation's formulation performance must be proven through experiments

VIII. PHARMACOLOGY NETWORK AND APPROACH

In this method idea about how P. longum works with multiple parts. Computational predictions need clear reporting of databases, selection rules, target prediction tools, network building, statistical analysis, and experimental validation. These should not be considered as proof of a mechanism on their own. [14,15,16]

IX. NANOTECHNOLOGY-BASED DELIVERY SYSTEMS

Low aqueous solubility, formulation instability, and first-pass metabolism are mentioned as issues for some parts of P. longum. Nanotechnology-based delivery systems are being looked at as possible ways to improve solubility, protect active components, change release patterns, or target specific tissues. [12,14,15,19]

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9.1. Solid lipid nanoparticles

Solid lipid nanoparticles may hold lipophilic compounds and affect how they are released and absorbed. Claims about better lymphatic transport or improved delivery to a certain organ need specific pharmacokinetic and biodistribution data from the formulation. [14,15,19]

9.2. Liposomes and cubosomes

Liposomes and cubosomes are lipid-based systems that could be used to deliver piperine or piperlongumine. Their suitability depends on how well they hold the compounds, their size and stability, how they release the substance, where they go in the body, their toxicity, and the method of administration. [14,15,19]

9.3. Transdermal systems and nano emulsions

Nano emulsions and transdermal carriers may be explored for applying drugs on the skin or through the body. The idea that a formulation avoids the digestive system or liver processing depends on the method used and how the product is made; long-lasting release and localized pain reduction must be shown, not just assumed. [14,15,19]

X. TOXICOLOGY AND SAFETY CONSIDERATIONS

The source describes mostly positive results from some animal toxicity tests at commonly used or tested doses, but also warns that piperine might change how other medicines are processed. Results from animal studies can't confirm safety in people, and findings for one extract or compound can't be automatically applied to other products. [13–15,18]

Extra care is needed for drug interactions, medicines with narrow therapeutic ranges, dosage, duration, extract standardization, and the chance that processing changes the chemical makeup. The source also mentions traditional warnings against long-term high-dose use of the raw material. These points should be backed by exact references and should not be taken as personal medical advice. [13,18]

XI. FUTURE DIRECTIONS AND RESEARCH

Several areas need attention from the reviewed topics:

(I) verifying the plant material and making extracts consistent;
(ii) confirming chemical identities and measuring key components;
(iii) improving consistency across extraction and testing methods;
(iv) separating findings from lab, animal, and human studies;
(v) looking into drug interactions with suitable pharmacokinetic studies;
(vi) checking computational predictions with experiments;
(vii) examining nano formulations for their stability, release, distribution, and safety; and
(viii) doing well-organized, ethically approved human studies if preclinical data supports it. [14,15]

XI. LIMITATIONS OF THE AVAILABLE EVIDENCE

The manuscript did not include a repeatable strategy for searching literature or tables with details about each study. Some treatment claims were not tied to specific primary studies, and several references were missing, repeated, or had placeholders. Therefore, the paper is a structured narrative rather than a complete evaluation of the evidence. All claims and references should be checked before submitting. [14,15]

XII. CONCLUSION

Piper longum L. is an important plant in traditional medicine with a wide range of reported chemicals and several areas of pharmacological study. Piperine is of special interest because it may affect how drugs are handled in the body, while piperlongumine has been studied in experimental cancer models. Extracts and components have also been investigated

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for their effects on inflammation, the digestive system, metabolism, the respiratory system, brain protection, and against infections.

However, the strength of the evidence varies a lot, and many potential uses are still in the early stages of research. Nanotechnology and computational methods provide opportunities for research, but the actual benefit in clinical settings will rely on reliable formulation techniques, thorough safety evaluations, and carefully planned human trials. [2,11,14,15,18]

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