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Literary study of *Piper longum* Linn., A Potent Bioavailability Enhancer

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ABSTRACT

Piper longum Linn. (*Pippali*), a well-known medicinal plant of the family Piperaceae, has been extensively used in Ayurveda and other traditional systems of medicine since antiquity. It is an important constituent of classical formulations such as *Trikatu* and is renowned for its *Deepana, Pachana, Rasayana, and Vatanulomana* properties. The present review aims to compile and critically analyze the available literature on the botanical description, traditional uses, Ayurvedic attributes, phytochemical constituents, pharmacological activities, and its significance as a bioavailability enhancer. Phytochemical investigations revealed the presence of diverse secondary metabolites including alkaloids (notably piperine), amides, lignans, flavonoids, essential oils, esters, and organic acids, which are responsible for its broad spectrum of biological activities. Experimental studies have demonstrated its antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, neuroprotective, anticancer, antihyperglycemic, and immunomodulatory effects. Recent advances highlight its application in green synthesis of metal nanoparticles and enhancement of oral bioavailability of co-administered drugs. This review emphasizes the therapeutic potential of Piper longum and supports its relevance in integrative medicine and future drug development.

Key words: *Pippali*, *Piper longum* Linn., Nanotechnology, Bioavailability enhancer

INTRODUCTION

Healing with medicinal plants is an ancient practice. Secondary metabolites of various plants have been traditionally utilized for the betterment of human-health. Plants belonging to genus Piper are amongst the important medicinal plants used in various systems of medicine. More than 1000 species belongs to this genus and *P. longum* is one of the most well-known species, including *Piper nigrum* and *Piper bettle*. *P. longum* forms an active constituent of the widely used Ayurvedic poly-herbal formulation —*Trikatu* (Johri et al., 1992)[1]. The word pepper is derived from the Sanskrit for long pepper (*pippali*). Long pepper (*Piper longum*), sometimes called Javanese, Indian, or Indonesian long pepper, is a flowering vine in the family Piperaceae cultivated for its fruit, which is usually dried and used as a spice. The fruits contain the alkaloid piperine, which contributes to their pungency. In Ayurvedic medicine, it is a potent *Rasayan Dravya* (good rejuvenator). *P. longum* stimulates the appetite and dispels gas from the intestines. An infusion of *P. longum* root is used after birth to induce expulsion of the placenta [2].

TAXONOMICAL CLASSIFICATION

According to Cronquist (1988)[3], the taxonomical classification of P. longum has been proposed as follows (Lawrence, 2017)[4]

Kingdom: Plantae.

Division: Magnoliophyta.

Class: Magnoliopsida.

Order: Piperales.

Family: Piperaceae.

Genus: Piper.

Species: longum

SYNONYMS: *Piper latifolium* Hunter, *P. saramentosum* Wall., *Chavica roxburghii* Miq, C.

VERNACULAR NAMES: English: Long pepper, Hindi: Pippali, Sanskrit: Pipali

HABITAT: The native of plant is considered to be South Asia and is found both wild as well as cultivated, throughout the hotter parts of India from central to the north-eastern Himalayas. The herb also grows wild in Malaysia, Singapore, Bhutan, Myanmar[5].

AYURVEDIC PROPERTIES OF PIPPALI [6]

Rasa : Katu, Tikta, Madhura.

Guna : Laghu, Snigdha.

Virya : Anushna.

Vipaka : Madhura.

Doshakarma: Kapha vata shamaka

ROGAGHNATA

It is described to be potent dravya used in various diseases such as - Kasa, Shvasa, Hikka, Aruchi, Agnimandya, Ajirna, Vibandha, Gulma, Udara vikara, Arsha, Yakridvikara, Pliha vriddhi, Krimiroga, Hriddourbalya, Pandu, Raktavikara, Amvata, Vatarakta, Kshaya, Yakshma, Shukradourbalya, Rajorodha, Kashtaprasava, Kushtha, Jirna jvara, Vishamajvara, Dourbalya in various classical lexicons.[7,8,9,10].

KARMA

Various pharmacological activities of Pippali such as- Kasahara, Shvasahara, Hikkanigrahana, Rasayana Medhya, Vatahara Mutrala, Dipana, Vatanulomana, Shulaprashamana, Mridurecana, Krimighna, Raktotkleshaka, Jantughna, Shrovirechana, Plihavriddhihara, Yakriduttejaka, Vishamajvara, Raktotkleshaka, Vrishya, Balya, Garbhashyasamkocaka in the ayurvedic literature. [11].

Prayojyanga : Phala, Mula [12]

Dose : Churna 500mg-1gm [12]

BOTANICAL DESCRIPTION:

Fig.1 *Piper longum* plant

Habit: A slender, aromatic climber with perennial woody roots.

Root: Root stock erect, thick, jointed, and branched.

Stem: Stems numerous, 0.6 -0.9m, ascending or prostrate (not climbing) much branched, stout, cylindrical, thickened above nodes, finely pubescent.

Leaves: Ovate, cordate, subacute, entire, glabrous.

Flowers: Flowers are unisexual, minute, sessile bracteate without perianth very densely packed in spikate inflorescences. The male & female spikes are on separate plants.

Fruit: Ovoid, yellowish orange, sunk in fleshy spike [14].

Fig.2 Unripe fruit of *Pippali*

Fig.3 Dried mature fruits of *Pippali*

TRADITIONAL USES:

Dried unripe fruits are used as an alternative to tonic. Decoction of immature fruits and roots is used in chronic bronchitis, cough and cold. Roots and fruits are also used as anti-dote in snake biting and scorpion sting [15]. An equal part of powdered seeds of *Embelia ribes*, fruit of *P. longum* L. and borax powder has been used as an Ayurvedic contraceptive [16]

PHYTOCHEMISTRY

P. longum contains a number of secondary metabolites of various classes, such as alkaloids, lignans, flavonoids, amides, esters, essential oils, and organic acids. Alkaloids are abundant phytochemicals in all major plant parts namely fruits, seeds, leaves, stems, and roots. Piperine was the first amide isolated from the Piper species that also contributes to P. longum's hot and pungent flavour (Lee, Shin, & Woo, 1984)[17]; Saraf & Saraf, 2014[18]

KNOWN PHARMACOLOGICAL ACTIVITIES [19]

Antiproliferative, anticancer, and antitumour activities, Neuro-pharmacological activity, Anti-Alzheimer's disease activity, Anti-Parkinson's disease activity, Antidepressant activity, Antistress activity, Central nervous system depressant activity, Nootropic effect, Anticonvulsant and antiepileptic activities, Antiinflammatory, analgesic, antiarthritic, and antiosteoporotic activities, Antihyperglycaemic activity, Antioxidant activity, Hepatoprotective activity, Antiulcer activity, Antibacterial activity, Antifungal activity, Antiparasitic activity, Scolicidal activity, Anthelmintic and insecticidal properties, Acaricidal activity, Antiamoebic activity, Mosquito larvicidal and adulticidal activities, Molluscicidal activity.

PIPER LONGUM IN GREEN SYNTHESIS AND NANOTECHNOLOGY

Nanotechnology is now widely used for synthesizing drugs in the pharmaceutical industry. Formulation of nanoparticles, nanospheres, nano-capsules, nano-emulsion, and nanosuspensions are few applications of nanotechnology in the field of nanomedicine [20]. Nanoparticles are physically and chemically altered to have high potency to act upon the biological cell structure of the body [21,22].

In an vitro study, Silver nanoparticles (AgNPs) which were synthesized using aqueous extract of P. longum leaves, showed potent antioxidant, radical scavenging, anticancer against Hela cell line, and larvicidal against A. stephensi, Aedes aegypti, and Mesocyclops thermocyclopoide activities which were characterized by UV–Vis, FE-SEM, XRD, and FTIRI (Yadav, Saini, Kumar, Pasi, & Agrawal, 2019)[23].

In an another study, silver nanoparticles prepared using P. longum catkin (flowers) extract, showed catalytic and antibacterial activities against mastitis causing bacteria S. aureus, P. aeruginosa, and B. subtilis (Jayapriya et al., 2019) [24] and food-borne pathogenic bacteria namely B. cereus, S. aureus, E. coli, Proteus mirabilis, K. pneumoniae, P. aeruginosa, and S. typhi (Huang et al., 2020) [25].

Jamila et al.,(2020) studied that the *P. longum* catkin extract were used to synthesize silver nanoparticles as well as copper oxide and nickel nanoparticles and were studied for their pharmacological activities which

proved that these nanoparticles exhibited anticancer, antioxidant, antimicrobial, and redox catalytic activities, characterized by UV–Vis, FTIR, SEM, and atomic force microscopy (AFM)[26].

All these above referenced experimental studies support the advantages of using simple and cost-effective bio green synthesis methods for manufacturing different metal nanoparticles with potent antioxidant, antimicrobial, catalytic, and cytotoxic activities which may be used for pharmaceutical and industrial purposes.

PIPER LONGUM AS BIOAVAILABILITY ENHANCER

Chemical substances known as "bioenhancers" are those that, when combined with pharmaceuticals, increase their bioavailability without having a synergistic impact on the drug itself. Toxicity, expense, poor bioavailability, and long-term medication administration all contribute to the need for bioenhancers, which aid in solving the majority of these issues.

Piperine, also known as 1-peperoyl piperidine, is an aromatic alkaloid produced by the Piper species. It was revealed in an in vivo study that, Piperine alters the lipid milieu and membrane dynamics at the site of absorption to improve permeability. The molecular nature of piperine makes it appropriate for inhibiting enzymes. By blocking several metabolising enzymes, it increases the bioavailability of many medications, including carbamazepine, curcumin, ciprofloxacin, ampicillin, metronidazole, oxytetracycline, and many more. As a result, piperine, a potent inhibitor of medication metabolism, effectively increases absorption.[27]

Various studies suggesting enhancement of Bioavailability of medicine by Piperine

- In a clinical study in epilepsy patients, the impact of piperine (20 mg orally) on the pharmacokinetics of carbamazepine (300 or 500 mg dose) was assessed. The administration of carbamazepine and carbamazepine combined with piperine, showed that the pharmacokinetic parameters from blood samples taken at regular intervals revealed that the concentration of carbamazepine was more in piperenie addition as compared to single carbamazepine which proved that piperine was responsible for raising the mean plasma concentrations compared in both dose groups. Also the injection of piperine, the 500 mg dosage group experienced a considerable rise in Cmax and tmax, which indicated They came to the conclusion that piperine could greatly improve carbamazepine's oral bioavailability, may be by reducing its excretion and/or boosting its absorption[28].
- Jin MJ, et al. (2010) studied whether or not piperine (10 or 20 mg/kg, given orally) increase the oral exposure of fexofenadine (10 mg/kg) in rats, findings showed that adding piperine to fexofenadine increased its oral exposure by 18% to 19% and its bioavailability by around twofold, which may be due to the piperine's effects were probably caused by its ability to block P-glycoprotein-mediated cellular efflux during intestinal absorption[29].
- Janakiraman K, et al(2011) studied the effect of addition piperine in oral formulations of ampicillin trihydrate, as bioenhancing capacity of piperine. It was observed that piperine showed an additive effect or a bioenhancing effect for the formulation[30].
- Shoba G. et al. (1998) investigated that Piperine at doses of 20 mg/kg for rats and 2 g for healthy human volunteers, increases curcumin's serum levels, degree of absorption, and bioavailability in both rats and people without having any negative effects[31]
- The bioavailability term is used to indicate the fraction of a dose that is orally administered and reaches the systemic circulation as an intact drug, then absorption and degradation occur with the help of local metabolites.
- The bioavailability of orally administered drugs is calculated by the ratio of the area under the curve (AUC) against the area for intravenous administration of the particular drug.
- In another study, it is found that Boswellic acids are well-known natural products, which have the capacity to retard inflammation effectively without any severe adverse effects. But, bioactivity and the therapeutic uses of boswellic acid are restricted owing to its poor pharmacokinetic properties. Piper longum extract was found to increase the bioavailability of boswellic acid ($p < .05$). The results confirmed that P. longum may be administered orally with boswellic acid together for effective therapeutic efficacy (Vijayarani et al., 2020)[32].

Possible Mechanism of Action of Piperine as a Bioenhancer as per some vivo studies:-

Possible mechanism of action of how Piperine works to enhance biological function are stated due to the increase in gastrointestinal absorption is caused by following factors:-

1. Bile acid assists in the creation of micelles, which are necessary for the absorption of lipids and lipid soluble medicines, thereby increasing solubility. Piperine increases bile acid secretion which are important for the absorption of lipids and lipid soluble medicines, simultaneously it also inhibits bile acid metabolism which leads to increased micelle formation, which are responsible for lipids and lipid soluble medicines absorption, thereby it increases the solubility of the medicines. This leads to improved absorption and solubility of the given medicine[33].
2. Piperine activates the gamma-glutamyltranspeptidase activity by interacting with intestinal epithelial cells leading to increased amino acid intake by the intestinal epithelial cells resulting in increased membrane permeability[34].
3. Piperine also helps to improve brush border membrane fluidity and microvilli length leading to increased surface area for absorption and motility[35].

These are some of the factors which explains the Bioenhancing capacity of P. longum.

DISCUSSION

In *charak samhita Pippali* is known for its *yogvahi guna* which can be looked as an bioavailability enhancer. That means *pippali* when combined with either combination of herbs enhances the property as compared to the single use of it. Piperine has been shown to enhance the bioavailability of structurally and theurapitacally diverse drug possibly by modulating membrane dyanamics due to its easy participate. On and increasing permeability. The study has been reported that trikatu (a combination drug of long pepper, ginger, black pepper) increases their bioavailability either by promoting rapid absorption of gastrointestinal tract or by protecting the drug being metabolised its first pass effect through liver after being absorbed or by combination of both of above said mechanism. This gives scientific validation of the yogvahi effect of pippali vis a vis as a bioavailabilty enhancer

The extensive therapeutic utility of *Piper longum* described in classical Ayurvedic texts finds substantial support in modern phytochemical and pharmacological research. Ayurvedic attributes such as *Katu rasa, Laghu–Snigdha guna, Anushna virya,* and *Madhura vipaka* explains its efficacy in Kapha-Vata disorders, respiratory ailments, digestive dysfunctions, metabolic diseases, and rejuvenative therapies. The traditional indications mentioned in *Charaka Samhita, Sushruta Samhita, Ashtanga Hridaya,* and *Bhavaprakasha Nighantu* closely correlate with experimentally validated pharmacological actions.

Phytochemical profiling of Piper longum reveals that alkaloids, particularly piperine, play a pivotal role in its biological activities. Piperine modulates drug-metabolizing enzymes, enhances gastrointestinal absorption, and exhibits antioxidant, anti-inflammatory, neuroprotective, and anticancer properties. Other constituents such as lignans, flavonoids, and essential oils contribute synergistically to its antimicrobial, hepatoprotective, and immunomodulatory actions.

The wide range of pharmacological activities, including neuropharmacological, anti-inflammatory, antioxidant, antihyperglycaemic, and anticancer effects, validates the traditional use of Piper longum as a Rasayana and Medhya drug.

Recent advances in green synthesis demonstrate its utility in the eco-friendly production of metal nanoparticles with significant biomedical applications. Additionally, its role as a bioavailability enhancer substantiates its *Yogavahi* property described in study of Boswellic acids , making it valuable in combination therapies. However, further clinical validation, standardization, and safety profiling are required for its widespread therapeutic application.

CONCLUSION

Piper longum Linn. is a medicinally significant plant in Ayurvedic medicine and increasing scientific validation. Its diverse phytochemical constituents, including piperine, are responsible for a wide spectrum of pharmacological activities. The plant's emerging role in green nanotechnology and as a bioavailability

enhancer further expands its therapeutic relevance. This review highlights the potential of *Piper longum* as a promising candidate for integrative medicine and future drug development. However comprehensive experimental and clinical studies are essential to fully harness its therapeutic benefits and ensure safe, effective utilization in modern healthcare.

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