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CRITICAL REVIEW ON VARIOUS ETHONOMEDICINAL AND PHARMACOLOGICAL ASPECTS OF *Piper longum* Linn. (LONG PEPPER or PIPPALI)

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Abstract

Piper longum Linn. (family piperaceae) is popularly known as long pepper. It is widely distributed in the tropical and sub-tropical regions of the world, throughout the Indian subcontinent, Sri Lanka, Middle Eastern countries and the Americas. The root and stem part of the *P. longum*, has been used for various Ayurvedic and Unani system of medicine. The fruits of the *P. longum* are used as a stomachic, liver tonic, aboartifacient, pungent, aphrodiasic, stomachic, laxative, anti-diarrhoeal, anti-dysenteric, anti-asthmatic, anti-bronchitis, abdominal complaints, in urinary discharges, tumours, diseases of the spleen, pains, inflammation, leprosy, insomnia, jaundice, and hiccoughs. The roots of *P. longum* are used for the treatment of heart diseases. An infusion of the root is used for parturition, to help in the eviction of the placenta. *P. longum* possesses several pharmacological properties like antibacterial, antifungal, insecticidal, antiulcer, antiplatelet, antiamoebic, hepatoprotective, adulticidal, anti-obesity, larvicidal, antidepressant, anticancer, anti-asthmatic etc. *P. longum* contain piperine as the major and active constituent, the piperine content is 3-5%. The fruits of *P. longum* possesss starch, protein and alkaloids, volatile oils, saponins, carbohydrates, and amygdalin.

Keywords: *Piper longum*, folk medicine, antimicrobial potential, pharmacological activities, phytochemistry

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INTRODUCTION

Piper longum Linn. (syn *P. latifolium* Hunter*, P. saramentosum* Wall*., Chavica roxburghii* Miq*)* is belongs to the family piperaceae. It is a flowering plant. *P. longum* commonly known as Indian long pepper, pippali or pipali. It is widely used as a spice and flavouring agent in preparation of a variety of herbal formulations [1-2]. *P. longum* has been used as a therapeutic agent in various diseases. The fruit and root of species *P. longum* are used as anti-irritant, analgesic, anti-asthma and bronchitis. Apart from root of and stem *P. longum* whole plants are also used for the treatment of variety of diseases conventionally [3].

Geographical distribution

P. longum is native to Indo-Malaya region. It is now mainly cultivated in India, Nepal, Indonesia, Malaysia and Sri Lanka. In our country, it is mostly cultivated in central Himalayas to Assam, Khasi and Mikir hills, lower hills of West Bengal and evergreen forests of Western Ghats from Konkan to Kerala and also from Car Nicobar Islands [4].

Plant description

P. longum is a perennial long, slender, climber with woody roots, creeping and jointed stem with fleshy fruits. Leaves arrangement is alternate, ovate shaped, apex acute to acuminate with entire margins [5]. Male spikes greenish-yellow, cylindrical, fleshy with minute flowers, female spikes, erect, yellow. The fruit spikes are cylindrical, oblong, berries red or black when ripe, globose with aromatic odour and pungent taste [6].

Classification

Kingdom- Plantae

Division- magnoliophyta

Order- piperales

Family- piperaceae

Genus- *Piper*

Species- *longum*

ETHNOMEDICINAL USES

The root and stem part of the *P. longum*, has been used for various Ayurvedic and Unani system of medicine. The fruits of the *P. longum* are used as a stomachic, liver tonic, aboartifacient, pungent, aphrodiasic, stomachic, laxative, anti-diarrhoeal, anti-dysenteric, anti-asthmatic, anti-bronchitis, abdominal complaints, in urinary discharges, tumours, diseases of the spleen, pains,

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inflammation, leprosy, insomnia, jaundice, and hiccoughs. The roots of *P. longum* are used for the management of heart diseases. An infusion of the root is used for parturition, to assist in the expulsion of the placenta. It appears to part take, in a minor degree of the stimulant properties of the fruit and also used as an alternative tonic in paraplegia, chronic cough, enlargement of the spleen and other abdominal viscera. *P. longum* has been used in a variety of compositions of drugs; boiled with ginger, mustard oil, butter milk and curds. It forms a liniment, used in case of paralysis. The roasted fruits of *P. longum* are beaten up with honey and given to treat rheumatism. The decoction of dried young fruits and root are of *P. longum* used in the form of decoction in the treatment of acute and chronic bronchitis [7-8].

PHARMACOLOGICAL USES

Insecticidal and acaricidal activity

The essential oil of the *P. longum* showed insecticidal and insect-repellant activity. *Cinnamomum zeylanicum* toxicities of two piperidine alkaloids (pipernonaline and piperoctadecalidine), isolated from *P. longum* were determined against five species of arthropod pests. Both of the alkaloids showed insecticidal activity [9-10].

Antiulcer activity

Agrawal *et al.,* (2000) [11] reported the antiulcer activity was demonstrated by water decoction of ginger making up one of the constituents of Mahakasyaya drugs along with water decoction of *P. longum* and colloidal solution of Ferula asafoetida has been reported to protect against CRS-, ASP- and PL- induced gastric ulcers in rats. Piperine, an alkaloid of *P. longum* inhibited gastric emptying of solids/liquids in rats and gastrointestinal transit in mice in a dose and time dependent mode. Gastric emptying inhibitory activity of piperine is independent of gastric acid and pepsin secretion [12].

Bioavailability enhancers

Piperine of *P. longum* shown to enhance the bioavailability of structurally and therapeutically varied drugs. It is maybe by modulating membrane dynamics due to its easy partitioning and raise in permeability of other drugs [13]. It was reported that piperine also enhance the oral bioavailability of phenytoin in humans [14-16].

Anti-snake venom activity

Shenoy *et al.,* (2013) reported the ethanol extract of *P. longum* and piperine showed the anti-snake venom performance against Russell's viper venom in embryonated fertile chicken eggs, mice and rats by using various models. The administration of *P. longum* extract and piperine

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significantly ($p<0.01$) inhibited venom induced lethality, haemorrhage, necrosis, defibrinogenation and inflammatory paw edema in mice in a dose dependent way [17].

Antiplatelet activity

Das *et al.,* (1998) reported the inhibitory property of the four acid amides piperine, pipernonaline, piperoctadecalidine, and piperlongumine, isolated from the fruits of *P. longum* were evaluated on washed rabbit platelet aggregation. These four tested acid amides dose-dependently inhibited platelet aggregation induced by collagen, arachidonic acid, and platelet-activating factor, but not that induced by thrombin [18].

Coronary vasodilation activity

Shoji *et al.,* (1986) reported the amide dehydropiperonaline analogue isolated from the fruit of *P. longum* has established the capability to induce coronary vasodilation [19].

Antifungal activity

Lee *et al.,* (2001) reported the essential oil isolated from the fruits of *P. longum* showed fungicidal activity against phytopathogenic *Pyricularia oryzae, Rhizoctonia solani, Botrytis cineria, Phytophthora infestans, Puccinia recondita,* and *Erysiphe graminis*. A piperidine alkaloid, pipernonaline, was isolated from the hexane fraction of *P. longum* showed a potent fungicidal commotion against *P. recondita* with 91% and 80% control values at the concentration of 0.5 and 0.25 mg ml−1, correspondingly [20].

Antiamoebic activity

The methanol extract of *P. longum* fruit was tested for their efficacy against *Entamoeba histolytica in vitro* and against experimental cecal amebiasis in *vivo* [21]. The ethanol extract and constituents piperine of *P. longum*, a pure compound, cured 90% and 40% of rats with caecal amoebiasis, correspondingly [22-23].

Adulticidal activity

The dose dependent adulticidal result of ethanol extract of ethanol extract of fruits of *P. longum* was experiential against *Stegomyia aegypti*. The various extracts of *P. longum* were demonstrated impressive adulticidal activity when tested on female mosquitoesley topical application [24].

Anti-obesity activity

Lee *et al.,* (2005) reported the pharmacological inhibition of acyl Co-A diaylglycerol acyltransferase has emerged as a possible therapy for the management of obesity. Compounds containing piperidine groups are measured potential acyl Co-A diacylglycerol acyltransferase inhibitors [25].

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Larvicidal activity

Ethanol extracts of *P. longum* was evaluated for the efficiency against early fourth instar larvae of *Aedes aegypti* mosquito using a larvicidal bioassay [26,27].

Antidepressant activity

The ethanolic fruit extract of *P. longum* yielded a piperine alkaloid and it has strong antidepressant like commotion, which is mediated in part through the inhibition of MAO activity. Treatment with piperine (6.25-25mM) for 72hours reversed the induced reduction of BDNF mRNA expression in cultured hippocampal neurons [28-30].

Anticancer and Antitumor activity

The alcoholic extract of *P. longum* (10mg/dose/animal) and piperine (1.14mg/dose/animal) inhibits solid tumor development in mice induced with Daltons lymphoma ascites cells and increases the life span of mice. Piperine also shown cytotoxic towards Doltons lymphoma ascites and Ehrlichascites carcinoma cells at 250mg/ml. Piplartine and piperine are the major constituents of *Piper longum* was shown to produce anti-tumor result on sarcoma 180 tumours transplanted in mice, it shown decrease of tumor weight in piplartine and piperine treated animals [31-33].

Anti-asthmatic activity

The extract of *P. longum* in milk reduced passive cutaneous anaphylaxis in rats and protected gunia pigs against antigen-induced bronchospasm [34-35].

Anti-diabetic activity

The aqueous extract of *P. longum* showed anti-hyperglycemic and anti-lipidperoxidative activities in sterptozotocin induced diabetic rat. Oral administration of dried fruits of *P. longum* has shown significant anti-hyperglycemic, anti-hyperlipidemic property in diabetic rats compared to that of the model reference during glibenclamide [36-37].

Hypocholestrolaemic activity

Piper analogue isolated from *P. longum* considerably inhibited the elevation of total serum cholesterol, and the total serum cholesterol to HDL-cholesterol ratio in rats fed with a high cholesterol diet. The unsaponicable fraction of the oil of *P. longum* also considerably decreased total serum cholesterol and hepatic cholesterol in hypercholesterolaemic mice [38-39].

Hepatoprotective activity

The plant extract of *P. longum* was studied in rodents for its hepatoprotective action against carbontertrachloride induced acute, chronic reversible and irreversible damage using morphological, biochemical and histopathologic parameters. The main piperine was found to

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protect against tertiary butyl hydroperoxide induced and carbontetrachloride induced hepatotoxicity by reducing lipid peroxidation by *in vitro* and *in vivo* methods [40-41].

Analgesic activity

Vedhanayaki *et al.,* (2003) reported the aqueous root extract of *P. longum* (200, 400, and 800/kg) was given orally to mice and rat to study its analgesic property. In rat the delay in reaction time to thermal stimulant was assessed. In mice the amount of writhing to chemical stimulus was assessed. The effect of the 400 and 800mg/kg doses of fruit were like to that of NSAID drugs ($p<0.0001$). Both ibuprofen (40mg/kg) and *P. longum* (800mg/kg) demonstrated 50% protection against writhing. The delay in reaction time to thermal stimulus was<6% for different doses of fruit as compared with 100% for pentazocaine. The results showed that the plant and root extract of *P. longum* produces a weak-opioid-type but potent non-steroidal anti-inflammatory drug type of analgesic [42].

Antiapoptotic activity

The hexane: ethanol (2:8) extract of *P. longum* showed anti-apoptosis and antioxidant activity through tunel assay and radical scavenger activity. The fruit extracts on GM-induced hair cell loss in basal, middle and apical regions in a neonatal cochlea cultures. The study accomplished that the fruit extract of *P. longum* showed anti-apoptosis and antioxidant activity. The petroleum ether extracts of the fruit decrease lipid peroxide levels and maintains glutathione content, demonstrates antioxidant activity [43-44].

Anti-inflammatory

The fruit extract of *P. longum* were reported to possess anti-inflammatory activity in carageanan rat paw edema. *P. longum* extract and piperine possess inhibitory activities on prostaglandin and leukotrienes Cox-1 inhibitory effect and thus exhibit anti-inflammatory activity [45-46]. Stohr *et al.,* (2001) reported that the *Piper* extracts and piperine have inhibitory activities on prostaglandin and leukotrienes COX-1 inhibitory effect and thus exhibit anti-inflammatory activity [47].

Immunomodulatory activity

Mananvalan and Singh (1979) reported the immunomodulatory potential of *P. longum* fruits extract has been evaluated by hoemagglutination titre, macrophage migration index, and phagocytic index in mice. A well-known ayurvedic preparation containing long pepper, pippali rasayana, was tested in mice infected with *Giardia lamblia* and found to produce significant activation of macrophages as shown by an increased macrophage migration index and phagocytic activity [48].

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Anti-arthritic activity

Yende *et al.,* (2010) reported anti-arthritic activity of *P. longum* in Complete Freund's adjuvant induced arthritis in rats where they illustrated that the aqueous extract of *P. longum* has the capability to significantly reduce the swelling of the paws which may be attributed to the immunomodulatory activity exhibited by piperine [49].

Protective myocardial activity

Mishra (2010) reported that piperaldehyde is one of the important constituent of *P. longum* which was isolated from the fruits of the *P. longum* by extracting it with methanol as solvent. Studies conducted revealed that the alcoholic extract and piperaldehyde shows significant DPPH scavenging activity and exert protective outcome in the myocardial narcotic rats. They activity protected myocardium from the harmful effects of lipid per oxidation and even maintained the glutathione levels to normal [50].

Antifertility activity

Lakhmi *et al.,* (2006) [51] reported that the hexane fraction of *P. longum* has potent antiimplantation activity accompanied by the mortality of animals. *P. longum* roots when used along with *Embelia ribes* seeds showed 100% anti-fertility activity in female albino rats [52]. It is believed that *P. longum* probably potentiates the contraceptive activity of other plant products, the feasibility of such a combination needs to be investigated further for the progress of a contraceptive for the female as reported in Ayurveda Garbhanivarana Aushadham used for both female and male [53] devoid of interfering with the activity of ovarian hormones on uterus [54].

Radioprotective activity

The radioprotective property of an ethanol extract of *P. longum* fruits were evaluated in Swiss mice. The extract attenuated the elevated levels of glutathione pyruvate transaminase, alkaline phosphatase and lipid peroxidation in the liver and serum of radiation-treated animals. The extract also restored glutathione production to offer radioprotection [55].

PHYTOCHEMISTRY

P. longum contain piperine as the major and active constituent, the piperine content is 3-5% (on dry weight basis) in *P. longum* [56]. The fruits of *P. longum* have starch, protein and alkaloids, volatile oils, saponins, carbohydrates, and amygdalin [57].

Alkaloids and amides

The fruit of *P. longum* contains a more number of alkaloids and related compounds, the most plentiful of which is piperine, followed by methyl piperine, pipernonaline, piperettine, asarinine,

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pellitorine, piperundecalidine, piperlongumine, piperlonguminine, retrofractamide A, pergumidiene, brachystamide-B, a dimer of desmethoxypiplartine, N-isobutyl decadienamide, brachyamide-A, brachystine, pipercide, piperderidine, longamide, dehydropipernonaline piperidine and tetrahydro piperine. Piperine, piperlongumine, tetrahydropiperlongumine, trimethoxy cinnamoyl-piperidine, and piperlonguminine have been found in the root. Newly recognized chemical constituents are 1-(3,4-methylenedioxyphenyl)1E-tetradecene, 3-(3,4-methylenedioxophenyl)propenal, piperoic acid, 3,4-di-hydroxy- biabola-1, 10-diene, eudesm-4-ene-1beta, 6-alpha-diol, 7-epi- eudesm-4-ene-1beta, 6beta-diol, guineesine, and 2E,4E-dienamide, -Nisobutylhenicosa-2,4,8-trienamide [58-59].

CONCLUSION

In various pathological conditions *P. longum* has been used as a therapeutic agent. The fruit and root of species *Piper longum* are used as anti-irritant, analgesic, anti-asthma and bronchitis. Apart from its root and stem whole plants are used for the treatment of variety of diseases traditionally. The fruits of the *P. longum* are used as a stomachic, liver tonic, aboartifacient, pungent, aphrodiasic, stomachic, laxative, anti-diarrhoeal, anti-dysenteric, anti-asthmatic, anti-bronchitis, abdominal complaints, in urinary discharges, tumours, diseases of the spleen, pains, inflammation, leprosy, insomnia, jaundice, and hiccoughs. The roots of *P. longum* are used for the treatment of heart diseases. An infusion of the root is used for parturition, to help in the expulsion of the placenta. *P. longum* possesses several pharmacological properties like antibacterial, antifungal, insecticidal, antiulcer, antiplatelet, antiamoebic, hepatoprotective, adulticidal, anti-obesity, larvicidal, antidepressant, anticancer, anti-asthmatic activities.

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