

Remedial merits of *Piper longum* Linn with astonishing antidiabetic potential

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Abstract

Over the past three decades, the number of people with diabetes mellitus (DM) has doubled globally, making it one of the most important public health challenges to all nations. This has been stimulating the development of novel and potentially more effective therapeutic approaches to treat the disease. Even after the availability of a massive amount of hypoglycemic drugs in conventional system, herbals are gaining much attention because of its spectacular therapeutic potential and also help to sustain the healthy condition of the body. In this review article, a highly valuable drug *Pippali* (*Piper longum*) has been evaluated on the basis of its pharmacognostical, pharmacological, and therapeutical background. The plant possesses significant antidiabetic activity. The systemic dysfunction associated with DM can also be cured by *Pippali*. Plant through exhibiting synergistic action gives a valuable response in hepatic, digestive, cardiac, and respiratory disorders. The purpose of this review is to enlighten all the remedial aspects of *P. longum* with a special focus on its antidiabetic potential.

Key words: Antidiabetic, diabetes mellitus, *Piper longum*, *Pippali*, *Prameha*

INTRODUCTION

Piper longum Linn. (Family Piperaceae), commonly known as long pepper, a slender, aromatic climber with perennial woody roots, occurring in hotter parts of India from central Himalayas to Assam and also cultivated in North East and many parts of the South.^[1] Long pepper is the unripe spike of the plant. The fruit, which is blackish green in color and shining in appearance generally sunk inside the fleshy spike, is the medicinally used part of the plant. The root, which is thick and branched, called as *pippali mula*, is also used medically.^[2] Pharmacological profile shows that the plant acts as antidiabetic, antihyperlipidemic, hepatoprotective, neuroprotective, cardioprotective, antibacterial, aphrodisiac, respiratory effective agent, and digestive agent and also more effectively as bio-enhancing agent.^[3] The above-mentioned activities of the plant occurs due to five basic pharmacological properties described in Ayurveda, i.e., *Rasa Panchaka* (*Rasa*, *Guna*, *Virya*, *Vipaka*, and *Prabhava*) along with due to the presence of several active phytoconstituents. *P. longum* fruit contains volatile oil, other minor alkaloids such as pipartine, piperlongumine, piperidine, starch, resin, and pungent alkaloid piperine.^[4] Piperine, which is the major active constituent,

constitutes about 3–5% (on dry weight basis) of the plant. The pungency of the fruits is mainly due to the presence of alkaloid piperine.^[3] Some studies reveal that fruit also contains some essential macro elements in a considerable percentage such as calcium 1230 mg/100 g, phosphorous 190 mg/100 g, and iron 62.1 mg/100 g.^[5] The roots of this plant contain piperine, pippalartin, piperlongumine, sterols, and glycosides.^[6]

The earliest known documentation of plant treatment in Indian literature is found in *Vedas* and *Pippali* has got its importance since the time of *Vedas*, then further continued in different *Puranas*, *Nighantus*, *Samhitas* and now in modern era, it has been widely used as a single herb and also as a constituent in different products available in market, thus exhibiting its therapeutic potential in several disorders.

Nowadays, due to irregular dietary habits and less physical activities, severe lifestyle disorders such as heart diseases, stroke, obesity, and diabetes mellitus (DM) are emerging

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Received: 07-07-2017

Revised: 22-09-2017

Accepted: 18-10-2017

speedily in human beings. The worldwide prevalence of DM has risen dramatically over the past two decades. Prevalence of type II DM is increasing worldwide much more rapidly than type I DM because of increasing obesity and reduced physical activity level of men and trends toward more industrialization.^[7] DM refers to a heterogeneous chronic metabolic disorder that shares the phenotype of hyperglycemia which is caused by a complex interaction of genetic, behavioral, and environmental factors. It results due to impaired insulin secretion or insulin resistance, decreased glucose utilization and increased glucose production.^[8,9] There is a critical need for the development of the new therapeutic agents that target the underlying pathogenic mechanisms involved in diabetes. In the field of phytomedicine, much interest has been focused on the development of alternative medicinal herbal preparations, which has the ability to cure and/or delay the progression of diabetes through different mechanisms. These compounds may provide a safer drug for treatment of diabetes. A plethora of literature is available to document the antidiabetic effects of plants and their preparations.^[10-12] In Ayurveda, it is advocated that regular intake of the fruit of *P. longum* in a fixed amount for a specific duration act as *Rasayana* (anti-aging agent) and enough capability to cure any diseases.^[13] In the present paper, it has been tried to document the chief therapeutic potentials of *P. longum* with special reference to its *Prameha-har* (antidiabetic) property. Necessary and relevant information regarding *Prameha* (DM) and *P. longum* has been extracted out from different sources (Textbooks of Ayurveda, Ayurvedic Pharmacopeia of India, Ayurvedic Formulary of India) and from different networking sites for the compilation of this article.

MATERIALS AND METHODS

Prameha in Ayurvedic Classics

An elaborative description regarding *Prameha* is available in different *ayurvedic* treatises such as greater triads (*Charak Samhita*, *Sushruta Samhita*, and *Ashtanga Hridayam*), lesser triads (*Madhava Nidan*, *Sharangdhara Samhita*, and *Bhavaprakasha*), and others such as *Harita Samhita*, *Bhel Samhita*, *Kashyapa Samhita*, *Gayadasa*, *Chakrapanidatta*, *Basvrajiyam*, *Yogaratnakara*, *Vangasena*, and *Bhaishajya Ratnavali*. *Prameha* is described as a disease in which increment in the quantity of urine along with an alteration in quality of urine takes place which is considered as “*Prabhuta avila Mutrata*” in ayurvedic literature.^[14] 20 types of *Prameha* have been described on the basis of *Dosha* involved in the pathogenesis and manifestation of the disease. It includes 10 types of *Kaphaj Prameha*, six types of *Pittaj Prameha*, and four types of *Vataja Prameha*.^[15] In *Bhel Samhita*, *Prameha* has been divided into two types, i.e., *Swakrita* and *Prakrita*.^[16] All *Pramehas*, if not treated properly with due course of time, get converted into *Madhumeha*.^[17] *Charak* has explained *Madhumeha* in types of *Vataja Prameha* as *Ojomeha*.^[18]

Pippali (*P. longum*) in Ayurvedic Classics

Although the description of *Pippali* was available since *Vedic* period, *Pippali* was more extensively used in *Puranas* as compared to *Vedas*. *Pippali* has been described in the context of *Vataja bheshaj* (which eliminates disorders caused due to *Vata dosha*) in *Atharva Veda*.^[19] In *Agni Purana*, properties of *Trikatu* has been described, in which *Pippali* is found to be useful in *Medoroga*, *Rajyakshama*, *Kasa*, *Shwasa* and *Gulma*, etc., diseases.^[20] *Acharya Charak* has elucidated the *Yogavahi karma* of *Pippali* in *Vimana Sthana* due to which it is used in various formulations either as a supportive ingredient or as an adjuvant.^[21] *Lodhrasava* and *Madhvasava* useful in *Prameha* consist of *Pippali* as one of the main ingredients.^[22] *Pippali* is a part of *Pippalyadi gana* which is indicated for digestive disturbance related disorders.^[23] *Sushruta* has mentioned that all *Katu Rasa Dravyas* are *Avrisha* but *Pippali* and *Sunthi* are exceptions to them.^[24] Among 426 *Dravyas* dealt in *Bhavaprakash Nighantu*, 47 *Dravyas* (herbs) are described as *Pramehahara* and *Pippali* is among one of them. *Haritakyadi varga* contains nine drugs having *Pramehaghana* activity, and *Pippali* is also one of them.^[25] *Pippali* is found to be useful in *Jirnajwara*, *Vishmajwara*, and *Naktandhya*. *Pippali* and *Madhu* (honey) as an adjuvant is beneficial in *Puranajwara* and *Shwasa Roga*.^[26] The Ayurvedic Pharmacopeia of India therapeutically indicated it in *Prameha* (DM), *Hikka* (Hiccough), *Kasa* (cough), and *Kustha* (skin diseases).^[27] In Ayurvedic Formulary of India, *Pippali* is being used in 324 formulations. Classical formulations are useful in *Prameha* containing *Pippali* as an ingredient are compiled in Table 1.

Scientific Validation of Various Therapeutic Properties of *P. longum*

Diabetes is a metabolic disorder which is mainly related to the disturbed liver metabolism. Disturbances in liver functioning lead to the initiation of a lot of other diseases and complications. *P. longum* as described in Ayurveda is a plant with sufficient potency which not only takes out diabetes from the body but also stops the augmentation of other complications by maintaining the functioning of body systems such as liver metabolism, respiratory diseases, gastrointestinal tract disturbances, heart problems, and antimicrobial activities. Hence, along with a description of antihyperglycemic effect of *P. longum*, it is necessary to highlight the additional important properties of the plant.

Antidiabetic Activity

P. longum can be used as an alternative remedy for the treatment of diabetes and oxidative stress associated diabetic complications. Oral administration of ethanolic extract of the drug for 45 days restored the blood glucose in diabetic rats which indicates that the extract stimulated the activities of the liver to maintain the normal homeostasis of blood glucose during diabetes.^[28] Aqueous extract of *P. longum* at a dose

Table 1: Classical formulations containing *Pippali* as an ingredient and used as *Pramehahara* (antidiabetic)

Formulations	Indications	References
<i>Eladi churna</i> ^[43]	<i>Pramehahara</i> (antidiabetic)	B. R. 37/41
<i>Mehamudgar Gutika</i> ^[44]	<i>Pramehahara</i> (antidiabetic), <i>Mutrakruccha</i> (dysuria), <i>Aruchi</i> (anorexia)	B. R. 37/64-68
<i>Meghanada Rasa</i> ^[45]	<i>Pramehahara</i> (antidiabetic)	B. R. 37/136-137
<i>Vidangadi loha</i> ^[46]	<i>Pramehahara</i> (antidiabetic) and all kinds of urinary disorders	B. R. 37/185
<i>Lodhrasava</i> ^[22]	<i>Pramehahara</i> (antidiabetic), <i>Pandu</i> (Anemia), <i>Aruchi</i> (anorexia)	C. Ci 6/43
<i>Madhvasava</i> ^[22]	<i>Pramehahara</i> (antidiabetic), <i>Pandu</i> (anemia), <i>Aruchi</i> (anorexia)	C. Ci 6/44
<i>Dantyasava and Bhallatakasava</i> ^[22]	<i>Pramehahara</i> (antidiabetic), <i>Pandu</i> (anemia), <i>Aruchi</i> (Anorexia)	C. Ci 6/45
<i>Navayas lauha</i> ^[47]	<i>Pramehahara</i> (antidiabetic), <i>Pandu</i> (anemia), <i>Kustha</i> (skin diseases)	S. Ci (12/11)

of 200 mg/kg.b.w in streptozotocin induced diabetic rats was found to possess significant antidiabetic activity after 6 h of the treatment.^[29] Oil of the plant leads to increment in body weight, liver glycogen content, plasma insulin along with decrement in glycosylated hemoglobin, and total plasma cholesterol, thus indicating its antidiabetic potential.^[30]

Cardioprotective Activity

Cardiovascular risks are more commonly associated with DM. *Pippali* is an effective cardioprotective agent as well. The methanolic extract of *P. longum* prevents the destructive effect on histopathological and biochemical parameters produced due to isoproterenol in a rat model having acute myocardial ischemia.^[31] Piperlongumine at different concentrations inhibited platelet aggregation induced by thromboxane A(2) receptor agonist U46619, but it slightly inhibited thrombin-induced one. It is assumed that piperlongumine inhibits platelet aggregation as a thromboxane A(2) receptor antagonist.^[32] Studies showed that alcoholic extract and piperonaldehyde exerts a protective effect on the myocardium of rats through preventing from the harmful effects of lipid peroxidation and also helps to maintain normal glutathione levels.^[33]

Hepatoprotective Activity

Alteration in lipid profile is commonly associated with the cases of diabetes. In this condition, *P. longum* may be helpful via acting as a hepatoprotective agent. Along with *P. nigrum*, it shows synergistic effect and found to be beneficial in viral hepatitis. If aqueous extract of *P. longum* and piperine administered along with normal doses of antitubercular drugs, it lowers down the rate of lipid peroxidation and increased the reduced glutathione levels also, thus exhibits its hepatoprotective action.^[34]

Bio-enhancing Activity

Bioavailability is the rate and extent to which therapeutically active substance enters systemic circulation and becomes available at the required site of action. Intravenous

administration of drugs shows maximum bioavailability, while oral administration yields a reduced percentage due to incomplete drug absorption and first-pass metabolism.^[35] *Pippali* has been considered as *Yogavahi* in *ayurvedic* classics. *Yogavahi* drug in combination with main drug exerts synergistic action and leads to enhancement in therapeutic potential of that drug. Piperine was found to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics due to its easy partitioning and increase in permeability of other drugs such as vasicine, indomethacin, and diclofenac sodium. Piperine exhibits potential to act as a bio-enhancing agent thus helps to reduce dose of metformin and also the adverse effects of it. In combination with subtherapeutic dose of metformin, it showed much better effect than therapeutic dose of metformin.^[36]

Antimicrobial and Antiamoebic Activity

In Ayurveda, *Pippali* has been considered as *Krimighna*, because of its *Katu Rasa*, *Ushna Virya*, and *Tikshana Guna*. The methanolic extract of fruit of the *P. longum* reduce the severity of cecal wall ulceration in mice caused by *Entamoeba histolytica*.^[37] Both roots and fruits of *P. longum* are effective against amoebiasis almost up to same extent.^[38] Different extracts of piper species against different bacterial pathogens such as *Staphylococcus albus*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Bacillus megaterium* and one fungus, i.e., *Aspergillus niger*, has been studied and it has been evaluated that they were exhibiting significant antibacterial activities while the aqueous extract did not show any antibacterial activity against the tested pathogens.^[39]

Respiratory Effective Agent

Most of the pharmacological and therapeutic actions of *P. longum* is due to the presence of alkaloid piperine and this piperine is also responsible for the effect on respiratory tract disorders. It has been found that isolated piperine produce antagonistic effect in respiratory depression produced by

morphine.^[40] A comparative study which has been conducted in between nalorphine and piperine to evaluate the antagonistic effect on morphine induced respiratory depression and analgesic effects. It was found that nalorphine antagonize both respiratory depression and analgesia produced due to morphine but piperine reversed only the respiratory depression and not the analgesic effect of morphine.^[41] Extract of the *P. longum* fruits in milk leads to reduction in passive cutaneous anaphylaxis in rats and protected guinea pigs against antigen-induced bronchospasm.^[42]

DISCUSSION

Prameha (diabetes) is not a single disease but rather a group of metabolic disorders which is characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with an absolute or relative deficiency in insulin secretion and/or insulin action.^[48] Therefore, a plant possessing hypoglycemic action along with hypolipidemic and antioxidant property when administered orally will be better for the management of diabetes. In Ayurveda, some of the plants have been identified which can stimulate beta cells to liberate insulin that further is the basic line of treatment of diabetes, and *P. longum* is among those identified plant materials.^[49] Deficiency in the production of insulin by the pancreas results in increased concentrations of glucose and other metabolites in the blood, which in turn damages many of the body's organs as liver, heart, blood vessels, kidney, etc.,^[50] and *P. longum* has exposed potent pancreatic enzymes activity.^[51] *P. longum* can act as an effective remedy in respiratory disorder. As per ayurvedic context, it has been described as *Kasahar* (cough), *Shwasahar* (breathing disorders), and *Hik kahar* (hiccough) which mainly occurs due to aggravated *Vata* and *Kapha dosha* and *Pippali* exhibits *Kapha* and *Vata dosha* hair property. In uncontrolled diabetes, glucose and lipids (fats) remain in the bloodstream and, with time, damage the body's vital organs and contribute to the generation of heart disease.^[48] Intake of antidiabetic drugs with cardiovascular diseases had more potential drug interactions than patients without cardiovascular disease in our study.^[52]

Prameha (diabetes) and liver disorders are very much interconnected to one another. DM might contribute to liver damage by promoting inflammation and fibrosis through an increase in mitochondrial oxidative stress mediated by adipokines.^[53] Garcia-Compean *et al.*, 2009, found that about 30% of patients with liver cirrhosis have DM which advocate that diabetes may be a risk factor for chronic liver disease and in the presence of hepatic disease, the metabolic homeostasis of glucose is impaired as a result of disorders such as insulin resistance, glucose intolerance, and diabetes.^[54] The liver is a central player in buffering plasma glucose contributing either by net hepatic glucose utilization or net hepatic glucose production depending on the plasma glucose level.^[55] *P. longum* has revealed hepatoprotective action^[56] and balances

enzymatic and non-enzymatic antioxidants levels by lessening oxidative stress which is the major contributor of diabetes.^[57] Nabi *et al.* have reported dual action of *Piper longum* by presenting antidiabetic (reducing blood glucose level) action as well as hepatoprotective (significantly reduced the level of triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, very LDL –cholesterol, and serum enzymes) action.^[29] Hence, it can be said that *Pippali* has a potential as an antidiabetic as well as also manage complicated factors associated with the disease.

CONCLUSION

In the present review article, an attempt has been made to assemble the thorough description on *Pippali* (*P. longum*) by enlightening its pharmacognostical, morphological, pharmacological, phytochemical, therapeutic, and nutritional values. While assessing various journals, manuscripts, and textbooks on this plant, we found that *P. longum* has exposed good action on liver protection, respiration system, antiamebic, and antibacterial activity as well as potent antidiabetic action. Although researchers on *P. longum* and its alkaloids has gained a special attention in recent times, there is a need of more well documented clinical trials and more laboratory work to isolate the active principles, their pharmacological actions and toxicity. Further studies on *P. longum* are required to isolate and characterize the bioactive antidiabetic principles from the plant which can, therefore, be used as an alternative remedy for the treatment of DM and oxidative stress associated diabetic complications.

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Source of Support: Nil. **Conflict of Interest:** Nil.