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PERSPECTIVES

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Overview for Various Aspects of the Health Benefits of *Piper Longum* Linn. Fruit

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Abstract
Herbal remedies have become popular, due in part to the lower risk of adverse reactions. Thousands of plants have been used traditionally to treat various diseases. Among them, species of the genus *Piper* are important medicinal plants used in various systems of medicine. The *Piper longum* fruit has been used in traditional medicine, including the Ayurvedic system of medicine. Although there are numerous indications for its use, controlled trials are needed to determine its efficacy. The primary constituents isolated from various parts of *P. longum* are piperine, piperlongumine, sylvatin, sesamin, diaeudesmin piperlonguminine, pipermonaline, and piperundecalidine. It is most commonly used to treat chronic bronchitis, asthma, constipation, gonorrhea, paralysis of the tongue, diarrhea, cholera, chronic malaria, viral hepatitis, respiratory infections, stomachache, bronchitis, diseases of the spleen, cough, and tumors. This study provides detailed information about the *P. longum* fruit, including phytochemistry, pharmacological profile and safety profile. In view of the commercial, economic, and medicinal importance of the *P. longum* plant, it is useful for researchers to study the plant in detail.

1. Introduction

The word pepper is derived from the Sanskrit word 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. Long pepper is a close relative of *P. nigrum*, which gives black, green, and white pepper and has a similar but generally hotter flavor. The fruits contain the alkaloid piperine, which contributes to their pungency. Another species of long pepper, *P. retrofractum*, is native to Java, Indonesia. When applied topically, it soothes and relieves muscular pains and inflammation. In Ayurvedic medicine, it is said to be a 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 [1].

The whole plant as well as plant parts such as the fruit are used traditionally, but detailed information regarding its use have not been compiled. This plant is inexpensive, readily available, and effective for many diseases, including cancer, inflammation, depression, diabetes, obesity, and hepatotoxicity.

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The aim of this article is to highlight recent advances in pharmacology and pharmacognosy research on *P. longum* plant, and to inform researchers about this plant to encourage its study [2].

This literature review included journals from the library and on-line, internet databases, search engines, websites [3–6], and books.

2. Background

P. longum was first written about by Hippocrates, who described it as a medicament rather than a spice. Long pepper reached Greece in the 6th or 5th century BCE, and long pepper was an important and well-known spice before European discovery of the New World. The history of black pepper is linked to (and often confused with) that of long pepper, although Theophrastus distinguished the two in the first work of botany. The Romans knew of both and often referred to either as just piper; Pliny erroneously believed that dried black pepper and long pepper came from the same plant. Round or black pepper began to compete with long pepper in Europe beginning in the 12th century and had replaced it by the 14th century. Today long pepper is a rarity in general commerce [7].

3. Geographical Distribution

The plant grows in evergreen forests of India and is cultivated in Assam, Tamil Nadu, and Andhra Pradesh. Long pepper is cultivated on a large scale in limestone soil and in heavy rainfall areas where relative humidity is high [1–2].

4. Plant Description

P. longum is a small shrub with a large woody root and numerous creeping, jointed stems that are thickened at the nodes (Figure 1). The leaves are alternate, spreading, without stipules and with blades varying greatly in size. The lowest leaves are 5–7 cm long, whereas, the uppermost are 2–3 cm long. Flowers grow in solitary spikes. The fruits, which grow in fleshy spikes 2.5–3.5 cm long and 5 mm thick, are oblong, blunt, and blackish-green. The mature spikes are collected and dried as the commercial form of pippali, and the root radix is known as pippalimula. There are three grades of piplamul: grade I with thick roots and underground stems fetch a higher price than grade II or III, which consist of thin roots, stems, or broken fragments. The commercial drug consists almost entirely of transversely cut pieces (length, 5–25 mm; diameter 2–7 mm), which are cylindrical, straight, or slightly curved; some have distinct, swollen internodes exhibiting a number of leaf and rootlet scars. The surface is a dirty light brown. The drug has a peculiar odor and a pungent bitter taste that produces numbness on the tongue [2,7–8].

Figure 1 (A) The *Piper longum* plant and (B) fruit.

4.1. Scientific classification [1]

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Piperales
Family:	Piperaceae
Genus:	*Piper*
Species:	*longum*
Botanical name:	*Piper longum*

4.2. Synonyms [8]

Arabic:	دار فلفل Dâr fulful
Bengali:	Piplamor
Chinese:	荜拨 Bi bo, 荜茇根 Bi ba gen
Dutch:	Langwerpige peper
English:	Indian long pepper, jaborandi pepper, long pepper
French:	Poivre long
German:	Bengalischer Pfeffer, Jaborandi-Pfeffer, Langer Pfeffer,
Gujuarati:	Pipli
Hindi:	Pipar, piplamul
Hungarian:	Bengáli bors
Italian:	Pepe lungo
Kannada:	Hippali, Lippali, Thippili
Malaya:	Magadhi, Pippali, Thippili, Tippili
Marathi:	Pimpli
Nepalese:	गज पिप्ल Gaj pipla, सानो पिप्ल Saano pipla
Portuguese:	Pimenta-longa
Swedish:	Långpeppar
Tamil:	Kandan lippilli, pippili, sirumulam, tippili, thippili
Telugu :	Pippallu
Turkish:	Dar biberi
Urdu:	Pippal

5. Principal Constituents

The fruit contains a large number of alkaloids and related compounds, the most abundant of which is piperine, followed by methyl piperine, pipernonaline, piperettine, asarinine, 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 identified 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(15)-ene-1beta, 6-alpha-diol, 7-epi-eudesm-4(15)-ene-1beta, 6beta-diol, guineesine, and 2E,4E-dienamide, (2E, 4E, 8E) -N-isobutylhenicosa-2,4,8-trienamide [1–2].

5.1. Lignans

The main lignans present in the fruits are sesamin, pulviatilol, and fargesin [1–2].

5.2. Esters

The fruits contain tridecyl-dihydro-p-coumarate, eicosanyl-(E)-p-coumarate, and Z-12-octadecenoic-glycerol-monoester [1–2].

5.3. Volatile oils

The essential oils of the fruit are a complex mixture. Excluding the volatile piperine, the three major components are caryophyllene, pentadecane (both about 17.8%), and bisaboline (11%). Others include thujone, terpinolene, zingiberene, p-cymene, p-methoxyacetophenone, dihydrocarveol, and vitamins A and E [1–2].

5.4. Organic acids

The major organic acids present are palmitic acid and tetrahydropiperic acid [1–2]. Other reported chemical constituents are listed in Table 1 [9–21].

6. Pharmacological Profile

The reported pharmacological activities include the following:

Anticancer	Hepatoprotective
Antioxidant	Anti-inflammatory
Immunomodulatory	Coronary vasodilation
Antimicrobial	Bioavailability-enhancing
Antiplatelet	Antifertility
Antihyperlipidemic	Antiobesity
Analgesic	Larvicidal
Adulticidal	Radioprotective
Melanin-inhibiting	Cardioprotective
Antidepressant	Antifungal
Antiamoebic	

6.1. Anticancer activity

The alcohol extract of *P. longum* (10 mg/dose/animal) and piperine (1.14 mg/dose/animal) inhibits solid tumor development in mice induced with Dalton's lymphoma ascites cells and increases the life span of mice. Piperine was also found to be cytotoxic towards Dalton's lymphoma ascites and Ehrlich ascites carcinoma cells at 250 μg/mL [22,23].

6.2. Antioxidant activity

P. longum exhibits promising antioxidant potential against free radical-induced oxidative damage. Petroleum ether extract of the root and piperine from roots of *P. longum* Linn. decrease lipid peroxide levels and maintain glutathione content, demonstrating antioxidant activity [24].

6.3. Hepatoprotective activity

The plant fruit extract was assessed in rodents for its hepatoprotective action against carbon tetrachloride-induced acute, chronic reversible and irreversible damage using morphological, biochemical, and histopathological parameters. The extract stimulates regeneration by restricting fibrosis, but offers no protection against acute damage or against cirrhosis. Piperine was found to protect against tertiary butyl hydroperoxide-induced and carbon tetrachloride-induced hepatotoxicity by reducing lipid peroxidation *in vitro* and *in vivo* [25–26].

6.4. Anti-inflammatory activity

A marked anti-inflammatory activity of *P. longum* fruit decoction has been reported using carrageenan-induced rat edema [19,27].

6.5. Immunomodulatory activity

The specific and nonspecific immunostimulatory actions of *P. longum* fruits have been evaluated by hemagglutination titer, macrophage migration index, and phagocytic index in mice. A well-known Ayurvedic preparation containing long pepper (pippali rasayana) was tested in mice infected with

Table 1 Other reported chemical constituents of *P. longum* [9–21]

Study no.	Reported chemical constituents	Part used	Reference(s)
1	Retrofractamide C, piperrolein B, pipernonaline, dehydropipernonaline, (2E,4Z,8E)/N/[9/(3,4/methylenedioxyphenyl)/2,4,8/nonatrienoyl] piperidine	Fruit	[9]
2	Pipataline, pellitorine, sesamin, brachystamide B, guineensine	Herb	[10]
3	Piperlonguminine	Whole plant	[11]
4	Piperine	Fruit	[12]
5	(2E,4E)/N/isobutyl/eicosa/2,4/dienamide, (2E,4E,14Z)/N/isobutyl/ eicosa/2,4,14/trienamide, (2E,4E,12Z)/N/isobutyl/ocatadeca/ 2,4,12/trienamide, pellitorine, piperanine	Fruit	[13]
6	Isodihydropiperlonguminine	Dried fruit	[14]
7	Piperidine	Fruit	[15]
8	Piperlongumine	Fruit	[16]
9	Methylpiperate	Fruit	[17]
10	Piperoctadecalidine	Fruit	[18]
11	3′,4′,5′-trimethoxycinnamate	Fruit	[19]
12	Cepharadione B, cepharadione A, cepharanone B, aristolactam	Root	[20]
13	Norcepharadione B, 2-hydroxy-1-methoxy-4H-dibenzo, quinoline-4, 5(6H)-dione, 10-amino-4-hydroxy-3-methoxyphenanthrene-l-carboxylic acid lactam [piperolactam A], 10-amino-4-hydroxy-2, 3-dimethoxyphenanthrene-l-carboxylic acid lactam [piperolactam B]	Root	[20]
14	Sylvatin, (+)-diaeudesmin and sesamin	Seed	[21]

Giardia lamblia and found to activate macrophages, as shown by an increased macrophage migration index and phagocytic index, indicating immunostimulatory activity [28].

6.6. Antimicrobial activity

Petroleum ether and ethyl acetate extracts of *P. longum* were found to exert antimicrobial effects against various microorganisms [29].

6.7. Antiplatelet activity

The inhibitory effects of the four acid amides piperine, pipernonaline, piperoctadecalidine, and piperlongumine, isolated from the fruits of *P. longum* L. were evaluated on washed rabbit platelet aggregation. All of the four tested acid amides dose-dependently inhibited washed platelet aggregation induced by collagen, arachidonic acid, and platelet-activating factor, but not that induced by thrombin [30].

6.8. Antihyperlipidemic activity

The ethanol extract of the *P. longum* L. fruit yields piperlonguminine, piperine, and pipernonaline as the main antihyperlipidemic constituents. They exhibit appreciable antihyperlipidemic activity *in vivo*, which was comparable to that of the commercial antihyperlipidemic drug simvastatin [31].

6.9. Analgesic activity

The aqueous suspension of *P. longum* root powder (200, 400, and 800 mg/kg) was given orally to mice and rat to evaluate it analgesic effects. The delay in reaction time to thermal stimulus was assessed in rats, and the amount of writhing to chemical stimulus was assessed in mice. The effects of the 400 and 800 mg/kg doses of *P. longum* were similar to that of nonsteroidal anti-inflammatory drugs ($p < 0.001$). Both ibuprofen (40 mg/kg) and *P. longum* (800 mg/kg) demonstrated 50% protection against writhing. The delay in reaction time to thermal stimulus was < 6% for different doses of *P. longum* as compared with 100% for pentazocine. This indicates that the plant root produces a weak opioid-type but potent nonsteroidal anti-inflammatory drug-type of analgesia [32].

6.10. Adulticidal activity

The dose-dependent adulticidal effect of ethanol extract of *P. longum* was observed against *Stegomyia aegypti*, a main vector of dengue and dengue hemorrhagic fever. The extracts also demonstrated impressive adulticidal activity when tested on female mosquitoes by topical application [33].

6.11. Melanin-inhibiting activity

Piperlonguminine from *P. longum* inhibits melanin production in melanoma B16 cells stimulated with

alpha-melanocyte-stimulating hormone, 3-isobutyl-1-methylxanthine, or protoporphyrin IX, where the compound exhibited stronger depigmenting efficacy. This effect was attributed to the inhibitory action of piperlonguminine on alpha-melanocyte-stimulating hormone signaling through cAMP to the cAMP-responsive element binding protein, which in turn regulates the expression of the microphthalmia-associated transcription factor, a key activator of tyrosinase expression. In this way the enzyme is inhibited internally, thereby suppressing the production of melanin [11].

6.12. Antidepressant activity

Ethanol extraction of *P. longum* fruits yields a known piperidine and piperine alkaloid, as a monoamine oxidase inhibitor. Thus the piper longum fruits represent a promising pharmacotherapeutic candidate against depression [34].

6.13. Antiamoebic activity

The fruits were tested for their efficacy against *Entamoeba histolytica in vitro* and against experimental cecal amebiasis *in vivo*. The ethanol extract and isolated piperine improved cecal amebiasis by 90% and 40%, respectively, in rats [35].

6.14. Coronary vasodilation

The amide dehydropipernonaline isolated from the fruit of *P. longum* L. has demonstrated the ability to induce coronary vasodilation [36].

6.15. Bioavailability enhancers

Piperine has been shown to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics, due to its easy partitioning and increasing permeability. The mechanism by which this compound enhances bioavailability is not understood. We hypothesize that this property may be attributed to increased absorption, which may be caused by altered membrane lipid dynamics and conformational change of enzymes in the intestine. Piperine also has been reported to enhance the oral bioavailability of phenytoin in humans [37–39].

6.16. Antifertility activity

The crude extract, various fractions, and the purified compound isolated from the active fraction of the powdered fruits of *P. longum* were studied for antifertility effects in female rats. The crude extract and its hexane fraction exhibited 100% and 86% efficacy, respectively (days 1–7 post coitum). On the other hand, the 1-butanol soluble, 1-butanol insoluble, and chloroform fractions were inactive. The benzene extract of *P. longum* Linn. fruit along with the methanol extract of the *Embelia ribes* berries inhibited pregnancy by 80% when administered to female rats [40].

6.17. Antiobesity activity

Pharmacological inhibition of acyl CoA diacylglycerol acyltransferase has emerged as a potential therapy for the treatment of obesity. Compounds containing piperidine groups are considered potential acyl CoA diacylglycerol acyltransferase inhibitors [41].

6.18. Larvicidal activity

Ethanol extracts derived from *P. longum* L. were evaluated for efficacy against early fourth instar larvae of *Aedes aegypti* mosquitoes using a larvicidal bioassay [15,42].

6.19. Radioprotective activity

The radioprotective property of an ethanol extract of *P. longum* fruits was 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 [43].

6.20. Cardioprotective activity

The effect of methanol extract of *P. longum* fruits was evaluated on adriamycin-induced cardiotoxicity (i.e., biochemical changes, tissue peroxidation damage, and abnormal antioxidant levels) in Wistar rats. Histopathological studies of the heart revealed degenerative changes and cellular infiltration in rats treated with adriamycin; however, pretreatment with *P. longum* reduced the intensity of these lesions. The results indicate that *P. longum* offers significant protection against adriamycin-induced oxidative stress and reduces cardiotoxicity by virtue of its antioxidant activity [44].

6.21. Antifungal activity

Fungicidal activity of *P. longum* L. fruit-derived materials toward six phytopathogenic fungi, *Pyricularia oryzae, Rhizoctonia solani, Botrytis cinerea, Phytophthora infestans, Puccinia recondita,* and *Erysiphe graminis* was tested using a whole plant method *in vivo*. This treatment was compared with synthetic fungicides (chlorothalonil, dichlofluanid,

and mancozeb) and four commercially available compounds (eugenol, piperine, piperlongumine, and piperettine) [45].

7. Classic Ayurvedic Preparations

Pippalyasavam
Vardhamana pippali
Causasti pippali
Pippali khanda
Sitopaladi churna
Guda pippali

8. Safety Profile of *P. Longum*

Because *P. longum* is widely used in cooking and traditional medicine, it is generally assumed to be safe in moderate doses. However, the fruits are reported to exert contraceptive activity in experimental models; therefore, its use during pregnancy and lactation should be avoided. Piperine may interfere with enzymatic drug biotransformation, resulting in the inhibition of hepatic aryl hydrocarbon hydroxylase and UDP-glucuronyltransferase, and altering the pharmacokinetic parameters of barbiturates and phenytoin. A single oral dose in experimental animals (3 g/kg body weight) and chronic toxicity studies for 90 days revealed no adverse effects. Studies of isolated constituents in mice reported LD_{50} values of piperine, piperlongumine and piperlonguminine as 56.2 ± 3.0, 110.1 ± 7.8, and 115.3 ± 9.5 mg/kg body weight, respectively. Thus, acute toxicity studies do not show any mortality or morbidity when 3 to 5 g/kg is administered to animals during pharmacological study; however, under certain conditions, such as pregnancy and lactation, the fruits of *P. longum* should be used cautiously because of potential interactions [46].

9. Conclusion

P. longum has demonstrated remarkable effects against numerous diseases and conditions, including cancer, inflammation, depression, diabetes, obesity, and hepatotoxicity. The plant markedly improves microbial infections, cardiac disease, and protects against the effects of radiation. The specific effects of the plant make it more useful for animals and human beings. Furthermore, the plant appears to be nontoxic, as no deaths have been reported with the use of high doses of the plant extracts. We conclude that this plant is safe and effective for use in various diseases. The plant is easily available, inexpensive, and free from adverse effects. Thus with the matter collected in this article we can scientifically work for various other pharmacological interrelated activities.

References

1. Kirtikar KR, Basu BD. *Indian Medicinal Plants*. Mumbai, India: Orients Longman, 1980:21–8.
2. Rastogi RP, Malhotra BN. *Compendium of Indian Medicinal Plants*. CDRI, Luckhnow and New Delhi, India: Nisc 1993: 504–857.
3. ScienceDirect. Available at: www.sciencedirect.com [Date accessed: April 24, 2011]
4. National Institutes of Health. National Center for Biotechnology Information. PubMed. Available at: www.pubmed.com [Date accessed: April 24, 2011]
5. Scirus search engine. Available at: www.scirus.com [Date accessed: April 24, 2011]
6. Google India. Available at: www.google.co.in [Date accessed: April 24, 2011]
7. Ayushveda health and lifestyle portal. Available at: http://www.ayushveda.com/herbs/piper-longum.htm [Date accessed: March 03, 2010]
8. Multilingual multiscript plant name database. Available at: http://www.plantnames.unimelb.edu.au/Sorting/Piper.html [Date accessed: March 03, 2010]
9. Lee SW, Rho MC, Park HR, Choi JH, Kang JY, Lee JW, et al. Inhibition of diacylglycerol acyltransferase by alkamides isolated from the fruits of *Piper longum* and *Piper nigrum*. *J Agric Food Chem* 2006;54:9759–63.
10. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. *Stat Methods Med Res* 2006; 15:547–69.
11. Kim KS, Kim JA, Eom SY, Lee SH, Min KR, Kim Y. Inhibitory effect of piperlonguminine on melanin production in melanoma B16 cell line by downregulation of tyrosinase expression. *Pigment Cell Res* 2006;19:90–8.
12. Hong SS, Han XX, Oh GJ, Lee KS, Lee MK, Hwang BY, et al. Piperine from the fruits of *Piper longum* with inhibitory effect on monoamine oxidase and antidepressant-like activity. *Chem Pharm Bull (Tokyo)* 2005;53:832–5.
13. Sun XX, Hodge JJ, Zhou Y, Nguyen M, Griffith LC. The *eag* potassium channel binds and locally activates calcium/calmodulin-dependent protein kinase II. *J Biol Chem* 2004; 279:10206–14.
14. Sunila ES, Kuttan G. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. *J Ethnopharmacol* 2004;90:339–46.
15. Yang YC, Lee SG, Lee HK, Kim MK, Lee SH, LEE HS. A piperidine amide extracted from Piper longum L. fruit shows activity against *Aedes aegypti* mosquito larva. *J Agric Food Chem* 2002;19:3765–67.
16. Chatterjee A, Dutta CP. Alkaloids of *Piper longum* Linn. I. Structure and synthesis of piperlongumine and piperlonguminine. *Tetrahedron* 1967;23:1769–81.
17. Lee SA, Hwang JS, Han XH, Lee C, Lee MH, Choe SG, et al. Methylpiperate derivatives from *Piper longum* and their inhibition of monoamine oxidase. *Arch Pharm Res* 2008;31: 679–83.
18. Park BS, Son DJ, Park YH, Kim TW, Lee SE. Antiplatelet effects of acidamides isolated from the fruits of Piper longum L. *Phytomedicine* 2007;14:853–5.
19. Kumar S, Arya P, Mukherjee C, Singh BK, Singh N, Parmar VS, et al. Novel aromatic ester from *Piper longum* and its analogues inhibit expression of cell adhesion molecules on endothelial cells. *Biochemistry* 2005;6;44:15944–52.

20. Desai SJ, Bharathi R, Mulchandani NB. Aristolactams and 4,5-dioxoaporphines from *Piper longum*. *Phytochemistry* 1988;27:1511–5.
21. Dutt CP, Banerjee N, Roy DN. Lignans in the seeds of *Piper longum*. *Phytochemistry* 1975;14:2090–1.
22. Anuradha V, Srinivas PV, Rao JM. Isolation and synthesis of isodihydropiperlonguminine. *Nat Prod Res* 2004;18:247–51.
23. Pradeep CR, Kuttan G. Effect of piperine on the inhibition of lung metastasis induced B16F/10 melanoma cells in mice. *Clin Exp Metastasis* 2002;19:703–8.
24. Natarajan KS, Narasimhan M, Shanmugasundaram KR, Shanmugasundaram ER. Antioxidant activity of a salt/spice/herbal mixture against free radical induction. *J Ethnopharmacol* 2006;105:76–83.
25. Koul IB, Kapil A. Evaluation of the liver protective potential of piperine, an active principle of black and long peppers. *Planta Med* 1993;59:413–7.
26. Christina AJ, Saraswathy GR, Robert SJ, Kothai R, Chidambaranathan N, Nalini G, et al. Inhibition of CCl4 induced liver fibrosis by *Piper longum* Linn. *Phytomedicine* 2006;13:196–18.
27. Choudhary GP. Mast cell stabilizing activity of *piper longum* Linn. *Indian J Allergy Asthma Immunol* 2006;20:112–6.
28. Tripathi DM, Gupta N, Lakshmi V, Saxena KC, Agrawal AK. Antigiardial and immunostimulatory effect of Piper longum on giardiasis due to *Giardia lamblia*. *Phytother Res* 1999; 13:561–5.
29. Ali AM, Alam NM, Yeasmin MS, Khan AM, Sayeed MA. Antimicrobial screening of different extracts of *Piper longum* Linn. *Res J Agr Bio Sci* 2007;3:852–7.
30. Iwashita M, Saito M, Yamaguchi Y, Takagaki R, Nakahata N. Inhibitory effect of ethanol extract of *Piper longum* L. on rabbit platelet aggregation through antagonizing thromboxane A2 receptor. *Phytomedicine* 2007;14:853–5.
31. Jin Z, Borjihan G, Zhao R, Sun Z, Hammond GB, Uryu T. Antihyperlipidemic compounds from the fruit of *Piper longum* L. *Phytother Res* 2009;23:1194–6.
32. Vedhanayaki G, Shastri GV, Kuruvilla A. Analgesic activity of *Piper longum* Linn. root. *Indian J Exp Biol* 2003;41:649–51.
33. Choochote W, Chaithong U, Kamsuk K, Rattanachanpicchai E, Jitpakdi A, Tippawangkosol P, et al. Adulticidal activity against *Stegomyia aegypti* (Diptera: Culicidae) of three Piper spp. *Rev Inst Med Trop Sao Paulo* 2006;48:33–7.
34. Lee SA, Hwang JS, Han XH, Lee C, Lee M, Choe SG, et al. Methylpiperate derivatives from *Piper longum* and their inhibition of monoamine oxidase. *Arch Pharm Res* 2008;31: 679–83.
35. Ghoshal S, Lakshmi V. Potential antiamoebic property of the roots of *Piper longum* Linn. *Phytother Res* 2002;16:689–91.
36. Shoji N, Umeyama A, Saito N, Takemoto T, Kajiwara A. Ohizumi Dehydropipernonaline, an amide possessing coronary vasodilating activity, isolated from Piper longum L. *J Pharm Sci* 1986;75:1188–9.
37. Pattanaik S, Hota D, Prabhakar S, Kharbanda P, Pandhi P. Effect of piperine on the steady-state pharmacokinetics of phenytoin in patients with epilepsy. *Phytother Res* 2006;20: 683–6.
38. Singh M, Varshneya C, Telang RS, Srivastava AK. Alteration of pharmacokinetics of oxytetracycline following oral administration of Piper longum in hens. *J Vet Sci* 2005;6:197–200.
39. Khajuria A, Thusu N, Zutshi U. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. *Phytomedicine* 2002;9:224–31.
40. Lakshmi V, Kumar R, Agarwal SK, Dhar JD. Antifertility activity of *Piper longum* Linn. in female rats. *Nat Prod Res* 2006;20:235–9.
41. Lee SA, Hong SS, Han XH, Hwang JS, Oh GJ, Lee KS, et al. Piperine from the fruits of Piper longum with inhibitory effect on monoamine oxidase and antidepressant/like activity. *Chem Pharm Bull* 2005;53:832–5.
42. Chaithong U, Choochote W, Kamsuk K, Jitpakdi A, Tippawangkosol P, Chaiyasit D, et al. Larvicidal effect of pepper plants on *Aedes aegypti* (L.) (Diptera: Culicidae). *J Vector Ecol* 2006;31:138–44.
43. Sunila ES, Kuttan G. Protective effect of *Piper longum* fruit ethanolic extract on radiation induced damages in mice: a preliminary study. *Fitoterapia* 2005;76:649–55.
44. Wakade AS, Shah AS, Kulkarni MP, Juvekar AR. Protective effect of *Piper longum* L. on oxidative stress induced injury and cellular abnormality in adriamycin induced cardiotoxicity in rats. *Indian J Exp Biol* 2008;46:528–33.
45. Lee SE, Park BS, Kim MK, Choi WS, Kim HT, Cho KW, et al. Fungicidal activity of pipernonaline, a piperidine alkaloid derived from long pepper, *Piper longum* L., against phytopathogenic fungi. *Crop Protection* 2001;20:523–8.
46. Chanda D, Shanker K, Pal A, Lugman S, Bawankule DU, Mani D, et al. Safety evaluation of Trikatu, a generic Ayurvedic medicine in Charles foster rats. *J Toxicol Sci* 2009;34:99–108.