Piperine- Review of Advances in Pharmacology

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ABSTRACT: Piperine, an alkaloid, is found in *Piper longum* L. and *Piper nigrum* L. The plants containing piperine are widely used in Alternative and Complementary Therapies for curing an array of disorders. Piperine obtained from botanical sources is about 98% pure. It is produced in the laboratory for chemical and medical purposes. Piperine is helpful in reducing inflammation, improving digestion, and relieving pain and asthma. It is reported to improve the production of serotonin, it may relieve stomach ulcerations. It improves the bioavailability of other nutritive substances including beta carotene, curcumin, selenium, pyroxidine, glucose, and amino acids. Extensive data has been complied in favour of piperine in a wide range of pharmacological studies. The review analyses recent advances in pharmacology research on piperine.

KEYWORDS: Piperine; bioavailability; pharmacology

Introduction

In recent years many researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to support function and treat diseases. In most cases, scientist has confirmed the veracity traditional experience and wisdom by discovering the mechanism of action of these plants. *Piper longum* L. and *Piper nigrum* L. (Piperaceae) are used in Indian traditional medicine (Singh et al., 1992) and as a spice globally. Piperine (C17H19NO3), the alkaloid is responsible for the pungency of *P. nigrum* L. and *P. longum* L (Singh et al., 1992). Piperine can be obtained from the oleoresin in the peppercorns. Piperine makes up about 5-7% of the peppercorns. It exhibits a wide variety of biological effects.

Antidepressant Activity

In one of the studies, Song et al., 2007 investigated the antidepressant effect of piperine in mice exposed to chronic mild stress procedure. Repeated administration of piperine for 14 days in doses of 2.5, 5 and 10 mg/kg reversed the chronic stress induced changes in sucrose consumption, plasma corticosterone level and open field activity. Furthermore, the decreased proliferation of hippocampal progenitor cells was ameliorated and the level of brain-derived neurotrophic factor in hippocampus of chronic stressed mice was up-regulated by piperine treatment.

In the another study, Wattanathorn et al., 2008 administered piperine to Wister male rats, at various doses ranging from 5, 10 and 20 mg/kg/day, body wt. (p.o.) for 4 weeks and the neuropharmacological activity (elevated plus maze, spontaneous locomotor behavior, forced swimming test, cognitive function) was determined after single, 1, 2, 3 and 4 weeks of treatment. The results showed that piperine during entire dosage range possessed anti-depression like activity and cognitive enhancing effect during entire treatment duration.

Bioenhancer Properties

Kulkarni et al., 2008 evaluated that simultaneous administration of piperine (2.5 mg/kg, i.p.) with curcumin (20 and 40 mg/kg, i.p.) which resulted in the potentiation of antidepressant activities. Zhao et al., 2007 noted the reversal of oxidative stress and hepatic dysfunction induced by beryllium. They observed that individual administration of gallic acid (50 mg/kg, i.p.) and piperine (10 mg/kg, p.o.) moderately reversed the altered biochemical variables, whereas the combination of these was found to completely reverse the beryllium-induced biochemical alterations and oxidative stress consequences. They concluded that gallic acid exerts a synergistic effect when administered with piperine. Nirala et al., 2008 evaluated the effect of piperine (10 mg/kg, 5 consecutive day, p.o.) individually and in combination with tifferron...
(300 mg/kg, i.p.) against beryllium (1 mg/kg/day, 28 days, i.p.) induced biochemical alteration and oxidative stress. They found that the combination of tiferron with piperine could reverse all the variables significantly towards the control. Vladimir et al., 1999 studied the effect of simultaneous administration of piperine (5mg) on serum concentration of β-carotene (15mg) in healthy volunteers for 14-days. The results indicate that there was a significant increase (P<0.0001) in serum β-carotene concentration when supplemented with piperine (49.8±9.6µg/dl vs 30.9±5.4µg/dl) compared to β-carotene plus placebo, respectively. There was 60% increase in area under curve of β-carotene plus piperine when compared with β-carotene plus placebo. Vladimir et al., 2000 studied the relative bioavailability of 90 mg and 120 mg of coenzyme Q10 simultaneous administered with piperine (5mg) or placebo in healthy adult male volunteers in single-dose experiment or in separate experiments for 14 and 21 days. The result of single and the 14th day dose study indicated smaller, but no significant increase in plasma concentration when compared with coenzyme Q10 plus placebo. Supplementation of 120 mg coenzyme Q10 with piperine for 21st days produces a statistically significant difference (p=0.0348), approximately 30% greater, area under the plasma curve than coenzyme Q10 plus placebo.

Bhutani et al., 2005 (b) examined the protective effect of piperine on DNA damage and activities of detoxifying enzyme such as glutathione peroxidase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione in the liver, heart, kidney, intestine and aorta were observed in rats. They concluded that simultaneous supplementation of high fat diet with piperine lowered thiobarbituric acid reactive substances, conjugated dienes and activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione in the liver, heart, kidney, intestine and aorta were observed in rats. They concluded that simultaneous supplementation of high fat diet with piperine lowered thiobarbituric acid reactive substances, conjugated dienes and activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione near those of control rats. Selvendiran et al., 2005 (a) revealed significant suppression (33.9-66.5%) in the micronuclei formation induced by benzo (a) pyrene and cyclophosphamide which was reduced following oral administration of piperine at doses of 25, 50 and 75 mg/kg in mice.

Durgaprasad et al., 2005 evaluated the effect of oral curcumin (500 mg) with piperine (5 mg) on the pain, and the markers of oxidative stress in patients with tropical pancreatitis for 6 wks. There was a significant reduction in the erythrocyte malonyldialdeyde levels following curcumin therapy compared with placebo, with a significant increase in glutathione levels. Lambert et al., 2004 reported that piperine (70.2 micromol/kg, p.o.) co-administered with (-)-Epigallocatechin-3-gallate (163.8 micromol/kg, p.o.) to male CF-1 mice increased the plasma C(max) and area under the curve by 1.3-fold compared to mice treated with Epigallocatechin-3-gallate only. It appears to be due to inhibiting glucuronidation and gastrointestinal transit.

Apoptosis inhibition

Choi et al., 2007 demonstrated that piperine (10-100 microM) protect House Ear Institute-Organ of Corti-1 cells against cisplatin-induced apoptosis through the induction of heme oxygenase-1 expression in dose- and time-dependent manner. The c-Jun N-terminal kinase pathway played an important role in piperine-induced heme oxygenase-1 expression.

Genotoxicity

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Antioxidant

Vijaykumar et al., 2004 studied the effect of simultaneous administration of piperine (0.02 g/kg, b.wt) plus high-fat diet (containing 20% coconut oil, 2% cholesterol, and 0.125% bile salt) for 10 days on levels of thiobarbituric acid reactive substances, conjugated dienes and activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione in the liver, heart, kidney, intestine and aorta were observed in rats. They concluded that simultaneous supplementation of high fat diet with piperine lowered thiobarbituric acid reactive substances, conjugated dienes and activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione near those of control rats. Selvendiran et al., 2005 (b) examined the protective effect of piperine on DNA damage and activities of detoxifying enzyme such as glutathione transferase, quinone reductase and UDP-glucuronosyl transferase in lung cancer bearing animals induced by Benzo (a) pyrene. They observed that supplementation of piperine (50 mg/kg, b.wt) enhanced the
activities of detoxification enzymes and reduced DNA damage as determined by single cell electrophoresis. Neelima et al., 2007 investigated the role of piperine in cadmium induced immuno-compromised marine splenocytes. Addition of piperine in various concentrations (1, 10 and 50 µg/ml) ameliorated oxidative stress markers, Bcl-2 protein expression, mitochondrial membrane potential, caspase-3 activity, DNA damage, splenic B and T cell population, blastogenesis and cytokines. The highest dose of piperine could completely abrogate the toxic manifestations of cadmium and the splenic cells behaved in similar way as the control cells.

Anti-platelet Effect
Park et al., 2007 isolated four acidamides (piperine, pipermonaline, piperoctadecalidine, and piperlongumine) from fruits of *Piper longum L.* and examined inhibitory effect on washed rabbit platelet aggression induced by collagen, arachidonic acid, platelet activating factor and thrombin. They showed dose dependent inhibitory activities on platelet aggression except for that induced by thrombin.

Anti-Inflammatory Activity
Sarvesh et al., 2007 demonstrated that piperine inhibits adhesion of neutrophils to endothelial monolayer due to its ability to block the tumor necrosis factor-α induced expression of cell adhesion molecules i.e. intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin. They observed that pretreatment of endothelial cells with piperine blocks the phosphorylation and degradation of IkBα by attenuating tumor necrosis factor-α induced IkB kinase activity. Pradeep et al., 2004 observed that piperine at 2.5, 5 and 10 µg/ml concentration inhibited the collagen matrix invasion of B16F-10 melanoma cells in a dose-dependent manner. It also significantly reduced the proinflammatory cytokines (such as IL-1β, IL-6, TNF-α, GM-CSF).

Antihypertensive effect
Taqvi et al., 2008 observed that intravenous administration of piperine caused a dose-dependent (1 to 10 mg/kg) decrease in mean arterial pressure in normotensive anesthetized rats; the next higher dose (30 mg/kg) did not cause any further change in mean arterial pressure. Piperine, in vitro study on rabbit heart causes a partial inhibition of force, rate of contraction and coronary flow. In rabbit aortic ring, piperine inhibited high K+ (80 mM) precontractions and partially inhibited phenylephrine, due to Ca2+ channel blockade. In Ca2+-free medium, piperine (1 to 30 microM) exhibited vasoconstrictor effect.

Hepatoprotective Effect
Matsuda et al., 2008 isolated piperine, of ethyl acetate-soluble fraction from methanolic extract and concluded that piperine, dose-dependently inhibited increase in serum GPT and GOT levels at doses of 2.5-10 mg/kg (p.o.) in D-galactosamine induced liver toxicity in mice, and suggested that this inhibitory effect depended on the reduced sensitivity of hepatocytes to tumor necrosis factor-α.

Antithyroid activity
Vijayakumar et al., 2006 concluded that when piperine (40mg/kg) was simultaneously administered with carbimazole (10 mg) for 10 days significant reduction in plasma lipids and lipoproteins levels occurred, except for high density lipoprotein, which was significantly elevated. Piperine supplementation also improved the plasma levels of apo A-I, T3, T4, testosterone, and I and significantly reduced apo B, TSH, and insulin to near normal.

Panda et al., 2003 administered piperine for 15 day at 0.25 & 2.50mg/kg/day, (p.o.) to adult male Swiss albino mice. They concluded that piperine at dose (2.50 mg/kg) lowered the serum levels of both the thyroid hormones, thyroxin (T 4) and triiodothyronine (T 3) as well as glucose concentrations with a concomitant decrease in hepatic 5'D enzyme and glucose-6-phosphatase (G-6-Pase) activity. However, no significant alterations were observed in animals treated with 0.25 mg/kg of piperine in any of the activities studied except an inhibition in serum T 3 concentration.

Fertility Enhancer
Pawinee et al., 1997 evaluated the effect of piperine on fertilization of egg in female hamsters from day 1st through day 4th of the oestrous cycle at dose of 50 and 100 mg/kg (b.wt, p.o). They observed that there was enhancement of fertilization, 85.4±4.1 and 82.8 ±4.8 at doses of 50 and 100mg/kg, respectively at 9 hr after artificial inseminated. However, examination of the embryos retrieved 48 hr after artificial insemination revealed no difference in the stage of embryonic development.

Antitumor activity
Manoharan et al., 2009 investigated the chemoprotective effect of piperine (50 mg/kg, b.wt, p.o, alternate days) against 7, 12 dimethylbenzo[a]anthracene (0.5% in liquid
paraffin, three times a week for 14 weeks) induced buccal pouch carcinoma of Syrian golden hamsters. They observed that piperine completely prevented the formation of oral carcinoma, probably due to its antilipidperoxidative and antioxidant potential as well as its modulating effect on the carcinogen detoxification process. Duessel et al., 2008 observed that piperine displayed an anti-proliferation effect at 24 hours and statistically significant inhibition at 48 and 72 hours at 100 - 200 µM concentration against cultured human colon cancer cells (DLD-1). Wongpa et al., 2007 investigated the influence of piperine on chromosomes in rat bone marrow. piperine administered to Wister male rats at dose of 100, 400 and 800 mg/kg, b. wt, (p.o) for 24 hrs then challenged with cyclophosphamide at a dose of 50 mg/kg, b. wt, (i.p.). They demonstrated that piperine at a dose of 100 mg/kg, gave a statistically significant reduction in chromosomal aberrations.

Antiasthmatic
Kim et al., 2009 induced asthma in Balb/c mice by ovalbumin sensitization. Piperine (4.5 and 2.25 mg/kg) was orally administered 5 times a week for 8 weeks and it was found that piperine-treated groups had suppressed eosinophil infiltration, allergic airway inflammation and airway hyperresponsiveness, and these effects were achieved by suppression of the production of interleukin-4, interleukin-5, immunoglobulin E and histamine.

Toxicity
Dogra et al., 2004 administered piperine (1.12, 2.25, and 4.5 mg/kg, p.o.) for 5 days consecutively to determine the immunotoxicity in Swiss male mice. They noted that piperine at 2.25 and 4.5 mg/kg caused a significant reduction in total leucocyte counts, increase in the percentage of neutrophils and suppressed the mitogenic response of B-lymphocyte to lipopolysaccharide. Treatment at highest dose, however, resulted in significant decrease in the weight of spleen, thymus and mesenteric lymph nodes, but not of peripheral lymph nodes. Since piperine at dose 1.12 mg/kg had no immunotoxic effect, it may be considered as immunologically safe "no observed adverse effect level dose".

Other Activities
Li et al., 2008 evaluated the inhibitory effects of piperine on caries-related bacteria and glucan on dental plaque in vitro. They concluded that piperine had >40% inhibitory effect on soluble glucan synthesis. Both insoluble and soluble glucan synthesis were inhibited by piperine. Veerreddy et al., 2004 prepared different formulations (lipid nanospheres of piperine, lipid nanosphere of piperine with stearylamine, pegylated lipid nanospheres of piperine) and evaluated them as antileishmanial in BALB/c mice infected with Leishmania donovani AG83, for 60 days. A single dose (5 mg/kg, i.v.) of piperine and different formulation were injected. Mice were sacrificed after 15 days of treatment with piperine or formulations and Leishmania donovani Unit was counted. They concluded that piperine reduced the parasite burden in liver and spleen by 38% and 31% after 15 days post infection, respectively. Lipid nanospheres of piperine reduced the parasite burden in liver and spleen by 63% and 52% respectively. Pegylated lipid nanospheres of piperine reduced the parasite burden in liver and spleen by 78% and 75% respectively. Lipid nanosphere of piperine with stearylamine reduced the parasite burden in liver and spleen by 90% and 85% respectively as compared to control. Volak et al., 2008 evaluated that piperine was a relatively selective noncompetitive inhibitor of CYP3A with IC50 = 5.5 +/- 0.7 microM, K(i) = 5.4 +/- 0.3 microM. Ononiuwa et al., 2002 evaluated that piperine produced a dose dependent (at 20 mg/kg, 22.2% and 142 mg/kg, 334.6% ) increase in gastric secretion in albino rats which may be due to stimulation of H2 receptors.

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