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Review Article

# Emerging Diverse Medicinal Properties of Piperine: A Review

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## Abstract

Piperine is the principle alkaloid present in *Piper nigrum* and *Piper longum* species of black pepper which has wide range of pharmacological activities. Piperine was used in the preparation of traditional medicines as well as in modern medicine. Piperine was found to have many pharmacological actions such as analgesic, anti-inflammatory, antioxidant, antitumor, anti-epileptic, anti-rheumatic, hepatoprotective, immunomodulatory effects and so on, in various animal models. The piperine use has been limited due to its low aqueous solubility. For the formulation of a wide range of poorly aqueous soluble drugs, solid lipid nanoparticles are used because of their biodegradable and biocompatible properties and low toxicity. Solid lipid nanoparticles possess unique properties like small size, large surface area and high drug loading ability. The solubility of piperine can be enhanced by formulating them as solid lipid nanoparticles by using different preparation techniques and it can be effectively used for its diverse applications as mentioned earlier.

**Keywords:** Anti-Oxidant Activity; Bio Enhancing Activity; Anti-Tumor Activity; Anti-inflammatory Effect

## Introduction

Black pepper is a food condiment used as medicine, preservative, perfume and also used in human diet. In 1819, Hans Christian Orsted was first isolated the piperine from the extract of pepper. It is a principle alkaloid present in *Piper nigrum* and it is widely utilised in the preparation of traditional medicines [1]. It is phenolic extract of black pepper which produces useful physiological effects [2]. The solubility of piperine is quite low in water (14 mg/ml) in contrast it shows very good solubility in alcohol (1 g/15 ml) and ether (1 g/1.7 ml) [3].

The extracted piperine is a yellowish crystalline substance having the melting point ranging from $128^0$ to $130^0$C. piperoylpiperidine is the chemical structure of piperine and the chemical formula is $C_{17}H_{19}NO_3$. It was determined as a very weak base. Piperidine and piperic acid are formed upon piperine decomposition with acid or alkali hydrolysis [4]. Piperine is passively diffused with a non-saturable absorption kinetics and is not influenced by any rate limiting factor [5].

In ancient times, piperine served as a natural medicine to treat the conditions such as rheumatism, pain, chills, influenza, muscle pains and fever. Coma, inefficient digestion, strep throat and migraine headache were relieved by black pepper tea [6]. Recent study on piperine demonstrated that it possesses anti-oxidant, chemo preventive, immunoregulatory, anti-cancer, stimulatory, anti-inflammatory and hepatic protection activities [7].

Piperine also found to have many activities in different investigations such as anti-microbial activity [8], and anti-ulcer activities [9]. In the previous studies it has been found to have anti mutagenic and anti-tumor properties. It increases the secretion of pancreatic enzymes, prevent oxidative damage, decreases lipid peroxidation and can increases the bioavailability of many drugs. It can be used in the treatment of rheumatoid arthritis due to its anti-inflammatory properties either alone or in combination with other herbal drugs [10].

CNS diseases like depression, epilepsy and neuro-degenerations can be managed when piperine is efficiently up taken by brain [11]. It is used as bioenhancer which is capable to boost the bioavailability either by stimulating absorption or by lowering the rate of metabolism of drugs such as phenytoin, tetracycline, rifampicin and sulfadiazine. It is promoting the bioavailability and hence found to have bio-transformative effects [12]. It can be used before radiotherapy to the cancer patients as protective agent against radiation [13]. It might be capable of reducing the levels of triglycerides, cholesterol and glucose in the blood, demonstrated by a recent study [14].

## Pharmacological actions of piperine

### Anti-oxidant and anti-tumor activity

Free radicals are the by-products of the normal body metabolism or they are obtained as a result of exposure to the radiation and some pollutants in environment. Rise in the levels of anti-oxidants in the tissue can protect the tissue from damage caused by free radicals. piperine possess antioxidant property. Apart from anti-oxidant property it can maintain the levels of catalase, superoxide dismutase, glutathione peroxidase, glutathione-s-transferase and glutathione and reduces the thiobarbituric acid reactive substances [15].

Piperine was evaluated for hepatotoxic effect and it is used in therapeutic formulations. Piperine exerts protection against tert-butyl hydroperoxide and carbon tetrachloride hepatotoxicity by decreasing both *in vitro* and *in vivo* lipid peroxidation, enzymatic leakage of GPT and AP and by preventing the degradation of GHS and complete thiols in the intoxicated mice. Silymarin, piperine showed a lower hepatoprotective potency [16]. The hepatic metabolic transformation of enzymes can be upregulated by piperine and hence it acts as chemoprotective agent [17].

Piperine was studied for its immunomodulatory and antitumor activity. Piperine has cytotoxic effect toward Daltons Lymphoma Ascites and Ehrlich Ascites Carcinoma cells at a concentration of 250 mcg/ml. *Piper longum* alcoholic extract and piperine inhibit the growth of solid tumor in mice with DLA cells and increase the life span of mice EAC tumor to 37.3% and 58.8%, piperine increased WBC count to 138.9%. piperine increased bone marrow cellularity and α-esterase positive cells [18].

Piperine inhibited the proliferation of human umbilical vein endothelial cells (HUVES) and G1/S transformation without causing cell death. Piperine inhibited the phosphorylation of ser 473 and Thr 308reduces of AKt (protein kinase B) a key endothelial cell function and angiogenesis regulator. In keeping with AKt inhibition as the basis for the action of piperine on HUVECS, inhibition of the phosphoinoside-3 kinase/ AKt signalling pathway with Ly-294002 also inhibited HUVEC proliferation and angiogenesis caused by collagen [19]. piperine has shown to possess remarkable tumor growth reduction activity irrespective of growth of tumor is either androgen-dependant or androgen-independent in prostate cancer cells of xenotransplanted nude mice model [20].

### Anti-inflammatory activity

Anti-inflammatory property refers to the capability of a substance to decrease swelling and inflammation [21]. Piperine along with hexane and ethanolic extracts of *Piper nigrum. L* are evaluated for analgesic and anti-inflammatory activity by using tail-immersion method, analgesy meter, hot plate and writhing test at a dose of 5 mg/kg piperine, 15 mg/kg of ethanolic extract and 10 mg/kg of hexane extract on rats. A significant analgesic activity was produced by piperine at low doses (5 and 10 mg/kg) and ethanolic and hexane extracts were also produced significant action [22].

Piperine administration can inhibit endotoxin shock induced by LPS, accumulation of leukocytes and TNF-α production. piperine acts by inhibiting LPS-induced type-1 IFN mRNA expression, and also inhibits the interferons regulatory factor-1 (IRF-1) and IRF-3 levels and phosphorylation and nuclear translocation of IR-3. It also reduced STAT-1 activation on IFN-α /β-treated cells [23]. Piperine was used to treat asthma in Balb/c mice and found that it produced eosinophil infiltration, allergic inflammation and hyper-responsiveness of airway by lowering the production of IL-4, IL-5, IGF and histamine. They also found that an increase in TGF-β in piperine treated groups [24].

## Bio-enhancing activity

It is used as bioenhancer which is having the ability to boost the bioavailability of co-administered medicinal substances. It acts as potent bioenhancer [25]. Either by stimulating the absorption or by lowering the rate of metabolism of drugs such as phenytoin, tetracycline, rifampicin and sulfadiazine. It is promoting their bioavailability and hence found to have bio-transformative effects [26]. Bile acid is responsible to form micelles in stomach to solubilise and absorb lipids and lipid soluble drugs. It increases the formation of micelles by increasing the production of bile acid and also inhibits the metabolism of bile acid [12].

Piperine can enhance the bioavailability by increasing the permeability at site of absorption through the modulation of lipid environment and membrane dynamics, piperine has suitable molecular structure for enzyme inhibition. It is a potent absorption enhancer and effective inhibitors of drug metabolism and it increase the bioavailability of carbamazepine, curcumin, ciprofloxacin, ampicillin, metronidazole, oxytetracycline and it also inhibits various metabolising enzymes [27]. Piperine has enhancing activity on the release of epinephrine [28]. It can rise the thyroid hormones levels in circulation [29].

## Other actions

- Piperine has been investigated on memory performance and neurodegeneration in adult Wister rats orally at a dose of 5,10 and 20 mg/kg body weight for a period of two weeks and found that it significantly enhanced the memory impairment and neurodegeneration in hippocampus. They found that the decreased lipid peroxidation and acetylcholinesterase enzyme may be the underlying mechanism [11].
- Piperine was found to have protective action against gastric ulcer in rats and mice when given at doses of 25, 50 and 100 mg/kg IG. It produced the protective activity in a dose dependent manner by reducing the gastric acid volume, gastric activity and pepsin A activity [9].

## Extraction methods of piperine

Piperine is thermolabile and photosensitive compound, proper steps to be taken to avoid its degradation during storage. The quantity of biologically active substances in the plant material extracts can be highly affected by the extraction methods. There are different methods of extraction are available to extract piperine from pepper.

Piperine was extracted by mixing 45 mg of black pepper powder and 60 ml of 95% ethanol to make a suspension which will be stored for overnight and then filtered using vaccum filtration method (maceration method) [30].

Piperine extracted with methanol as solvent using Soxhlet apparatus. A thimble containing 40 gm of plant material was kept for continuous extraction for about 22h. from thimble a weighed sample of 40 gm was introduced into a double bypass Soxhlet apparatus (DBSA) connected with two distillation flask through inverted Y shaped joints and extraction was performed with 500 ml of methanol for 12h. Finally piperine is isolated on purification of methanolic extract over silica gel column [31]. These approaches can be used for piperine extraction efficiently but they are also associated with demerits like long procedures, less yields and use of large quantity of solvent and heat reflux extractions involves degradation of active principles [32].

Enzyme assisted super critic $CO_2$ extraction of piperine by mixing the powder of black pepper with lyophilised enzyme and subjected to both batch and continuous mode of extraction has been performed. The sample matrix is kept under the supercritical condition of $CO_2$ at $60^0$C and 300 bars pressure for static time. Then the piperine extraction is commenced at a fixed flow rate of $CO_2$. But in continuous mode flow of $CO_2$ through sample material is maintained at 1 L/min. in batch mode, enzyme has more incubation time to act on starch while in continuous mode there is no static time of contact of starch with enzyme. The best yield of extract and phytochemical properties were obtained at $60^0$C and 300 bars pressure among all experimental runs [33].

A glass vessel with flat bottom having length of 13 cm and internal diameter of 5 cm was kept at a distance of 2.5 cm from the bottom of ultrasound bath which is constant throughout the experiment. To this vessel, a mixture containing 5 gm of *Piper longum* powder and 50 ml of ethanol is added and irradiated by ultra sound for 30 minutes. This process yields 5.8 mg of piperine per 1 gm of powder [34].

1g of dry sample powder was mixed with 10 ml of different ionic liquid solutions and these solutions are kept in ultrasonic water bath. 1-alkyl-3-methyimidazolium ionic liquid are dissolved in deionised water to get ionic liquid solution. After ultrasonication, suspension was cooled and filtered through a Busher funnel to extract piperine [35].

| S. No. | Name of the Formulation | Claimed pharmacological activity | Animal model used | Reference |
|---|---|---|---|---|
| 1. | Olive oil suspension of piperine | Hepatoprotective activity | Male Swiss mice (20-22gm) | Kaul., *et al.* 1992 [16] |
| 2. | Piperine powder | Hepatic detoxication and chemo preventive property | Swiss albino mice | Singh., *et al.* 1993 [17] |
| 3. | 1% gum acacia suspension of piperine | Immunomodulatory and anti-tumor property | Balb/c mice | Sunila., *et al.* 2003 [18] |
| 4. | piperine | Reduction of androgen dependent and androgen independent tumour growth | Nude mice model xeno-transplanted with prostate cancer cells | Samikutty., *et al.* 2013 [20] |
| 5. | Oral piperine | Analgesic and anti-inflammatory effect | Swiss albino mice | Tasleem., *et al.* 2014 [22] |
| 6. | Oral piperine | Reduction of LPS-induced inflammatory responses | C57BL/6 mice | Bae., *et al.* 2010 [23] |
| 7. | Oral piperine | Reduction of asthma | Balb/c mice | Kim., *et al.* 2008 [24] |
| 8. | Piperine nanoparticles | Anti-epileptic effect along with enhanced oral bioavailability | Sprague dowley rats, zebrafish, male Kunming mice | Tianzing., *et al.* 2019 [36] |
| 9. | Piperine oral solution | Protection against neurodegeneration and cognitive impairment | Male wistar rats | Chonpathompikunlert., *et al.* 2009 [11] |
| 10. | Polymeric encapsulated piperine | Analgesic and anti-inflammatory activity | In vitro studies | Yeseminbudama*., et al.* 2019 [37] |
| 11. | Piperine solid lipid nanoparticles | Anti rheumatoid arthritis activity | Rats | M.R.Bhaleker*., et al.* 2017 [38] |
| 12. | Piperine pellets | Anti-oxidant activity | - | Vijaykumar., *et al.* 2014 [15] |

**Table 1:** Information on different formulations of piperine and their pharmacological activity.

| Study | Piperine activities |
|---|---|
| Traditional | Rheumatism, Cold and Cough, Muscle Pains, Diuretic, Flu, Saliva Stimulant, Antispasmodic, Antiseptic, Dyspepsia, Migraine Headache Reductant, Poor Digestion, Coma, Strep Throat, Blood Purifier, Analgesic, Anti-Toxic, Diabetic, Antipyretic, Carminative, Appetite Stimulant. |
| Animal studies | Metastatic Inhibitor, Enzyme Activity Stimulant, Anti-Microbial, Anti-Fertility Effects, Bio-Transformative Effects, Hepato-Protective Effect, Digestive Stimulant Effect, Anti-Ulcer Action, Anti-Amoebic Action, Drug Metabolism Inhibitor, Anti-Diarrheal, Anti-Fibrotic Effect, Anti-Fungal, Acaricidal, Anti-Oxidant, Glutathione Reduction. |
| Human studies | Gastro-Intestinal Stimulant, Anti-Asthmatic, Anti-Oxidant, Parietal and Pepsin Secretion, Reduction of High Fat Diet Induced Oxidative Stress, Anti-Carcinogenic, Antihyperlipidemic, Anti-Diabetic, Lipid Metabolism Accelerator, Food Absorption Enhancer, Anti-Inflammatory and Anti-Cancer Effects. |
| Cell studies | Immunomodulatory Activity, Reduction of Antibody in Serum, Drug Bioavailability Enhancer, Anti-Oxidant, Lung Metastasis Inhibitor, Lipid Peroxidation Enhancer, Increase of WBC, Increase of Hypersensitivity Response, Enzymatic Activity Enhancer. |

**Table 2:** Various activities of piperine from traditional uses to recent investigations.

## Conclusion

Piperine is thermolabile and photosensitive compound, proper steps to be taken to avoid its degradation during storage. The quantity of biologically active substances in the plant material extracts can be highly affected by the extraction methods. There are different methods of extraction are available to extract piperine from pepper.

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