

**PIPERINE: DELIGHTFUL SURPRISE TO THE BIOLOGICAL
WORLD, MADE BY PLANT “PEPPER” AND A GREAT
BIOAVAILABILITY ENHANCER FOR OUR DRUGS AND
SUPPLEMENTS.**

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Article Received on
30 June 2014,

Revised on 25 July 2014,
Accepted on 20 August 2014

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ABSTRACT

Several of the common spices consumed as food adjuncts to impart flavour, aroma and colour to foods are also documented to exhibit several health beneficial physiological effects¹. The beneficial physiological effects of the black pepper (*Piper nigrum*) are incidentally attributable to their active principles piperine (the biting principle of black pepper)¹. Piperine is a major ingredient of black pepper and long pepper, which are widely used as a spice and in Ayurvedic medicine. Piperine {[1-5-(1, 3)-benzodioxol-5-yl)-1-oxo-2, 4-pentadienyl]-piperidine}, an alkaloid responsible for the pungency of black pepper & long pepper. Systemic pharmacological studies on

piperine have revealed that this compound elicited diverse pharmacological activities; analgesic, anti-pyretic, anti-inflammatory, anti-convulsant & CNS-depressant activities. Piperine {[1-5-(1, 3)-benzodioxol-5-yl)-1-oxo-2, 4-pentadienyl]-piperidine}, an alkaloid responsible for the pungency of black pepper & long pepper. Systemic pharmacological studies on piperine have revealed that this compound elicited diverse pharmacological activities; analgesic, anti-pyretic, anti-inflammatory, anti-convulsant & CNS-depressant activities. Black pepper is used not only in human dietaries but also for a variety of other purposes such as medicinal, as a preservative, and in perfumery. Many physiological effects of black pepper, its extracts, or its major active principle, piperine, have been reported in recent decades. Dietary piperine, by favorably stimulating the digestive enzymes of pancreas,

enhances the digestive capacity and significantly reduces the gastrointestinal food transit time.

KEY WORDS : Bioenhancer, Piperine,

INTRODUCTION

Piperine is a pungent substance found in plants of the Piperaceae family – including *Piper nigrum* (black pepper) and *Piper longum* (long pepper). These peppers have been used in Ayurvedic medicine for the treatment of various diseases and discomforts^[1]. Piperine is the *trans-trans* isomer of 1-piperoyl piperidine^[2]. Their major active constituent, piperine, possesses various pharmacological actions including antioxidant,^[3-5] anti-inflammatory,^[6,7] and antihypertensive effects^[8], antihyperlipidemic activity.^[9,10] Piperine is also known to exhibit a variety of biological activities which includes antipyretic activity (Parmar et al., 1997), fertility enhancement (Piyachaturawat and Pholpramool, 1997), antifungal activity (Navickiene et al., 2000), antidiarrhoeal activity (Bajad et al., 2001b), antioxidant activity (Mittal and Gupta, 2000; Naidu and Thippeswamy, 2002; Vijayakumar et al., 2004; Gulcin, 2005; Selvendiran et al., 2005a; Jain and Mishra, 2011), antimetastatic activity (Pradeep and Kuttan, 2002), antithyroid activity (Panda and Kar, 2003; Vijayakumar and Nalini, 2006), antimutagenic activity (El-Hamss et al., 2003; Srinivasan, 2007; Wongpa et al., 2007), antitumor activity (Sunila and Kuttan, 2004; Srinivasan, 2007; Manoharan et al., 2009), antidepressant activity (Lee et al., 2005; L Wattanathorn et al., 2008), antiplatelet activity (Park et al., 2007), analgesic activity (Pooja et al., 2007), hepatoprotective activity (Matsuda et al., 2008), antihypertensive activity (Taqvi et al., 2008) and antiasthmatic activity (Kim and Lee, 2009). Piperine exhibits a toxic effect against hepatocytes (Koul and Kapil, 1993) and cultured hippocampal neurons (Unchern et al., 1997), Reproductive toxicity in swiss albino mice (Daware et al., 2000) and immunotoxicity (Dogra et al., 2004). Black pepper suffers with certain side effects when taken orally, like it causes gastro intestinal disturbances and stomach upset. The reason for this may be the availability of whole amount of the drug at a time.

PHARMACOGNOSY OF PEPPER

Synonym : Pepper

Biological source

Dried ripe fruit of perennial climbing vine *Piper nigrum* Linn.

Family : Piperaceae



Figure : 1 Plant of Piper nigrum , Figure : 2 Dried fruit of Piper nigrum

Geographical source

It is indigenous and cultivated in Indonesia, Brazil, Malaysia, Sri Lanka .

India ranks first in cultivation of this drug.

Cultivated and collection

Pepper is cultivated by plants raised from second year and survive upto 15 years. The seed raised plant starts fruiting after 7-8 year and can even survive upto 60 years. The cuttings are planted in March-April by keeping the distance of 3-4 meters in either direction.

Macroscopic character

Colour : Blackish –Brown or grayish-black.

Taste : Pungent and Aromatic.

Diameter : 3.5-6 mm

Surface structure

coarsely reticulate wrinkled with remains of stigma at apex.

Microscopic character : The Transverse section of drug shows :-

Tubular epidermal cells followed by thin walled parenchymatous hypodermis with rectangular stone cells. The inner pericarpic layer is brown coloured and is made up of sclerenchyma.

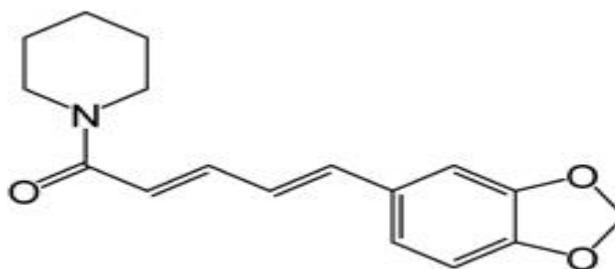
Seed coat layer is attached to it and is reddish brown.

Chemical constituent

Pepper contains an alkaloid piperine (5-9 %), volatile oil (1-2.5%)

Pungent resin (6.0%)

Piperidine and starch (30%)

Structure of piperine

Formula: C₁₇H₁₉NO₃

Percent Composition by mass :

C= 71% O= 17% H=6% N=5%

Type of Bonding: Piperine has predominantly covalent bonds. However, with its large amount of hydrogen atoms it has been hydrogen bonds as well.

Specific gravity : 0.898 – 0.900

Optical rotation : -3° to -5°

Refractive index : 1.4539 -1.4977

Molar Mass: 285.34 grams

Density: .0861 grams

Melting Point: 128°C - 132°C

Purity in Nature : 98% in piper nigrum. Can only be attained in 100% purity through processing in the laboratory.

Preparation of extracts

1. Pippali piper longum fruit powder was dissolved in 50% methanol and incubated at room temperature (28–30°C) for 16 h.
2. The supernatant collected by centrifugation at 14,000 rpm was dried in vacuum, designated as methnolic extract.
3. This was further fractionated using n-hexane, soluble fraction dried under vacuum and designated as n-hexane extract.
4. The insoluble fraction was further dissolved in chloroform, the supernatant was separated by using a separator funnel. The lower fraction was dried under vacuum^[38],



Identification test

1. The piperine (in mcL) is subjected on to the precoated and activated (kept the plates in oven for 1hr at 700C) silica gel TLCplate.
2. The mobile phase is Toluene: Ethyl acetate in 70:3 ratios and the detecting agent is Vanillin Sulphuric acid reagent.
3. After the TLC run and spraying the detecting agent the yellow spots of piperine were identified visually Rf value can be calculated.

Phytochemical parameters of Black pepper^[39]

PARAMETER	LIMIT
Total ash	Not more than 5.5% w/w
Water soluble ash	Not more than 4.5 % w/w
Acid insoluble ash	Not more than 1.0% w/w
Water soluble extractive	Not less than 15% w/w
Methanol soluble extractive	Not less than 8% w/w
Loss on drying	Not more than 4 % w/w

Chemical tests

10 mg of Piperine crystals were dissolved in 10ml ethanol and this solution is used as sample for chemical tests^[15,16]

Method

Dragendroff's test	Orange brown ppt
Mayer's test	Cream coloured ppt
Hager's test	Yellow ppt
Wagner's test	Reddish brown ppt

Preparation of standard calibration Curve

The calibration curve is obtained by dissolving piperine in distilled water and further dilution are made using distilled water and absorbance measured spectro photometrically at 343 nm.

pH value^{11,13}

A small quantity of Piperine is dissolved in ethanol and its pH can be checked by using a pH meter and it is found to be 7.9.

Mechanism of action of piperine

There are two possible explanations for the role of piperine in drug bioavailability:

(a) Non-specific mechanisms

Mainly promoting rapid absorption of drugs and nutrients, e.g. increased blood supply to the gastrointestinal tract, decreased hydrochloric acid secretion which prevents breakdown of some drugs, increased emulsifying content of the gut, increased enzymes like γ -glutamyl transpeptidase which participate in active and passive transport of nutrients to the intestinal cells, and

(b) Non-specific mechanisms inhibiting enzymes

Participating in biotransformation of drugs, preventing their inactivation and elimination (Majeed et al., 1998).

Piperine increases the bioavailability of many substances

1. Piperine has the remarkable ability to manipulate all four of these mechanisms.
2. It inhibits a number of enzymes responsible for metabolizing drugs and nutritional substances.
3. It stimulates the activity of amino-acid transporters in the intestinal lining.
4. It inhibits p-glycoprotein, the 'pump' protein that removes substances from cells.
5. It decreases the intestinal production of glucuronic acid, thereby permitting more of the substances to enter the body in active form.

Substances for which piperine has been directly shown to increase bioavailability :

Substances	Substances
barbiturates	pyrazinamide
beta-carotene	rifampicin
coenzyme Q10 (CoQ10)	selenium
curcumin(extract from turmeric)	sulfadiazine
dapsone	thiophylline
ethambutolisoniazid	vitamin B-6
nalorphine	
propranolol	
pyrazinamide	

Piperine reduces bioavailability of some substance

Metabolizing of a substance converts it into a more active (rather than less active) form – for example, a prodrug that gets converted into an active form in the body piperine may increase the bioavailability of the original substance by slowing its conversion to its metabolite and thus decrease the amount of the active metabolite. In effect, piperine would be reducing the availability of the desired substance. Piperine Inhibit the metabolic enzymes that would otherwise deactivate many substances, it also has the ability to induce the body's production of certain of these enzymes. The net effect in some cases would be to increase, rather than decrease, the rate at which certain substances get metabolized in the body, thereby decreasing their bioavailability .

Example of drug metabolizing enzyme

Drug Metabolizing Enzymes	References
Arylhydrocarbon Hydroxylase (AHH)	Atal et al. ^[15] , Singh et al. ^[66]
Uridine Diphosphate- (UDP-) Glucuronyl Transferase	Atal et al. ^[15] , Singh et al. ^[66]
Ethylmorphine-N-Demethylase	Atal et al. ^[15] , Singh et al. ^[66]
Ethoxycoumarin-O-Deethylase	Atal et al. ^[15] , Singh et al. ^[66]
Hydroxy-Benzo (a) Pyrene Glucuronidation	Atal et al. ^[15] , Singh et al. ^[66]
UDP-Glucose Dehydrogenase (UDP-GDH)	Reen et al. ^[16]
Lipoxygenase	Stöhret al. ^[67]
Cyclooxygenase-1	Stöhret al. ^[67]
Cytochrome P450	Atal et al. ^[15] , Singh et al. ^[66] , Bhardwaj et al. ^[17]

Piperine Used As A Bioenhancer For Various Activity

Anticytotoxic activity

Singh et al., 1994

Reported Inhibition of aflatoxin B1 induced cytotoxicity and genotoxicity in chinese hamster cells by piperine was reported by **Reen et al. (1997)**. A significant suppression (33.9-66.5%) in the micronuclei formation induced by benzo(a)pyrene and cyclophosphamide was reduced following oral administration of piperine at doses of 25, 50 and 75 mg/kg in mice.

Mechanism of action

Piperine reduces the aflatoxin B1 induced cytotoxicity and micronuclei formation in rat hepatoma cells in concentration dependent manner. It is capable of counteracting aflatoxin B1 toxicity by suppressing cytochromes P450 mediated bioactivation of the mycotoxin

Antiapoptotic activity

The antiapoptotic efficacy of piperine has been demonstrated against cisplatin induced apoptosis via heme oxygenase-1 induction in auditory cells (**Choi et al., 2007**). Gallic acid exerts a synergistic effect when administered with piperine and provides a more pronounced therapeutic potential in reducing beryllium induced hepatorenal dysfunction and oxidative stress consequences (**Zhao et al., 2007**).

Mechanism of action

Piperine can reverse the corticosterone induced reduction of brain derived neurotrophic factor mRNA expression in cultured hippocampal neurons (**Li et al., 2007**). Piperine contains pentacyclic oxindole group which is effective for immunomodulation. This immunomodulation activity is due to its multi-faceted activities such as antioxidative, antiapoptotic and restorative ability against cell proliferative mitogenic response, thymic and splenic cell population and cytokine release (**Pathak and Khandelwal, 2008**)

Antimutagenic activity

Mona A. M et al 2009 Swiss albino male mice were orally administered piperine at the doses of 5, 10 and 15mg/kg b. wt. for three consecutive days then treated with mitomycin C (MMC) intraperitoneally at a dose of 1mg/kg b. wt. Twenty-four hours thereafter, all animals were sacrificed and samples were collected from somatic and germ cells for chromosomal aberrations (CA) and sister chromatid exchanges (SCEs). Piperine inhibited the frequency of SCEs induced by MMC in bone marrow cells. This inhibition reached to 41.82% with piperine (15mg /kg b.wt.). The number of chromosomal aberrations induced by MMC in mouse splenocytes and spermatocytes decreased gradually with increasing the dose of piperine. The percentage of inhibition of chromosomal aberrations was 50% and 40.78% in splenocytes and spermatocytes, respectively.

Mechanism of action

piperine inhibited frequency sister chromatid exchanges. The rate of chromosomal aberration decreases with the use of piperine.

Antiarthritic activity

Jun Soo Bang, Da Hee Oh et al 2009 The levels of IL6, matrix metalloproteinase (MMPs), cyclo-oxygenase 2 (COX-2), and prostaglandin E2 (PGE₂) were investigated by ELISA and RT-PCR analysis. The analgesic and antiarthritic activities of piperine were investigated on

rat models of carrageenan-induced acute paw pain and arthritis. The former were evaluated with a paw pressure test, and the latter by measuring the squeaking score, paw volume, and weight distribution ratio. Piperine was administered orally to rats at 20 and 100 mg/kg/day for 8 days. Piperine inhibited the expression of IL6 and MMP13 and reduced the production of PGE₂ in a dose dependant manner at concentrations of 10 to 100 µg/ml. In particular, the production of PGE₂ was significantly inhibited even at 10 µg/ml of piperine. Histological staining showed that piperine significantly reduced the inflammatory area in the ankle joints.

Mechanism of action

Piperine inhibited the expression of IL6 and MMP13 and reduced the production of PGE₂

Hepatoprotective activity

Prashant Sahu et al 2012 piperine loaded chitosan microspheres to evaluate enhanced hepatoprotective activity in paracetamol induced hepatotoxic mice model. Piperine was extracted from Pippali Piper Longum. Solvent evaporation method was employed to fabricate the microspheres. Optical microscopy demonstrated that the formulation was spherical and had smooth texture with no drug crystals or microsphere aggregation. Formulations containing 2 mg piperine were administered orally to the animal model. In paracetamol induced hepatotoxic mice model, SGOT and SGPT level demonstrated no significant elevation in the blood by the microspheres formulation. The histopathology and enzyme level results suggested that microsphere formulation can passively target hepatoprotective drug to the liver.

Mechanism of action

Piperine inhibited increase in serum GPT and serum GOT. The rate of inhibition on dose of piperine. It is suggested that inhibitory effect due to reduced sensitivity of hepatocytes to tumor necrosis factor α .

Antivitaligo activity

Vitiligo is a pigmentation disorder in which melanocytes (the cells that make pigment) in the skin are destroyed. As a result, white patches appear on the skin on different parts of the body. It has been proved that Piperine, an alkaloid from black pepper has the repigmenting capacity. Use of Piperine in Vitiligo not only reduces UV Radiation but also prevents side effects. Drug targeting at the skin where the melanocytic proliferation is intended was achieved 69.06%. The topical formulation was physically stable throughout the shelf life.

Mechanism of action

Antirheumatoid activity

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the chronic inflammation of synovial joints which results in severe bone destruction.. It is reported that chloroform extracts of *P. longum* inhibited the TNF- α -induced expression of intercellular adhesion molecule-1 (ICAM-1) furthermore, extract inhibited the adherence of neutrophils to endothelial monolayer by inhibiting the TNF- α -induced expression of ICAM-1, Vascular cell adhesion molecule-1 (VCAM-1) and E-selectin in a dose- and time- dependent manner. Also, extracts of *P. longum* significantly inhibited the TNF- α -induced activation of NF-kB 21 aqueous extract of *P. longum* significantly suppressed the swelling of the paws.

Mechanism of action

Piperine is a potent inhibitor of the mixed function oxygenase system and nonspecific inhibition of cytochrome P450 isoenzymes^[11]. The constituents of piper species have inhibitory activity on prostaglandin and leukotriene biosynthesis in vitro. Chronic inflammation involves the release of number of mediators like cytokines (IL-1 β and TNF- α) and interferon's. These mediators are responsible for the pain, destruction of bone and cartilage that can lead to severe disability . TNF- α - induced free radical generation like H₂O₂ activates inflammatory signalling pathway, including NF-kB in vascular cells, and regulating the expression of cell adhesion molecules on endothelial cells and hence play an important role in various inflammatory diseases.

Antiasthmatic drug

Seung-Hyung Kim et al 2009 the effect of piperine on airway hyper-responsiveness, pulmonary eosinophilic infiltration, various immune cell phenotypes, Th2 cytokine production, immunoglobulin E and histamine production in a murine model of asthma. Asthma was induced in Balb/c mice by ovalbumin sensitization and inhalation. Piperine (4.5 and 2.25 mg/kg) was orally administered 5 times a week for 8 weeks. piperine effectively treats asthma is based on a reduction of Th2 cytokines (interleukin-4, interleukin-5), eosinophil infiltration, and by marked reduction of thymus and activation regulated chemokine, eotaxin-2 and interleukin-13 mRNA expression (especially transcription of nuclear factor- β dependent genes) in lung tissue, as well as reduced interleukin-4, interleukin-5 and eotaxin levels in bronchoalveolar lavage fluid, and histamine and ovalbumin-specific immunoglobulin E production in serum.

Mechanism of action

Asthma is recognized as a chronic lung disease by increased airway hyper-responsiveness and mucus production that leads to episodes of wheezing, coughing and shortness of breath (Annesi-Maesano, 2005). This may be due to liberation of endogenous and intrinsic mediators like bradykinin, chemokines, histamine, leukotrienes, **nitric oxide**, platelet activating factors and prostaglandins (Spina, 2000). Allergic asthma is a chronic inflammatory process occurring due to exposure of allergen resulting in the activation of T-lymphocytes with subsequent release of inflammatory mediators. Immuno-modulating agents are useful in the treatment of asthma by inhibiting the antigen-antibody (AG-AB) reaction and there by inhibiting the release of inflammatory mediators (Tripathi, 2003).

Antibacterial activity

Pavithra vani karsha et al 2009 evaluate the antibacterial activity of piperine by Disc diffusion method. The zone of inhibition was measured for both acetone and DCM extract of Pepper. It was found that Gram Positive bacteria more susceptible than Gram negative bacteria. The acetone extract of pepper displayed excellent inhibition on the growth of Gram positive bacteria.

Mechanism of action

Piperine show excellent bactericidal activity at 250 ppm for gram positive bacteria and gram negative bacteria. Leakage of UV₂₆₀ and UV₂₈₀ absorbing material (mainly nucleic acid and protein) occur. Pepper alter the membrane permeability resulting the leakage of UV₂₆₀ and UV₂₈₀ cause cell death.

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