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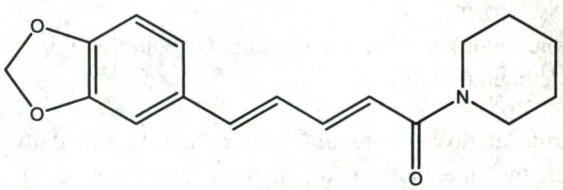
Piperine

DESCRIPTION

Piperine is an alkaloid found naturally in plants belonging to the *Piperaceae* family, such as *Piper nigrum* L, commonly known as black pepper, and *Piper longum* L, commonly known as long pepper. Piperine is the major pungent substance in these plants and is isolated from the fruit of the black pepper and long pepper plants. Piperine comprises 1 to 99% of these plants. The term black pepper is used both for the plant *Piper nigrum* and the spice that is mainly in the fruit of the plant.

Piperine is a solid substance essentially insoluble in water. It is a weak base that is tasteless at first, but leaves a burning aftertaste. Piperine belongs to the vanilloid family of compounds, a family that also includes capsaicin, the pungent substance in hot chili peppers. Its molecular formula is $C_{17}H_{19}NO_3$, and its molecular weight is 285.34 daltons. Piperine is the trans-trans stereoisomer of 1-piperoylpiperidine. It is also known as (*E, E*)-1-piperoylpiperidine and (*E, E*)-1-[5-(1, 3-benzodioxol-5-y1)-1-oxo-2, 4-pentdienyl] piperidine. It is represented by the following chemical structure:



Piperine

Black pepper and long pepper have been used in Ayurvedic medicine for the treatment of various diseases. One such preparation is known by the Sanskrit name trikatu and consists of black pepper, long pepper and ginger. Another preparation, known by the Sanskrit name pippali, consists of long pepper. It is thought that piperine is one of the major bioactive substances of these Ayurvedic remedies. Black pepper has also been used in traditional Chinese medicine to treat seizure disorders. A derivative of piperine, antiepilepsirine, has also been used in China to treat seizure disorders. Some recent research suggests that piperine may enhance the bioavailability of some drugs and nutritional substances.

ACTIONS AND PHARMACOLOGY

ACTIONS

Piperine may have bioavailability-enhancing activity for some nutritional substances and for some drugs. It has putative anti-inflammatory activity and may have activity in promoting digestive processes. It has recently been shown to have melanocyte stimulatory activity and antivitiligo activity, when applied topically.

MECHANISM OF ACTION

Piperine has been demonstrated to increase the serum levels and lengthen the serum half lives of some nutritional substances, such as coenzyme Q_{10} and beta-carotene. The mechanism of this action is unknown. It is speculated that piperine may act as a so-called thermonutrient and increase the absorption of certain nutritional substances from the gastrointestinal tract by producing a local thermogenic action. There is no evidence for this.

Piperine has also been found to increase the serum levels and lengthen the serum half lives of some drugs, such as propanolol and theophylline. The mechanism is thought to be by inhibition of certain enzymes involved in the biotransformation of the affected drugs. Piperine has been found to be a nonspecific inhibitor of drug and xenobiotic metabolism. It appears to inhibit many different cytochrome P450 isoforms, as well as UDP-glucuronyltransferase and hepatic arylhydrocarbon hydroxylase and other enzymes involved in drug and xenobiotic metabolism.

The mechanism of piperine's putative anti-inflammatory activity may be accounted for, in part, by piperine's possible antioxidant activity. There are a few studies suggesting that piperine may inhibit lipid peroxidation. Piperine has been shown to stimulate the secretion of the digestive enzymes pancreatic amylase, trypsin, chymotrypsin and lipase in rats. However, piperine appears to have this activity when administered with other spice bioactives, such as capsaicin and curcumin, and not when administered by itself.

The antivitiligo action of piperine is not completely understood.

PHARMACOKINETICS

The pharmacokinetics of piperine in humans remains incompletely understood. In rats, piperine is absorbed following ingestion, and some metabolites have been identified: piperonylic acid, piperonyl alcohol, piperonal and vanillic

acid are found in the urine. One metabolite, piperic acid, is found in the bile. Human pharmacokinetic studies are needed.

INDICATIONS AND USAGE

Piperine, in appropriate doses, may be useful in increasing the bioavailability of some drugs and nutrients. There is very preliminary evidence suggesting that piperine may aid in the digestion of food. There is also preliminary evidence that it may have some anticonvulsant, anticarcinogenic and anti-inflammatory properties. On the other hand, there is also preliminary evidence that it might be carcinogenic and cytotoxic in some circumstances and that it might interfere with reproductive processes and have negative effects on sperm. When applied topically, piperine shows antivitiligo activity.

RESEARCH SUMMARY

There are *in vitro*, animal and human studies demonstrating that piperine can significantly increase the bioavailability of numerous drugs and some nutritional supplements. Reportedly, it has demonstrated this effect with some antimicrobial, antiprotozoal, antihelmintic, antihistaminic, non-steroidal anti-inflammatory, muscle-relaxant and anticancer drugs, among others. It has also increased the bioavailability of coenzyme Q_{10}, curcumin and beta-carotene.

In humans given 2-gram doses of curcumin alone, levels of curcumin in serum were undetectable to very low one hour post-administration. Concomitant administration of 20 mg of piperine was said to significantly increase absorption and bioavailability (by 2000%). Similar results were reported in rats.

In a double-blind crossover study, 5 mg of piperine daily for 14-day periods resulted in significant increases in serum beta-carotene levels. The same dose of piperine produced similar results in another study, this one involving coenzyme Q_{10}.

The claim that piperine may aid in the digestion of food is based on some experimental animal data showing that dietary piperine seems to enhance pancreatic amylase lipase, trypsin and chymotrypsin activity.

The claim that piperine may have some anticonvulsant activity comes, in part, from China, where the substance is used in an effort to treat some forms of epilepsy. In mice, piperine injected intraperitoneally inhibited clonic convulsions induced by kainate. It did not significantly block seizure activity induced by L-glutamate, N-methyl-D-aspartate or guanidinosuccinate.

In a rat intestinal model, piperine was said to provide protection against oxidative changes induced by a number of chemical carcinogens. In another study, this one *in vitro*, piperine reportedly reduced the cytotoxicity of aflatoxin B1 in rat hepatoma cells.

Piperine exhibited significant anti-inflammatory activity in carageenan-induced rat paw edema and in some other experimental models of inflammation. In one animal study, piperine reduced liver lipid peroxidation, acid phosphatase and edema induced by carageenan.

On the negative side, piperine has shown some evidence of being mutagenic and potentially carcinogenic under some circumstances. It has reportedly given rise to mutagenic products on reaction with nitrites. This causes concern since nitrites and piperine may be consumed simultaneously. Risk might increase with high-dose piperine supplementation. In another study, piperine appeared to enhance the bioavailability of aflatoxin B1 in rat tissues. And in yet another study, piperine was found to be cytotoxic to cultured brain neurons. Piperine was said to be non-mutagenic, however, in a study examining effects of the substance on the germ cells of Swiss albino mice.

In a recent study utilizing albino rats, piperine, given at doses of 5 and 10 mg/kg body weight for 30 days, resulted (at the 10-mg/kg dose level) in significant reduction in the weights of testes and accessory sex organs as well as severe damage to seminiferous tubules. The 5-mg/kg dose resulted in partial degeneration of germ cells.

Decreased mating performance, decreased fertility and anti-implantation activity, along with some other adverse reproductive events, were observed in mice given very high doses of piperine.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Piperine is contraindicated for those who are hypersensitive to any component of a piperine-containing preparation.

PRECAUTIONS

Pregnant women and nursing mothers should avoid piperine supplementation.

Piperine at doses generally higher than 15 mg daily may affect the metabolism of a wide range of drugs and xenobiotics (see Interactions). In some cases, doses lower than 15 mg daily may affect the metabolism of these substances. Those using the drugs listed in Interactions should exercise caution in the use of piperine supplements.

Piperine may form mutagenic and possibly carcinogenic substances with nitrites. Those who eat processed food containing nitrites and nitrates as food preservatives should exercise caution in the use of piperine supplements.

ADVERSE REACTIONS

The typical dose of piperine in nutritional formulas is 5 milligrams, and doses of 15 milligrams daily are rarely exceeded. No adverse reactions have been reported with these doses. Piperine, if exposed to the tongue, is tasteless at first but leaves a burning aftertaste.

INTERACTIONS

DRUGS

Piperine, usually at a dose of 20 mg or greater, has been shown to inhibit the metabolism of the following drugs: propanolol, theophylline, phenytoin, sulfadiazene, rifampicin, isoniazid, ethambutol, pyrazinamide and dapsone. This list is not inclusive. Piperine is a nonspecific inhibitor of drugs and xenobiotics. Most drugs metabolized via cytochrome P450 enzymes would likely be affected by piperine.

NUTRITIONAL SUPPLEMENTS

Piperine at a dose of 5 mg daily has been found to enhance the absorption of beta-carotene and coenzyme Q_{10}. At a dose of 20 mg daily, it has been found to enhance the absorption of curcumin. Piperine may also enhance the absorption of vitamin B_6, vitamin C and the mineral selenium in the form of L-selenomethionine.

FOOD

Piperine may enhance the absorption of beta-carotene, vitamin B_6, Vitamin C and L-selenomethionine found in certain foods.

DOSAGE AND ADMINISTRATION

The content of piperine in black pepper ranges from 5 to 9%. The daily consumption of piperine in populations that use black pepper regularly is approximately 17 to 31 milligrams daily.

Piperine is available in stand-alone supplements and in combination products. A typical dose is 5 mg daily.

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