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## Phytosterols

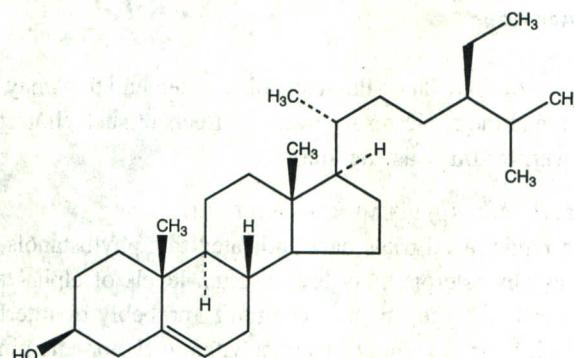
### DESCRIPTION

Phytosterols (also see Phytostanols and Beta-Sitosterol), widely found in the plant kingdom, are chemically similar to cholesterol. Cholesterol, however, only occurs in animals and is not found in plants. The cyclopentanoperhydropentanethrene ring structure of the sterol molecule is common to all sterols; the differences are primarily in the structure of the side chains.

Phytosterols are present in the diet. Typical daily dietary intakes of phytosterols range from 100 to 300 milligrams. It is higher in vegetarians. There are over 40 phytosterols, but beta-sitosterol is the most abundant one, comprising about 50% of dietary phytosterols. The next most abundant phytosterols are campesterol (about 33%) and stigmasterol (about 2 to 5%). Other phytosterols found in the diet include brassicasterol, delta-7-stigmasterol and delta-7-avenasterol.

Beta-sitosterol differs from cholesterol by the presence of an ethyl group at the 24<sup>th</sup> carbon position of the side chain. In the case of campesterol, this position is occupied by a methyl group. Chemically, the phytosterols are classified as 4-

desmethylsterols of the cholestane series. Beta-sitosterol has the following chemical structure:



Beta-sitosterol

Phytosterols are potentially atherogenic like cholesterol, but except in the rare genetic disorders, sitosterolemia and cerebrotendinotic xanthomatosis, they are not. This is because so little of the phytosterols are absorbed. On the other hand, phytosterols can lower cholesterol levels. As early as 1951, it was shown that phytosterols lowered cholesterol in chickens, and subsequently they were found to lower cholesterol in humans. Recently, functional foods containing phytosterols have become available. These functional foods are in the form of margarines, spreads and salad dressings. In the case of most of these products, phytosterols are found esterified with long-chain fatty acids. These phytosterols are derived from soybean oil and are mainly beta-sitosterol, campesterol and stigmasterol.

Phytosterols are also known as plant sterols and, owing to their large sitosterol content, are sometimes called sitosterol. Phytosterols are virtually insoluble in aqueous media and are poorly soluble in lipid media. Esterification of phytosterols with long-chain fatty acids increases their lipid solubility.

### ACTIONS AND PHARMACOLOGY

#### ACTIONS

Phytosterols have cholesterol-lowering activity.

#### MECHANISM OF ACTION

The mechanism of the cholesterol-lowering activity of phytosterols is not fully understood. Phytosterols appear to inhibit the absorption of dietary cholesterol and the reabsorption (via the enterohepatic circulation) of endogenous cholesterol from the gastrointestinal tract. Consequently, the excretion of cholesterol in the feces leads to decreased serum levels of this sterol. Phytosterols do not appear to affect the absorption of bile acids.

It is believed that phytosterols displace cholesterol from bile salt micelles. Another proposed mechanism is the possible



inhibition of the rate of cholesterol esterification in the intestinal mucosa.

#### PHARMACOKINETICS

Supplemental esterified phytosterols, following ingestion, undergo hydrolysis in the small intestine, catalyzed by such enzymes as cholesterol esterase, to yield the phytosterols beta-sitosterol, campesterol and stigmasterol. Of course, unesterified phytosterols do not undergo hydrolysis. About 5% of the ingested beta-sitosterol and about 15% of the campesterol are absorbed and transported via the portal circulation to the liver where some fraction of these phytosterols is glucuronidated. The phytosterols are excreted either in the free or glucuronidated form mainly via the biliary route.

#### INDICATIONS AND USAGE

Phytosterols may be indicated for the management of hypercholesterolemia.

#### RESEARCH SUMMARY

Phytosterols have been compared with phytostanols to assess their relative efficacy in lowering total cholesterol and LDL-cholesterol. These studies confirm that both are effective in lowering these lipids. A recent review concluded that plant sterols and stanols, in the studies analyzed, reduce, on average, total cholesterol by 10% and LDL-cholesterol by 13%. They have no significant effect in either HDL-cholesterol or triglycerides. (See Phytostanols.)

Given ongoing positive results in studies of phytosterols, the United States National Cholesterol Education Program recommends dietary phytosterol supplementation of 2 grams daily for cholesterol reduction. It is believed that this will lower LDL-cholesterol by approximately 10%.

#### CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

##### CONTRAINDICATIONS

Phytosterol supplementation is contraindicated in those with the rare genetic disorders sitosterolemia and cerebrotendinotic xanthomatosis.

##### PRECAUTIONS

Phytosterol supplementation should be avoided by pregnant women and nursing mothers.

##### ADVERSE REACTIONS

Adverse reactions are mainly mild gastrointestinal ones, including occasional indigestion, feeling of fullness, gas, diarrhea and constipation. Phytosterol supplementation is generally well tolerated.

#### INTERACTIONS

##### DRUGS

None known to date. Phytosterol supplementation may be additive to the cholesterol-lowering effects of such cholesterol-lowering drugs as the statins.

#### NUTRITIONAL SUPPLEMENTS AND FOOD

Some randomized trials have indicated that phytosterols may lower serum levels of alpha- and beta-carotene, lycopene and vitamin E, probably by interfering with their absorption. Neither vitamin A nor vitamin D levels appear to be affected by phytosterol ingestion. There are no data yet available on the effect of phytosterols on other carotenoids (lutein, zeaxanthin), flavonoids or polyphenols.

#### OVERDOSAGE

No reports of overdosage.

#### DOSAGE AND ADMINISTRATION

Phytosterols are available in the form of fatty acid esters in some functional food products, including margarines, spreads and salad dressing. Unesterified phytosterols are available in capsules. Doses of the phytosterol esters range from 1.12 to 2.24 grams daily. Doses of the unesterified phytosterols are about 1 gram daily. Capsules, if used, should be taken with meals.

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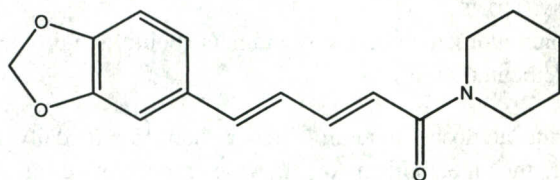
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## Piperine

### 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-yl)-1-oxo-2, 4-pentadienyl] 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, antiepileptine, 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 antivertigo 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<sub>10</sub> and beta-carotene. The mechanism of this action is unknown. It is speculated that piperine may act as a so-called thermogenutrient 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 propranolol 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 antivertigo 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