

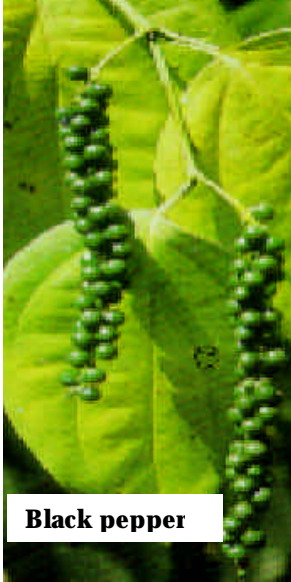
THE MEDICINAL USES OF PEPPER

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The history of the Pepper family



Members of the botanical family Piperaceae were among the first cultivated plants¹. Black pepper (*Piper nigrum*) and long pepper (*Piper longum*) are the best known species in this family and are probably among the most recognized spices in the world. Black pepper alone accounts for about 35% of the world's total spice trade. In addition, black pepper and long pepper have been used medicinally for centuries. In recent years, extensive research data on the phytochemistry and unique pharmacological actions of these plants have also become available.

The Materia Medica of Ayurveda, which dates back to 6,000 B.C., has many references advocating the use of pepper in a variety of ailments, particularly those

pertaining to the gastro-intestinal tract.^{2,3,4,5,6,7,8,9}

The earliest travelers from Europe who visited India described pepper cultivation on the Malabar coast.¹⁰ Theophrastus mentions two kinds of pepper in the fourth century B.C., (most likely these were black pepper and long pepper).¹⁰ Discorides in the first century A.D. mentions black pepper and long pepper as well as white pepper, which is simply black pepper seed with its peel or pericarp removed. Black pepper and long pepper were among the spices from India on which the Romans levied import duty at Alexandria, around A.D. 176.¹¹ Pepper is mentioned by Roman writers in the fifth century A.D. It is said that Attila the Hun demanded, among other items, 3,000 lbs. of pepper as ransom for the city of Rome.¹¹

Centuries later, the high cost of pepper led the Portuguese¹⁰ to seek their own sea passage to India. The Portuguese were successful in this mission and monopolized the spice trade until the 18th century.¹ In January 1793, an agreement was made between the Rajah of Travancore and the Crown of England. The Rajah was to supply large quantities of pepper to the Bombay Government in return for arms, ammunition and European goods. This is known historically as the "Pepper Contract".

From the 16th to the 18th centuries, the struggle for control of the Far Eastern spice producing regions became so intense that wars were fought between Portugal, Holland, and England. By the end of the 18th century, the United States entered the world trade for spices, bartering its salmon, flour, and soap for tea, coffee and spices.

One reason spices in general, and pepper in particular, became so important in international trade was their popular culinary role. In those times, tough, heavily salted long-stored meat was standard fare, and spice additives made these meats more palatable, while simultaneously masking off-flavors.

The Chemical Constituents of Pepper

Piperine is the active principle of black pepper (*Piper nigrum* L.) and long pepper (*Piper longum* L.). This is also the principal alkaloid of these plants. The piperine content is 3-9% and 3-5% (on dry weight basis) in *P. nigrum* and *P. longum* respectively.

Structure of piperine

Chemical names:

1- piperoyl piperidine

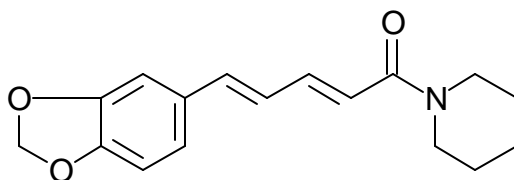
(E,E) 1-[5-(1,3-Benzodioxol-5-yl)-1-oxo-2, 4-pentadienyl]piperidine

Molecular weight: 285.33

Percentage composition:

C= 71.55% H=6.71% N=4.91% O=16.82%

Molecular structure:



Method of extraction⁴⁸

Piperine can be isolated from the oleoresin of *P. nigrum* or *P. longum*. The powdered fruits of the plant are extracted with dichloromethane at room temperature with stirring for 12 hours. The extract is filtered, concentrated in vacuum, and then the residue is purified on an alumina column. Pure piperine can also be obtained by crystallization from ethanol, which may be required for food and/or medicinal usages. Piperine is obtained directly from the crude

residue in lesser amounts by extraction in alcohol, filtration and successive crystallization.

Pepper: One of the most common herbs in Ayurveda

Piper species have been used in traditional medicine for intermittent fevers and to promote the secretion of bile. They are also recommended for neurological, broncho-pulmonary and gastrointestinal disorders, (including dyspepsia, flatulence, constipation and hemorrhoids).^{2,3,4,5,6,7,8,9} In Ayurveda, black pepper, long pepper and ginger are often used together in equal proportions in a preparation known as “trikatu”, a Sanskrit word meaning “three acrids”.⁸ Out of 370 compound formulations listed in the Handbook of Domestic Medicines and Common Ayurvedic Remedies, 210 contain either trikatu or its individual ingredients.⁸ According to Ayurveda, the three acrids collectively act as “kapha-vatta-pitta-haratwam” which means “correctors of the three humors (doshas) of the human organism”.

Pepper in the treatment of fever and malaria

The advantage of utilizing black pepper (as opposed to the standard quinine) in the treatment of refractory intermittent fevers, which are symptomatic of malarial infections, was reported by Dr. C. S. Taylor in The British Medical Journal, September 1886.¹⁰ At a 1983 symposium in Bombay, India entitled “Therapeutic Approaches to Malaria” sponsored by Ciba Geigy, Ltd., long pepper was discussed as a possible treatment for chronic malaria.¹² It was reported that long pepper was used for patients with chronic malaria with splenomegaly (enlarged spleen). Long pepper fruits were given in an increasing dose from 3 to 30, starting with 3 and increasing daily by 3 fruits. Subsequently the dose was decreased from 30 to 3 fruits, by reducing 3 fruits daily. Long pepper was boiled in milk and water and drunk once a day in the early morning. Drinking this decoction reportedly caused cessation of malarial parasite multiplication and regression of splenomegaly.

In traditional Chinese medicine, black pepper has been used for the treatment of epilepsy.¹³ Based on this traditional application, a new antiepileptic drug called Antiepilepsine has recently been synthesized by Chinese researchers.¹³ Antiepilepsine is a chemical relative of piperine, the main alkaloid phytochemical found in plants of the family *Piperaceae*. In traditional Middle Eastern medicine, black pepper has been used as a nerve tonic. Recently, the analeptic (nervous system stimulant) properties of piperine have been studied. Based on this research, piperine has been used successfully to counteract morphine-induced respiratory depression in experimental animals.¹⁴

The application of pepper in respiratory diseases

Long pepper, and to a lesser extent trikatu, have been used in the treatment of asthma and chronic bronchitis in Ayurveda and Unani medicine.¹⁰ In a study

involving 240 children of different age groups suffering from frequent asthma attacks, long-term administration of long pepper fruits significantly reduced the frequency and severity of the attacks.¹⁵ Twenty-five patients in the study group showed no recurrence of asthma attacks, 161 showed clinical improvement, 47 did not benefit from the treatment, and 7 patients deteriorated. In another study, 20 pediatric patients with asthma received long pepper in doses ranging from 9.35 to 15.75 gm daily for several weeks. As a result of this treatment all patients showed clinical improvement.¹⁶

Bioavailability enhancement : a significant application of pepper

The use of black pepper, long pepper, or trikatu is traditionally well-known in the treatment of a variety of gastrointestinal disorders, and all three act to improve digestion. In the 1920's Bose, an acknowledged author of "Pharmacographia Indica", reported an enhanced antiasthmatic effect of an Ayurvedic formula containing *vasaka* (*Adhatoda vasica*) when administered with long pepper.¹⁷ In his "Pharmacopoeia Indica", Bose describes examples of his preparation which consists of juice from the *vasaka* leaves boiled with sugar, long pepper and butter; then this mixture was added to honey and given as a treatment for asthma.

Through sustained experimentation and observation, ancient practitioners discovered herbal agents, such as pepper, which could increase the digestibility and efficacy of both nutrients and herbal drugs. The main purpose of trikatu's incorporation into numerous Ayurvedic formulations was most probably to enhance the efficacy of pharmacologically active ingredients. Several groups of investigators now attribute this bioavailability enhancing property of pepper to its main alkaloid, piperine. Piperine is an alkaloid with the molecular formula $C_{17}H_{19}O_3N$, which on hydrolysis with alkali gives piperic acid and piperidine.¹⁸ The piperine content of pepper is directly proportional to its pungency.

The biological properties of piperine have been extensively studied only in recent years.^{19,20} The proposed mechanism for the increased bioavailability of drugs co-administered with piperine is attributed to the interaction of piperine with enzymes that participate in drug metabolism, such as mixed function oxidases found in the liver and intestinal cells. Interaction with the synthesis of drug chelating molecules in the body such as glucuronic acid has also been proposed. Piperine may also interact with the process of oxidative phosphorylation, or the process of activation/deactivation of certain metabolic pathways, slowing down the metabolism and biodegradation of drugs. This action of piperine results in higher plasma levels of drugs, rendering them more available for pharmacological action.

One of the first scientific experiments to confirm that pepper could enhance the bioavailability of drugs was performed in the late 1970's by Atal and coworkers at the Regional Research Laboratory, Jammu-Tawi in India.¹⁹ These experiments

revealed that *Piper longum* co-administered to rats orally with the drugs vasicine and sparteine increased the blood levels of vasicine by 232% and sparteine by more than 100% as compared to control animals who did not receive *P. longum*.

In subsequent experiments, piperine has been proven to enhance the bioavailability of a number of drugs including rifampicin, phenytoin, propranolol and theophylline.^{21,22,23} A patent based on the drug bioretentive property of piperine (Indian Patent No. 1232/DEL/89) recommends the use of piperine in combination with drugs to improve their effectiveness.²⁴

This successful use of piperine to increase bioavailability of certain drugs has created interest in the area of nutrient and food absorption, since nutritional deficiencies due to poor gastrointestinal absorption are an increasing problem in developing countries as well as in Western nations. In developing countries, overall gross malnutrition may be the culprit. However, in Western nations, poor gastrointestinal absorption is increasing due to a larger percentage of elderly people in the population, as well as an increasing incidence of “junk food diets”, allergies, gastric ulcers, and chronic yeast infections (Candidiasis).

Beta-carotene absorption has been shown to be variable among humans, with some individuals consistently absorbing it well while others do not. Recently, an original bioavailability study showed that a standardized extract of black pepper (Bioperine[®]), increases gastrointestinal absorption of beta-carotene in humans.²⁵ Bioperine[®] is 98% pure piperine obtained through a proprietary extraction process, from pepper.²⁵ A small amount of Bioperine[®] (5 mg) combined with a formula containing 15 mg of beta-carotene, given as a food supplement once a day, increased almost twofold the blood levels of beta carotene in human volunteers (Fig. 1). These results indicate that Bioperine[®] possesses the potential to increase the bioavailability of nutrients as well.

Bioperine[®] was effective in increasing nutrient absorption with a dose several times lower than that commonly used to bioenhance blood levels of a drug. Incidentally, the dose of piperine which increased the bioavailability of beta - carotene was several times lower than the estimated amount of piperine consumed daily in the diet by an average individual in the USA.²⁶ Similar bioavailability enhancement was observed on co-administration of other nutrients including Coenzyme Q₁₀²⁷, L(+)-Selenomethionine, Vitami B₆, Vitamin C (with propranolol hydrochloride) and herbal extracts such as Curcumin with Bioperine[®]²⁸.

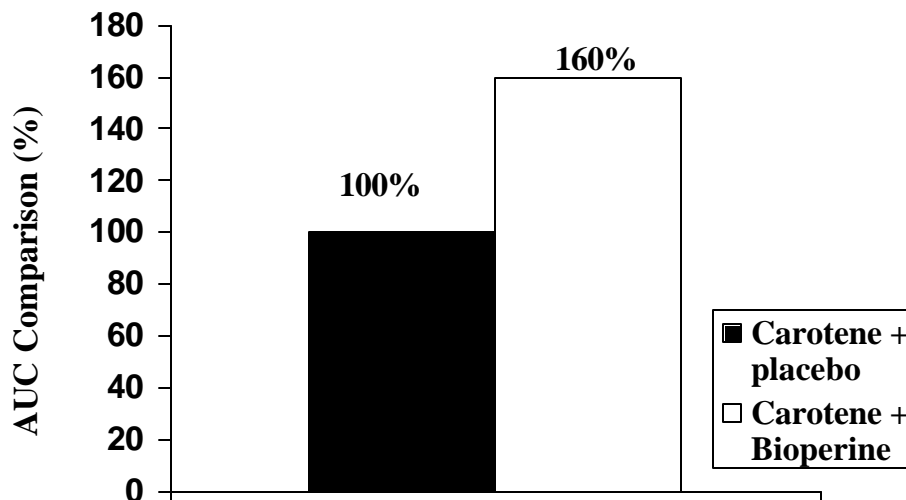


FIGURE 1: BIOAVAILABILITY ENHANCEMENT OF BETA-CAROTENE BY BIOPERINE[®]: PERCENTAGE COMPARISON OF AUC (AREA UNDER THE CURVE) FOLLOWING SUPPLEMENTATION

Pepper’s “hot” taste, “hot” feel, and its thermogenic effect

Almost everyone recognizes that the black pepper sprinkled on their food makes it taste spicy or “hot”. The hot flavor is even stronger when the pepper is used fresh. Pepper’s heat is no accident—it is a manifestation of the biological activity of some of the phytochemicals found in pepper, most notably piperine.

Black and long peppers stimulate the skin as well as the tongue, thus they are also useful for topical application. They have broad antimicrobial, anti-parasitic and insecticidal properties. Peppers have been traditionally used as local anesthetics, but the mechanism of this analgesic (pain-relieving) action has only been recently described.²⁹ Piperine is thought to be the main phytochemical responsible for the analgesic action of pepper. It is believed that piperine acts in a similar (but not identical) way to another well-known pungent phytochemical, capsaicin, the principal pungent principle found in cayenne peppers (*Capsicum annuum*). Black and various red peppers, including cayenne, chilli, and paprika, are all spicy but are not related botanically. According to one concept, piperine may deplete sensory nerves of the neurotransmitter called “Substance P”²⁹. This action may cause local desensitization to pain stimuli. It has been proposed that Bioperine[®] acts through thermoreceptors, both locally in the skin nerve endings, and systemically, throughout the nervous system. This, in turn, interferes with pain stimulus transmission and causes desensitization of pain receptors.²⁵

The proposed mechanism through thermoreceptors, which are sensors of heat energy in the body, may shed light on the thermogenic (heat-generating) action of pepper and piperine. The thermogenic effect of piperine and other

components of spices such as capsaicin, gingerol and shogaol is now broadly discussed as a new application of spices traditionally known for their body temperature regulating properties. Thermogenesis is now scientifically linked to body metabolism and the metabolic rate. The higher the metabolic rate, the more heat energy is being produced by the body. Could it be that thermoregulation by piperine is a mechanism through which metabolism can be regulated, including the metabolization of nutrients and drugs? Considering the profound effects of piperine on nutrient absorption when given orally in a dose as small as a few milligrams, piperine deserves to be called a “supernutrient” and based on its possible thermogenic effect on the body, it might also be dubbed a “thermonutrient”.³⁰

Although the concept of thermogenesis was not recognized in Ayurvedic medicine, there existed an empirical use of certain combinations of herbs and minerals specifically targeted to improve the digestibility of food. Traditionally, black pepper and its close relative long pepper are used in combination with ginger in trikatu (three acids), a remedy used for a broad range of gastrointestinal disorders^{31,32}. The sharp tasting principles in trikatu are used to increase the protective gastrointestinal mucous secretion, a long-standing Ayurvedic treatment which has proven successful for both acute and chronic gastrointestinal conditions.

Indeed, recent experimental evidence shows that piperine has anti-inflammatory and antioxidant properties³³. Piperine may facilitate nutrient absorption by alleviating inflammatory conditions at the site of absorption. The mechanisms behind the beneficial action of piperine as one of the principal ingredients of numerous digestive formulas employed by Ayurveda needs to be further investigated. Particular emphasis needs to be placed on the traditional sense of restoring gastrointestinal function as means of preventing disease and improving overall nutrition. Black pepper and long pepper are thus potentially useful herbs in the management of a variety of respiratory and gastrointestinal problems.

Future research on pepper may well retrace the origin and evolution of the properties which attracted attention to pepper in ancient times. Pliny commented some 2,000 years ago: “it is quite surprising that the use of pepper has come so much in fashion, its only desirable quality being a certain pungency; and yet it is for this that we import it all the way from India!”¹⁰

This pungency of pepper is now understood to be a byproduct of the biological properties of piperine, which can apparently regulate neurohormones, thereby increasing thermogenesis, or the production of heat by the body. Scientific research has now revealed that the “hot” pepper taste is due to the production of heat energy. The biological mechanism of piperine is strongly linked to its hot taste, further validating its representation as a nutraceutical or “functional food”.

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