Capsiate and Capsaicin

DESCRIPTION

Capsiate, a nonpungent capsaicin analogue, and its dihydro and nordihydro derivatives, dihydrocapsiate and nordihydrocapsiate, respectively, are the major capsinoids of the nonpungent red pepper cultivar CH-19 Sweet. The capsinoids are fatty acid esters of vanillyl alcohol and are lipophilic.

Capsaicin, the main pungency compound of hot chili peppers, and its dihydro and nordihydro derivatives, dihydrocapsaicin and nordihydrocapsaicin, respectively, are the major capsaicinoids of hot chili peppers.

A number of health benefits have been ascribed to capsaicin and its derivatives, including anticancer activity, anti-inflammatory activity, anti-obesity activity and analgesia. Topical capsaicin is used in the treatment of postherpetic neuralgia, osteoarthritis and painful diabetic neuropathy. However, the strong pungency of these substances and potential for neurotoxicity limit their use in food, nutritional supplements and pharmaceuticals.

The pungency of chili peppers ranges from the coolness of bell and sweet pepper varieties to the mild to moderate heat of serranos to the earth-scorching habaneros, and has to do with the amount of capsaicin present in the chili pepper. In 1912, the chemist Wilbur Scoville developed a measure of the pungency of chili peppers which became known as the Scoville Organoleptic Test. The test, called a dilution-taste procedure, relies on the tongue of an experienced chili taster to determine the degree of heat (or Scoville unit) of the chili pepper. Recently, the experienced tongue has been replaced by HPLC (high pressure liquid chromatography) and ASTA (American Spice Trade Association) units. The ASTA units are then converted to Scoville units.

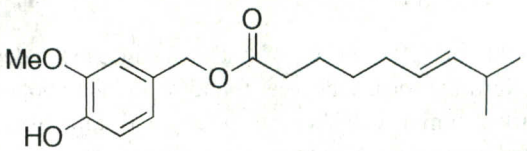
Scoville heat levels for a few chili peppers are: bell/sweet pepper varieties (*Capsicum annuum)*, 0 Scoville Heat Units (SHU); ancho peppers (*Capsicum annuum)*, 1,000-3,000 SHU; serrano peppers (*Capsicum annuum)*, 4,000 SHU; New Mexican peppers (*Capsicum annuum*), 5,000 SHU; jalapeño peppers (*Capsicum annuum*), 5,000-25,000 SHU; cayenne peppers (*Capsicum annuum*), 23,000 SHU; Thai peppers (*Capsicum annuum)*, 60,000 SHU; Tabasco peppers (*Capsicum frutescens*), 120,000 SHU; habanero peppers (*Capsicum chinense*), 200,000-300,000 SHU. The present Guinness Book of World Records holder is the Bhut Jolokia (*Capsicum frutescens*) chili from India, which weighed in at a blistering 1,001,304 SHU.

The SHU for pure capsaicin, the major pungent substance of the *Capsicum* family (hot chili peppers) is 16 million SHU, as is that of dihydrocapsaicin. The SHU of nordihydrocapsaicin is 9.1 million. In contrast to the capsaicinoids, capsinoids are not pungent and have SHUs well below 100. Capsinoids are found in the various *Capsicum* species, but in very small amounts. A few years ago, a nonpungent cultivar of *Capsicum annuum* L was identified in Thailand. This cultivar was called CH-19 Sweet and was found to have much more capsiate in its fruit, as well as other capsinoids, than had ever before been found in chili peppers. CH-19 Sweet is virtually devoid of capsaicin and other pungent capsaicinoids. The SHU of CH-19 Sweet is well below 100.

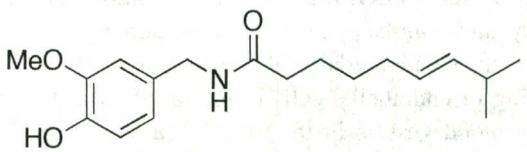
The major capsinoids in CH-19 Sweet are capsiate (4-hydroxy-3-methoxybenzyl (*E*)-8-methyl-6-nonenoate; CAS No. 205687-01-0), dihydrocapsiate (4-hydroxy-3-methoxybenzyl 8-methylnonanoate; CAS No. 205687-03-2), and nordihydrocapsiate (4-hydroxy-3-methoxybenzyl 7-methyloctanoate; CAS No. 220012-5-3).

The capsinoids have an ester bond instead of the amide bond normally found in capsaicinoids between the vanillyl moiety and fatty acid chain. The difference between the sensory properties of capsaicin and capsiate is due to the way the vanillyl and acyl moiety of the basic structural motif is linked: by an amide bond in capsaicin-like compounds and by an ester bond in capsiate-type compounds.

The term capsiate is used either for the substance capsiate itself or for mixtures of capsiate with its analogues dihydrocapsiate and nordihydrocapsiate. The chemical structures below are described within this monograph.



Capsiate



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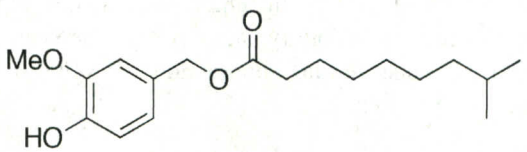
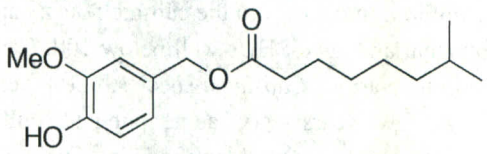


Dihydrocapsiate



Nordihydrocapsiate

ACTIONS AND PHARMACOLOGY

ACTIONS

Capsiate may have an anti-obesity effect. Capsiate has chemopreventive and anticancer potential.

MECHANISM OF ACTION

A two-week study with male mice administered capsiate (10 mg/kg body weight) reported increased metabolic rate and promotion of fat oxidation at rest. It was found that the two-week treatment of capsiate increased the levels of UCP-1 (uncoupling protein 1) and mRNA in brown adipose tissue (BAT), and UCP-2 (uncoupling protein 2) mRNA in white adipose tissue (WAT). Another study in mice by the same group found that continuous administration of capsiate suppressed body fat accumulation. Capsiate in the form of CH-19 Sweet extract has been reported to increase body temperature and oxygen consumption in humans.

A hypothetical model to explain the above results is as follows: Capsiate and other capsinoids activate TRPV1 (transient receptor potential vanilloid 1, the capsaicin receptor) found on the digestive tract surface, leading to activation of the sympathetic nervous system followed by activation of UCP-1 in BAT, UCP-3 in skeletal muscle and activation of lipolysis in WAT.

Capsinoids target a variety of pathways in cancer development. Nordihydrocapsiate was found to induce apoptosis in the Jurkat tumor cell line. Capsiate and dihydrocapsiate inhibited angiogenesis in human umbilical vascular endothelial cells. These capsinoids inhibited vascular endothelial growth factor (VEGF)-induced proliferation, chemotactic motility and capillary-like tube formation of primary cultured human endothelial cells. In addition, they inhibited sprouting of endothelial cells in the rat aorta and formation of new blood vessels in the mouse Matrigel plug assay in response to VEGF. VEGF, expressed by many cancer cell types and certain tumor stromal cells, is a potent proangiogenic factor that functions in tumor vascular development. The angiogenesis inhibitory activity of the capsinoids appears to be due to the suppression of VEGF-induced activation of Src kinase.

PHARMACOKINETICS

Pharmacokinetic studies with ^{14}C-labeled synthetic dihydrocapsiate have been performed in rats and with an oral ingestion of CH-19 Sweet extract in healthy male volunteers. ^{14}C dihydrocapsiate is rapidly absorbed from the gastrointestinal tract, and radioactivity is found in several different tissues. Radioactivity reaches Cmax in plasma 0.67 hours after administration of a single dose of ^{14}C dihydrocapsiate. The apparent half-life is 2.4 hours. The dihydrocapsiate metabolites are excreted in the urine, bile and feces. Maximum concentrations of radioactivity were observed in most tissues two hours following single dose administration. Metabolism of dihydrocapsiate occurs very quickly after single dose administration, and it is thought that the metabolism takes place in the gastrointestinal tract, the intestinal mucosa and the liver. Metabolites include vanillyl alcohol, the glucuronide of vanillyl alcohol, the sulfate of vanillyl alcohol and the sulfate of vanillic acid.

Capsaicin is known to inhibit CYP3A4 (cytochrome P450 3A4). However, capsiate, dihydrocapsiate and nordihydrocapsiate were not found to inhibit CYP3A3 in human liver microsomes.

Further pharmacokinetic studies with single doses and repeated doses of dihydrocapsiate in both experimental animals and humans are necessary in order to completely elucidate the pharmacokinetics of the capsinoids.

INDICATIONS AND USAGE

Capsiate is said to have many of the same indications as its hotter cousin, capsaicin. Claims for it include: prevention and treatment of some cancers, anti-inflammatory, immunomodulator, useful in treating rheumatoid arthritis and other autoimmune diseases, analgesic, weight loss promoter, and athletic endurance enhancer.

RESEARCH SUMMARY

Recent research, principally in Japan, indicates that capsiate may be useful in inhibiting the pathologic angiogenesis (blood vessel formation) that characterizes and sustains some cancers. This evidence encompasses both *in vitro* and *in vivo* animal and human experiments which, while still very preliminary, show promising results. Like the pungent ("hot") capsaicin, cool capsiate demonstrates an ability to inhibit the vascular endothelial growth factor that promotes abnormal angiogenesis. Other dietary phytochemicals (eg, curcuminoids, resveratrol, etc.) have demonstrated similar abilities but, according to one group of Japanese researchers, capsiate is more potent in this regard.

It is hoped that this nonirritating capsaicinoid analogue will have broad-spectrum anti-inflammatory applications, for which capsaicin itself shows preliminary promise. The research that could establish it as efficacious in rheumatoid arthritis, psoriasis, diabetic retinopathy, atherosclerosis, hyperthyroidism and other conditions remains to be done. Already, however, there is evidence, based upon animal inflammation models, that capsiate may be effective in

preventing and ameliorating such conditions as septic shock and inflammatory bowel disease. *In vitro* and animal experiments are yielding early evidence of positive immunomodulatory effects that could have broad, positive implications.

Analgesic effects have not been established.

A few recent studies, again from Japan, suggest that capsiate, like capsaicin, may have thermogenic effects that could promote weight loss. There is a suggestion in this work that capsiate activates the sympathetic nervous system along pathways that increase energy expenditures at a level that inhibits the accumulation of fat. These findings have been observed in both animal and human experiments. One small human study compared male subjects matched to control subjects (and controlled for diet, smoking and several other relevant variables) over a period of just two weeks. In that time frame a significant reduction in body fat was reported among those receiving portions of CH-19 Sweet pepper prior to meals (0.4 grams per kilogram of body weight in the form of uncooked pepper three times per day) compared with the matched controls who did not receive the capsiate-containing sweet pepper. Unlike capsaicin, which has also been postulated to have weight-loss properties, capsiate did not, in these studies, accelerate heart rate or increase blood pressure. More rigorous follow-up, with larger cohorts, is warranted.

Another Japanese study demonstrated that mice that received orally administered capsiate were able to swim significantly longer than similar mice not fed capsiate. This suggests that the substance could promote athletic endurance. There was evidence in this study of enhanced fat oxidation and carbohydrate sparing. The experimentals showed increased residual muscle glycogen, higher serum free fatty acid concentration and significantly lower lactic acid concentration, as well as a lower respiratory exchange ratio during both rest and exercise, all consistent with the potential for greater physical endurance. This intriguing pilot study also needs follow-up.

In general, capsiate replicates many of the apparently beneficial effects of capsaicin but without the concomitant irritating properties than many researchers believe have impeded the use of these substances. It is hoped that capsiate will now provide a more attractive alternative and promote further research with capsaicinoids.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Capsiate and all of the capsinoids are contraindicated in those hypersensitive to any component of a capsinoid preparation.

PRECAUTIONS

Those with chronic cough syndromes, including chronic cough due to the use of angiotensin-converting enzyme (ACE) inhibitors, may notice an increase in coughing when using capsinoids. To date, this has not been reported, but since capsinoids as well as capsaicin are agonists for the ligand-gated cation channel TRPV1, it is something to watch out for.

ADVERSE REACTIONS

There have been no reports of adverse events in those taking capsiate supplements.

INTERACTIONS

No interactions between capsiate and other dietary supplements, pharmaceuticals or foods have been reported.

OVERDOSAGE

There are no reports of overdosage in those taking capsiate supplements.

DOSAGE AND ADMINISTRATION

The presently marketed capsiate supplement contains one milligram per capsule, and the recommended dosage is three capsules every morning. The supplement contains the three capsinoids: capsiate, dihydrocapsiate and nordihydrocapsiate. Optimal dosage of capsiate is unknown. One human study using 30 milligrams of capsiate showed no adverse events.

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Carnosine

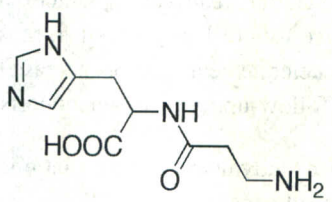
DESCRIPTION

Carnosine is a dipeptide comprised of the nonprotein amino acid beta-alanine (see Beta-Alanine) and the protein amino acid L-histidine. The dipeptide was first detected in 1900 by the chemists Gulewitsch and Amiradgibi in Liebig's meat extract. Liebig's meat extract was developed in 1840 by the German organic chemist Baron Justus von Liebig as a cheap and nutritious meat substitute for those who couldn't afford the real thing. It is a molasses-like black spread that contains only reduced meat stock and salt. It was widely used, including by European middle-class households, the Allied Forces of World War II and by the explorer Sir Henry Morton Stanley on his trip to Africa when he was searching for David Livingston. It is still marketed.

In addition to its presence in Liebig's meat extract, carnosine is also found in fairly high concentrations in vertebrate excitable tissues, including CNS tissue and skeletal muscle. Although the exact function of carnosine still remains unclear, it has been demonstrated to function as an antioxidant, an antiglycating agent and a skeletal muscle pH buffer, helping to delay muscle fatigue. It is a putative neurotransmitter and it is even speculated that carnosine might possess "antiaging" activity. It appears to be the first neuropeptide discovered.

Carnosine is chemically described as (2*S*)-2-(3-aminopropanoylamino)-3-(3*H*-imidazol-4-yl)propanoic acid. It is also known as beta-alanyl-L-histidine, beta-alanylhistidine and L-carnosine, and it is sometimes referred to as ignotine (in Australia) and karnozin (in Russia). Its CAS Registry Number is 305-84-0. Carnosine is a member of the histidine-containing dipeptide family. The other members include anserine (beta-alanyl-L-1-methylhistidine), also found in excitable tissues, balenine or ophidine (beta-alanyl-L-3-methylhistidine) and homocarnosine (gamma-amino-butyryl-histidine).

Carnosine is represented by the following chemical structure.



Carnosine

Carnosine's empirical formula is $C_9H_{14}N_4O_3$, its molecular weight is 226.23, its second pKa is 6.83, and it is soluble in water (one gram dissolves in 3.1 milliliters of water). Carnosine is found in skeletal muscles and CNS tissues at concentrations ranging from 2millimolar (2mM) to 25millimolar (25mM) or 0.45 mg per ml to 5.65 mg per ml. The dipeptide is synthesized in muscle and nervous tissues from beta alanine and L-histidine via the enzyme carnosine synthetase, which requires adenosine triphosphate (ATP). Vegetarian diets are lacking in carnosine, but carnosine is synthesized in the muscles and nervous tissues of vegetarians. N-acetylcarnosine eye drops are available, which are used by some for their putative anticataract action.

The predominance of carnosine and anserine in skeletal muscle is species-dependent. There is essentially no anserine in human muscle. In beef, turkey, pigs and goat, carnosine concentrations are higher than anserine concentrations. In chicken and rabbit skeletal muscle, anserine predominates. The human quadriceps contains about 362 mg of carnosine per 100 grams of tissue, a chicken breast, about 278 mg per