The mechanism of hesperetin's possible vasoprotective action is unclear. Hesperetin has been shown to decrease microvascular permeability. It may protect endothelial cells from hypoxia by stimulating certain mitochondrial enzymes such as succinate dehydrogenase.

The mechanism of hesperetin's possible anticarcinogenic action is also unclear. It may be accounted for, in part, by hesperetin's possible antioxidant activity. Other possibilities include inhibition of polyamine biosynthesis and inhibition of lipoxygenase and cyclo-oxygenase.

PHARMACOKINETICS

Hesperetin is typically administered as hesperidin. See Hesperidin.

INDICATIONS AND USAGE

Hesperetin may be helpful in lowering cholesterol and, possibly, otherwise favorably affecting lipids. *In vitro* and animal research also suggests the possibility that hesperetin might have some anticancer effects and that it might have some anti-aromatase activity, as well as activity against *Helicobacter pylori.* More research will be required before hesperetin is indicated for any of these situations.

RESEARCH SUMMARY

Like hesperidin, hesperetin has shown some favorable effects on lipids, but, unlike hesperidin, this research has so far been confined to *in vitro* and animal studies. In the best-designed of the animal studies to date, hesperetin significantly lowered plasma cholesterol levels (but not triglyceride levels) in rats fed a high-cholesterol diet.

No conclusions can yet be drawn from early animal work that suggests hesperetin-induced anticancer effects. Similarly, isolated studies showing anti-aromatase and anti-*Helicobacter pylori* activity *in vitro* need follow-up.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

See Hesperidin.

DOSAGE AND ADMINISTRATION

Hesperetin is typically administered as hesperidin. See Hesperidin.

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Hesperidin

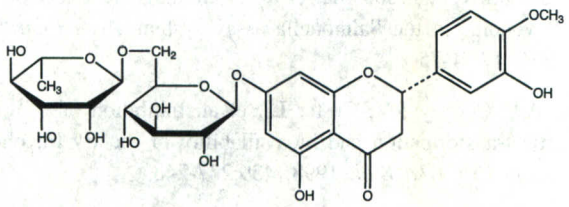
DESCRIPTION

The flavonoid hesperidin is a flavanone glycoside (glucoside) comprised of the flavanone (a class of flavonoids) hesperitin and the disaccharide rutinose. Hesperidin is the predominant flavonoid in lemons and oranges. The peel and membranous parts of these fruits have the highest hesperidin concentrations. Therefore, orange juice containing pulp is richer in the flavonoid than that without pulp. Sweet oranges *(Citrus sinensis)* and tangelos are the richest dietary sources of hesperidin. Hesperidin is classified as a citrus bioflavonoid.

Hesperidin, in combination with a flavone glycoside called diosmin, is used in Europe for the treatment of venous insufficiency and hemorrhoids. Hesperidin, rutin and other flavonoids thought to reduce capillary permeability and to have anti-inflammatory action were collectively known as vitamin P. These substances, however, are not vitamins and are no longer referred to, except in older literature, as vitamin P.

Hesperidin is a solid substance with low solubility in water. It is, however, much more soluble in water than its aglycone hesperetin. Hesperidin's molecular formula is $C_{28}H_{34}O_{15}$, and its molecular weight is 610.57 daltons.

The disaccharide of hesperidin, rutinose, is comprised of the sugars rhamnose (6-deoxy-L-mannose) and glucose. Hesperidin is also known as hesperetin 7-rhamnoglucoside, hesperetin-7-rutinoside and (S)-7-[[6-0-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl] oxy]-2, 3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one. Hesperidin is represented by the following chemical structure:



Hesperidin

ACTIONS AND PHARMACOLOGY

ACTIONS

Hesperidin may have antioxidant, anti-inflammatory, anti-allergic, hypolipidemic, vasoprotective and anticarcinogenic actions.

MECHANISM OF ACTION

Although some studies indicate that hesperidin has antioxidant activity *in vivo*, others do not demonstrate antioxidant activity *in vitro*.

The possible anti-inflammatory action of hesperidin is probably due to the possible anti-inflammatory action of its aglycone hesperetin. Hesperetin appears to interfere with the metabolism of arachidonic acid as well as with histamine release. Hesperetin appears to inhibit phospholipase A2, lipoxygenase and cyclo-oxygenase. There is evidence that hesperetin inhibits histamine release from mast cells, which would account for the possible anti-allergic activity of hesperidin.

Again, the possible hypolipidemic effect of hesperidin is probably due to hesperetin's possible action in lipid lowering. Hesperetin may reduce plasma cholesterol levels by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, as well as acyl coenzyme A: cholesterol acytransferase (ACAT). Inhibition of these enzymes by hesperetin has been demonstrated in rats fed a high cholesterol diet.

The mechanism of hesperidin's possible vasoprotective action is unclear. Animal studies have shown that hesperidin decreases microvascular permeability. Hesperidin, itself or via hesperetin, may protect endothelial cells from hypoxia by stimulating certain mitochondrial enzymes, such as succinate dehydrogenase.

The mechanism of hesperidin's possible anticarcinogenic action is also unclear. One explanation may be the inhibition of polyamine synthesis. Inhibition of lipoxygenase and cyclo-oxygenase is another possibility.

PHARMACOKINETICS

There is not much known about the pharmacokinetics of hesperidin in humans. It is unclear if hesperidin itself is absorbed from the intestine intact as a glycoside. The aglycone hesperetin is detected in the serum following ingestion and may be formed prior to or following absorption. Hesperetin may undergo glucuronidation in the wall of the intestine, as well as in the liver. Hesperetin is detected in the urine within three hours after ingestion of hesperidin. Urinary excretion appears to be the major route of excretion of the aglycone. Not much more is known about the metabolism of hesperidin.

INDICATIONS AND USAGE

Hesperidin has demonstrated some ability to favorably affect lipids and to treat some vascular disorders in humans. Other claims made for hesperidin are based on *in vitro* and animal studies. These include claims that hesperidin is useful in cancer and immune disorders. There are also claims that hesperidin is an anti-allergen and anti-inflammatory agent based on results from animal experiments.

RESEARCH SUMMARY

In several animal studies, hesperidin has significantly increased HDL-cholesterol while lowering total lipid and triglyceride plasma levels. A recent clinical trial tested the effects of hesperidin-rich orange juice in 25 subjects with elevated cholesterol levels. Subjects drank one glass of orange juice daily for four weeks, two glasses daily for four weeks and three glasses daily for four weeks. By the third phase of the study, HDL levels in these subjects increased 21% and the LDL/HDL ratio dropped 16%. Folate levels significantly increased. This was interpreted as a positive result, as well, since folate has been shown to cause declines in levels of homocysteine which, at high levels, is believed to increase the risk of heart disease.

These positive effects, attributed by the researchers to the hesperidin content of orange juice, persisted throughout a five-week washout period that followed the conclusion of testing. During that period, subjects were asked not to drink any juice.

Hesperidin has demonstrated antihypertensive and diuretic effects in both normotensive rats and spontaneously hypertensive rats. It has also shown some ability to protect against ischemia-reperfusion tissue damage in some animal models.

In combination with micronized diosmin, hesperidin has significantly improved acute internal hemorrhoids of pregnancy in a clinical open trial.

Anticancer, antimutagenic and immune-modulating effects have been seen with the use of hesperidin in numerous *in vitro* and animal studies. Among the cancers investigated in these studies are esophageal, colon, urinary bladder and skin cancers. In one study that compared the cancer-inhibiting effects of a number of dietary flavonoids and bioflavonoids,

hesperidin, hesperetin and catechin were said to be the most potent. More research is needed.

Similarly, more research is warranted to see whether preliminary animal studies suggesting that hesperidin may have significant antiallergenic and anti-inflammatory effects will have clinical relevance.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Hesperidin is contraindicated in those who are hypersensitive to hesperidin or any component of an hesperidin-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid use of supplemental hesperidin at doses higher than may be found in some multivitamin preparations (about 20 mg) unless such use is recommended by a physician.

ADVERSE REACTIONS

Supplemental hesperidin is usually well tolerated. Adverse reactions include gastrointestinal ones, such as nausea.

INTERACTIONS

NUTRITIONAL SUPPLEMENTS

Vitamin C: The interaction between flavonoids, such as hesperidin and hesperetin, and vitamin C is unclear. It has been believed for some time that flavonoids work synergistically with vitamin C, enhancing the absorption of the vitamin and preventing its oxidation. However, recent research indicates that flavonoids, such as hesperetin, may actually inhibit the uptake of vitamin C into cells. More research is needed to clarify this issue.

OVERDOSAGE

There are no reports of overdosage.

DOSAGE AND ADMINISTRATION

Hesperidin is present in such nutritional supplements as vitamin C with bioflavonoids. Typical dose in these products is about 20 mg. Hesperidin is available in hesperidin-complex supplements. Doses for this type of supplement are usually 500 mg to 2 grams daily. In Europe, hesperidin is available for the management of venous insufficiency and hemorrhoids in a combination product with diosmin. A 500-mg dose of this combination product is comprised of 50 mg of hesperidin and 450 mg of diosmin. Dose for this mixed flavonoid product, for the above conditions, is 1 to 3 grams daily. Another flavonoid, hesperidin methyl chalcone, is often marketed in formulations with hesperidin. This is a different flavonoid, and very few studies have been performed using it. A good source of hesperidin is orange juice containing pulp.

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Hexacosanol

DESCRIPTION

Hexacosanol is a 26-carbon, long-chain, saturated primary alcohol. Along with other long-chain alcohols, such as docosanol, octacosanol and triacontanol, it belongs to a family of organic compounds called fatty alcohols. It is a component of vegetable waxes and is found in wheat germ oil, rice bran oil and wool wax, among other things.