in the synthesis of acetylcholine in the central nervous system.

Oxaloacetate may enter the gluconeogenic pathway, which can lead to the production of glucose and glycogen. It is believed that the putative antiobesity effect of hydroxycitric acid is due to suppression of fatty acid and fat synthesis. In addition, hydroxycitric acid is thought to suppress food intake via an anorectic effect. This is believed to be accounted for by hydroxycitric acid's stimulation of liver gluconeogenesis.

PHARMACOKINETICS

There is little reported on the pharmacokinetics of hydroxycitric acid in humans. Animal studies indicate that it is absorbed via the gastrointestinal tract and transported to the liver and other body tissues. There are no reports indicating if the marketed hydroxycitric acid is transported into liver cells in humans.

INDICATIONS AND USAGE

Claims are made that hydroxycitric acid is an effective weight-loss agent. These claims are not presently supported by well-controlled studies.

RESEARCH SUMMARY

A suggestion from animal work that hydroxycitric acid might be an effective antiobesity agent has not been confirmed in human studies. A recent well-controlled trial of hydroxycitric acid failed to produce any significant weight loss compared with placebo. This was a 12-week double-blind study in which overweight subjects were randomized to receive 1500 milligrams of hydroxycitric acid daily or placebo.

In another recent study, also conducted double-blind, placebo-controlled and randomized, researchers sought to see whether hydroxycitric acid supplementation could increase fat oxidation in human subject. The researchers found no significant effect.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to a hydroxycitric acid-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid hydroxycitric acid supplements. Because of the theoretical possibility that hydroxycitric acid might affect the formation of acetylcholine in the brain, those with dementia syndromes, including Alzheimer's disease, should avoid hydroxycitric acid. Those with diabetes should be cautious about using hydroxycitric acid.

ADVERSE REACTIONS

In a 12-week weight loss study comparing hydroxycitric acid, 1500 milligrams daily, against a placebo, the number of reported adverse reactions was not significantly different between the placebo group and hydroxycitric acid groups.

OVERDOSAGE

There are no reports of overdosage.

DOSAGE AND ADMINISTRATION

Hydroxycitric acid is available in *Garcinia cambogia* extracts. Some products contain hydroxycitric acid in the lactone form, which has not shown activity in animal models. There are products available that are free of the lactone form. Typical doses are about 1500 milligrams (as hydroxycitric acid) daily.

LITERATURE

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Hydroxyethylrutosides

DESCRIPTION

Hydroxyethylrutosides (HR) refer to a mixture of semi-synthetic derivatives of the flavonoid rutin. Rutin is a naturally occurring flavonol glycoside comprised of the flavonol quercetin and the disaccharide rutinose (see Rutin). Hydroxyethylrutosides are comprised of the mono-, di-, tri- and tetrahydroxyethyl derivatives of rutin and are prepared by the hydroxyethylation of the phenolic groups of rutin.

Formulations, mainly consisting of the trihydroxyethyl derivative of rutin, are used in Europe, Mexico and other Latin American countries for the treatment of such venous disorders as varicose veins and hemorrhoids. The generic name for these formulations is troxerutin.

Trihydroxyethylrutoside, the principal flavonoid in troxerutin, is also known as 7, 3′, 4′-tris [O- (2-hydroxyethyl)]rutin, trioxyethylrutin and 2- [3, 4-bis (2-hydroxyethoxy) phenyl]-3 [[6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl]oxy] -5-hydroxy-7- (2-hydroxyethoxy) -4*H*-1-benzopyran-4-one. It is a solid, yellow substance that is soluble

in water. Its molecular formula is $C_{33}H_{42}O_{19}$, and its molecular weight is 742.69 daltons.

ACTIONS AND PHARMACOLOGY

ACTIONS

Hydroxyethylrutosides may have venoprotective, vasoprotective and antioxidant actions.

MECHANISM OF ACTION

The mechanisms of the possible veno- and vasoprotective actions of HR are not clear. During blood stasis, such as occurs during venous insufficiency, hypoxic conditions can activate endothelial cells. The activation of endothelial cells may result in phospholipase A2 activation, leading to the release of inflammatory mediators, neutrophil adhesiveness to the endothelium with subsequent release of superoxide anions and leukotriene B4, and depletion of ATP. At least *in vitro*, HR appear to inhibit some of these processes, such as the activation of phospholipase A2 and the recruitment and activation of neutrophils. HR may have reactive oxygen and nitrogen species scavenging activity, which could also contribute to the possible protective effects. It is unclear, however, what the active forms of HR are *in vivo*.

PHARMACOKINETICS

There is little known about the pharmacokinetics of HR in humans. Radioactive labeling studies indicate that HR are absorbed from the intestine following absorption and that the major route of HR excretion is via the biliary-enteric route. However, it is unclear how much HR are absorbed intact—that is, as the glycosides—and it is also unclear what the metabolic fate of HR is following absorption.

INDICATIONS AND USAGE

Hydroxyethylrutosides have demonstrated significant efficacy in the treatment of venous insufficiency and related disorders. There is preliminary evidence that HR might be useful in some with Meniere's disease.

RESEARCH SUMMARY

A meta-analysis of randomized, placebo-controlled trials using HR in the treatment of chronic venous insufficiency found improvement in HR-treated subjects, compared with placebo, as measured by significant disappearance of the following symptoms: pain, cramps, tired legs, swelling and restless legs.

In another review of the therapeutic efficacy of HR, the substance was found to show "promise as a useful additional option for the management of edema and other symptoms of chronic venous insufficiency." Positive effects were confirmed in venous insufficiency associated with pregnancy and lymphoedema. Reductions in retinal vascular permeability have been seen in HR-treated patients with diabetic retinopathy, and HR have been shown, in other studies, to be efficacious in treating some women with hemorrhoids of pregnancy.

Finally, there is a double-blind, placebo-controlled, crossover study showing significant, positive HR effects in the treatment of subjects with well-defined Meniere's disease. Dose in this trial was 2 grams of HR daily for three months. Side effects were few.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Hydroxyethylrutosides are contraindicated in those hypersensitive to any component of an HR-containing product.

PRECAUTIONS

HR should be avoided by pregnant women and nursing mothers unless they are prescribed by physicians.

ADVERSE REACTIONS

HR are generally well tolerated. Gastrointestinal side effects, such as nausea, are occasionally reported.

DOSAGE AND ADMINISTRATION

Troxerutin (trihydroxyethylrutoside) is available is some combination products. It is used in Europe and Latin American countries in the management of varicose veins and hemorrhoids. Doses used for these conditions range from 500 mg to 2 grams daily.

LITERATURE

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Hydroxytyrosol

DESCRIPTION

Olive oil is the principal fat component in the Mediterranean diet and its consumption has been associated with a lower incidence of coronary heart disease (CHD), some cancers, including prostate, breast and colorectal cancer, and other