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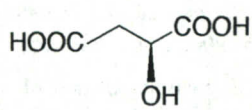
Malic Acid

DESCRIPTION

Malic acid, an alpha-hydroxy organic acid, is sometimes referred to as a fruit acid. This is because malic acid is found in apples and other fruits. It is also found in plants and animals, including humans. In fact, malic acid, in the form of its anion malate, is a key intermediate in the major biochemical energy-producing cycle in cells known as the citric acid or Krebs cycle located in the cells' mitochondria.

Malic acid, also known as apple acid, hydroxybutanedioic acid and hydroxysuccinic acid, is a chiral molecule. The naturally occurring stereoisomer is the L-form. The L-form is also the biologically active one. There is some preliminary evidence that malic acid, in combination with magnesium, may be helpful for some with fibromyalgia. Malic acid sold as a supplement is mainly derived from apples and, therefore, is the L-form. L-malic acid has the following chemical structure:



L-malic Acid

ACTIONS AND PHARMACOLOGY

ACTIONS

Malic acid, in combination with magnesium, has putative antifibromyalgic activity.

MECHANISM OF ACTION

The mechanism of malic acid's putative antifibromyalgic activity is unknown.

PHARMACOKINETICS

Malic acid is absorbed from the gastrointestinal tract from whence it is transported via the portal circulation to the liver. There are a few enzymes that metabolize malic acid. Malic enzyme catalyzes the oxidative decarboxylation of L-malate to pyruvate with concomitant reduction of the cofactor NAD+ (oxidized form of nicotinamide adenine dinucleotide) or NADP+ (oxidized form of nicotinamide adenine dinucleotide phosphate). These reactions require the divalent cations magnesium or manganese. Three isoforms of malic enzyme have been identified in mammals: a cytosolic NADP+-dependent malic enzyme, a mitochondrial NADP+-dependent malic enzyme and a mitochondrial NAD(P)+-dependent malic enzyme. The latter can use either NAD+ or NADP+ as the cofactor but prefers NAD+. Pyruvate formed from malate can itself be metabolized in a number of ways, including metabolism via a number of metabolic steps to glucose. Malate can also be metabolized to oxaloacetate via the citric acid cycle. The mitochondrial malic enzyme, particularly in brain cells, may play a key role in the pyruvate recycling pathway, which utilizes dicarboxylic acids and substrates, such as glutamine, to provide pyruvate to maintain the citric acid cycle activity when glucose and lactate are low.

Clearly, the metabolism of malic acid is complex and what any of the above has to do, if anything, with malic acids' putative activity in those with fibromyalgia is entirely unclear.

INDICATIONS AND USAGE

Malic acid may help some with fibromyalgia.

RESEARCH SUMMARY

Results have been mixed in studies of malic acid's possible effects in those with fibromyalgia. In a double-blind, placebo-controlled crossover study, subjects with primary fibromyalgia syndrome were randomized to receive a combination of 200 milligrams of malic acid and 50 milligrams of magnesium per tablet (three tablets twice a day) or placebo for four weeks. This was followed by a six-month, open-label trial with dose escalating up to six tablets twice a day. Outcome variables were measures of pain and tenderness, as well as functional and psychological measures.

No clear benefit was observed for the malic acid/magnesium combination in the lower-dose blinded trial. But in the open-label trial, at higher doses, there were significant reductions in the severity of all three primary pain/tenderness measures. Follow-up is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to a malic acid-containing product.

PRECAUTIONS

Because of lack of long-term safety studies, supplementary malic acid should be avoided by pregnant women and lactating mothers. See Magnesium.

INTERACTIONS

None reported for malic acid. See Magnesium.

DOSAGE AND ADMINISTRATION

The doses used in the fibromyalgia studies were L-malic acid, 1200 to 2400 milligrams daily, and magnesium, 300 to 600 milligrams daily.

LITERATURE

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Manganese

DESCRIPTION

Manganese is an essential trace mineral in animal nutrition and is believed to be an essential trace mineral in human nutrition, as well. Manganese is a metallic element with atomic number 25 and an atomic weight of 54.94 daltons. Its chemical symbol is Mn. Manganese exists in the oxidation states Mn^{2+} or Mn(II) and Mn^{3+} or Mn(III) under physiological conditions.

Dietary manganese-deficiency in animals results in a wide variety of structural and physiological defects, including growth retardation, skeletal and cartilage malformations, impaired reproductive function, congenital ataxia due to abnormal inner ear development, optic nerve abnormalities, impaired insulin metabolism and abnormal glucose tolerance, alterations in lipoprotein metabolism and an impaired oxidant defense system.

Manganese deficiency states have not been well documented in humans. There is one report of a man maintained for four months on a manganese-deficient diet and also given magnesium-containing antacids. The symptoms which occurred included a decrease in serum cholesterol, depressed growth of hair and nails, scaly dermatitis, weight loss, reddening of his black hair and beard and impaired blood clotting. He responded to a diet containing manganese. In another report, men fed a low-manganese diet manifested low serum cholesterol levels and dermatitis. Short-term manganese supplementation did not reverse these symptoms.

In still another report, young women fed a manganese-poor diet were found to have mildly abnormal glucose tolerance and increased menstrual losses of manganese, calcium, iron and total hemoglobin. Finally a child on long-term total parenteral nutrition (TPN) lacking manganese manifested bone demineralization and impaired growth that were corrected by supplementation with manganese.

Manganese is the preferred metal cofactor for glycosyltransferases. Glycosyltransferases are important in the synthesis of glycoproteins and glycosaminoglycans (GAGs or mucopolysaccharides). Glycoproteins are involved in the synthesis of myelin and the clotting factors, among other things. Manganese-containing metalloenzymes include manganese superoxide dismutase, the principal antioxidant enzyme of mitochondria, arginase, pyruvate carboxylase and glutamine synthetase.

The richest dietary sources of manganese include whole grains, nuts, leafy vegetables and teas. Manganese is concentrated in the bran of grains which is removed during processing. Mean intakes of manganese worldwide range from 0.52 to 10.8 milligrams daily.

ACTIONS AND PHARMACOLOGY

ACTIONS

Manganese may have antioxidant activity. Manganese has putative anti-osteoporotic and anti-arthritic activities.

MECHANISM OF ACTION

Manganese ions have been found to scavenge hydroxyl and superoxide radicals. The mechanism of binding of manganese ions to these reactive oxygen species is not known. Manganese is a crucial component of the metalloenzyme manganese superoxide dismutase (MnSOD). MnSOD is found in mitochondria and is the principal constituent of the mitochondrial oxidant defense system. Rats and mice fed manganese-deficient diets are found to have reduced MnSOD activity in heart muscle and nervous tissue. They also have mitochondrial abnormalities and pathological changes in these tissues. The pathological changes are thought to result from oxidative damage due to the decreased activity of MnSOD which normally would protect against this damage.