

FDA warns against consuming dietary supplements containing tiratricol.

ADVERSE REACTIONS

Reported adverse reactions include fatigue, lethargy, profound weight loss and severe diarrhea. Tiratricol has also been reported to cause abnormal thyroid function tests.

INTERACTIONS

DRUGS

Anticoagulants (oral). The hypoprothrombinemic effect of anticoagulants, such as warfarin, may be potentiated.

Sympathomimetic agents. There is a possible increased risk of coronary insufficiency in those with coronary artery disease.

Thyroid drugs (levothyroxine, triiodothyronine, thyroid). Concomitant use of tiratricol with these thyroid drugs is likely to produce additive effects.

LABORATORY TESTS

Tiratricol is likely to alter thyroid function tests, including TSH, T_4 and T_3 .

OVERDOSAGE

There have been no reports of overdosage with tiratricol. Excessive doses of tiratricol theoretically may result in a hypermetabolic state indistinguishable from thyrotoxicosis.

DOSAGE AND ADMINISTRATION

Tiratricol is not recommended for use as a dietary supplement.

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Tocotrienols

DESCRIPTION

Tocotrienols comprise one of the two groups of molecules belonging to the vitamin E family, the other group being the tocopherols. Tocotrienols and tocopherols are sometimes collectively called tocopherols. Just as there are four natural tocopherols, alpha-, beta-, gamma- and delta-tocopherol, there are also four natural tocotrienols, alpha-, beta-, gamma- and delta-tocotrienol. The tocotrienols differ from the tocopherols in the chemical nature of the side chain or tail. Tocopherols have a saturated phytyl side chain, whereas tocotrienols have an unsaturated isoprenoid or farnesyl side chain possessing three double bonds.

The major source of tocotrienols are plant oils, and the richest sources are palm oil, rice bran oil, palm kernel oil and coconut oil. Tocotrienols are also found in such cereal grains as oat, barley and rye. Vegetable oils, such as those from canola, cottonseed, olive, peanut, safflower, soybean and sunflower, contain little to no tocotrienols. However, those oils do contain tocopherols. Corn oil has small amounts of tocotrienols.

All of the natural tocotrienols are fat-soluble, water-insoluble oils. The tocotrienols, as well as the tocopherols, possess chain-breaking, peroxyl radical scavenging activities. In contrast to tocopherols, tocotrienols inhibit the rate-limiting enzyme of the cholesterol biosynthetic pathway beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase.

The four natural tocotrienols are characterized by the number of methyl groups and their position in the chromanol ring. Alpha-tocotrienol has three methyl groups located on positions 5, 7 and 8 of the chromanol ring; beta-tocotrienol has two methyl groups located on positions 5 and 8 of the ring; gamma-tocotrienol has two methyl groups located on positions 7 and 8 of the ring and delta-tocotrienol has one methyl group located on position 8 of the ring.

While tocopherols have three chiral centers, tocotrienols have only one chiral center. Therefore, each tocotrienol has two stereoisomeric possibilities in comparison with eight such possibilities for each of the tocopherols. The natural tocotrienols exist as d-stereoisomers: d-alpha-tocotrienol, d-beta-tocotrienol, d-gamma-tocotrienol and d-delta-tocotrienol.

ol. The chiral center in the tocotrienol structure is at the point where the isoprenoid side chain bonds to the chromanol ring, the 2 position of the ring. The natural tocotrienols are E, E in reference to the geometric configuration of the double bonds of the side chain.

D-Alpha-tocotrienol is also known as 2R, 3'E, 7'E-alpha tocotrienol and is abbreviated alpha-T₃; d-beta-tocotrienol is known as 2R, 3'E, 7'E-beta-tocotrienol and abbreviated beta-T₃; d-gamma-tocotrienol is known as 2R, 3'E, 7'E-gamma-tocotrienol and abbreviated gamma-T₃; delta-tocotrienol is known as 2R, 3'E, 7'E-delta-tocotrienol and abbreviated delta-T₃. Tocotrienols are presently available in nutritional supplement form as mixed tocotrienols. Typically, the gamma form is the most abundant one in the mixture.

Occasionally tocotrienol is used in the singular but refers to the entire group of natural tocotrienols.

ACTIONS AND PHARMACOLOGY

ACTIONS

Tocotrienols have antioxidant activity. They may also have hypocholesterolemic, anti-atherogenic, antithrombotic, anti-carcinogenic and immunomodulatory actions.

MECHANISM OF ACTION

All the tocotrienols are lipid soluble, chain-breaking, peroxy radical scavengers. As such, they can protect polyunsaturated fatty acids (PUFAs) within membrane phospholipids as well as PUFAs within plasma lipoproteins, such as low density lipoproteins, from lipid peroxidation. Which of the tocols have the highest antioxidant activity is still open to debate. For many years, alpha-tocopherol was thought to be the most potent antioxidant in the vitamin E family. Some studies have shown tocotrienols to be more effective inhibitors of both lipid peroxidation and protein oxidation than alpha-tocopherol. In these same studies, the order of antioxidant potency was gamma-tocotrienol followed by the alpha and delta tocotrienol homologues. Gamma-tocopherol is a peroxynitrite scavenger, and gamma-tocotrienol may be, as well. The possible greater antioxidant activity of the tocotrienols, compared with alpha-tocopherol, may be accounted for by a more efficient interaction of the chromanol ring with reactive oxygen species, a higher recycling efficiency of the chromanol radicals of the tocotrienols and a more uniform distribution of the tocotrienols in cellular membranes. In any case, alpha-tocopherol is the dominant tocol in human plasma and tissue, and, therefore, would be expected to be the dominant antioxidant form, as well.

Tocotrienols inhibit the rate-limiting enzyme of the cholesterol biosynthetic pathway, beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase. Tocopherols do not have this activity. This hypocholesterolemic effect of tocotrienols is accounted for by the tocotrienol isoprenoid side-

chain's ability to increase the concentration of cellular farnesol. Farnesol is derived from mevalonate, the product of the HMG-CoA reductase reaction. Farnesol, post-transcriptionally, suppresses HMG-CoA reductase synthesis and enhances the proteolytic catabolism of this enzyme. This mechanism is different from that of the statin hypocholesterolemic drugs (atorvastatin, cerivastatin, fluvastatin, lovastatin and pravastatin) which are competitive inhibitors of the enzyme. Gamma-tocotrienol and delta-tocotrienol are significantly more active than alpha-tocotrienol in suppressing HMG-CoA reductase activity.

The possible anti-atherogenic activity of tocotrienols can be accounted for by a few mechanisms. These include inhibition of LDL oxidation, suppression of HMG-CoA reductase activity and inhibition of platelet aggregation. Additional possible mechanisms include tocotrienol-mediated reduction of plasma apolipoprotein B-100 (apoB) levels, reduction of lipoprotein (a) [Lp (a)] plasma levels and inhibition of adhesion molecule (e.g., ICAM-1 and VCAM-1) expression and monocyte cell adherence. High plasma levels of apoB as well as Lp (a) are considered risk factors for coronary artery disease.

Tocotrienols' possible antithrombotic effect may be due to tocotrienols' (especially gamma-tocotrienol's) inhibition of thromboxane B₂ synthesis, as well as their suppression of plasma levels of platelet factor 4.

Tocotrienols have been found to inhibit the growth of several tumor cell lines in culture, including both estrogen receptor-negative and estrogen receptor-positive human breast cancer cells. The mechanism of this effect is unclear, but there is some speculation about it. Tocotrienols may upregulate apoptosis in these lines. Another possible mechanism may relate to tocotrienols' post-transcriptional suppression of HMG-CoA reductase. The suppression of mevalonate synthesis depletes tumor tissues of farnesyl pyrophosphate and geranylgeranylpyrophosphate. These intermediates in the cholesterol biosynthetic pathway play important roles in growth control-associated proteins. Suppressing the production intermediates could result in suppression of prenylation of the oncogene ras protein. Post-translational farnesylation of Ras is required for the cytoplasmic localization of the active Ras p21 to the cell membrane, enabling this oncogene to stimulate growth and induce malignant transformation.

PHARMACOKINETICS

The efficiency of absorption of tocotrienol is low and variable. Absorption from the lumen of the small intestine is lower on an empty stomach than with meals. Prior to their absorption, tocotrienols are emulsified with the aid of bile salts and form micelles with dietary fats and products of lipid hydrolysis. Tocotrienols, after absorption into the entero-

cytes, are secreted by these cells into the lymphatics in the form of chylomicrons. The chylomicrons are transported by the lymphatics to the circulation where they are metabolized to chylomicron remnants. Some tocotrienols are transferred to various tissues, including adipose tissue, muscle and possibly the brain. Chylomicrons transfer tocotrienols to HDL, which, in turn, transfers them to LDL and VLDL. These remnants can also acquire apolipoprotein E, which directs them and the tocotrienols they contain to the liver for further metabolism.

Chylomicron remnants are taken up by the liver. Tocotrienols do not bind very well to the hepatic alpha-tocopherol transfer protein. It is this protein that is involved in the secretion from the liver of alpha-tocopherol in VLDLs. Very little tocotrienol is secreted by the liver to the circulation in VLDLs.

Some tocotrienol is metabolized, and the metabolites are excreted in the urine. Fecal excretion is the main route of excretion of oral tocotrienols. Fecal excretion products include non-absorbed tocotrienols and tocotrienols that may be excreted by the biliary route.

INDICATIONS AND USAGE

Indications and uses of the tocotrienols are, generally, the same as those of vitamin E. (See Vitamin E.) The tocotrienols may, in some conditions, be more potent and, in others, less potent than vitamin E, but research related to this issue is preliminary. There are some data suggesting that tocotrienols may have greater hypolipidemic effects than the tocopherols. The tocotrienols show some promise in inhibiting breast cancer and some other malignancies, though this work, too, is preliminary. Tocotrienols were reported, in one recent animal study, to promote healing of ethanol-induced gastric lesions.

RESEARCH SUMMARY

There is evidence, in animal models, that tocotrienols decrease serum cholesterol levels. Both total and LDL-cholesterol levels have been significantly reduced in swine, 44% and 60% respectively. Serum cholesterol levels were lowered 29% in hypercholesterolemic chickens fed a tocotrienol-enriched diet. In some animal studies, it has also inhibited platelet aggregation.

In some small, case-controlled human trials, tocotrienol preparations showed an ability to reduce cholesterol, principally LDL-cholesterol, while leaving HDL-cholesterol essentially unchanged. Despite good results in these studies and in animal and *in vitro* studies, coupled with epidemiological data suggesting that high tocotrienol status confers protection against cardiovascular disease, some recent, small studies have not been quite as promising.

In one randomized, placebo-controlled trial of 50 subjects with cerebrovascular disease (including carotid stenosis), a daily supplement containing 64 milligrams of alpha-tocopherol and 160 milligrams of gamma-tocotrienol failed to produce any positive lipid effects. The lack of effect persisted even when the dose was boosted to 96 milligrams of alpha-tocopherol and 240 milligrams of gamma-tocotrienol.

But, even though there was no lipid-lowering effect, the treated group showed improvement, compared with controls receiving placebo in terms of ultrasonographically measured rate of progression and, in some cases, regression of carotid stenosis. It was hypothesized that the treatment might have inhibited protein kinase C stimulation and may thus have prevented proliferation of smooth muscle cells among other possible mechanisms of action.

More recently, another randomized, double-blind, placebo-controlled study found no lipid effects from a supplement containing 35 milligrams of tocotrienols and 20 milligrams of alpha-tocopherol in 20 men with slightly elevated lipid concentrations. Larger studies, perhaps using higher doses of tocotrienols in subjects with more pronounced hyperlipidemia, are needed.

In one small, double-blind, crossover study of hypercholesterolemic subjects, 200 milligrams of a tocotrienol-enriched fraction of palm oil daily for four weeks significantly lowered total cholesterol, LDL-cholesterol, Apo B, thromboxane, platelet factor 4 and glucose. The crossover confirmed these findings.

Subsequently, both gamma-tocotrienol and the same tocotrienol-enriched fraction of palm oil described above were tested in more hypercholesterolemic subjects. Both supplements produced significant cholesterol reduction in these subjects. Gamma tocotrienol (200 milligrams daily) was more effective than the palm oil preparation (which contained 40 milligrams of alpha-tocotrienol and 60 milligrams of delta-tocotrienol).

Gamma and delta-tocotrienols, but not alpha- and gamma-tocopherols, have shown significant tumor-inhibition activity in several *in vitro* studies. In one of these, a tocotrienol-rich fraction of palm oil significantly inhibited the growth of a human breast cancer cell line, whereas alpha-tocopherol did not. Additional *in vitro* studies have demonstrated that tocotrienols inhibit the growth of human breast cancer cells in culture irrespective of the estrogen receptor status of the cells. It has been suggested by some researchers that tocotrienols might productively be combined with tamoxifen as a breast cancer treatment. The efficacy and safety of such a combination have not been tested, but the potential for such a treatment might be considerable, particularly with respect

to treating hormone-responsive breast cancer that has become resistant to tamoxifen and other antiestrogens.

Tocotrienols have shown experimental activity against a number of other cancers. Research continues.

Recently, a tocotrienol-enriched fraction of palm oil was found to enhance the healing of ethanol-induced gastric mucosal lesions in rats. It was not, however, able to prevent such injuries. It was hypothesized that tocotrienols may abet healing through inhibition of lipid peroxidation. Further study is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Tocotrienols are contraindicated in those with known hypersensitivity to these substances.

PRECAUTIONS

Those on warfarin should be cautious in using doses of tocotrienols greater than 100 milligrams daily and, if they do so, they should have their INRs carefully monitored and their warfarin dose appropriately adjusted if indicated. Likewise, those with vitamin K deficiencies, such as those with liver failure, should be cautious in using doses of tocotrienols greater than 100 milligrams daily. Tocotrienols should also be used with caution in those with lesions with a propensity to bleed (e.g., bleeding peptic ulcers), those with a history of hemorrhagic stroke and those with inherited bleeding disorders (e.g., hemophilia).

High dose tocotrienol supplementation (greater than 100 milligrams daily) should be stopped about one month before surgical procedures and may be resumed following recovery from the procedure.

Those taking iron supplements should not take tocotrienols and iron at the same time.

ADVERSE REACTIONS

Tocotrienol supplements have only recently been introduced in the nutritional supplement marketplace. No adverse reactions have been reported.

INTERACTIONS

DRUGS

Antiplatelet drugs, such as aspirin, dipyridamole, eptifibatide, clopidogrel, ticlopidine, tirofiban and abciximab: Tocotrienol supplementation may potentiate the effects of these antiplatelet drugs.

Cholestyramine: may decrease tocotrienol absorption.

Colestipol: may decrease tocotrienol absorption.

Isoniazid: may decrease tocotrienol absorption.

Mineral oil: may decrease tocotrienol absorption.

Neomycin: may impair utilization of tocotrienols.

Orlistat: is likely to inhibit tocotrienol absorption.

Statins: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin: The possible cholesterol-lowering action of tocotrienols may be additive to that of the statins.

Sucralfate: may interfere with tocotrienol absorption.

Warfarin: Tocotrienol doses greater than 100 milligrams daily may enhance the anticoagulant response of warfarin. Monitor INRs and appropriately adjust warfarin dose if necessary.

NUTRITIONAL SUPPLEMENTS

Desiccated ox bile: may increase the absorption of tocotrienols.

Iron: Most iron supplements contain the ferrous form of iron. This form can oxidize tocotrienols, marketed in their unesterified forms, to their pro-oxidant forms if taken concomitantly.

Medium-chain triglycerides: may enhance absorption of tocotrienols if taken concomitantly.

Phytosterols and phytosterols, including beta-sitosterol and beta-sitosterol: may lower plasma tocotrienol levels.

FOOD

Olestra: is likely to inhibit the absorption of tocotrienols. Alpha-tocopherol is the only member of the vitamin E family that is added to olestra.

HERBS

Some herbs, including ginkgo and garlic, possess antithrombotic activity, and tocotrienols, if taken concomitantly with these herbs, may enhance their antithrombotic activity.

OVERDOSAGE

Tocotrienol overdosage has not been reported in the literature.

DOSAGE AND ADMINISTRATION

Presently marketed forms of tocotrienols contain mixed tocotrienols in their unesterified forms. These products typically contain d-alpha-tocotrienol, d-gamma-tocotrienol and d-delta-tocotrienol. Gamma-tocotrienol is usually the major tocotrienol in these preparations, which are marketed in the form of softgel capsules (tocotrienol is an oil).

Doses of 200 to 300 milligrams daily, with food, have been used in clinical trials studying possible cholesterol-lowering activity of tocotrienol.

The unesterified forms of tocotrienols, as well as tocopherols, are susceptible to oxidation and should therefore be stored in tightly closed, opaque containers in a cool, dry

place. Tocotrienols should not be taken concomitantly with iron supplements.

LITERATURE

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Transgalacto-Oligosaccharides

DESCRIPTION

Transgalacto-oligosaccharides (TOS), also known as galactooligosaccharides (GOS), are a mixture of oligosaccharides consisting of D-glucose and D-galactose. Transgalacto-digosaccharides are produced from D-lactose via the action of the enzyme beta-galactosidase obtained from *Aspergillus oryzae*.

TOS are not normally digested in the small intestine. They are, however, fermented by a limited number of colonic bacteria. This could lead to changes in the colonic ecosystem in favor of some bacteria, such as bifidobacteria, which may have health benefits, including protection against certain cancers and lowering of cholesterol levels. TOS and other non-digestible oligosaccharides are sometimes referred to as bifidogenic factors.

Substances such as TOS that promote the growth of beneficial bacteria in the colon are called prebiotics. Prebiotics are typically non-digestible oligosaccharides.

ACTIONS AND PHARMACOLOGY

ACTIONS

Transgalacto-oligosaccharides may have antitumor, antimicrobial, hypolipidemic and hypoglycemic actions. They may also help improve mineral absorption and balance.