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

LITERATURE

Elson CE. Suppression of mevalonate pathway activities by dietary isoprenoids: protective roles in cancer and cardiovascular disease. *J Nutr.* 1995; 125(6 Suppl):1666S-1672S.

Guthrie N, Gapor A, Chambers AF, Carroll KK. Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and—positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. *J Nutr.* 1997; 127:544S-548S.

Kamat JP, Devasagayam TP. Tocotrienols from palm oil as inhibitors of lipid peroxidation and protein oxidation in rat brain mitochondria. *Neurosci Lett.* 1995; 195:179-182.

Kamat JP. Sarma HD, Devasagayam TPA, et al. Tocotrienols from palm oil as effective inhibitors of protein oxidation and lipid peroxidation in rat liver microsomes. *Mol Cell Biochem.* 1997; 170:131-137.

Mc Intyre BS, Briski KP, Tirmenstein MA, et al. Antiproliferative and apoptotic effects of tocopherols and tocotrienols on normal mouse mammary epithelial cells. *Lipids.* 2000; 35:171-180.

Mensink RP, van Houwelingen AC, Kromhout D, Hornstra G. A vitamin E concentrate rich in tocotrienols had no effect on serum lipids, lipoproteins, or platelet function in men with mildly elevated serum lipid concentrations. *Am J Clin Nutr.* 1999; 69:213-219.

Nesaretnam K, Guthrie N, Chambers AF, Carroll KK. Effects of tocotrienols on the growth of a human breast cancer cell line in culture. *Lipids.* 1995; 30:1139-1143.

Nesaretnam K, Stephen R, Dils R, Dabre P. Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status. *Lipids.* 1998; 33:461-469.

Parker RA, Pearce BC, Clark RW, et al. Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hdroxy-3-methylglutaryl-coenzyme A reductase. *J Biol Chem.* 1993; 268:11230-11238.

Pearce BC, Parker RA, Deason ME, et al. Inhibitors of cholesterol biosynthesis. 2. Hypocholesterolemic and antioxidant activities of benzopyran and tertrahydronaphthalene analogues of the tocotrienols. *J Med Chem.* 1994; 37:526-541.

Quereshi AA, Bradlow BA, Manganello J, et al. Response of hypercholesterolemic subjects to administration of tocotrienols. *Lipids.* 1995; 30:1171-1177.

Quereshi AA, Pearce BC, Nor RM, et al. Dietary alpha-tocopherol on hepatic 3-hydroxy-3-methlyglutaryl coenzyme A reductase activity in chickens. *J Nutr.* 1996; 126:389-394.

Quereshi AA, Quereshi N, Hasler-Rapacz JO, et al. Dietary tocotrienols reduce concentrations of plasma cholesterol, apolipoprotein B, thromboxane B2 and platelet factor 4 in pigs with inherited hyperlipidemica. *Am J Clin Nutr.* 1991; 53(Suppl):1042S-1046S.

Serbinova E, Khwaja S, Catudioc J, et al. Palm oil vitamin E protects against ischemia reperfusion injury in the isolated perfused Langendorff heart. *Nutr Res.* 1992; 12(Suppl 1):S203-S215.

Theriault A, Chao J-T, Wang Q, et al. Tocotrienol: a review of its therapeutic potential. *Clinic Biochem.* 1999; 32:309-319.

Theriault A, Wang Q, Gapor A, Adeli K. Effects of gamma-tocotrienol on ApoB synthesis, degradation, and secretion in Hep G2 cells. *Arterioscler Thromb Vasc Biol.* 1999; 19:704-712.

Tomeo AC, Geller M, Watkins TR, et al. Antioxidant effects of tocotrienols in patients with hyperlipidemia and carotid stenosis. *Lipids.* 1995; 30:1179-1183.

Wang Q, Theriault A, Gapor A, Adeli K. Effects of tocotrienol on the intracellular translocation and degradation of apolipoprotein B: possible involvement of a proteasome independent pathway. *Biochem Biophys Res Commun.* 1998; 246:640-643.

Watkins T, Lenz P, Gapor A, et al. Gamma-tocopherol as a hypocholesterolemic and antioxidant agent in rats fed atherogenic diets. *Lipids.* 1993; 28:1113-1118.

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.

MECHANISM OF ACTION

The possible antitumor activity of TOS might be accounted for by the possible antitumor action of butyrate, one of the substances produced from TOS in the colon. Butyrate, the anion of the naturally occurring short-chain fatty acid butyric acid, is produced by bacterial fermentation of TOS in the colon. Studies suggest that butyrate induces growth arrest and cell differentiation and may upregulate apoptosis, three activities that could be significant for antitumor activity. Interestingly, butyrate also appears to inhibit vascular smooth muscle cell proliferation, at least in the rat, an activity that could have relevance with regard to a possible antiatherogenic role. TOS may promote the growth of favorable bacterial populations, such as bifidobacteria, in the colon. Bifidobacteria may inhibit the growth of pathogenic bacteria, such as *Clostritium perfringens* and diarrheogenic strains of *Escherichia coli.*

There is evidence, again from rat studies, that butyrate may suppress cholesterol synthesis in the liver and intestine. Propionate, another short-chain fatty acid produced from the bacterial fermentation of TOS in the colon, may reduce plasma free fatty acids. This might be good for blood glucose and insulin sensitivity in the long term, since high levels of plasma free fatty acids lower tissue glucose utilization and induce insulin resistance. Propionate may also aid in lowering cholesterol levels in some by possibly inhibiting HMG-CoA reductase.

TOS, similar to dietary fiber, may bind/sequester such minerals as calcium and magnesium in the small intestine. The short-chain fatty acids (acetate, propionate, butyrate) formed from the bacterial fermentation of TOS may facilitate the colonic absorption of calcium and magnesium ions. This could have both bone- and cardiovascular-health benefits.

PHARMACOKINETICS

Under normal conditions, following ingestion of TOS, no digestion of these oligosaccharides takes place in the small intestine. A small amount of TOS may undergo some acid hydrolysis in the stomach. TOS are fermented in the colon by bifidobacteria and some other bacteria to produce the short-chain fatty acids acetate, propionate and butyrate. Lactate is also produced. Acetate, propionate and butyrate that are not metabolized in colonocytes are absorbed from the colon and transported via the portal circulation to the liver. These short-chain fatty acids are extensively metabolized in hepatocytes. Acetate, propionate and butyrate that are not metabolized in hepatocytes are transported by the circulation to various tissues, where they undergo further metabolism. Butyrate is an important respiratory fuel for the colonocytes and is metabolized in them to CO_2 and H_2O. Energy is produced (ATP) from the catabolism of butyrate. Those with ileostomies may have a microbial population colonizing their ileums. In those cases, TOS could be fermented by some of the bacteria to short-chain fatty acids and lactic acid.

INDICATIONS AND USAGE

Transgalacto-oligosaccharides are being investigated for possible protective effects against colorectal cancer and infectious bowel diseases, for modulation of lipids and prevention of bone loss. Animal research suggests a role for TOS in those situations, but there is still little substantial clinical research.

RESEARCH SUMMARY

TOS, through their stimulation of bifidobacteria, have shown some protective effects against colorectal cancer and infectious bowel diseases in animal and *in vitro* experiments. TOS inhibit putrefactive bacteria (*Clostridium perfringens*) and pathogenic bacteria, such as *Escherichia coli, salmonella, listeria* and *shigella.*

A recent human study showed that supplemental TOS (in doses of 7.5 and 10 grams daily) are completely fermented in the human colon but that they did not, in this study, beneficially change the composition of the intestinal microflora. Another study, however, did show some alteration in the fermentative activity of colonic flora in humans given 10 grams of TOS per day for 21 days.

TOS have demonstrated some preliminary positive effects on calcium absorption and lipid metabolism in animal studies. Reduced serum triglyceride levels have been noted. A significant TOS hypocholesterolemic effect was observed in ovariectomized rats that had elevated total cholesterol at baseline. This same study also demonstrated a significant positive TOS effect on calcium absorption and prevention of bone loss in these animals. The stimulatory effect of TOS on calcium absorption has been observed in additional studies. Research continues.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Transgalacto-oligosaccharides are contraindicated in those who are hypersensitive to any component of a TOS-containing product.

PRECAUTIONS

Because of absence of long-term safety studies, pregnant women and nursing mothers should exercise caution in the use of TOS supplements.

Those with lactose intolerance should be cautious in the use of TOS supplements.

ADVERSE REACTIONS

Doses of 10 grams daily are well tolerated. Higher doses may cause some gastrointestinal symptoms, such as flatulence, bloating and diarrhea.

INTERACTIONS

NUTRITIONAL SUPPLEMENTS

TOS may enhance the colonic absorption of calcium and magnesium supplements if used concomitantly with them.

Probiotics. The possible beneficial effects of TOS may be enhanced if used in combination with probiotics.

FOODS

TOS may enhance the colonic absorption of calcium and magnesium in foods.

DOSAGE AND ADMINISTRATION

Transgalacto-oligosaccharides are available in Japan and Europe as nutritional supplements and as functional foods. They are also expected to enter the U.S. marketplace. Typical dosage is about 10 grams daily, usually taken in divided doses.

LITERATURE

Bouhnik Y, Flourié B, D'Agay-Abensour L, et al. Administration of transgalacto-oligosaccharides increases fecal bifidobacteria and modifies colonic fermentation metabolism in healthy humans. *J Nutr.* 1997; 127:444-448.

Chonan O, Matsumoto K, Watanuki M. Effect of galactooligosaccharides on calcium absorption and preventing bone loss in ovariectomized rats. *Biosci Biotechnol Biochem.* 1995; 59:236-239.

Chonan O, Watanuki M. Effect of galactooligosaccharides on calcium absorption in rats. *J Nutr Sci Vitaminol (Tokyo).* 1995; 11:95-104.

Ito M, Deguchi Y, Matsumoto K, et al. Influence of galactooligosaccharides on the human fecal microflora. *J Nutr Sci Vitaminol (Tokyo).* 1993; 39:635-640.

Vanadium

DESCRIPTION

Vanadium is a metallic element with atomic number 23 and atomic symbol V. Vanadium is a transition element that exists in several oxidation states, including +2, +3, +4 and +5. Vanadium compounds are striking for their varied colors. For this reason, vanadium was first named panchromium. The element chromium, another colorful element, is vanadium's next-door neighbor to the left in the periodic table. Vanadium is widely found in nature in the form of minerals, as well as in living matter, such as the human body. In living matter, vanadium is found mainly as the tetravalent vanadyl cation and the pentavalent vanadate form.

Nutritional essentiality for humans has not been established for vanadium. Vanadium-deficiency states have been reported in some animals. Goats fed diets deficient in vanadium had an elevated spontaneous abortion rate and depressed milk production, and approximately 40% of kids from these goats died between days 7 and 91 of life, with some deaths preceded by convulsions. Only 8% of kids from vanadium-supplemented goats died during the same period. Rats fed vanadium-deficient diets were found to have decreased growth.

Vanadyl and vanadate compounds act as insulin-mimetics and are being studied as potentially orally active replacements for insulin. However, these substances are poorly absorbed from the gastrointestinal tract, and the amounts needed for an effective oral dose are likely to be toxic. Vanadium-containing compounds are being developed for the treatment of diabetes with higher therapeutic-to-toxicity ratios. Such compounds include peroxovanadiums, bis(picolinato) oxovanadium and the vanadium ligand L-glutamic acid gamma-monohydroxamate.

Typical diets supply less than 30 micrograms of vanadium daily. The average daily dietary intake of vanadium is approximately 15 micrograms. Foods rich in vanadium include black pepper, mushrooms, shellfish, parsley, dill seed and some prepared foods. Foods low in vanadium include fresh fruits and vegetables, oils and beverages.

Tetravalent vanadium compounds are sometimes designated as vanadium (IV) and pentavalent vanadium compounds are designated as vanadium (V).

ACTIONS AND PHARMACOLOGY

ACTIONS

Vanadium salts have insulin-mimetic activity, and vanadium compounds are being studied as potentially orally active replacements for insulin. The doses of supplemental vanadium that may affect blood glucose levels are potentially toxic, and supplemental vanadium is not recommended for the management of diabetes, hyperglycemia, hypoglycemia or insulin resistance.

MECHANISM OF ACTION

Vanadium salts mimic most of the effects of insulin *in vitro* and also induce normoglycemia and improve glucose homeostasis in insulin-deficient and insulin-resistant diabetic rodents *in vivo*. Vanadium salts appear to have these effects via alternative pathways not involving insulin receptor tyrosine kinase activation or phosphorylation of insulin receptor substrate. Vanadium's mechanisms of action appear to involve inhibition of protein-phosphotyrosine phosphatase and activation of nonreceptor protein-tyrosine kinases.

PHARMACOKINETICS

The absorption of dietary vanadium and supplemental vanadium (usually vanadyl sulfate) is poor, and most ingested vanadium is excreted in the feces. It is estimated that less than 5% of dietary vanadium is absorbed. Most