ACTIONS AND PHARMACOLOGY

ACTIONS

Alkoxyglycerols have putative antiproliferative and immunomodulatory activities.

MECHANISM OF ACTION

The mechanism of the putative antiproliferative and immunomodulatory actions of alkoxyglycerols is not known. Speculative mechanisms include protein kinase C inhibition, macrophage activation and natural killer cell activation.

PHARMACOKINETICS

Ether glycerols, when absorbed, may be incorporated into plasmalogens and alkylacyl glycerophospholipids. Little is available on the specific pharmacokinetics of the shark oil alkoxyglycerols in humans.

INDICATIONS AND USAGE

Support for claims that the alkoxyglycerols are indicated for the prevention and treatment of any cancer or for the treatment of wounds and inflammatory conditions in humans is limited and unsystematic. There is little support for claims that they are immune-enhancing in humans.

RESEARCH SUMMARY

This shark-liver oil derivative has been touted as an effective anti-cancer treatment. Unfortunately, there is little evidence to support this claim, at least for humans. There is scant evidence it inhibits tumor growth or reduces cancer mortality in humans. It should in no way be relied upon in the treatment of any form of cancer. Similarly, there is little evidence to support claims that this substance is useful for treating wounds and inflammatory conditions. Neither has it been demonstrated in appropriate human clinical studies that it has immune-enhancing effects. There are some *in vitro* and animal studies reporting antiproliferative and immunomodulatory effects for these substances, and perhaps alkoxyglycerols may eventually have a role to play in adjuvant management of certain types of cancer. However, this would need to be established by well-designed, double-blind, placebo-controlled trials, which have not yet been done.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to an alkoxyglycerol-containing product.

PRECAUTIONS

Those with cancer who are interested in alkoxyglycerols should discuss their use with their physicians. Under no circumstance should they be relied upon as principle elements in the management of their disease. Pregnant women and nursing mothers should avoid alkoxyglycerol supplements.

ADVERSE REACTIONS

Mild gastrointestinal symptoms, including diarrhea, have been reported.

DOSAGE AND ADMINISTRATION

There are no typical doses. Those who use shark liver oil products are cautioned that some preparations may contain high amounts of vitamins A and D.

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Alpha-Amylase Inhibitor (Phaseolamin)

DESCRIPTION

The enzyme pancreatic alpha-amylase plays a major role in the digestion of the starch. Starch is comprised of two polysaccharides—amylose and amylopectin. Amylose is comprised of long unbranched chains of D-glucose units bound in alpha (1>4) linkages. Amylopectin is a highly branched structure, also made up of D-glucose units. The backbone glycosidic linkages are alpha (1>4), as in amylose, but the branch points have alpha (1>6) glycosidic linkages. Pancreatic alpha-amylase hydrolyzes alpha (1>4) linkages randomly to produce maltotriose, oligosaccharides, maltose and some D-glucose. Alpha-amylase cannot hydrolyze alpha (1>6) linkages, which occur at the branch points of amylopectin, consequently forming a highly branched core called limit dextrin. A debranching enzyme—alpha (1>6) glycosidase—hydrolyzes the alpha (1>6) linkages at the branch points producing D-glucose. The brush border of the cells lining the lumen of the small intestine contains enzymes that covert oligosaccharides and disaccharides to D-glucose. Alpha-glucosidases convert maltose and maltotriose to D-glucose. D-glucose is then the major end product of the digestion of starch.

The regulation of plasma glucose levels and of glucose metabolism is one of the most important homeostatic mechanisms in the body. In a normal situation, some of the D-glucose formed from starch digestion is stored as glycogen in the liver and some is metabolized to produce biological energy. This occurs when an appropriate amount of non-resistant insulin is secreted in response to the glucose formed via digestion. Under conditions of insulin resistance, postprandial serum glucose is abnormally elevated and less glucose goes into the production of glycogen and into the pathways that produce biological energy, among other metabolic events. A way of rectifying this abnormal situation would be to decrease the amount of D-glucose produced from carbohydrate digestion, slowing down its absorption and consequently diminishing postprandial excursions of insulin and D-glucose. One way of doing that might be to inhibit the enzyme pancreatic alpha-amylase.

Alpha-amylase inhibitors are found in many plants and are abundant in cereals and legumes. A major impetus for research and discovery of these inhibitors is their potential as bioinsecticides. Three different isoforms of an alpha-amylase inhibitor are found in the common bean *Phaseolus vulgaris*. These isoforms are designated alphaAI-1, alphaAI-2 and alphaAI-3.

AlphaAI-1 was purified and analyzed in the mid 1970s and found to be a glycoprotein having a molecular weight of 45 kDa (kilo Daltons) to 50 kDa. This glycoprotein was named phaseolamin in recognition of its origin. Later, it was determined that this glycoprotein had a molecular weight of 56.7 kDa, that it was composed of two kinds of glycopeptide structures, alpha and beta, and that it had a tetrameric structure, $alpha_2beta_2$.

AlphaAI-1 inhibits animal alpha-amylase and forms the basis of a dietary supplement that was introduced into the dietary supplement marketplace in the early 1980s. It was called a "starch blocker," with claims that it would lower plasma glucose levels and also help in weight reduction. However, even though it was demonstrated in some animal studies to have a serum glucose-lowering effect, and even though alpha-amylase inhibition seemed like a good bet for an agent that would result in a decreased release of glucose and insulin, phaseolamin did not appear to work in humans and almost disappeared from the marketplace. However, phaseolamin had a rebirth in the early 2000s that coincided with an increased interest in low-carbohydrate diets for weight management.

ACTIONS AND PHARMACOLOGY

ACTIONS

Alpha-amylase inhibitor (phaseolamin) has possible hypoglycemic activity and possible anorexigenic activity.

MECHANISM OF ACTION

Phaseolamin has demonstrated alpha-amylase activity, *in vitro,* and in animal studies. Further, inhibition of pancreatic alpha-amylase might be expected to demonstrate less of an increase in plasma glucose and plasma insulin levels following a meal, and possibly even a modest weight reduction effect. Parallels might be drawn between a pancreatic alpha-amylase inhibitor and two drugs that inhibit a related enzyme (alpha-glucosidase) in the digestion of starch—acarbose (a maltotetrose derivative) and miglitol (N-hydroxyethyl-1-deoxynojirimycin, a monosaccharide-like substance). Both of these drugs reduce fasting and postprandial serum glucose levels and have a modest effect on weight reduction. The possible mechanism of action of these substances is unclear, but may be due to energy loss from increased colonic fermentation of oligosaccharides and maltose and/or may be due to adiponectin elevation caused by these drugs, among other possibilities. Gastrointestinal side effects, including flatulence, abdominal cramping, borborygms, bloating, diarrhea and nausea, are common in those who use acarbose or miglitol and have to do with undigested carbohydrates entering the large intestine and undergoing fermentation to short-chain fatty acids and the gases methane and hydrogen. Interestingly, these adverse effects have rarely been reported in those using phaseolamin, suggesting the possibility that very little or no inhibition of alpha-amylase is taking place *in vivo*. These gastrointestinal symptoms would very likely occur if undigested starch were to enter the large intestine to be fermented by its bacterial microflora. In this way, the undigested starch would be acting like resistant starch (see Resistant Starch).

Assuming that the inhibition of alpha-amylase does have a weight reduction effect, the mechanism of action of this effect is unclear. It is known that a reduction in postprandial insulin secretion, by preventing rebound hypoglycemia, can have a favorable effect on appetite control. There are other possibilities and it is conceivable that this might occur via yet unknown mechanisms.

The phaseolamin marketed in the 1980s as a "starch blocker" to control hyperglycemia and obesity showed little or no effect on plasma glucose levels or on weight. It was thought that was because the preparations at the time were very crude, had many impurities and little of the alpha-amylase inhibitor. The "new" alpha-amylase inhibitor is said to have no impurities and to have much higher alpha-amylase activity.

Much research and evidence-based clinical trials are needed in order to determine if the new, reformulated phaseolamin has a role in postprandial glucose control and weight management.

PHARMACOKINETICS

Little is known about the pharmacokinetics of phaseolamin. Most importantly, research is needed on the stability of phaseolamin in the stomach and small intestine.

INDICATIONS AND USAGE

There is some evidence that alpha-amylase inhibitor, a so-called "starch blocker" derived from the common white kidney bean (*Phaseolus vulgaris*), may have hypoglycemic and anorexigenic actions and might thus be of benefit in the prevention and treatment of diabetes and obesity. A suggestion that this substance might be protective against colorectal cancer is, at this point, based entirely upon a theoretical mode of action that remains to be demonstrated.

RESEARCH SUMMARY

So-called starch blockers have been marketed for some time as antiobesity and antidiabetic agents. The claim has been that these starch blockers interfere with the breakdown of complex carbohydrate, reducing or prolonging its digestibility and thus reducing carbohydrate absorption, as well as reducing postprandial glucose and insulin levels. There are *in vitro* as well as *in vivo* animal and human data to support this hypothesis, but studies have yielded mixed results over the years. The inconsistency of these results has been attributed by one recent reviewer of the relevant literature to inefficient extraction methods that resulted in products with impurities and low alpha-amylase inhibiting activity. Newer, improved extraction techniques have resulted in purer, more potent products.

Various rat studies using kidney beans or alpha-amylase inhibitor have demonstrated reduced food intake and subsequent modest weight loss. There is some evidence that prolonged administration of the inhibitor is necessary in order to get any meaningful results. Clinical studies have been few, have again reported mixed results and, when positive, have mostly reported what the authors of a review article called "subtle weight loss." It appears that more research is needed in order to establish that alpha-amylase inhibitor has consistent, significant appetite-suppressing/weight-reducing effects.

Rats have exhibited reduced postprandial glucose levels when given amylase inhibitor with or before starch-containing meals. Reductions have also been observed in some human subjects similarly treated. Decreased serum insulin levels have been found in both normal and diabetic rats fed amylase inhibitor. There is sufficient preliminary data to warrant further study of the possible beneficial effects of alpha-amylase inhibitor in diabetes.

The suggestion that alpha-amylase inhibitor might have some protective effects against colon cancer is purely hypothetical but may be worthy of further investigation.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Products containing alpha-amylase (phaseolamin) should not be used by anyone who is allergic to any component of a phaseolamin-containing product.

PRECAUTIONS

Those with type 2 diabetes who wish to try phaseolamin should do so only with a physician's approval and supervision.

Pregnant women and nursing mothers should avoid the use of phaseolamin.

ADVERSE REACTIONS

If phaseolamin does inhibit pancreatic alpha-amylase, the following gastrointestinal adverse events may be expected: flatulence, abdominal cramping, borborygms, bloating, diarrhea and nausea.

INTERACTIONS

DRUGS

None known.

FOODS

No known interactions.

DIETARY SUPPLEMENTS

No known interactions.

OVERDOSAGE

No reports.

DOSAGE AND ADMINISTRATION

Phaseolamin is available in 500mg and 600mg capsules. Those who use phaseolamin take two pills either once a day in the morning before meals, or two pills before or with each meal.

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Alpha-Lipoic Acid

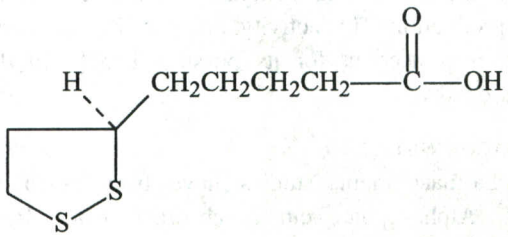
DESCRIPTION

Alpha-lipoic acid, also known as thioctic acid, is a disulfide compound that is a cofactor in vital energy-producing reactions in the body. It is also a potent biological antioxidant. Alpha-lipoic acid was once thought to be a vitamin for animals and humans. It is made endogenously in humans—the details of its synthesis are still not fully understood—and so it is not an essential nutrient. There are, however, certain situations, for example, diabetic polyneuropathy, where alpha-lipoic acid might have conditional essentiality. And recent research indicates that the antioxidant roles of alpha-lipoic acid may confer several health benefits. Alpha-lipoic acid is found widely in plant and animal sources.

Most of the metabolic reactions in which alpha-lipoic acid participates occur in mitochondria. These include the oxidation of pyruvic acid (as pyruvate) by the pyruvate dehydrogenase enzyme complex and the oxidation of alpha-ketoglutarate by the alpha-ketoglutarate dehydrogenase enzyme complex. It is also a cofactor for the oxidation of branched-chain amino acids (leucine, isoleucine and valine) via the branched-chain alpha-keto acid dehydrogenase enzyme complex.

Alpha-lipoic acid is approved in Germany as a drug for the treatment of polyneuropathies, such as diabetic and alcoholic polyneuropathies, and liver disease.

Alpha-lipoic acid contains a chiral center and consists of two enantiomers, the natural R- or D- enantiomer and the S- or L- enantiomer. Commercial preparations of alpha-lipoic acid consist of the racemic mixture, i.e. a 50/50 mixture of the R- and E-enantiomers. It is represented by the following chemical structure:



Alpha-Lipoic acid

Alpha-lipoic acid has a variety of names. In addition to being known as alpha-lipoic acid and thioctic acid, it is also known as lipoic acid, 1,2-dithiolane-3-pentanoic acid; 1,2-ditholane-3-valeric acid; 6,8-thiotic acid; 5-[3-C1,2-dithiolanyl)]-pentanoic acid; delta-[3-(1,2-dithiacyclopentyl)] pentanoic acid; acetate replacing factor and pyruvate oxidation factor. Alpha-lipoic acid is water-insoluble.

Although the details of its synthesis have yet to be worked out, alpha-lipoic acid is synthesized in mitochondria; octanoic acid and L-cysteine (for its sulfur) are precursors in its synthesis.

ACTIONS AND PHARMACOLOGY

ACTIONS

Alpha-lipoic acid has biological antioxidant activity, antioxidant recycling activity and activity in enhancing biological energy production.

MECHANISM OF ACTION

Alpha-lipoic acid and its reduced metabolite, dihydrolipoic acid (DHLA), form a redox couple and may scavenge a wide range of reactive oxygen species. Both alpha-lipoic acid and DHLA can scavenge hydroxyl radicals, the nitric oxide radical, peroxynitrite, hydrogen peroxide and hypochlorite. Alpha-lipoic acid, but not DHLA, may scavenge singlet