


Nozawa H. Xanthohumol, the chalcone from beer hops (Humulus lupulus L.), is the ligand for farnesoid X receptor and ameliorates lipid and glucose metabolism in KK-A(y) mice. *Biochem Biophys Res Commun.* 2005;336(3):754-761.


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**Xylitol**

**DESCRIPTION**

Xylitol is classified as a “sugar alcohol.” It has similar sweetness to sucrose, but in a strict chemical sense it is not really a sugar; it is a polyhydroxy alcohol. A sugar is defined chemically as a polyhydroxy aldehyde (eg, glucose) or a polyhydroxy ketone (eg, fructose). However, since “sugar alcohol” is the term commonly used, including by the FDA, for xylitol and other polyhydroxy alcohols, that is the term that will be used in this monograph. Xylitol is a five-carbon acyclic polyhydroxy alcohol, or polyol (pentitol), named for its corresponding aldehyde, the sugar xylose. Xylitol is found naturally in small quantities in fruits and vegetables, including plums, strawberries, raspberries and rowan berries. It is also found in corn husks, mushrooms and oats. Xylitol was first derived from the complex carbohydrate xylan from birch trees in Finland, where it was called birch sugar, or koivusokeri. About 5 to 10 grams of xylitol are made daily in the human body, from its corresponding aldose xylose and from its corresponding ketose xylulose.
Xylitol was first popularized in Europe as a safe sweetener for diabetics. It is now widely used as a low-calorie sweetener and for several health conditions. These include caries, middle ear infections (otitis media), and sinus infections, among other health concerns. Currently, most of the world supply of xylitol is derived from corn sources and reportedly comes mainly from China.

Xylitol is also known as xylo-pentane-1,2,3,4,5-pentol, (2R,3R,4S)-pentane-1,2,3,4,5-pentanol, 1,2,3,4,5-pentahydroxy-pentane, xylite, and birch sugar (see above). Its molecular formula is C₅H₁₀O₅, its molecular weight is 152.15, and its CAS registration number is 87-99-0. Xylitol is written without an L or a D prefix owing to the symmetry of the molecule. Xylitol is represented by the following chemical structure.

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CH₂OH
H－OH
HO－H
H－CH₂OH
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Xylitol

When chewed in the form of gum, xylitol has a cooling effect in the mouth, which is accounted for by the endothermic reaction that occurs when xylitol is dissolved. Sportswear is available that uses xylitol infused into the fabric in order to absorb the heat coming from perspiration. The energy content of xylitol is 2.4 kcal per gram. In comparison, the energy content of sucrose is 4 kcal per gram.

The FDA allows the claim to be made that the noncariogenic carbohydrate sweetener xylitol present in the food does not promote tooth decay, and may reduce the risk of tooth decay. Other "sugar alcohols" considered noncariogenic include sorbitol, mannitol, lactitol, isomalt (a disaccharide composed of the sugar glucose and the sugar alcohol mannitol), erythritol, and hydrogenated starch hydrolysates (a mixture of several sugar alcohols). Also, the claim is allowed for the sugars tagatose (a monosaccharide) and isomaltoolose (a disaccharide that is a natural constituent of honey). This is because the FDA was convinced that isomaltoolose and tagatose were not fermented by oral bacteria to an extent sufficient to lower dental plaque pH to levels that would contribute to the erosion of dental enamel.

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Xylitol is a low-calorie sweetener, suitable for use by diabetics. Xylitol has anticariogenic activity and may have antimicrobial activity against middle ear infections (otitis media), nasal and sinus infections, and pulmonary infections. It also may have antiosteoporotic activity. Xylitol may have some benefits for the treatment of the inborn errors of metabolism, such as myoadenylate deaminase deficiency and glucose-6-phosphate dehydrogenase deficiency.

**MECHANISM OF ACTION**

**Anticariogenic activity:** Dental caries are the localized destruction of susceptible dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates. The disease process starts within the bacterial biofilm also known as dental plaque. The bacteria that comprise the biofilm are mainly *Streptococcus mutans, Streptococcus sobrinus* and *Lactobacillus* spp.

These bacteria ferment sugars such as sucrose, producing lactic acid. Lactic acid causes local pH to fall, resulting in the demineralization of tooth tissues. If the diffusion of calcium, carbonate and phosphate out of the tooth is allowed to continue, caries will eventually form. This process can be reversed in its early stages through uptake of calcium, phosphate and fluoride. Fluoride works by causing diffusion of calcium and phosphate into the tooth, which remineralizes the crystalline structure of the lesion. The rebuilt crystalline surfaces are composed of fluoridated hydroxyapatite and fluorapatite, which is much more resistant to acid attack than is the original structure.

Administration of xylitol is another way of preventing dental decay. There are now many human studies, beginning in 1970 in Finland, testing the effect of xylitol on the growth of dental plaque and the formation of dental caries. In the early studies, diets containing xylitol were compared with diets containing sucrose or fructose. In later studies, xylitol was presented to the subjects in the form of chewing gum. In most cases, xylitol was demonstrated to decrease the formation of dental caries. *Streptococcus mutans*, the major cariogenic bacterium in the mouth, is able to transport xylitol into the cell. It does this via the fructose phosphotransferase system. Once inside, xylitol is phosphorylated to xylitol-5-phosphate. *S. mutans* cannot ferment the five carbon structure of xylitol to form lactic acid as it can six- and 12 carbon sugars. *S. mutans* has to expel xylitol-5-phosphate in order to survive. This futile energy-consuming xylitol cycle is thought to be responsible for the inhibition of the growth of the cariogenic bacteria, both *in vitro* and *in vivo*. Xylitol was also thought to prevent the adhesion of the biofilm to the teeth.

**Antiosteoporotic:** Animal studies found that xylitol prevents experimental osteoporosis and improves the properties of bones and collagen. The mechanism of these effects is unclear, and more research is warranted. There is some evidence that xylitol increases calcium absorption independent of the effect of vitamin D.
**Low-calorie sweetener:** The energy content of xylitol is 2.4 kcal per gram. In comparison, the energy content of sucrose is 4 kcal per gram. Xylitol and sucrose have equal levels of sweetness and there is no after taste with xylitol, which is to say that, in addition to its reduced calories, xylitol has excellent organoleptic ("mouth feel") qualities for a sugar substitute. Xylitol has been an excellent sugar substitute for diabetics. Following its ingestion, there is little change in plasma glucose and insulin levels.

**Nasal and sinus infections:** Preliminary studies with xylitol suggest that it also may have some utility against nasal and sinus infections. More research is required to establish this effect. The mechanism of action of such an effect should be similar to that described for xylitol and otitis media (see below).

**Otitis media:** Xylitol has been found to be effective in preventing acute otitis media (middle ear infection) by up to 42% when administered either in the form of chewing gum or as a syrup. Otitis media develops when bacteria from the nasopharynx—usually Streptococcus pneumoniae, whose growth is known to be inhibited by xylitol—enter the middle ear through the Eustachian tube. The mechanism of the inhibitory effect is not completely known. Possibilities include: Xylitol is known to have anti-adhesive effects on both S. pneumoniae and Haemophilus influenzae, which are mediated by its effect on the cell wall of the bacteria; xylitol is an unsuitable source of energy for these bacteria (see: Anticariogenic activity, above); xylitol causes a marked reduction in the intracellular redox state due to the rapid production of NADH and NADPH in the polyol dehydrogenase reaction. This could improve the oxidative burst in polymorphonuclear leukocytes with consequent bacterial killing via reactive oxygen species.

**Pulmonary infections:** A study reported in the Proceedings of the National Academy of Sciences (PNAS) has introduced still another way of accounting for the antimicrobial effect of xylitol. It appears that the surface of the airways is covered by a thin layer of liquid. This liquid contains a number of antimicrobial substances, including lysozyme, lactoferrin, secretory leukoproteinase inhibitor, human beta defensins 1 and 2, secretory phospholipase A2 and cathelicidin LL-37. These substances form part of the pulmonary defense system, killing the small numbers of bacteria that are constantly being deposited on the pulmonary airway surface. Importantly, the antibacterial activity of most of these substances is salt sensitive. An increase of the salt concentration in the liquid layer inhibits the antibacterial activity of most of the above agents. The study suggested that xylitol delivered to the airway surface appears to lower the salt concentration, thus enhancing the innate antibacterial defense system. Further study is needed to test this interesting hypothesis.

**Xylitol and myoadenylate deaminase deficiency:** Myoadenylate deaminase (muscle AMP deaminase) deficiency is an inborn error of metabolism disorder that is manifested by muscle weakness and cramping after exercise, decreased muscle mass, hypotonia and generalized weakness in some cases. The diagnostic test is based on the lack of an exertional increase in plasma ammonia in patients and was based on the fact that AMP (adenosine phosphate) deaminase is the major ammonia-producing enzyme in skeletal muscles. AMP is comprised of adenine, ribose and phosphate. Ribose is essential in the synthesis of DNA, RNA and ATP, among many other important biological molecules. In myoadenylate deaminase deficiency, some ribose is effectively lost from the metabolic pool and may create a storage deficiency of this crucial metabolite. It was reported that when oral ribose was administered before and after exercise to a patient with this disorder, exercise-related symptoms diminished.

Xylitol can be converted metabolically to ribose, and there is a report that xylitol was beneficial to one patient when administered orally at 15 grams to 20 grams daily.

**Xylitol and glucose-6-phosphate dehydrogenase deficiency:** Red blood cell glucose-6-phosphate dehydrogenase deficiency (G6PD) is a widespread genetic disorder. Hemolytic anemia is the most serious feature of this disease. The disease is characterized biochemically by a low or almost absent G6PD and an abnormally low red blood cell reduced glutathione (GSH) level. This is because a normal glucose-6-phosphate dehydrogenase is necessary for the production of NADPH, which in turn maintains glutathione in its reduced state. GSH is the major intracellular buffer against oxidative stress, and a deficiency of red blood cell GSH makes the cell very vulnerable to any oxidative threat. In G6PD, the production of NADPH is impaired.

It turns out that the NADP-linked xylitol dehydrogenase is found in red blood cells and that its enzyme activity is normal in most G6PD-deficient red blood cells. Xylitol was demonstrated to preserve GSH levels in vitro (rabbit red blood cells) and in vivo (rabbits with deficient GSH) and to prevent hemolysis of the red blood cells. Further research in this promising area is certainly warranted.

**PHARMACOKINETICS**

Many details of the pharmacokinetics of xylitol are still missing. After ingestion, xylitol is absorbed slowly from the small intestine and a portion passes into the large intestine where it is fermented by the microflora of the gut to the short-chain fatty acids, acetate, propionate and butyrate, and the gases hydrogen, hydrogen sulfide, carbon dioxide and
methane. The portion that is absorbed from the small intestine is distributed to several tissues in the body, but mainly to the liver. In the liver, xylitol is converted to xylitol-5-phosphate. Xylitol-5-phosphate is converted to xylulose-5-phosphate via a polyol dehydrogenase reaction; this metabolite enters the pentose phosphate cycle to be further metabolized.

**INDICATIONS AND USAGE**

Some, though not all, studies indicate that xylitol, a sugar alcohol found in a number of fruits and vegetables, is an effective anticaries agent. There is some support for claims that xylitol has significant antimicrobial effects and may be useful in treating and preventing otitis media and some lung and nasopharyngeal infections. Scant preliminary *in vitro* and animal data suggest possible contributions to bone, skin and colon health.

**RESEARCH SUMMARY**

Xylitol has been promoted for some time as an effective anticaries agent and is sold in the form of gum and other products advertised to protect dental health. Evidence that xylitol gums are any better than gums sweetened with sorbitol or other sugar alcohol is inconsistently demonstrated in clinical trials that have sought to assess the effects of these gums on tooth decay. One review of the literature found that the claimed superiority of xylitol was not demonstrated in two out of four clinical trials comparing the anticaries potential of xylitol with that of sorbitol-sweetened gums. These reviewers, in fact, concluded that, to the extent any positive effect was observed, it was more likely due to the stimulation of salivary flow, which was roughly equal irrespective of the type of gum chewed. They did not, however, entirely rule out the possibility of a relevant xylitol-related antimicrobial effect. Some studies have found that xylitol does, indeed, significantly suppress some oral bacteria, specifically *Streptococcus mutans*, but it has not been conclusively demonstrated that this effect significantly impedes the formation of dental caries. One can say, however, that xylitol is highly unlikely to promote caries, as certain sugars are known to do. More research will be required to definitively determine whether xylitol is superior to sorbitol as an anticaries agent.

A number of recent studies suggest that xylitol may have significant antimicrobial effects that could be clinically beneficial in a number of circumstances. One of these studies, performed double-blind and placebo-controlled, demonstrated that xylitol, whether administered in a gum or in a syrup, was significantly superior to xylitol-devoid chewing gum and xylitol-devoid syrup in preventing acute otitis media (AOM) in healthy children. The study continued for three months, during which time the experimental subjects received 8.4 to 10 grams of xylitol daily. Whereas 41% of the children who received control syrup experienced at least one incident of AOM, only 29% of those receiving xylitol syrup were similarly affected. Occurrence of AOM decreased by even more among those taking the xylitol gum versus those using the non-xylitol gum. Given the apparent efficacy of xylitol in this study and the high economic costs of AOM, further research is needed and warranted.

Numerous animal studies have demonstrated additional antimicrobial effects. In a recent trial, xylitol-supplemented nutrition was found to enhance bacterial killing and prolong survival of rats in experimental pneumococcal sepsis. A finding of the study was enhanced neutrophilic leukocyte function. A previous report had demonstrated that parenteral administration of xylitol could significantly improve survival of rats suffering intestinal sepsis. A study in which xylitol was shown to enhance bacterial killing in the rabbit maxillary sinus led the researchers to conclude that xylitol might be useful in some cases of human sinusitis. Far more study will be required to establish this.

In one double-blind, placebo-controlled clinical trial, xylitol was sprayed for four days into each nostril of volunteers. Compared with saline-administered controls, the experimental subjects receiving the xylitol spray exhibited significantly decreased numbers of nasal coagulase-negative *Staphyloccocus*. This research further revealed some evidence suggesting that xylitol might be of benefit in cystic fibrosis through positive effects in the human airway. Again, more research is needed and warranted.

In a study utilizing an *in vitro* colon simulator, another group of researchers reported positive effects of xylitol on the metabolic activity and patterns of colon microbes, suggesting that the sugar alcohol might have some benefit on colonic health. Other, similarly very preliminary *in vitro* and animal research has pointed toward possible positive effects of xylitol on bone and skin. One study showed that dietary xylitol helped protect against weakening of bone biomechanical properties in an experimental model of postmenopausal osteoporosis. The same group subsequently demonstrated improved bone biomechanical properties in xylitol-fed, aged male rats. Clinical trials are needed to see whether xylitol can have any bone-strengthening effects in humans. Similarly, a finding that long-term dietary xylitol supplementation increases the synthesis of collagen in the skin of aging rats needs further exploration and extension into clinical inquiry.

**CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS**

**CONTRAINDICATIONS**

Xylitol is contraindicated in those who are hypersensitive to any component of a xylitol-containing product.
PRECAUTIONS
Those who develop gastrointestinal symptoms (flatus, bloating, diarrhea) with the use of xylitol should start with lower doses and slowly go up in dose. Those receiving whole body radiation or radiation to the gastrointestinal tract should avoid xylitol until they have completed their course of radiation. Those with diarrhea-prominent irritable bowel syndrome should begin the use of xylitol at low doses and increase the dose as tolerated.

ADVERSE REACTIONS
Doses of xylitol up to 30 to 60 grams daily are usually well tolerated. Higher doses may cause gastrointestinal symptoms, such as flatulence, bloating and diarrhea, in an unadapted user. Adapted users have gone up to 400 grams daily without any side effects. The most common side effect is flatulence. Some may have side effects at lower doses, eg, a person with diarrhea-prominent irritable bowel syndrome.

There are a couple of reports of dogs having serious adverse events after ingesting xylitol. In one report, eight adult dogs were evaluated for treatment of lethargy, vomiting, widespread petechial, ecchymotic, or gastrointestinal hemorrhages, hyperglycemia, hyperbilirubinemia and thrombocytopenia. Three dogs were euthanized, two dogs died, two dogs made a complete recovery, and one dog was recovering, but was lost to follow-up. In another report, a 9-month old Labrador retriever developed hypoglycemia and seizures after ingesting a large quantity of gum sweetened with xylitol. There have been other reports of dogs becoming hypoglycemic after consuming xylitol. There are no such reports for humans.

INTERACTIONS

DRUGS
No known interactions.

FOODS
No known interactions.

NUTRITIONAL SUPPLEMENTS
Arginine-containing mints have been found to have anticariogenic activity secondary to their ability to buffer the acid produced by cariogenic bacteria. Mints containing a combination of xylitol and arginine may give better anticariogenic effects that the use of either alone.

OTHER
The combination of xylitol and the use of fluoride toothpastes may give better anticariogenic effects than the use of either alone.

OVERDOSAGE
No reports.

DOSAGE AND ADMINISTRATION
Xylitol is available as chewing gum, as a nasal wash, in bulk as a sugar substitute and as mints. For dental benefits, 4 to 12 grams of xylitol daily are used. The chewing gum and mints typically contain about 1 gram of xylitol in each piece. One can start by chewing one piece four times a day for a total of 4 grams and work up from there to a total of 12 to 15 grams daily. For prevention of otitis media, 8.5 to 10 grams of chewing gum or syrup was used taken in five divided doses over a course of two months a study.

LITERATURE
Yeast Beta-D-Glucan

DESCRIPTION

Beta-D-glucans are nondigestible polysaccharides widely found in nature in such sources as cereal grains, including oats and barley, as well as in yeast, bacteria, algae and mushrooms. Beta-D-glucans are primarily located in the cell walls. Yeast beta-D-glucan is marketed as a nutritional supplement. The yeast beta-D-glucan in the supplement is a polyglucose polysaccharide derived from the cell walls of baker's yeast or Saccharomyces cerevisiae.

Yeast beta-D-glucan, usually referred to as yeast beta-glucan, consists of straight-chain and branched polymers. The straight-chain structures are (1/3)-beta-D-linked glucose polymers and (1/6)-beta-D-linked glucose polymers. The branched polymers consist of a (1/3)-beta-D-linked backbone containing varying degrees of (1/6)-beta branches. Yeast beta-glucan is sometimes designated as beta 1, 3/1, 6-glucan.

Yeast beta-glucan appears to have immunomodulatory properties. It can bind to various cells of the non-specific immune system, such as macrophages and neutrophils. PGG-glucan or poly- [1, 6]-beta-D-glucopyranosyl- [1,3]-beta-D-glucopyranose is a genetically modified Saccharomyces cerevisiae beta-glucan. It is being evaluated in clinical studies as an immunomodulatory agent and a biological response modifier.

Zymosan is the name of a cell wall preparation derived from Saccharomyces cerevisiae, which contains beta (1/3)-glucan, beta (1/6)-glucan and other components of the cell wall, such as chitin and mannoprotein. Zymosan's immunological effects are mainly attributed to the beta-glucans.

ACTIONS AND PHARMACOLOGY

ACTIONS

Yeast beta-glucan may have immunomodulatory and lipid-lowering activity.

MECHANISM OF ACTION

Most of the studies done with yeast beta-glucan have been performed in tissue culture, in animals and with PGG-glucan, which is administered parenterally. Yeast beta-glucan can bind to a beta-glucan receptor in macrophages and stimulate the production of such cytokines as TNF (tumor necrosis factor)-alpha and IL (interleukin)-I beta. Binding to the beta-glucan receptor may also induce the release of such reactive oxygen species as superoxide anions and hydrogen peroxide. Yeast beta-glucan may also stimulate such cells as neutrophils NK (natural killer cells) and LAK (lymphokine-activated killer) cells. All of the above stimulation effects may result in antimicrobial and tumoricidal activities.

Research on PGG-glucan indicates that it interacts with receptors on monocytes and neutrophils. It is thought that this interaction primes these cells for production of cytokines and other immune-modulating substances when they are needed. In this sense, yeast beta-glucan may be considered an immune system primer.

The possible immunomodulatory effects of oral yeast beta-glucan remain unclear. Yeast beta-glucan is an indigestible polysaccharide and very little hydrolysis of it takes place in the stomach or small intestine. There is some digestion of yeast beta-glucan that does take place in the large intestine.