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Review

Health effects of erythritol

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Abstract

Erythritol (1,2,3,4-butanetetrol) is a non-caloric C4 polyol made by fermentation that has a sweetness 60–70% that of sucrose. The safety of erythritol has been consistently demonstrated in animal and human studies. Erythritol has a higher digestive tolerance compared to all other polyols because about 90% of the ingested erythritol is readily absorbed and excreted unchanged in urine. Erythritol is used in a wide range of applications for sweetening and other functionalities, e.g., in beverages, chewing gum and candies. In this review, we summarise the health effects of erythritol described in the literature. We focus on studies involving the anti-cariogenic and endothelial protective effects of erythritol. We conclude that erythritol could be of great importance and could be considered to be the preferred sugar substitute for a rapidly growing population of people with diabetes or pre-diabetes to reduce their risk of developing diabetic complications.

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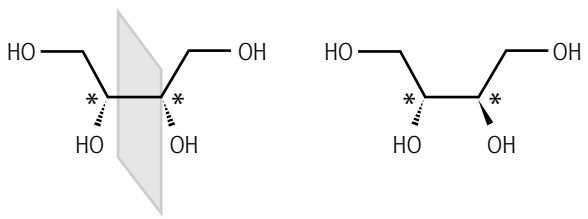
General characteristics

Erythritol (1,2,3,4-butanetetrol) is a four-carbon sugar alcohol, or polyol, and a meso-butanetetrol (Fig. 1). It occurs naturally in some mushrooms, some fruits (e.g., watermelon, grapes and pears) and in fermented foods including wine, cheese, sake and soy sauce [1, 2]. Consumption of erythritol nat-



2R,3S-1,2,3,4-butanetetrol
erythritol

2R,3R-1,2,3,4-butanetetrol
D-threitol

Figure 1 Two possible stereoisomers of 1,2,3,4-butanetetrol are shown. On the left: erythritol, the 2R,3S isomer. Although this compound contains two asymmetric carbon atoms, the overall molecule is achiral because it contains an intramolecular plane of symmetry. This plane of symmetry is absent in the compound on the right, D-threitol, which is therefore chiral: it has an enantiomer (mirror image) L-threitol (not shown)

urally occurring in foods has been estimated to be 80 mg/day (~1.3 mg/kg body weight/day) in the United States [2]. Erythritol is also found endogenously in human and animal tissues and body fluids including blood, urine and cerebrospinal fluid [2]. Erythritol is a white, anhydrous, non-hydroscopic and crystalline substance. It is 60–70% as sweet as sucrose [3]. Although erythritol was first isolated in 1852, it took until 1990 for it to be marketed as a new natural sweetener in Japan. Currently, the use of erythritol in foods has been approved in more than 60 countries. The range of applications includes as a tabletop sweeteners and in beverages, chewing gum, chocolate, candies and bakery products [3].

Manufacturing process

Large-scale production of erythritol uses fermentation. Pure glucose, sucrose or glucose from maize (as a source of starch) is used as a starting material. Starch is extracted from the maize, and through hydrolysis the starch chains are broken down into glucose molecules, which are fermented into erythritol using an osmophilic yeast, like *Moniliella pollinis*. After fermentation, yeast cells and other impurities are removed by filtering. Once the fermentation broth is filtered, erythritol is purified by ion exchange resin, activated charcoal and ultrafiltration. In the last step, crystallisation, the broth is cooled down and erythritol precipitates from the solution yielding crystals with over 99% purity [3, 4].

Safety

A number of toxicological studies have been performed to evaluate the safety of erythritol. These have been extensively discussed in reviews by Bernt et al. and Munro et al. [2, 5].

In summary, based on acute toxicity studies, erythritol is classified as essentially non-toxic after oral administration. Subchronic studies further support the safety of erythritol. Chronic studies (up to 2 years) revealed that erythritol has no effect on survival or carcinogenicity [2, 5].

Even at high doses (up to 16 g/kg body weight), erythritol does not affect reproductive performance or fertility of parental rats. In addition, no adverse effects on the developing foetus were observed [2, 5–7]. Erythritol does not have mutagenic potential, as observed in the Ames test and chromosomal aberration test [2, 5, 8, 9].

In summary, animal toxicological studies and clinical studies have consistently demonstrated the safety of erythritol. Therefore, it is not expected that erythritol will cause adverse effects under the conditions of its intended use in food.

Metabolic fate

The metabolic profile of erythritol is not like that of any other polyol, which gives rise to some of erythritol's unique properties. Erythritol is readily and virtually completely absorbed from the small intestine via passive diffusion similar to fructose. Fructose transport can also occur via GLUT2 transport with absorption enhanced in the presence of glucose due to greater GLUT2 insertion in the apical membrane as SGLT1 transports glucose. This explains the enhanced absorption of fructose in the presence of glucose. In addition, the presence of glucose has been shown to enhance paracellular flow due to the opening of tight junctions resulting in increased absorption of small solutes [10]. Enhanced GLUT2 insertion and enhanced paracellular flow in the presence of glucose has been hypothesised to be the same pathway with altered functions in the absence/presence of glucose. However, this hypothesis does not support the differences noted for minor increases in small solute transport compared to the greatly enhanced transport of fructose when glucose is present [11, 12]. As erythritol is readily absorbed on its own, the impact of the presence of glucose on erythritol absorption would be minimal and has not been investigated to date. After absorption, erythritol is distributed throughout the body, with maximum plasma concentrations occurring within the first 2 h of digestion. Up to 90% is excreted unchanged in the urine [5, 13, 14]. Unabsorbed erythritol may be subjected to microbial

fermentation in the colon. However, studies with ^{13}C-erythritol showed no increase in breath $^{13}CO_2$ and H_2, which indicated that erythritol was not metabolised by the host [15]. The inability of faecal flora to metabolise erythritol was confirmed in *in vitro* studies with fermentation times of up to 24 h [15, 16]. The potential for erythritol fermentation exists with exceedingly high doses, much greater than those represented with current intake [17].

Erythritol has much higher digestive tolerance than other polyols. This can mainly be attributed to the fact that it is readily absorbed and only a small fraction reaches the colon. Other polyols are poorly absorbed, which can provoke undesirable intestinal effects when they are consumed in excessive quantities. These effects can occur due to gas formation by fermentation (leading to flatulence) or as a result of osmotic effects (leading to laxative effects). Gastrointestinal responses of persons ingesting erythritol at up to 0.8 g/kg body weight were comparable to those of sucrose [13]. Repeated ingestion of erythritol at daily doses of 1 g/kg body weight did not show more frequent gastrointestinal effects than sucrose, indicating that erythritol was well tolerated [18]. When 35 g of erythritol was consumed in a drink, it was well tolerated, while at a dose of 50 g, only significant increases in borborygmi and nausea were observed. The consumption of 35 and 50 g of xylitol in the same study induced significant gastrointestinal distress [19]. The maximum dose of erythritol not causing laxation was calculated to be 0.80 g/kg body weight for females and 0.66 g/kg for males [20]. However, the maximum dose is also dependent on the delivery method. Consumption of erythritol with solid foods is tolerated at a higher intake level than with beverages, because digestion of food products is slower, providing a longer period for absorption to occur [19].

Because of its metabolic profile, erythritol does not provide energy to the body and therefore has a caloric value of 0 calories/g [3]. In addition, erythritol does not raise plasma glucose or insulin levels and can therefore be regarded as safe for diabetic patients. No effect on plasma glucose or insulin levels was observed within 3 h after ingestion of 1 g/kg body weight erythritol [14]. Ingestion of 0.3 g/kg body weight erythritol did not influence serum glucose or insulin levels, whereas the same dose of glucose rapidly increased these levels [21].

Health effects

Dental health

Mutans streptococci play an important role in the development of dental plaque. They attach to the biofilm on teeth and produce glucosyltransferase. This enzyme is responsible for the synthesis of insoluble glucan plaque material. Glucans and the bacteria accumulate on the teeth and are known as dental plaque. When large amounts of plaque form on teeth in the presence of sugar, the mutans streptococci produce lactic acid. The acid weakens tooth enamel through demineralisation, ultimately causing dental caries [3, 22].

When erythritol was incubated with a range of mutans streptococci species, no lactic acid production was observed. Furthermore, it was not used for growth or plaque formation by the mutans streptococci [23]. Another study showed that erythritol inhibited the growth of several strains of mutans streptococci strains [24]. A study by Hashino et al. showed that erythritol has inhibitory effects on *Porphyromonas gingivalis* and *Streptococcus gordonii* heterotypic biofilm development via several pathways, including a decrease in DNA/RNA synthesis, decreased extracellular matrix production and alterations of dipeptide acquisition and amino acid metabolism [25].

This was also supported by an *in vivo* study into the effects of 6-month use of erythritol, xylitol and glucose (in the form of chewable tablets and toothpaste). Erythritol and xylitol led to a significant reduction in the amount of plaque and saliva levels of mutans streptococci. In addition, a reduction in the amount of dental plaque was observed in subjects that had received erythritol and xylitol [24]. A 3-year clinical trial also found that erythritol pro-

motes dental health [26]. In this study, initially, 7–8-year-old children were given erythritol, xylitol or sorbitol candies containing 7.5 g of the polyol daily for three years. Erythritol consistently reduced the amount of dental plaque during the follow-up period. In addition, the plaque of erythritol-receiving subjects showed a reduction in the levels of acetic acid, propionic acid and lactic acid. Furthermore, erythritol consumption led to lower salivary and plaque mutans streptococci counts compared with other groups. This long-term study also investigated the impact of polyol consumption on dental caries development [27]. It was found that less children in the erythritol group developed enamel or dentin caries over the three years (4.6% vs. 5.5% in the sorbitol and 5.8% in the xylitol group). In addition, in the erythritol group, a lower number of enamel caries tooth surfaces developed to dentin caries (1.3% vs. 1.7% in the sorbitol and 2.0% in the xylitol group). Furthermore, the time to development of enamel/dentin and dentin caries lesions (surfaces) was statistically significantly longer in the erythritol group compared to the sorbitol or xylitol group. These studies demonstrate that erythritol can reduce the risk of dental caries development.

Antioxidant properties

It is well known that the polyol mannitol is a hydroxyl radical scavenger [28, 29]. Since erythritol closely resembles the structure of mannitol, den Hartog et al. investigated the hydroxyl radical scavenging capacity of erythritol and several other polyols with a test tube assay. A correlation between the number of hydroxyl groups in the investigated compound and its rate constant for the reaction with hydroxyl radicals was found. Erythritol proved to be an excellent hydroxyl radical scavenger, with a rate constant of 1.18×10^{9} M^{-1} s^{-1} [30].

In the same study, the ability of erythritol to scavenge superoxide radicals was investigated in a test tube assay. Erythritol proved to be inert towards superoxide radicals, probably because it lacks a major structural requirement for superoxide scavengers. The ability of erythritol to scavenge radicals in a cellular system was tested with a haemolysis assay. Erythritol delayed radical-induced haemolysis in red blood cells in a concentration-dependent manner [30].

The reaction of erythritol with hydroxyl radicals was also demonstrated in an *in vivo* model using diabetic rats. The rats were fed 1000 mg/kg per day for a period of 3 weeks after diabetes was induced by streptozotocin. The urine of the rats was investigated for the presence of two oxidative metabolites of erythritol: erythrose and erythrulose. The amount of erythrose in the urine was highest in the diabetic group fed with erythritol, indicating that erythritol scavenged hydroxyl radicals produced during hyperglycaemia in these rats [30].

In another *in vivo* study, by Yokozawa et al., antioxidant properties of erythritol were also investigated [31]. Several doses of erythritol (100, 200 and 400 mg/kg body weight) were orally administrated to streptozotocin-induced diabetic rats for 10 days. The highest dose resulted in a decrease of 5-hydroxymethylfurfural (5-HMF) levels, a marker for the extent of glycosylation of serum protein. In addition, thiobarbituric acid reactive substances levels of serum, liver and kidney were lower in the groups that received erythritol, indicating a reduction of lipid peroxidation (a marker of oxidative stress). This study also found a reduction in serum, liver and kidney glucose levels and a reduction in serum creatinine when rats were given erythritol. They conclude that erythritol is able to affect glucose metabolism and reduce lipid peroxidation and kidney damage caused by hyperglycaemia [31].

Endothelial protective effects

Most of the complications that arise from chronic hyperglycaemia find their origin in damaging the endothelium, a thin layer of cells lining the cardiovascular system [32–34]. The endothelium plays an important role in numerous physiological functions with one of the most important endothe-

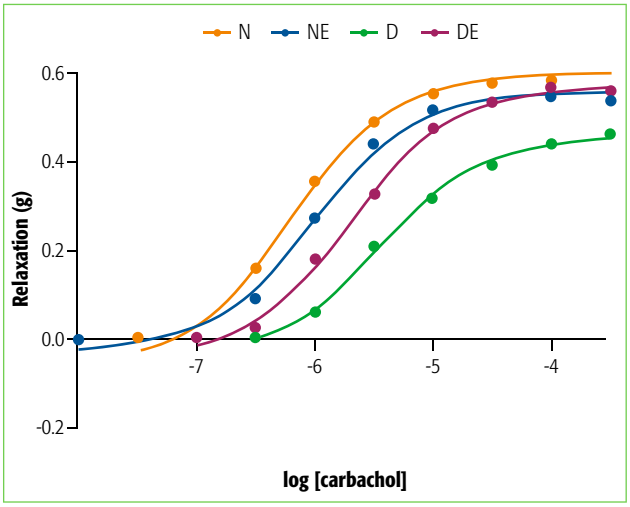


Figure 2 Carbachol concentration–response curves recorded with aortic rings from normoglycaemic rats (N), diabetic rats (D), normoglycaemic rats that had consumed erythritol (NE) and diabetic rats that had consumed erythritol (DE). In diabetic rats, the *ex vivo* carbachol response is smaller and requires higher concentrations than in control rats. Erythritol prevents the loss of response to carbachol, thus maintaining endothelium-dependent vascular relaxation. Adapted from den Hartog et al. [30].

lium-derived mediators being the soluble gaseous radical nitric oxide (NO), responsible for vascular relaxation. Endothelial dysfunction occurs when the endothelium loses its physiological properties. This has been linked to diabetes through the demonstration of impaired endothelial-dependent vasodilatation [35].

The study of den Hartog et al. also focused on the effect of erythritol on endothelial function. This was investigated in rings prepared from the thoracic aorta. Carbachol concentration response curves were recorded for the different groups (Fig. 2). In diabetic rats, the *ex vivo* carbachol response is smaller and requires higher concentrations than in control rats. This indicates that the endothelium of these rats is damaged. Since the carbachol response is mediated by NO, the diabetic rats seem to be incapable of generating sufficient NO to induce maximum relaxation. In diabetic rats fed with erythritol, the carbachol response curve was similar to control rats, indicating that the loss of endothelium-dependent vascular relaxation was prevented by erythritol in these rats [30].

To further investigate the endothelium protective effect, a study in endothelial cells was performed [36]. The cells were exposed to normal and high glucose concentrations and targeted and transcriptomic approaches were used to examine the effect of erythritol under these conditions. Overall, it was found that erythritol by itself (i.e., under non-diabetic conditions) has no effect on the endothelial cells. However, under high glucose conditions, erythritol was able to reverse a number of deleterious effects. The most striking observation was that erythritol reversed the direction of change of 148 of the 153 transcripts altered by high glucose incubation. Another finding was that erythritol did not seem to affect single endpoints, but rather had an effect on multiple targets – a mode of action which is not uncommon for natural compounds [37, 38].

A pilot study on the effects of erythritol in patients with type 2 diabetes also revealed protective effects on vascular function [39]. In this study, 24 subjects consumed 12 g of erythritol three times daily for 4 weeks. Subjects were tested at baseline and after 4 weeks. In addition, acute and acute-on-chronic effects before and 2 h after consumption of 24 g erythritol at baseline and follow-up visit were measured. Acute consumption of erythritol improved small vessel endothelial function as measured by fingertip peripheral arterial tonometry (EndoPAT). Chronic erythritol consumption showed a decrease in central pulse pressure and a trend towards a lower carotid-femoral pulse wave velocity. These findings suggest that erythritol can reduce arterial stiffness and improve small vessel endothelial function. However, this was a pilot study without a control group and a modest sample size. To validate the findings of this study, a randomised, placebo-controlled study is required [39].

Conclusion

Erythritol is a non-caloric bulk sweetener which has been shown in multiple studies to reduce the

risk of caries development. As erythritol does not influence glucose or insulin levels, it is a good alternative for sugar in patients with diabetes as well as for people needing or desiring to manage blood sugar levels due to prediabetes or compromised carbohydrate metabolism. In addition, diabetes patients could benefit from the vascular effects of erythritol described above. It is expected that in non-diabetic subjects the endothelium will not be affected by erythritol. However, in diabetic subjects, where the endothelium is under diabetic stress, erythritol could shift a variety of damage and dysfunction parameters to a safer side, as observed in the *in vitro*, *ex vivo* and *in vivo* studies. Erythritol can therefore be regarded as a compound that has protective effects on the endothelium under high glucose conditions, leading to a prevention or delay in onset of diabetic complications.

The characteristic of erythritol of having small effects on multiple targets may also prove to be beneficial. A compound with a strong biological effect is less suitable for chronic supplementation, as is needed in diabetes. The alternative is to use a compound with mild protective effects like erythritol. Erythritol could therefore be of great importance and could be considered to be the preferred sugar replacer for a rapidly growing population of people with diabetes or pre-diabetes to reduce their risk of developing diabetic complications.

Conflict of interest

This research was financially supported by Cargill Inc. Cargill is a manufacturer of erythritol and the employer of Peter de Cock, Douwina Bosscher and Angela Bonnema. Daniëlle Boesten, Gertjan den Hartog and Aalt Bast received funding from Cargill.

Human and Animal Rights

This review article does not contain any studies with human or animal subjects performed by any of the authors.

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