

The Latest on Sugar Substitutes of the Alditol Type with Special Consideration of Erythritol and Xylitol—Rectifications and Recommendations

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Abstract

Sugar substitution with low-calorie carbohydrates constitutes a well-grounded approach to controlling energy intake to prevent obesity or certain diseases, and reducing the incidence of bacteria-associated diseases such as dental caries. This review discusses latest applications of alditol-type sugar substitutes with emphasis placed on erythritol (a tetritol) and xylitol (a pentitol). Especially xylitol has been shown to exert interesting biochemical effects (such as ammonia formation) in the dental biofilm. Understanding the oral biologic processes involved presumes referring to certain physicochemical aspects of alditols (such as complex formation with Ca(II), protein stabilization, hydroxyl radical scavenging, and others), which will be briefly discussed. This review also comments on the gastrointestinal effects associated with enteral administration of alditols, discusses the synergy between chlorhexidine and alditols, and the use of alditols in periodontal treatments (i.e. non-sweet applications of alditols), and focuses on European Union regulations on sugar substitutes. The article also attempts to rectify defective information regarding these sweeteners. A part of this information has passed unnoticed, since the data involved were published in supplements to regular volumes in the 1970s. The present review emphasizes the oral biologic significance of the xylitol-associated shift observed in the biology of the oral biofilm (dental plaque): from carbohydrate dominance to one where nitrogen metabolism plays an important role.

Keywords: Sugar substitutes; Sugar alcohols; Alditols; Erythritol; Xylitol; D-Mannitol; Sorbitol (D-glucitol); Oral Biology; Dental biofilm (dental plaque)

Introduction

The scientific literature is replete with articles and reviews [1-3] on sugar substitutes, reflecting the popularity of low-calorie sugar-free foods. Sugar substitutes are used to reduce energy intake and to limit obesity, coronary heart disease, diabetes, dental caries and other health conditions, and continue to receive increased attention in sweetener research. Several non-sweet applications of sweeteners have been proposed, for example, in periodontal therapy. The sugar substitutes discussed in the present review include sugar alcohols (polyols) among which the simple alditols are currently used in surprisingly numerous medical, cosmetic, techno-chemical, and similar applications. Xylitol-based infusion therapy currently comprises one of the largest single applications of this alditol. Xylitol-containing chewing gums have also been employed in various medical studies related to cognitive function, mastication, drug delivery, physiologic tests, and other [4].

Health-care professionals should be aware of the different dietary applications of sugar substitutes and of the advent of new sweeteners. Some sugar substitutes of the alditol type, such as xylitol, provide only about 2.4 kcal/g of sweetener, whereas the energy available to the human body from erythritol is virtually zero, as compared to approximately 4 kcal/g for sugar. Owing to the lower sweetness of D-arabitol and ribitol, these alditols have received less attention in food applications, although these pentitols play important roles in various biological processes.

The objective of the present article is to review recent developments in the study of sugar substitutes of the alditol type. “The latest” also includes re-evaluation of dated information that has escaped the attention of current researchers, and rectification of previous reviews. In the former category, certain oral biologic effects of xylitol must be revisited, while in the latter a recent Cochrane Review [5], on xylitol serves as an example. These viewpoints represent gaps of knowledge that presume re-evaluation.

The present text will focus on the oral biologic effects of alditol-type sweeteners. Understanding these effects presumes referring to physicochemical properties of alditols, which will be concisely reviewed. Owing to the current interest in erythritol (a tetritol) and xylitol (a pentitol), these alditols will receive more attention. Finally, carbohydrates with deviating configuration will be briefly discussed. This review hopefully remind readers about the inseparable relationship between oral health and general health.

Health Benefits of Erythritol

Erythritol is currently approved and marketed in more than sixty countries worldwide [6]. This authorization implies the oral safety of erythritol, as demonstrated in toxicological tests in experimental animals and man. The recent dental erythritol trial in Estonia [7], stemmed from earlier animal studies [8], and prior theoretical consideration of dietary alditols as potential sugar surrogates [9]. At the same time, erythritol was shown to decrease the adherence of polysaccharide-forming oral streptococci [10], adherence of cells onto glass surfaces declined in the presence of 0.13 mol/L (2%) and 0.26 mol/L (4%) erythritol and xylitol. A Chinese study suggested that, compared with xylitol, erythritol in low concentrations had a weaker effect on bacterial growth and acid production of *Streptococcus mutans* (or mutans streptococci, MS), while having a stronger effect in high

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concentrations [11], the low concentrations ranged from 0.5% to 2%, while the high concentrations ranged from 8% to 16%.

Erythritol at 10% had an inhibitory effect on the metabolomic profiles and microstructure of biofilm composed of *Porphyromonas gingivalis* and *S. gordonii* [12]. The most effective reagent to reduce the substrata of these organisms was erythritol, compared with xylitol and D-glucitol (sorbitol). It was suggested that erythritol functions via several pathways. These include suppression of bacterial growth resulting from DNA and RNA depletion, attenuated extracellular matrix production, and alterations of dipeptide acquisition and amino acid metabolism.

The above-mentioned [7] school program revealed that a lower number of dentin caries teeth and surfaces was found in the erythritol group than in the xylitol or sorbitol groups. Time to the development of caries lesions was longest in the erythritol group. The study featured certain drawbacks: use of polyol candies within a relatively short 5h period daily, restriction of the number of sucking episodes to three per day, and use of the test items on only about 200 days/year. Tests on dental plaque and whole-mouth saliva suggested, however, that erythritol reduced their cariogenic potential.

Duane [13], reviewed a study of another group of researchers [14], and stated that there was no evidence of caries reduction in a school program with xylitol and erythritol lozenges. However, the subjects used the test items only three times a day, the overall consumption level of xylitol being 4.7 g (with 4.6 g maltitol), and the daily erythritol level being 4.5 g (with 4.2 g maltitol). Both the frequency of use and the amount of xylitol and erythritol seemed to be too low in this child cohort. The study subjects lived in a fluoridated area and exhibited low caries activity. The intervention lasted only 9 to 21 months (the final caries diagnoses were made 48 months after the start of the programme). These study features call into question the conclusions [13]. The shortcomings largely resulted from the local conditions at the study venue.

Synergistic Effects—Comments on Crossover Study Designs

The validity of some study designs may be called into question as a result of the possibility of synergy between fluoride and xylitol effects on the cells of MS [15]. An earlier study showed that xylitol augmented the metabolic effects on MS of low levels of fluoride [16]. Petin et al. [17] designed a mathematical model to describe, optimize, and predict a synergistic interaction between fluoride and xylitol on acid production by MS. These considerations receive support from an earlier suggestion that the cells of MS possess at least two glucose transport systems, one of which is fluoride-insensitive [18]. Other studies reported that xylitol prolonged the effect of chlorhexidine therapy on MS [19]. Chlorhexidine and xylitol appeared to act synergistically on MS and *S. sanguis* [20]. Synergistic inhibition of streptococcal biofilm by ribose and xylitol has been reported [21]. In another dental field, Han et al. [22] showed that xylitol inhibits inflammatory cytokine expression induced by *P. gingivalis*.

Synergy between xylitol and erythritol may also have been involved in their effects on the growth of oral bacteria [6,23]; the mechanism of the inhibitory effect of erythritol versus xylitol on the growth of MS differed. It is possible that their combinations are effective in caries limitation. Meurman [24], in his study on synergy between chlorhexidine and fluoride, referred to one Norwegian and one Dutch study where the authors concluded that the existence of synergy

between fluoride and xylitol was a true phenomenon in the oral cavity. Combinations of chlorhexidine and xylitol were suggested to be of value in maternal post-partum caries therapy [25]. Xylitol and fluoride had an additive effect in the reduction of dental erosion *in vitro* [26], and xylitol and funoran (a sulphated polysaccharide present in seaweeds) had a similar effect in the promotion of tooth remineralization [27].

“Blind” reliance on crossover study designs employed in clinical trials with sweeteners may invalidate their conclusions [28]. This stems from the reported long-term effects of xylitol. In studies involving the comparison of sugar alcohols, the crossover requirement calls for changing the regimens of the study cohorts following treatments of suitable duration. In case the substances tested exert long-term effects, no washout period will be able to completely nullify the effects of the previous treatment; the effects will overlap. Reservations against the above blind reliance thus result from observations that xylitol, antibiotic agents, and fluoride may exert long-term effects on oral bacteria. Such instances call into question the appropriateness of the washout periods between treatments.

All dental xylitol studies have not reached positive clinical and oral biologic findings. Long-term field experience has shown that in most cases failure to demonstrating such effects can be explained in terms of the following features of the studies in question:

- Use of caries-resistant study cohorts or cohorts with extremely low caries experience.
- Use of too small study cohorts.
- Use of too low concentrations of xylitol in experimental products.
- Use of too short intervention. Low caries experience presumes longer intervention.
- Use of too short or too infrequent daily exposure to xylitol.
- Simultaneous use of other caries-limiting agents and strategies (such as fluorides).
- Use of too insensitive analytical or diagnostic procedures.
- Inadequate compliance of subjects and/or families.
- Use of a single analytical procedure (such as total protein or nitrogen assay) to assess the growth of dental plaque. Ideally, gravimetry, clinical, microbiological, biochemical, and other methods should be used simultaneously (*vide infra*).

Biochemical Manifestations in the Oral Cavity

Studies on the effect of sweeteners on dental biofilm (dental plaque) are necessary surrogate investigations of long-term, expensive clinical trials; the quantity and quality of dental biofilm normally reflect its cariogenic potential. Plaque studies can lead to misinformation unless the entire complex biochemistry of this biofilm is considered. In some studies plaque quantification has been based on its nitrogen content, a measure that should never be exploited in plaque mass assessments. Namely, during xylitol consumption, the levels of protein and nitrogen present in plaque increase owing to biochemical expedience. In the presence of xylitol, and when the microorganisms are deprived of their normal six-carbon-based energy sources (such as glucose), plaque-forming oral bacteria increase their overall nitrogen metabolism and the formation of ammonia, urea, and free amino acids, and induce the liberation of increased amounts of proteolytic enzymes [29].

The xylitol-associated increase in the levels of free amino acids and ammonia was for the first time demonstrated in the whole-mouth saliva of subjects who were fed large quantities of xylitol (approximately 67 g daily) over a period of two years [30-32]. The ammonia levels in the xylitol group were 46% higher compared with the group receiving no xylitol. Amino acid analyses of whole-mouth saliva of the same subjects showed that the consumption of xylitol was associated with increased amounts of amino acids in saliva, regardless of the chemical type of amino acid involved (Table 1). The levels of basic amino acids (such as arginine, histidine and lysine) were increased remarkably. The xylitol-associated increase in the whole-mouth saliva ammonia levels during xylitol consumption is also depicted in Table 2; 60 day consumption of relatively small amounts of xylitol increased the ammonia levels significantly regardless of the way the ammonia levels were calculated. It has been suggested that the elevated ammonia and amino acid levels may partly counteract the reduction of pH values in the dental plaque interface. It is possible that such biochemical reactions in the dental biofilm contribute to the reduced cariogenicity of the xylitol diet. The increase of the serine and threonine levels was also remarkable (Table 1).

	Sucrose	Xylitol
A. Aliphatic amino acids		
1. Containing hydrocarbon residues (ala, val, gly, leu, ile)	147.8 (1.0)	232.5 (1.6)
2. Containing OH-groups (ser, thr)	22.1 (1.0)	36.9 (1.7)
3. Containing carboxyl (-COOH) groups	42.6 (1.0)	53.6 (1.3)
4. Containing -CONH ₂ groups (asp-NH ₂ , glu-NH ₂)	11.7 (1.0)	18.5 (1.6)
5. Containing -NH ₃ groups (lys, arg)	43.3 (1.0)	69.6 (1.6)
6. Containing sulphur (met, cys)	17.0 (1.0)	23.0 (1.4)
B. Containing Π-electron rings (his, tyr, phe [try])	105.4 (1.0)	143.1 (1.4)
C. Containing imino acid residues (pro, OH-pro)	54.4 (1.0)	90.0 (1.6)
D. Containing polar residues (arg, asp, asp-NH ₂ , glu, glu-NH ₂ , his, lys, ser, tyr, thr, [cys])	213.3 (1.0)	303.3 (1.4)
E. Containing nonpolar residues (ala, val, gly, ile, met, pro, [try], phe, [cys])	231.1 (1.0)	354.4 (1.5)
F. Neutral amino acids (ala, asp-NH ₂ , val, glu, glu-NH ₂ , leu, ile, met, ser, thr, try, phe, pro, [cys])	375.4 (1.0)	521.3 (1.4)
G. Acidic amino acids (asp, glu, tyr, [cys])	68.1 (1.0)	91.2 (1.3)
H. Basic amino acids (arg, his, lys)	111.5 (1.0)	184.7 (1.7)

Table 1: Evidence for xylitol-associated increase in the amino acid content of whole-mouth saliva after 12-16.5 month continuous xylitol administration in human volunteers (approximately 67 g xylitol daily in the form of mixed food). The amino acids are grouped in view of their chemical and physical nature [30]. The values shown are means of 3–5 separate analyses (in μmoles/L). The numbers in parentheses stand for the relative content of the amino acids involved (giving the value of 1.0 to the sucrose group). Note the role of basic amino acids and those containing a hydroxyl group.

Ammonia, mean ± SD n=14	Beginning	30 days	60 days
μmol/ml saliva	3.7 ± 1.1	5.0 ± 2.5 [*]	5.3 ± 1.8 ^{**}
μmol/mg protein	3.2 ± 1.2	3.9 ± 1.7	4.1 ± 1.3 ^o
Ammonia, pooled samples of 14 subjects			
μmol/ml saliva	2.6	2.8	5.4
μmol/mg protein	1.6	1.8	3.7

Table 2: Evidence for the xylitol-associated increase in whole-mouth saliva ammonia levels. Human subjects consumed, on average, 20 g xylitol daily in the form of chewable troches (99.9% xylitol and 0.1% sodium stearate) after main meals. Whole-mouth saliva was collected by paraffin-stimulation at baseline, and after 30 and 60 days. ^oApproaches significance; ^{*}p<0.05; ^{**}p<0.01. The comparison were made with baseline values. Adapted from Pakkala et al. [111].

At the same time, the overall carbohydrate metabolism, including the activity levels of invertase-sucrase enzymes, increased [31-33]. These enzymes may be regarded as caries markers, since the reaction products of these enzymes are acid-forming sugars. However, from the cariologic point of view, the most important properties of plaque—its quantity, volume, and adhesiveness—decrease simultaneously as the ammonia levels increase. Therefore, although plaque protein and nitrogen assays are excellent methods in the characterization of plaque chemistry, such procedures cannot be used to evaluate the mass, volume, or cariogenicity of oral biofilm. Instead, a combination of gravimetry (of fresh plaque), clinical plaque indices, and use of disclosing stains with photography, microbiologic MS tests, and related procedures should be applied simultaneously.

The above situation is graphically depicted in Figure 1 (left panel) which offers a historic view of the effects of dietary sweeteners on the quantity of dental plaque [33]. This example warns against using a single chemical method, although impeccable per se, to quantify dental plaque. The illustration strongly emphasizes the fact that plaque nitrogen or protein contents may not measure plaque mass. Consequently, sugar substitutes can have remarkable effects on oral biology, such as the balance between carbohydrate and nitrogen metabolism of the dental biofilm. For example, storing cells of MS in the presence of 0.25% xylitol resulted in a ten-fold increase in overall extracellular proteolytic activity of the cells compared with storage in 0.25% glucose [29]. These observations on ammonia, amino acids, proteolytic activity, and sucrose-splitting enzymes have passed unnoticed, since most data were published in supplements to regular journal volumes in the 1970s. Recalling these early observations can thus be regarded as justified.

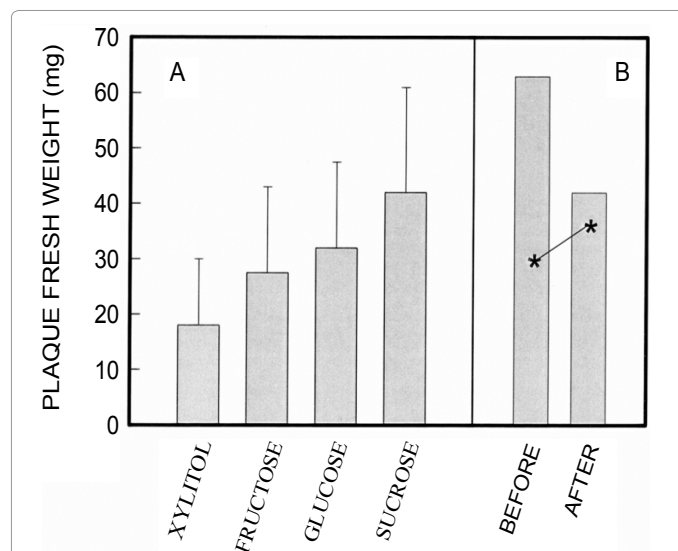


Figure 1: “The latest” resulting from ignoring older research findings. The illustration shows a historic plaque (dental biofilm) assessment study from the early 1970s (Panel A) and results of a later study (Panel B). A: Effect of dietary sweeteners on the formation of dental plaque (means ± S.D) after consumption of the listed sweeteners for four days (20 g/day) in the form of candies and as a sweetener in coffee or tea [33]. The subjects (n=12–16 per group) refrained from oral hygiene for four days after which a gravimetric study of total plaque was carried out. B: Unpublished results from the author’s laboratory. Subjects (n=12) used xylitol gum five times a day over a period of one month (daily consumption level: 6.7 g). Plaque was quantitated before and after xylitol usage, in both cases following a two-day no-oral-hygiene period (means; the S.D. values were similar to those in Panel A). The plaque total protein content (asterisks) increased from 1.1 ± 0.2 to 1.4 ± 0.2 mg/ml (means ± S.D.) in the aqueous plaque suspension investigated (made in 0.9% NaCl), but the amount of plaque itself decreased. Therefore, the protein content did not measure plaque mass.

Although other polyols were not tested, it is likely that other non-glucose polyols exert similar effects on dental plaque (Figure 1).

Studies carried out with dental biofilm have resulted in at least two internationally significant resolutions. On April 27, 2009, the European Union Scientific Panel on the substantiation of health claims related to sugar-free chewing gum approved the following claim: “Chewing gum sweetened with 100% xylitol has been shown to reduce dental plaque. High content/level of dental plaque is a risk factor in the development of caries in children”. The International Association of Paediatric Dentistry (IAPD) published the following resolution: “Policy on the Use of Xylitol in Caries Prevention is intended to assist oral healthcare professionals make informed decisions about the use of xylitol-based products in caries prevention”.

Non-sweet Applications of Sweeteners

Some caloric sweetening agents have gained use in applications where the sweetness of the molecule plays no role. Traditional subgingival root scaling with hand tools has been regarded as technically demanding. Air-polishing with erythritol powder can reduce tissue loss on root surfaces while causing less pain for patients [34-37]. Erythritol can also be used with chlorhexidine [37]. Erythritol powder provided comparable or better results than the frequently used glycine powder. Erythritol-treated tooth sites were less frequently positive for *Aggregatibacter actinomycetemcomitans* [36]. The non-cariogenicity and sweetness of erythritol may be additional benefits in these treatments.

Erythritol, xylitol and D-glucitol were used as dentine primers [38]. Contraction gap formation was completely prevented in aqueous solutions of 37.5% erythritol; alditols are always used at very high concentrations in this type of research. Ethylene glycol was most effective. Earlier studies showed that esterification of methacrylate with erythritol prevented the formation of a contraction gap by a commercial light-activated resin composite [39]. Xylitol-farnesol combinations can be of value in root-canal rinsing. In a study; investigating the biocompatibility of dental restorative materials, ascorbic acid increased, in a dose-dependent manner, the toxic effects of most of the restorative materials tested [40]. However, D-mannitol was found to neutralize the toxicity of ascorbic acid.

Xylitol was successfully tested in a nasal spray for the alleviation of cystic fibrosis conditions [41], middle-ear infections, asthma, sinus infections, and infections of the upper respiratory tract [42]. In the case of cystic fibrosis, xylitol reduced the salt concentration of airway surface liquid, and was suggested to enhance bacterial killing. These and other medical uses of xylitol have been summarized elsewhere [9,43]. The first use of xylitol in the prevention of otitis media in children was implemented by the team of Uhari [44], spurred by the Turku Sugar Studies showing xylitol to reduce the growth of MS [45].

Selected Physicochemical and Bioinorganic Properties of Alditols

Alditol-induced stabilization of proteins

For the understanding of oral biologic effects of alditols, it is important to get acquainted with their physicochemical properties. The following paragraphs will discuss physical and bioinorganic processes such as protein stabilization, hydration of alditols, complexation, and hydroxyl radical scavenging, that may help explain the clinical observations made with alditols.

It has been known for several decades that sugars and polyols can protect protein structures and biological cells from damage caused by heating, freezing, and loss of solubility during drying [46-48]. Polyols thus stabilize the α -helix and β -structures of proteins. The dependencies of the denaturation temperatures of most tested proteins on the chain-length of polyols support the view that polyol-induced stabilization of proteins is predominantly mediated through the strengthening of hydrophobic interactions of proteins on the structure of water [47]. Different alditols exert different influences on the structure of water. The extent of stabilization by sugars and polyols can be explained by their different influences on the structure of water. The difference between the partial molar volume of the polyol and its van der Waals volume has been used as a rough quantitative measure of the structure-making or structure-breaking effect. There is a linear relation between this quantity and the magnitude of the stabilizing effect ΔT_m . The magnitude of the stabilizing effect naturally also depends on the nature of the protein.

When a linear alditol (such as erythritol or xylitol) is added to an aqueous solution of a protein (as in whole-mouth saliva), some alditol molecules will migrate from the bulk solvent phase into the hydration layer of the protein molecule. This migration will result in the formation of a new hydration phase involving both the water of hydration and the penetrated alditol. The new hydration layer will protect and stabilize the protein molecule against denaturing forces [47-49]. However, significant differences exist between individual alditols in their ability to protect protein structures. The linear alditols appear to stabilize hydrophobic interactions more effectively and the peptide-peptide hydrogen bond less effectively with increasing hydroxymethyl chain length of alditols [47]. There are also other restrictions, since while 60% D-glucitol retained the pyrroline-5-carboxylate synthase activity fully for 30 min at 37°C, with xylitol and glycerol being also effective, sucrose, ethylene glycol, and polyethylene glycol were ineffective [50].

All natural alditols stabilize protein structures, but to varying degree. Some of the body's niches where the concentration of alditols can reach levels high enough meaningful for protein stabilization, include the alimentary tract, the oral cavity, the nasopharyngeal space, and the middle ear (in the latter compartment, the osmotic effect of an alditol can play an important role). Habitual consumption of dietary alditols may attribute to the stabilization of the calcium phosphate systems present in oral fluids and surface enamel of the teeth, and also to the stabilization of salivary proteins several of which participate in body's defence.

The ability of alditols to stabilize body proteins has; however, not been measured *in vivo*. Laboratory investigations have nevertheless shown that the hydration of protein molecules in alditol-water mixtures reveal important differences between individual alditols; the xylitol system displays exceptionally small preferential hydration parameters compared with other polyols [47] (*vide infra*). Considering the entry of alditols into tissue compartments, one must recall that the xylitol molecules, once present in the circulation, can rapidly diffuse into cells (because insulin is not required). The net result is xylitol's large distribution volume in the body.

Later studies on alditol-induced molten globule (MG) of cytochrome c provide further evidence: alditols can induce the MG state of cytochrome c at acidic conditions, the effect being stronger with increasing the concentration of OH groups of alditols [51]. Significant differences can in this regard be encountered between individual alditols. The results demonstrated in general that alditols can stabilize the MG state of this protein through the enhanced hydrophobic

interaction (preferential hydration mechanisms), which overcomes the electrostatic repulsion between charged residues. The alditol-induced stabilization of the invertase (from *Candida utilis*) is of interest since this enzyme, along with sucrase, can be considered one of the sucrose-attacking catalysts that may play a role in oral biology. Glycerol, xylitol, and D-glucitol were effective invertase-stabilizing agents [52]. The solvent-enzyme interaction showed preferential exclusion of the alditol molecules from the protein domain, leading to preferential hydration of the protein.

The stability of collagen against guanidine denaturation depends on the number of OH groups of the alditol present; the protective effect seems to decrease in the order from erythritol to xylitol to D-glucitol [53]. Sugars and alditols were also shown to protect collagen [54]. The extent of stabilization has been discussed in terms of sugars' and alditols' different influences on the structure of water. The hydroxymethyl chain length of alditols and equatorial OH groups of the sugars has been found to be decisive factors for their stabilizing effect on collagen structure. The presence of OH groups in the solvent is also in this case important for stabilization, owing to the formation of additional stabilizing hydrogen bonds. Thus, the total OH group concentration is of importance in the protective effect of alditols [55]. This view was supported by Turner et al. [56] who emphasized the importance of the orientation of OH groups as a determining factor in effective cryopreservation. Glycerol was most effective. When ribitol, erythritol, and glycerol which have similar stereochemical arrangement of OH groups were compared at the same molarity (0.4 M) and with equivalent OH numbers, higher survival was achieved when the total number of OH groups present was the same as in glycerol [56]. Protein stabilization by carbohydrates (which included xylitol, D-glucitol, and lactitol) for formulation of pharmaceutical products received detailed protein-chemistry examination by Pavišić et al. [57].

The relative concentration of OH groups of alditols indeed seems to play a role ubiquitous in biological systems. For example, the influence of several alditols (ethylene glycol, glycerol, erythritol, xylitol, and D-glucitol) present as water-activity-depressing agents in the synthesis of the tripeptide gly-gly-pheNH₂ linearly depended on the concentration of OH groups in the reaction media, suggesting that the modification of the catalytic behaviour of the enzyme (papain, displaying also esterase activity) involved indeed depended on the number of OH groups present in those alditol molecules, and on their water-activity depressing power [58,59]. In the case of α -chymotrypsin studied at 60°C, the enhancement of the thermal stability was proportional to the molecular size of the additive, being ethylene glycol < glycerol < erythritol < xylitol < D-glucitol. (However, as is customary in several comparisons of homologous alditols, ethylene glycol may form a deviation from the rule.) The above results nevertheless reveal important differences between individual alditols in various biological systems, and that alditols are excellent cosolvents by virtue of maintaining both the solvophobic interactions essential for the native structure and the preservation of the water shell around the protein molecule [59]. The OH groups of the cosolvent molecules were thus responsible for the microenvironmental change of the solvent (water) structure. These OH groups also reduce the mobility of the water molecules, thus favoring the shift of the above papain-catalyzed reaction to the synthetic direction (*vide infra*) [58].

The thermal stability of RNase A increased with increasing concentrations of maltitol, its stabilizing ability being comparable with maltose, but less than D-glucose and D-glucitol [60]. When the denaturation of RNase A and lysozyme by guanidine HCl was followed in the presence and absence of glycerol and D-glucitol, the

result indicated competing solvent effects of alditols and guanidine HCl on the structure of the proteins [61]. In the water-protein-alditol system, protein is preferentially hydrated to elevate its chemical potential, predominantly owing to the unfavourable interaction of alditol molecules with the exposed nonpolar amino acid residues. Consequently, alditols stabilized the protein structure through strengthening of the hydrophobic interaction, competing with the effect of guanidine HCl.

The participation of alditols in the synthesis of peptides can be reflected in increased thermostability and synthetic capability of the enzyme involved. The above-mentioned synthesis of gly-gly-pheNH₂ was accelerated and the enzyme's half-life increased in the presence of ethylene glycol, glycerol, erythritol, xylitol, and D-glucitol [58]. A linear relationship between the increase in the synthetic/hydrolytic activity ratio and the overall concentration of OH groups in the reaction media was obtained. The alditols, as water-activity-depressing agents enhance the synthetic capability of papain in a way which was directly proportional to the molecular size of the alditol molecule and its water-activity-depressing power.

The alditol-associated protein stabilization and protection against thermal denaturation often presumes the use of relatively high alditol levels. Certain stabilization processes may require up to 30% glycerol concentration [52], although discernible protection can be found at lower alditol levels. High alditol levels are inconceivable in the intracellular compartment or the in the vascular system, whereas the required high alditol levels can be regarded as fully realistic in the oral cavity, elsewhere in the gastrointestinal tract, in liver and kidney metabolism (frequently encountered in parenteral nutrition), and elsewhere in the body when locally higher alditol concentrations are customarily exploited (such as in certain cosmetic products), and in the treatment of foods to improve their quality.

Owing to the ability of xylitol to affect the water structure, the presence of high intracellular concentration of xylitol in yeast (*Saccharomyces cerevisiae*) before and after dehydration of the cells coincided with a higher viability of the cells after a dehydration/dehydration cycle [62].

The thermostabilization effect of alditols has occasionally turned out to be inferior to that of simple inorganic salts or organic substances. For example, MgSO₄, trehalose, and citric acid retained the activity of the so-called "protective antigen" (ingredient of the vaccine against anthrax) better than D-glucitol and xylitol which were not very effective [63].

Hydration properties of alditols

Alditols have been widely used as sweeteners and preservatives in foods. The use of alditols as "tissue-friendly" humectants in cosmetic products and dentifrices is also popular. Some of these uses depend on the way the alditol molecules interact with water which is the preferred physiological solvent. Studies on hydration have shown that the hydration water can display lower or higher mobility when compared with pure water. In literature, this has been casually referred to as 'structure-making' or 'structure-breaking' effect, respectively. It has been suggested that 'positive' and 'negative' hydration are probably more suitable descriptions of the true phenomena involved [64].

Computational simulation studies of alditols have shown that remarkable differences exist, for example, between xylitol and D-glucitol. There is a relatively strong hydration of xylitol. From the point of view of hydration dynamics, xylitol should be classified as positively hydrated

with an extended effect on the environment [64]. The stable linear conformation suggested for xylitol results from xylitol-water interactions. The xylitol molecule exhibits a perturbational effect on water structure. Other common alditols such as erythritol, D-mannitol, and D-glucitol have been found to exhibit negative hydration. Accordingly, xylitol can be expected to protect foodstuffs (for example, against non-enzymatic browning and ascorbic acid destruction) more effectively than the above hexitols do. This protective effect has been observed to correspond at 24°C to the series D-glucose>xylitol>D-mannitol>D-glucitol [64]. Indeed, measurements of the ratio (R) between the residence time of water near a given oxygen atom of xylitol and the residence time of water near another water molecule in the bulk, have shown a positive ratio (R>1) for all oxygen atoms of xylitol [64]. The average R (1.19) is noticeably higher than for D-glucitol (0.39). In the xylitol molecule, even carbon atoms display a hydrophilic-like behaviour, which speaks for a clear effect of the strong hydration structure of the neighbouring OH group. The above simulation studies showed that xylitol adopts in water a single straight conformation and is positively hydrated.

Microorganisms capable of growing at low water activity levels can accumulate alditol molecules which may increase to a high intracellular concentration. The alditols thus act as compatible solutes allowing metabolic functioning. Such molecules can be regarded as osmoregulators. However, at the same time the alditol molecules, by virtue of their high number of OH groups can participate in the intracellular water structure, thereby preserving the hydration of the cellular biopolymers [65]. Based on these considerations, Chirife et al. [66] determined the water activity (a_w) levels of several alditols from the following equation:

$$a_w = x_1 \exp(-K x_2^2) \quad (\text{equation 1})$$

where x_1 and x_2 are molar fractions of water and alditol, respectively, and K is a correlation constant. The values of K depended remarkably on the chain length and molecular configuration of the alditol (Figure 2). Therefore, alditols do not behave similarly in their reactions with water molecules. The predicted and experimental water activity levels also depended on the molality of the aqueous alditol solution, as shown

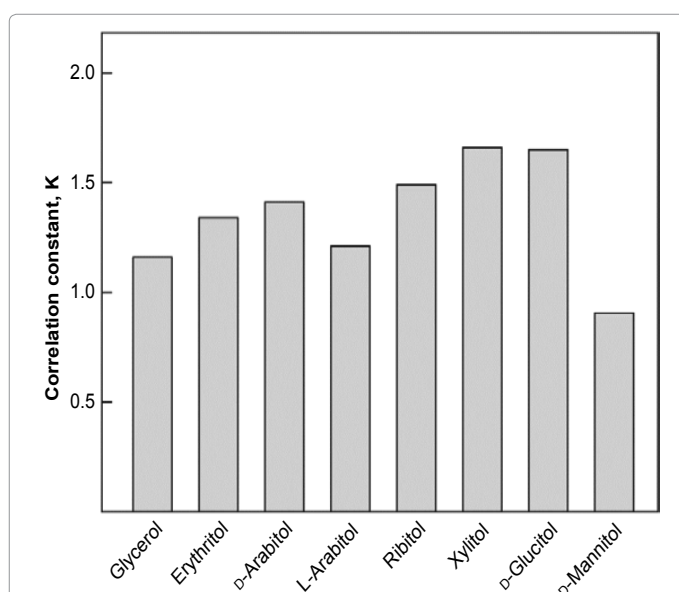


Figure 2: Values of the correlation constant, K (equation 1) for certain alditols at 25°C, revealing significant differences between different alditol molecules regarding their interaction with water molecules. Reproduced with permission [66].

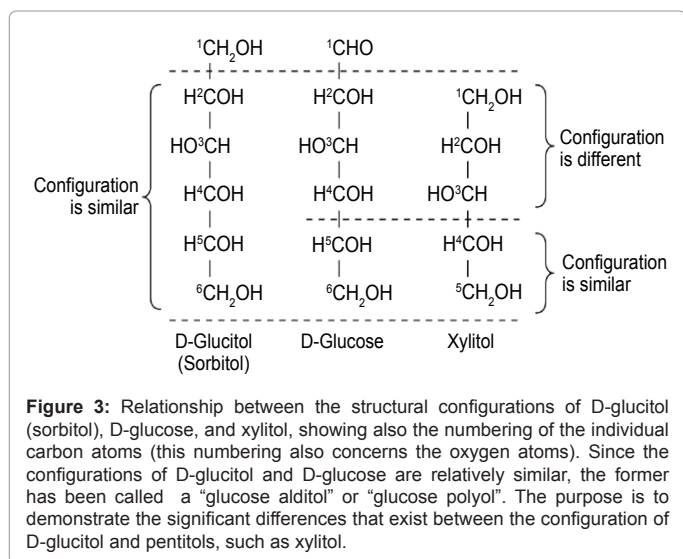
for xylitol and ribitol [66]. Furthermore, the average non-dimensional free energy and volume parameters greatly depended on the alditol in question [66]. The hydration number is a measure of the number of water molecules that have a relatively long residence time with the solute and hence tend to move with it rather than with bulk water [67]. The hydration of alditols can be considered to take place by solute-solvent hydrogen bonding and by non-specific hydration of apolar species.

Hydration of alditols most likely to plays a role in their effects as dentine primers (vide supra); the bonding efficacy of dentine adhesives was investigated in the presence of alditols [68]. Although the required alditol levels are by far higher than those normally used in biomedical studies, this study nevertheless speaks for the existence of important differences between alditols, especially since glycerol, xylitol, or D-glucitol did not display the above preventive effect. Apatite cement containing poragen has been used in the fabrication of biporous apatite which has gained attention as a bone substitute material. Addition of D-mannitol improved the setting reaction and mechanical strength of apatite [68], owing to its satisfactory dissolution behaviour and its biocompatibility, and because it did not inhibit the compositional transformation to apatitic material. It should also be mentioned that OH radical reactions with erythritol, D-arabitol, and D-mannitol are much faster than the NO_3 and SO_4^- radical reactions [69].

Complexation

During the past forty years, a large number of works concerning the complexation of metal cations with sugars and alditols have been published. Complexes of dietary alditols with Fe(II), Fe(III), Ca(II), Cu(II), and other metal cations are interesting owing to their contribution to various biological processes. The alditol molecules can be regarded as carriers of metal ions in the transport of Ca(II) and Fe(II,III) through the gut wall, in remineralization of demineralised enamel caries lesions (by facilitating the flux of Ca(II) from saliva and plaque fluid into calcium-deficient tooth sites), and in other reactions. However, there are substantial differences between alditols to form such metal complexes; alditols are not identical in this sense. The stability constants of alditol-metal complexes depend, among other things, on the size (chain length) and detailed conformation of the alditol molecule. The metal-centred structures may carry a negative or positive charge. In general, alditols form stronger complexes than do monosaccharides [70]. The process of complex formation in aqueous solution is essentially a displacement of one set of ligands, i.e. water molecules of the aqua complex, by another set, e.g. a diol [70].

The tridentate ligand (H-C-OH)₃ present in the xylitol molecules seems to be responsible for the complexation phenomenon (Figure 3; involving carbon atoms C² through C⁴). This arrangement reacts with various polyvalent cations and oxyacids in a most likely reversible reaction. Using the numbering of individual atoms shown in Figure 3, it appears that the preferential complexation sites of xylitol, arabitol, and D-glucitol with Ca(II) can be identified as (O₂,O₃,O₄), (O₁,O₂,O₃), and (O₂,O₃,O₄), respectively [71]. The site specificity of complexation of the various alditols shows that the strength of complex formation markedly depends on the configuration of the ligand. Consequently, the magnitude of the complex constant in reactions alditol + Ca(II) differs significantly from alditol to alditol [71,72]. In complex formation, the number of deprotonated OH groups of the alditol seems to be equal to the stoichiometric amount of OH⁻ present in the solution. The number of such groups is smaller in pentitols than in hexitols. It is likely that in an aqueous solution (as in whole-mouth saliva and gut lumen), only one Ca(II) ion interacts with pentitols and hexitols.



Xylitol serves as an example of symmetric alditols. The molecule is symmetric, while, for example, D-glucitol and D-arabitol are unsymmetrical alditols. The symmetry of the xylitol molecule causes differences in its complexation abilities compared with other alditols. Based on ¹H-NMR studies [71], it appears that, in the complexed state, the xylitol molecule will be held in a more rigid conformation than the unsymmetric alditols do, rendering an almost ideal "zig-zag" structure possible. Angyal et al. [73] determined that the xylitol molecule is predominantly in the 'sickle' form. Under normal experimental conditions only a portion of xylitol can be present as a metal complex.

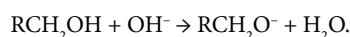
Based on experiments with the Eu³⁺, it appears that the behaviour of D-glucitol on complexing is similar to that of xylitol. One end of the D-glucitol molecule has the same configuration as xylitol; the other end, with an erythro configuration, may not be very well suited for complexing with Eu³⁺ [73]. Angyal et al. also estimated that about 10% of xylitol was present as an Eu(III) complex under the conditions used. The complexed portions of D-glucitol and D-mannitol were calculated to be 28.6% and 16.7% for Ca(II), respectively [70], under slightly different conditions. For erythritol, xylitol, and ribitol, the complexed portions were 16.0, 23.1, and 7.4, respectively, for Ca(II). Using the method of Briggs [70], the percentages of complexed ligands were for Ca(II) as follows: xylitol, 22; D-glucitol, 25; D-mannitol, 19; and galactitol, 21 [74]. In general, the highest percentage figures for the above alditols have been measured for Cu(II) complexes. Cu(II) complex formation with xylitol in alkaline solutions was studied by Norkus et al. [75].

The vicinal threo, threo-triol sequence (H-C-OH)₃ of the xylitol molecule is naturally also present in D-glucitol; both alditols contain this triad arrangement and form complexes which are reasonable stable under physiologic conditions (stronger than, for example, D-mannitol and galactitol, which contain an all erythro-, threo/erythro, erythro configuration; threo and erythro indicate the presence of two asymmetric carbon atoms [71]. Examples of this reaction type are the formation of complexes between xylitol and Ca(II) which can be considered to have biological significance also in the oral cavity and in the gut lumen; this possibility must be re-emphasized.

D-Mannitol is the electrophoretically slowest hexitol (i.e. showing the least degree of interaction with Ca(II) ions), but nevertheless, forms the most stable complex with partially hydrated Ca(II) ions in Ca(38) NaY-zeolites (followed by L-iditol, D-glucitol, and dulcitol [76]. It is

necessary to point out; however, that the alditol-Ca(II) interactions are often weak with short reaction times compared with those between Ca(II) and organic acids such as oxalic acid, citric acid, EDTA, etc. Accordingly, the dietary alditols do not act as demineralizing agents in studies on the mineral loss in dental caries and in dental erosion, but, instead, as factors that de facto stabilize the salivary calcium phosphate systems, favouring remineralization of caries lesions.

The pentitols and hexitols differ sometimes remarkably also when affected by other inorganic reactions. In several instances the substrate may readily undergo oxidation, the rate of which greatly depends on the alditol. For example, the kinetics of oxidation of xylitol and galactitol by hexacyanoferrate(III) ion in aqueous alkaline media depends on the alditol; the oxidation patterns differed significantly [77]. Both oxidation reactions followed first-order kinetics with respect to hydroxide ion, but with xylitol this was true only for lower OH⁻ concentrations, whereas with galactitol the first-order kinetics rule applied even up to manifold variation. At lower NaOH-concentrations the rate constants of oxidation of xylitol and galactitol were 0.0128 and 0.0170 mol⁻²L²s⁻¹, respectively. The reaction progresses via an alkoxide ion, the end products being dicarboxylic acids. The difference between xylitol and galactitol was remarkable. An alkoxide ion is formed most likely owing to ionization of alcohols in presence of alkali:



Complex-formation between dietary alditols and certain heavy metals deserve attention. All investigations so far published seem to indicate that ingestion of alditols does not increase the deposition of cadmium and lead in mammals and avian species. White Leghorn cockerels fed 20% xylitol or 20% sucrose in drinking water showed no interaction between xylitol and the absorption of ²⁰³Pb [78]. In contrast to this, xylitol may decrease the intestinal absorption of lead in female mice, by increasing the intestinal transit of the metal. The male mice did not respond this way, indicating the need of further research [78].

The complexation phenomenon has been exploited in a large number of chemical analytical methods. For example, the determination of boron as boric acid (in ophthalmologic eye solutions) is based on the complexation reaction between D-glucitol and boric acid [79]. Use of chromatography on poly(styrene-co-divinylbenzene) resins has been used to study the stability of metal complexes with xylitol and D-glucitol [80].

In some instances both complexation and OH⁻ radical formation (vide infra) are simultaneously responsible for the biological effects observed. Although such radicals can be present in an alditol-containing medium, sometimes complexation alone explains the results obtained. For example, the inhibitory effect of D-mannitol on metal-catalyzed oxidation of human relaxin most likely resulted from complexation of transition metal ions rather than HO[•] scavenging [81].

Alditol complexes with Pd(II) showed differences between tetrutols on one hand and pentitols and hexitols on the other [82]. In the case of pentitols and hexitols (D-arabitol, ribitol, xylitol, galactitol, and D-mannitol), the metalated tetra-anions were stabilized by intramolecular hydrogen bonds, which uniformly connected an alkoxide acceptor to the OH donor group located at the δ-carbon atom. As a consequence of hydrogen bonding, the open-chain alditol ligands became rigid.

An interesting application of complex formation between molybdenum and alditols was presented in a Russian paper on differentiation and identification of *Actinomyces* to subdivide them

into groups according to their sensitivity to myo-inositol, D-mannitol, D-glucitol, D- and L-arabitol, xylitol, and galactitol [83]. The alditols were termed “unassimilated polyols”. Clearly, highly specific alditol properties were involved. Partly related to these findings were the distinctly different effects of alditols on complexation with Molybdate ions; this reaction was found to invalidate the classical Lowry and Lopez phosphorus assay [84].

Hydroxyl radical scavenging

Reactive oxygen species are constantly formed in biological systems. Tissues and cells both in the animal and plant kingdom are normally protected against this oxidative stress by means of various innate molecular mechanisms. Alditols can play a role in both endogenous and exogenous protection against oxidative stress. Exogenous protection in this case means addition of alditol molecules to the reaction environment. Although, Gillbe et al. [85] stated that the possibility of preventing such chemistry inside cells with therapeutic doses of D-mannitol “at present seem remote”, Shen et al. [86] reported that the chloroplast location of D-mannitol can supplement endogenous radical-scavenging mechanisms and reduce oxidative damage to cells by HO[•].

Formation of reactive hydroxyl radicals (OH[•]) can be catalyzed by metal cations, such as Fe(II) and Cu(II). Such radicals can react violently with most biomolecules by means of hydroxylation, oxidation, or hydrogen abstraction. The consequences of such reactions include protein damage (even denaturation), and destruction of biomembranes and DNA molecules. Cell death constitutes the most serious consequence. Free radical scavengers and antioxidants can protect biomolecules against damage by interacting with the latter before the radical reacts with the biomolecule.

Studies on the redox and oxygenation equilibria of alditol complexes with metal cations have suggested that the metal-alditol complexes may activate molecular oxygen [87]. It was observed that addition of D-glucitol enhanced the catalytic activity of manganese for the oxygen-alkali pulping process in the manufacturing of paper. This was considered to result from an effective increase in the solubilization and activation of molecular oxygen by stable Mn-alditol complexes [88]. One of the reaction products is the peroxide ion. This type of complex formation occurs via two vicinal OH groups of the polyhydroxy ligand.

D-Mannitol was shown to exhibit antioxidant properties [88]. Later, erythritol, xylitol, and D-glucitol were reported to display free-radical-scavenging ability [89]. Hematoporphyrin monomethyl ether causes photodynamic damage (HMME-PDT) in HeLa cells by means of reactive oxygen species. D-Mannitol protected HeLa cells from the apoptosis and necrosis caused by HMME-PDT and also inhibited HMME-PDT-mediated Ca(II) elevation [90]. Although a large body of scientific papers has appeared in this area, there is scant information on the relative free-radical-scavenging ability of alditols. Theoretical reasoning suggests that the ability to activate molecular oxygen depends on the size of the alditol molecule, i.e. on the number of OH groups present in the molecule. This property may contribute to the prevention of certain disease conditions. Free radical stress can play a significant role in endothelial cell dysfunction which in turn can affect wound healing seen in diabetes mellitus and several other diseases.

Various analytical methods are available for the determination of OH[•] levels. A simple and specific procedure is based on the use of N-[³H]benzoylglucylglycylglycine as a probe for detecting OH[•] [91]. When this substance was oxidized by OH[•] (produced from aerated solutions of L-ascorbic acid), the process was blocked by typical OH[•]

scavengers, such as glycerol and D-mannitol. D-Mannitol also inhibited the phototoxicity caused by antibacterial fluoroquinolones (levofloxacin and moxifloxacin) on red blood cells [92]. Hydrogen peroxide (H₂O₂) has been shown to act as a signalling molecule involved in several cellular functions. H₂O₂ activates the extracellular signal-regulated kinase (ERK) in ileal smooth muscle cells [93]. This activation process was blocked by pretreatment with D-mannitol, suggesting that metal-catalyzed free radical formation may mediate the initiation of signal transduction by H₂O₂. Examples of the DNA-protecting effects of D-mannitol are numerous [94].

Wound healing is characterized by aerobic and anaerobic glycolysis which is the source of lactic acid present in the lesion. The lactate anion can form chelates with iron, a process that may in turn produce HO[•]. Using cultured dermal fibroblasts, it was found that 15 mM lactic acid retarded cell proliferation and that D-mannitol and catalase abolished this inhibitory effect of high lactic acid level [95]. In other oxidative stress situations, involved in exposure to Pb(II), induction of HO[•] was reduced by D-mannitol [96], while the production of HO[•] by norepinephrine and Cu(II) was reduced by D-mannitol in a study on neuronal norepinephrine uptake by undifferentiated PC12 cells [97]. This study was prompted by the observation that cardiac norepinephrine uptake is reduced in congestive heart failure. Photodynamic treatment (PDT) can also elicit a diverse range of cellular responses, including oxidative stress. In a study on human epidermal carcinoma, D-mannitol abolished PDT-stimulated intracellular oxidative stress [98]. Reactive oxygen species, including HO[•], may also be associated with gastric ulcer. D-Mannitol suppressed the formation of these radicals in a rat study [99].

The HO[•] scavenging activity of D-mannitol is manifested in an interesting fluoride-associated reaction. Iron-containing cultures of the brown-rot basidiomycete fungus *Gloeophyllum striatum* degrade 2-fluorophenol with a relatively good yield of fluoride. This dehalogenation process is strongly inhibited by D-mannitol [100]. Enzyme protein inactivation by low- and high-frequency ultrasound was substantially decreased in the presence of D-mannitol, suggesting that the inactivation was associated with HO[•] formation [101].

Finally, one should recall that the Fenton system inhibits various enzymes of pathogenic bacteria, such as the topoisomerase I of *Trypanosoma cruzi* and *Crithidia fasciculata*; D-mannitol can protect the system [102]. The Fenton system consists of either H₂O₂/Fe(II) or H₂O₂/Cu(II). The Fenton system can generate reactive oxygen species which act synergistically with UV-radiation in causing oxidative damage to cells [103]. In such case D-mannitol can help restore the original status of the cells. Fenton reaction-stimulated HO[•] formation may be involved in the development of diabetic complications which are associated with abnormally high D-glucitol levels in tissues (formed enzymatically from D-glucose by an aldose reductase). Aldose reductase inhibitors have been studied to treat the problem [104].

In some instances the free radical scavenging ability of D-mannitol can elicit untoward responses. For example, artemisinin has been used as an agent to treat malaria. The compound causes antiangiogenic effects, raising the level of intracellular reactive oxygen species, and could also be exploited in cancer treatment [105]. D-Mannitol and vitamin E reversed the artemisinin-induced antiangiogenic effects (including inhibition of hypoxia-inducing factors). D-Mannitol (at 20 mM) also blocked the sodium selenate-induced reduction of infection caused by *Cryptosporidium parvum* in bovine fallopian tube epithelial cell culture [106]. The role of erythritol and xylitol in these reactions is not known.

Comments on Gastrointestinal Effects Caused by Dietary Alditols

Xylitol and D-glucitol are used in chewing gums, troches and other related products aimed at reducing the incidence of dental caries. Physiologically and physicochemically, these substances are normally absorbed slowly from the intestinal lumen and may cause osmotic diarrhea in some individuals if the amounts consumed are too high. Such symptoms may occur especially in subjects unaccustomed to sugar alcohols. The occurrence of diarrhea, however, depends on a multitude of factors such as the person's weight, the composition and structure of the rest of the simultaneously consumed diet, state of fasting, the type of food that contains the sugar alcohols—liquid and solid consumables normally have different effects—state of fasting, and other factors. What is even more decisive is the molecular structure of the ingested alditol. The size and symmetry of the alditol molecule, and the number of hydroxyl groups present in the molecule, significantly influence the behavior of each alditol along the entire length of the alimentary tract. It is possible that these causative factors are not known to all health-care workers.

Despite the many positive effects of dietary alditols, their consumption is frequently linked also to irritable bowel syndrome (IBS) and abnormal flatulence, which affect quality of life negatively and result in a considerable economic burden in terms of health-care costs. Therefore, dentists, physicians and other health-care workers should be made to understand where to focus their attention when communicating with patients, detecting false opinions and misconceptions about diarrhea, flatulence, IBS, and constipation, and correcting them on the basis of scientific evidence and long-term clinical experience [107]. It is necessary to emphasize that osmotic diarrhea occasioned by excessive consumption of carbohydrates and alditols is not a disease, but rather a simple physicochemical response of the intestinal tract to the presence of slowly absorbed carbohydrates or polyols in the gut lumen. The present author is working on a review dealing with alditol-associated gastrointestinal reactions. The following recommendations and instructions were abstracted from that text, and are based on publicly available scientific articles. The instructions primarily concern clinical practitioners working at dental and medical offices:

- Various gastrointestinal discomforts have been known to humans for thousands of years.
- Osmotic diarrhea, catharsis, meteorism, flatulence, and borborygmy (borborygmus) are terms that frequently appear in this context.
- Osmotic diarrhea often results from the consumption of too-large doses of dietary polyols such as xylitol, D-glucitol, D-mannitol, maltitol, lactitol, isomalt, and others. Also other related substances, such as the raffinose-family oligosaccharides, and lactose, may cause similar effects. Raffinose-like carbohydrates are normal constituents in leguminous plants, such as soya.
- Alditols, along with some oligosaccharides, have also received attention in food and nutrition research owing to their prebiotic properties and other health benefits. IBS and functional constipation serve as examples of common gastrointestinal disorders whose treatment may benefit from the application of alditols and oligosaccharides.
- Osmotic diarrhea occasioned by excessive consumption of

these substances is not a disease, but a simple physicochemical response to the presence of slowly absorbed carbohydrates in the gut lumen. The presence of these solutes in the lumen will draw water from surrounding tissues.

- The capacity of the common alditols to cause osmotic diarrhea depends on their molar mass, symmetry of the molecule and, thus, on the detailed configuration of the alditol molecule.
- Consumption of the small-molecular dietary alditol, erythritol, does not normally lead to any gastrointestinal changes, while that of hexitols (D-glucitol and D-mannitol) may cause changes in adults already at 10 to 20 g daily consumption levels. Xylitol is much better tolerated, the largest safe doses ranging widely, normally from 20 g to 70 g per day. However, significant variation may occur. Consumption of disaccharide sugar alcohols maltitol, lactitol, and isomalt may also lead to gastrointestinal disturbances.
- The quantity of xylitol currently recommended for caries limitation is about 10 g/day or more for adults and about half that for infants older than 3 to 4 years; younger infants have received smaller quantities under parental guidance.
- European Union recommends that daily ingestion of 20 g of D-mannitol and 50 g of D-glucitol in the form of commercial food products should bear a warning statement about possible laxative effects.
- Researchers have not always paid attention to study conditions, such as comparing administration of xylitol in plain water versus as part of regular fiber-containing meals or snacks. Tolerance to xylitol present in beverages normally causes diarrhea at lower xylitol levels than when present in solid food. Use of xylitol in a beverage (apart from as a sweetener in tea or coffee) cannot be recommended.
- Adaptation to tolerate increasing quantities of xylitol has been observed in all long-term feeding trials. The adaptive changes may take place in the gut flora and by enzyme induction in the liver.
- The dietary alditols and disaccharide polyols possess undeniable utility value in dietary and medical applications. Therefore, health-care professionals should be aware of restrictions and recommendations regarding their safe and appropriate use.

Comments on a Cochrane Review

A recent Cochrane Review entitled Xylitol-containing products for preventing dental caries in children and adults [5], attracted attention in the media. These reviews are generally highly valued and often provide thoroughly analyzed information on research papers in a particular scientific discipline. In this instance, the opposite was true, as shown below.

- The report included a total of ten studies. In five of them, the daily xylitol doses were significantly smaller than the recommended lowest amounts found in several studies to be caries-limiting.
- Three trials used xylitol toothpaste. Such products normally provide only negligible amounts of xylitol for caries prevention. Toothpaste studies should never be compared with oral consumption of xylitol, such as use of chewable gums and troches.

- The two Costa Rica toothpaste studies listed in the Review do not even mention the xylitol dosage used.
- One of the remaining five studies used adults while four studies employed children. One study was carried out in children with excellent dental health. In such cases, it is impossible to observe any xylitol effect, or the effect of any other intervention procedure. In two studies, a xylitol syrup and “xylitol tooth wipes” were tested in infants. The results were encouraging, supporting the use of xylitol. However, tooth wipes and dentifrices are cosmetic devices and should not be compared with enteral administration of food items. In two further studies, xylitol troches were used. One of them was groundlessly regarded by the Cochrane Review as suffering from “high overall risk of bias”.
- The review included the Swedish Lycksele study in infants, where the daily xylitol levels were understandably quite low.
- A qualified review should establish inclusion and exclusion criteria. This decision normally results in a selection of studies that have been executed “correctly”, i.e., the review will generally include only controlled, randomized and blinded studies. Some indexing services list dentally-related xylitol studies that currently amount to more than 750, with “xylitol and caries” studies amounting to at least 500. Xylitol data have been accepted by The European Food Safety Authority, EFSA [108,109] (vide infra), and the International Association of Paediatric Dentistry (IAPD). For caries-limiting xylitol effects to occur, the daily xylitol levels and the daily frequency of use must be sufficiently high, i.e., at least 5 g, and preferably more (10–15 g in individuals with poor oral hygiene and craving sweets). In several studies, the xylitol regimen was unnecessarily impoverished (vide supra regarding shortcomings in study planning). Researchers planning clinical trials with sugar substitutes should consult reviews discussing failures to demonstrate caries reduction [4,9,32]. Xylitol selectively affects the metabolism of caries-inducive MS.

Consequently, the ten studies chosen for review were not comparable. It is likely, of course, that the Cochrane editors were aware of the above “shortcomings”. Such systematic reviews are conducted according to the widely recognized handbook.

EU-accepted health claims for sweeteners

Consumers should be able to make their food choices based on reliable and accurate information. The European Food Safety Authority (EFSA) has been influential in establishing the currently accepted health claims on sweeteners used in sugar-free chewing gums (SFCG) [4,108]. The sugar replacers currently permitted in EU-approved health claims for SFCG include intense sweeteners (such as aspartame and sucralose), erythritol, xylitol, sorbitol, mannitol, maltitol, lactitol, isomalt, polydextrose, D-tagatose, and isomaltulose. For SFCG, Article 13.1 contains three claims related to tooth mineralization, neutralization of plaque acids, and reduction of oral dryness, and a fourth claim for SFCG with carbamide concerning neutralization of plaque acids. Article 14.1 enounces a “plaque reduction” claim for gum sweetened with 100% xylitol. Two other claims for xylitol-containing SFCG relate to neutralization of plaque acids and reduction of tooth demineralization. The current EU-based legislation allows manufacturers to make claims for 100% xylitol gum to “reduce the risk of tooth decay”. The use of SFCG in medical and oral physiologic tests has become popular. Table-

top sweeteners and foods formulated with sugar replacers are useful in achieving healthier diets in relation to overall carbohydrate and energy intake [109]. This is important considering the increasing prevalence of diseases such as dental caries, obesity, and diabetes.

Are carbohydrates with deviating configuration of any use in the control of oral biofilms?

The carbohydrate portion of the human diet is normally based on D-sugars, such as D-glucose and D-fructose. The use of D and L is based on the configurational differences between monosaccharides. Such sugars are not necessarily dextrorotatory and levorotatory. Therefore, D and L do not designate optical rotational properties. Aldoses and ketoses of the L series are mirror images of their D counterparts. If the sign of rotation of a specific monosaccharide is to be included in naming the compound, it is designated by the italic letters *d* and *l*, or by (+) and (–). This particular nomenclature detail must be emphasized, since the literature on sweeteners has included papers on “levorotary” sugars, leaving readers uncertain as to whether configurational differences or true rotary properties (i.e. the ability to rotate the plane of polarized light) were meant. L sugars are found in nature, but they are not as abundant as D sugars. The L-forms may interfere with metabolic reactions involving D sugars. This possibility must have constituted the impetus for a recent study on “levorotary” carbohydrates and xylitol [110], which were advocated as potential agents for controlling dietary oral biofilms. The authors regarded their test compounds as enantiomers, a term which indicates configurational differences, not rotatory ones. Anyway, adhesion of the cells of *S. mutans* and *Candida albicans* was subdued in the presence of xylitol and certain L-sugars, notably L-glucose and L-mannose. This line of research is well-grounded and suggests that certain L-sugars may have potential use in dental applications.

In spite of the possible advent of L-sugars in dentally relevant consumer products, new information on “old” D-sugars, such as D-tagatose and D-psicose continues to emerge. Both of them occur in small amounts in natural products and have been promoted as tooth-friendly dietary sweeteners. The United States Food and Drug Administration (FDA) regards each as a safe dietary ingredient.

Conclusions

The consumption of fermentable, mostly hexose-based sugars, such as glucose, fructose, and sucrose, can be associated with certain dental problems, such as dental caries. Research and chemical technology have provided synthetic intense sweeteners and special carbohydrates whose consumption has helped curb pathological developments. Erythritol and xylitol have been found to be effective in caries prevention. The sugar alcohol family of sweeteners provides versatile applications within the entire odonto-stomatologic discipline. Evaluation of research publications presumes thorough knowledge of the physicochemical properties of the polyols involved. Evaluation of study papers and review articles on sweeteners also requires vigilant and impartial perusal of the interpretations and data presented; surveys may have been based on a small number of publications, which attempt to compare incompatible treatment procedures. Because the manifestation of dental caries and periodontal disease is often “sluggish” and “deceptive”, new and truly long-term clinical trials are warranted using disease-prone patient cohorts in non-fluoridate environments, with incomplete access to dental care, and with poor oral hygiene habits. Obviously, this type of studies can no longer be implemented owing to ethical reasons.

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