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Review

Spotlight on erythritol as a non-nutritive sweetener: Applications, implications and complications in human health

Erythritol as a non-nutritive sweetener

Syed Imran Ali Shah[1], Mohammed Hussain Alanazi[2], Majed Nidaa Ashammari[2]
[1] Department of Biochemistry, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan
[2] College Pharmacy, University of Hafr Al Batin, Hafar Al Batin, Saudi Arabia

Abstract
Non-nutritive sweeteners (NNS) are popular as sugar alternatives. Erythritol, in the last few years, has been extensively used as potentially safe NNS of choice for people with diabetes mellitus and obesity. However, its indiscriminate use has been questioned owing to potential health risks. The present review analysed the physicochemical properties of erythritol and explored the metabolism of erythritol, focusing on pathways of endogenous erythritol synthesis, absorption and elimination. The current work deliberated upon the metabolic impact, gastrointestinal effects and influence on gut microbiota as well as the recent recommendation by WHO against the long term use of erythritol for weight management owing to the potential cardiovascular complications. The need for further research to establish guidelines for the use of erythritol as a NNS is highlighted.

Keywords
Non-Nutritive Sweeteners, Artificial Sweeteners, Low-Calorie Sweeteners, Erythritol, Diabetes Mellitus, Obesity, Weight Management

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Corresponding Author: Syed Imran Ali Shah, Department of Biochemistry, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan.
E-mail: s.shah10@alumni.imperial.ac.uk P: +92 337 142 95 96
Corresponding Author ORCID ID: https://orcid.org/0000-0002-0833-0771
Other Authors ORCID ID: Mohammed Hussain Alanazi, https://orcid.org/0009-0004-2341-9207 · Majed Nidaa Ashammari, https://orcid.org/0009-0009-1176-3867

Introduction

Non-nutritive sweeteners (NNS), also known as artificial sweeteners or low-calorie sweeteners, are sugar substitutes that are used to provide sweetness to foods and beverages without adding calories. They are generally sweeter than table sugar (sucrose), so only small amounts are needed to achieve the desired sweetness [1]. NNS are often used by people who are looking to reduce their calorie intake, manage their blood sugar levels, or simply prefer the taste of sweet foods and beverages [2]. While NNS sweeteners are generally considered safe for consumption, there is ongoing debate about their potential health effects and concerns about their long-term use [3]. Erythritol has gained prominence as a potentially safe NNS; however, despite its advantages and regulatory approval, recent research prompts consideration of potential harmful effects associated with erythritol consumption. This review aims to assess the existing body of literature pertaining to erythritol usage, delineating knowledge gaps and elucidating how comprehensive analyses can contribute to its effective utilization as a NNS.

Material and Methods

In conducting this review, an extensive literature search was performed utilizing the terms "non-nutritive sweeteners" and "erythritol" for a focused exploration of databases, including PubMed, Google Scholar, and Web of Science. Articles with duplicate or redundant content were eliminated through an assessment of their titles. Following the keyword search, data extraction involved examination of the retrieved articles, considering their titles, abstracts, and full texts when necessary to identify pertinent information.

Non-nutritive sweeteners

There are several commonly used NNS, including aspartame, sucralose, saccharin, stevia, neotame, acesulfame potassium and a variety of sugar alcohols. Aspartame is often used in diet sodas, chewing gum, and other low-calorie foods [4]. Sucralose, derived from table sugar (sucrose), is commonly used in diet sodas, baked goods, and other low-calorie foods [5]. Saccharin is one of the oldest NNS and is often used in diet drinks, table sweeteners, and baked goods [6]. Stevia, a natural sweetener derived from the stevia plant, is often used in natural and organic foods, as well as in low-calorie and sugar-free products [7]. Neotame is similar to aspartame and it is often used in baked goods, desserts, and other low-calorie foods [8]. Acesulfame potassium, also known as Ace-K, is used in diet drinks, chewing gum, and other low-calorie foods [9]. Sugar alcohols, also known as polyols, are derived carbohydrates commonly used as artificial sweeteners. They are structurally similar to sucrose but are not fully absorbed in the small intestine, thus they contribute fewer calories and have a lower glycemic index [10, 11]. Xylitol, a sugar alcohol of the five-carbon monosaccharide xylose, is commonly used in sugar-free gum and mints due to its ability to prevent tooth decay. It is also used in baking as a sugar substitute [12, 13]. Sorbitol, a sugar alcohol of glucose, is commonly used in sugar-free candies, chewing gum, and diet drinks [14]. Erythritol, a sugar alcohol of the four-carbon monosaccharide erythrose, is commonly used as a sugar substitute in foods and beverages [13]. Mannitol, a reduction product of mannose, is less commonly used as a sugar substitute due to its laxative effects when consumed in large amounts. It is administered intravenously to reduce intracranial pressure in patients with traumatic head injuries due to its action as an osmotic diuretic [14]. Isomalt, produced from hydrogenation of isomaltulose, is commonly used in sugar-free hard candies, chewing gum, and chocolate. It has a lower glycemic impact than common sugar and does not promote tooth decay [15, 16]. Lactitol is a sugar alcohol derived from lactose and is commonly used as a sugar substitute in chocolate, baked goods, and ice cream [17]. The key chemical characteristics of these sweeteners are summarized in Table 1.

Erythritol

Erythritol is about 70% as sweet as table sugar (sucrose), but has almost no calories and does not raise blood glucose levels in the same way as sugar does [18]. Erythritol is generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA)

Table 1. Comparison of various non-nutritive sweeteners

Sweetener	Chemical Nature	Chemical Formula	Molar mass (g/mol)	Glycemic index*	Caloric value (kcal/g)	Sweetness compared to sucrose
Acesulfame-K	Potassium salt of 6-methyl-1,2,3- oxathiazine-4(3H)-one 2,2-dioxide	$C_4H_4KNO_4S$	201	0	0	~200x
Aspartame	Dipeptide of L-phenylalanine and L-aspartic acid linked through methyl ester bond	$C_{14}H_{18}N_2O_5$	294	0	4	~200x
Stevia	Stevia leaves contain active glycosides stevioside and rebaudioside	a.$C_{38}H600_{18}$	a.804	a.0	a.0	a.~140x
		b.$C_{44}H_{70}O_{23}$	b.967	b.0	b.0	b.~240x
Neotame	Dipeptide of N-(3,3-dimethylbutyl)-L-aspartic acid and methyl L-phenylalanate	$C_{20}H_{30}N_2O_5$	378	0	0	~8000x
Saccharin	Benzoic sulfamide	$C_7H_5NO_3S$	183	0	3.6	400x
Sucralose	Disaccharide of dichlorodideoxyfructose and chlorodeoxygalactose	$C_{12}H_{19}Cl_3O_8$	397	0	0	~600x
Erythritol	Four-carbon polyol	$C_4H_{10}O_4$	122	0	0.2	~0.8x
Sorbitol	Six-carbon polyol	$C_6H_{14}O_6$	182	9	2.7	~0.6x
Mannitol	Six-carbon polyol	$C_6H_{14}O_6$	182	0	1.6	~0.7x
Xylitol	Five-carbon polyol	$C_5H_{12}O_5$	152	13	2.4	~1x
Isomalt	Disaccharide of sugar alcohols gluco-sorbitol and gluco-mannitol	$C_{12}H_{24}O_{11}$	344	2	2	~0.6x
Lactitol	Glycosyl alditol consisting of beta-D-galactopyranose and D-glucitol	$C_{12}H_{24}O_{11}$	344	3	2	~0.4x

*Glycemic index: A value from 0 to 100 assigned to a dietary ingredient / food item, with pure glucose arbitrarily allocated a rank of 100, which denotes the relative increase in blood glucose level two hours post-prandial.

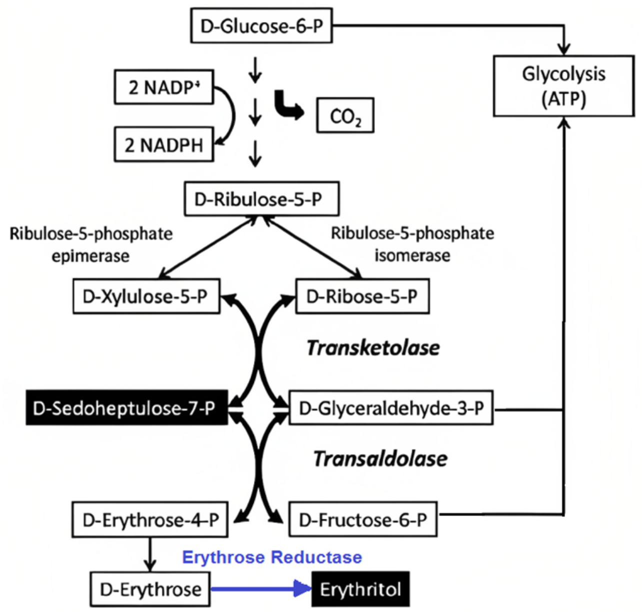

Figure 1. Endogenous synthesis of erythritol in humans via the pentose phosphate pathway

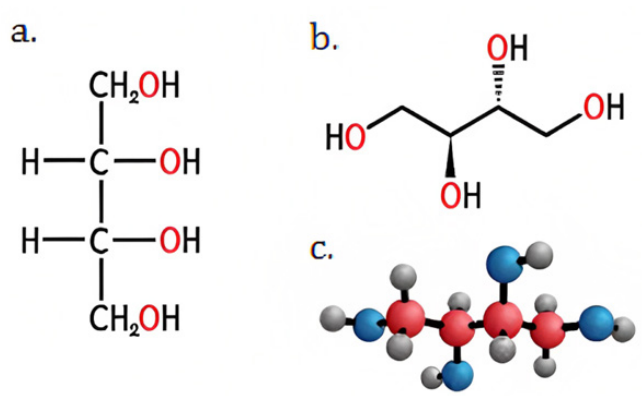

Figure 2. Structure of erythritol molecule.
(a. Fischer's straight chain projection, b. Haworth's simple three-dimensional projection, c. Ball-and-stick model; carbon: red, hydrogen: grey, oxygen: black)

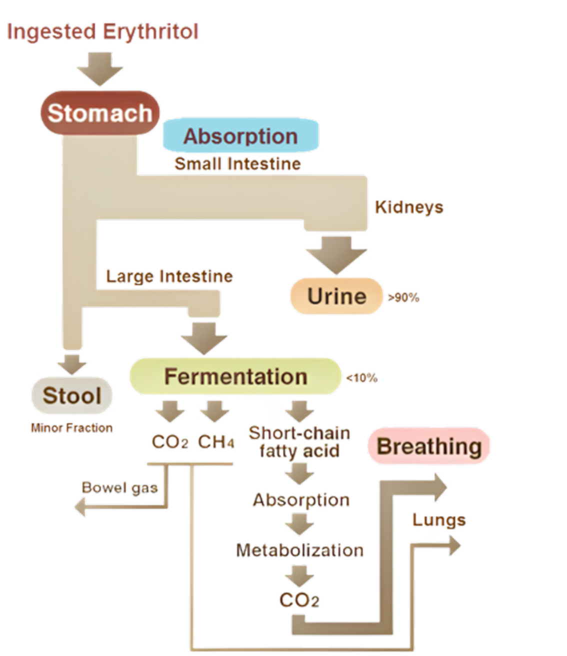

Figure 3. Digestion, absorption, metabolism and elimination of ingested erythritol

and is approved for use in many countries around the world [19].

Sources and Synthesis

Erythritol occurs naturally in some fruits, such as watermelon, grapes, and pears, as well as in some fermented foods, such as soy sauce, wine, and cheese [20]. However, the vast majority of erythritol used commercially is synthesized from natural sugars via a fermentation process that involves using specific strains of yeast, such as Moniliella pollinis or Trichosporonoides megachiliensis Yarrowia lipolytica, Aureobasidium and Pseudozyma tsukubaensis. Once the fermentation is complete, erythritol is separated from the fermentation broth via filtration and purification using ion-exchange resins and activated carbon [21, 22]. A small amount of erythritol is also synthesized endogenously in humans through the pentose phosphate pathway (Figure 1) [23].

Physicochemical properties

Erythritol is a four-carbon sugar alcohol or polyol, which belongs to a group of organic compounds called derived carbohydrates. Its chemical formula is C4H10O4, and it has a molecular weight of 122.12 g/mol (Table 1). Erythritol is classified as a tetritol, meaning it contains four carbon atoms. It has a unique molecular structure that consists of four hydroxyl (-OH) groups, with one of the carbon atoms bonded to two of these groups. The remaining two -OH groups are located on the adjacent carbon atoms (Figure 2) [18, 20]. The chemical structure of erythritol gives it several unique properties. Its four hydroxyl groups allow it to bind with water molecules, giving it a cooling effect on the tongue when consumed. It is resistant to fermentation by oral bacteria, which reduces the risk of tooth decay. Erythritol has a white, crystalline appearance and is water-soluble [24, 25].

Digestion and absorption

Erythritol is digested and absorbed differently than regular sugar (sucrose). When consumed, it passes largely unchanged through the digestive system and is absorbed into the bloodstream from the small intestine (Figure 3). Erythritol is passively absorbed through the intestinal wall and into the bloodstream, without the need for digestive enzymes [26]. Only 10% of erythritol is not absorbed and remains available for colonic fermentation and potential production of short-chain fatty acids (Figure 3). Therefore, it does not cause the digestive discomfort that is sometimes associated with other sugar alcohols, such as bloating or diarrhea, when consumed in moderate amounts [13, 25]. Recent studies have demonstrated erythritol to cause a dose-dependent slowing of gastric emptying, increased sense of fullness and stimulation of the release of gut hormones including cholecystokinin (CCK), active glucagon-like peptide-1 (aGLP-1) and peptide tyrosine tyrosine (PYY) [27-29].

Effect on gut microbiota

The intestinal microbiome is crucial for human health as it contributes to metabolism, immunity and growth. It is influenced by diet, and its composition and function can change quickly. Erythritol is neither fermented by gut microbiota nor does its consumption have a substantial impact on it. Erythritol does not produce lactic acid or organic acids when incubated with gut bacteria and it is also non-fermentable by freshly collected human fecal microbiota [30]. In vitro testing of erythritol on gut microbiota representatives also did not show any impact on bacterial growth. However, when tested using a human gut microbial community, erythritol led to an increase in the production of butyric and pentanoic acids which are by products of bacterial fermentation [31].

Metabolism and excretion

Absorbed erythritol reaches the liver through the portal circulation but is minimally metabolized there. Instead, it enters the systemic circulation and is taken to the kidneys for excretion (Figure 3). A dose ranging study has shown a small amount of ingested erythritol to be converted into erythronate which has recently been identified as a product of oxidative stress resulting from metabolic imbalance [32]. A study in murine cell lines has shown erythritol's ability to protect against non-alcoholic fatty liver diseases (NAFLD) due to its function as an antioxidant, via activation of nuclear factor E2-related factor 2 (Nrf2) signaling pathway which can lead to the inhibition of endoplasmic reticulum stress and hepatic lipid accumulation [33]. Erythritol is primarily excreted from the body via the kidneys without undergoing significant metabolism. The rate of renal excretion of erythritol is dose-dependent, meaning that the more erythritol that is consumed, the more is excreted in the urine. Renal clearance of erythritol has been shown to be nearly 50% that of creatinine, indicating tubular reabsorption of erythritol by the kidney [28].

Effects on human metabolism

Multiple previous studies shown that consumption of artificial sweeteners including erythritol does not have any adverse impact on serum lipid profile [34]. The findings from a murine study suggested that erythritol can effectively mitigate metabolic disorders associated with a high-fat diet by increasing short-chain fatty acids (SCFA) and modulating innate immunity. Consumption of erythritol by mice on a high-fat diet showed a lowering of body weight, improved glucose tolerance, and increased energy expenditure as well as reduced hepatic fat deposition, smaller adipocytes, and improved inflammatory profile in the small intestine. Erythritol supplementation led to higher concentrations SCFA, specifically acetic acid, propanoic acid, and butanoic acid, in the serum, feces, and white adipose tissue, as well as reduced inflammation in the colon, suggesting a potential anti-inflammatory effect [35]. A recent study by Witkowsky et al. investigated the relationship between erythritol and the risk of atherothrombotic disease. They initially conducted untargeted metabolomics studies in a group of patients undergoing cardiac risk assessment and found that elevated levels of erythritol and other polyol sweeteners were associated with a higher risk of major adverse cardiovascular events over a three-year period. This association was subsequently confirmed in independent validation cohorts consisting of stable patients undergoing elective cardiac evaluation. Physiological levels of erythritol were also shown to increase platelet reactivity and promote thrombosis. Ingestion of erythritol was reported to cause significant and sustained increases in plasma erythritol levels, exceeding thresholds associated with heightened platelet reactivity and thrombosis potential [36]. These findings highlight the potential risks associated with erythritol and underscore the need for further investigation into its long-term safety [37].

Glycemic control in diabetes mellitus

Erythritol has been suggested to be beneficial for glycemic control in people with diabetes mellitus. Erythritol has a low glycemic index, thereby it does not cause spikes in blood glucose levels following ingestion, and does not adversely impact insulin sensitivity [38-40]. Furthermore, a study investigating the potential role of erythritol in controlling postprandial blood glucose levels in diabetes mellitus (DM) reported that erythritol administration in diabetic mice demonstrated anti-postprandial hyperglycemic effects. Erythritol was shown to competitively inhibit α-glucosidase, a carbohydrate digestive enzyme, through electrostatic interactions involving specific amino acid residues at the enzyme's active site [41]. A recent interventional study in streptozocin induced diabetic mice showed that 8 weeks of erythritol administration caused reduction in body weight, fluid and water intake, blood glucose, serum aminotransferases, serum creatine kinase and creatinine. Serum insulin level, lipid profile, glucose tolerance ability and pancreatic β-cell function were also improved [42]. Another study in young mice showed prolonged erythritol consumption had no adverse effect on body weight, composition, or glucose tolerance despite substantially high blood erythritol levels [43].

Anti-oxidant effects

Erythritol has been reported to possess the ability to scavenge free radicals and reduce oxidative stress [44]. A recent study tested erythritol for its antioxidant and glucose-regulating properties. In vitro assays highlighted its radical scavenging activity and inhibition of alpha-amylase and alpha-glucosidase enzymes. Molecular docking confirmed its interaction with these enzymes. Erythritol administered to diabetic rats also resulted in improved glucose tolerance, reduced blood glucose levels, and enhanced antioxidant status [45]. A recent murine study in diabetic models has also shown that erythritol reduced oxidative stress [42].

Weight Management

Erythritol has been used for weight management due to its low caloric value and ability to provide sweetness without contributing to weight gain or obesity. Some studies have shown erythritol to reduce adiposity and weight gain [18, 46, 47]. Additionally, a satiating effect of erythritol has also been documented. Since the sweetness of erythritol is less than sucrose as compared to other NNS which have very high sweetness, erythritol is used at high osmolarity to achieve sweetness to sucrose, which allows it to increase satiety at common doses. Osmolarity modulates satiety-related hormones leading to reduced hunger independently of caloric content [48]. However, owing to the safety concerns raised by findings from recent studies, the World Health Organization (WHO) has advised against the use of NNS for controlling body weight. Recent guidelines state that long-term use of NNS is associated with an increased risk of type 2 diabetes, cardiovascular diseases and mortality [49, 50].

Conclusion

Overall, erythritol is a low-calorie sugar substitute that has minimal impact on metabolism. It does not lead to spikes in blood glucose following ingestion, is not dependent on insulin, and has antioxidant properties. These properties make erythritol a potentially safe NNS for patients with diabetes mellitus. However, recent evidence on long term use of erythritol suggests its association with an increased risk of cardiovascular complications. This prompted WHO to issue a statement advising avoidance of the use of NNS for weight management owing to the concerns of elevated cardiovascular and metabolic risks associated with their long term use. In light of these recent developments, further studies are needed to fully understand the impact of erythritol on human health. There is a dire necessity for adequately powered double-blind, randomized controlled trials to assess the safety and investigate the dual nature of erythritol. In the interim period, caution should be exercised in the consumption of NNS including erythritol.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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