

## Review of Xylitol as a Sweetener For Diabetes Patients

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Submitted: 15-05-2022

Revised: 20-05-2022

Accepted: 25-05-2022

**ABSTRACT:** Diabetes mellitus belongs to a group of metabolic diseases that is indicated by a high level of sugar that occurs due to abnormalities in the process of insulin secretion or insulin action. Diabetes mellitus can have an impact on organ damage, especially in the heart, eyes, blood vessels, and liver which then becomes a complication disease. This high prevalence can be attributed to the lifestyle of the Indonesian people in consuming foods that contain sugar. Various artificial sweeteners today such as saccharin, aspartame, cyclamate, synthetic sorbitol, dulcin, nitropropoxy-aniline provide a higher level of sweetness at a relatively cheap price but have a negative effect on the body. Xylitol is a polyol sweetener that exhibits a sweetness intensity equivalent to that of sucrose with several benefits such as dental protection, weight control, glycemic control, and antimicrobial effects.. The purpose of this review is to provide information about xylitol and its use in the pharmaceutical field, especially for diabetics.

**KEYWORDS:** Diabetes, Sweetener, Xylitol,.

### I. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders indicated by high blood sugar levels. In the absence of effective treatment, DM can cause complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. Chronic hyperglycemia can cause vascular, nerve damage, resulting in microvascular, macrovascular, and neuropathic complications. Prediabetes is an abnormal condition of glucose levels that are not high enough to approach the threshold [1]. The value of sugar levels is high if fasting blood sugar levels are 126 mg/dl. Metabolic disorders in this disease are also associated with abnormalities in carbohydrate, fat, and protein metabolism. It is known, diabetes mellitus is the main cause of blindness in the age range of 20 to 74 years, and contributes to the growth of end-stage kidney disease. As a result, this disease accounts for up to 82,000 cases of amputations each year. When compared to the 10 countries that have the highest number of cases, Indonesia is in 7th position in

2019. Based on Basic Health Research, diabetes cases in Indonesia reached 2% in 2018, this value has increased from 1.5% in 2018. 2013 [2] Based on the International Diabetes Federation in 2019, there are 3 classifications of diabetes mellitus:

#### Diabetes Mellitus Type 1

Diabetes Mellitus Type 1 (DM type 1) is caused by at least or no insulin produced by the beta cells of the pancreas. Autoimmune reactions in the body are a strong reason for type 1 diabetes mellitus so the body's defenses do not function normally and attack cells in the body, especially cells that produce insulin. The cause of this disease can be genetic or environmental. The percentage of diabetes 1 from other types of diabetes is about 10%. Starting from young to old age can be attacked by this type of diabetes. Treatment of type 1 diabetes through insulin injections is given routinely every day with the aim of maintaining blood glucose levels and this should not be missed. Type 1 diabetes mellitus is a genetic disease that can be inherited from family members, but it is very rare.

#### Diabetes Mellitus Type 2

This type of diabetes is a very universal type, known to up to 90% of existing diabetes cases. This type is generally indicated by insulin resistance, where the body is no longer sensitive to insulin because insulin does not work normally, blood glucose levels continue to rise. In some people this can interfere with the work of the pancreas, causing the body to produce less insulin so that the value of blood sugar levels becomes higher than normal (hyperglycemia). Type 2 diabetes is mainly diagnosed in adults and children because of the increasing number of diabetes cases due to physical activity and poor diet. The main treatment for type 2 diabetes is a healthy diet, doing regular physical activity and controlling and managing ideal body weight, and taking the necessary medications to manage the drop in sugar levels.

#### Genstational Diabetes Mellitus (GDM)

Gestational Diabetes Mellitus (GDM) develops during pregnancy. If DM is diagnosed

before pregnancy then it is not included in GDM but pregnancy with DM disease. The increase in insulin resistance is caused by hormonal irregularities that occur during the pregnancy phase.

### Therapy

The aim of DM therapy is to prevent or delay the development of long-term micro and macrovascular complications including retinopathy, neuropathy, diabetic kidney disease. Other goals can relieve symptoms of hyperglycemia, minimize hypoglycemia and other side effects, minimize treatment burden, and maintain quality of life. There are 2 therapeutic steps for patients with diabetes mellitus, namely non-pharmacological therapy and pharmacological therapy [1].

Non-pharmacological therapy include medical nutrition therapy, increasing physical activity, and education, and self-management support for people with diabetes.

#### a) Medical Nutrition Therapy

A healthy eating plan that is moderate in calories and carbohydrates and low in saturated fat (ie >7% of total calories) with all the essential vitamins and minerals is recommended. Weight loss or weight maintenance is an important element in many patients with type 2 diabetes. An initial weight loss goal of at least 5% should be targeted at all overweight or obese patients through calorie restriction.

#### b) Increase physical activity

Diabetic patients need to do regular physical activity. It is known that aerobic exercise can provide an increase in insulin sensitivity, provide a slight improvement in glycemic control in the majority of individuals, reduce the risk of heart disease, aid in weight maintenance or loss. Physical activity goals include at least 150 minutes per week of moderate (maximum heart 50%-70% rate) intensity exercise at least 3 days a week.

#### c) Education and Self-Management Support for Diabetics.

Consistent long-term diabetes control requires patients to understand their disease and participate in routine self-management strategies to control it.

Pharmacological therapy is carried out by taking drugs that can reduce blood glucose levels. Here are some drug options that can be used [3].

- Insulin

Regular insulin acts with a relatively long onset when administered subcutaneously (SC), to achieve optimal glucose levels it takes 30 minutes before meals and to avoid delayed postmeal hypoglycemia.

- Biguanide

One example of this class of drugs is metformin, which acts on insulin sensitivity of the liver and peripheral (muscle) tissue, making it more sensitive and increasing the effect of glucose uptake in the blood.

- Sulfonylureas

Sulfonylureas exert a hypoglycemic action by stimulating insulin secretion in the pancreas.

The high prevalence of diabetes in Indonesia can be attributed to the lifestyle of the Indonesian people in consuming foods that contain sugar. Currently, various artificial sweeteners such as saccharin, aspartame, cyclamate, synthetic sorbitol, dulcin, nitropropoxy-aniline are now an option for sweeteners in food or pharmaceutical preparations because they can provide a higher level of sweetness at relatively low prices. However, consuming this sweetener continuously will have a negative effect on the body. It is known in a study conducted by Setiady et al in 2019[4], the consumption of a combination artificial sweetener between cyclamate and saccharin increased fasting blood glucose in male rats. In addition, in addition to causing diabetes mellitus, artificial sweeteners are at risk of disturbing other health and causing cancer.

In a histopathological study conducted by Utomo et al in 2012[5], it was found that the administration of artificial sweeteners (sodium saccharin and cyclamate) at a dose of 5 mg/Kg body weight every day for 30 days in male mice had an impact on liver cell damage of 0.52-0.56%. changes and at a dose of 15 mg/Kg body weight every day for 30 days had an impact on liver cell damage by 35.72%.

Based on the risk of artificial sweeteners on health, it is necessary to conduct a study on the development of sugar that is safe for health. Xylitol is one of the sugar alcohols consisting of 5 carbon chains. Xylitol has been used for many years in a wide variety of foods, beverages, and pharmaceutical preparations. Sugar alcohol is a low-carbohydrate nutritional sweetener with lower blood sugar levels and can be metabolized without insulin. Sugar alcohol does not have the effect of increasing blood sugar. Therefore, sugar alcohol can be an alternative to sugar intake for diabetics

## Sweetener

Sweeteners can be grouped into [6]:

### 1) Natural Sweetener

Natural sweeteners are present or produced naturally, without the addition of chemicals, derived from superior fruits, natural sugars, and starches in vegetables, trees, seeds, nuts, and roots. The following are examples of natural sweeteners namely maple syrup, honey, stevia, molasses, coconut sugar, date sugar, agave nectar, and xylitol

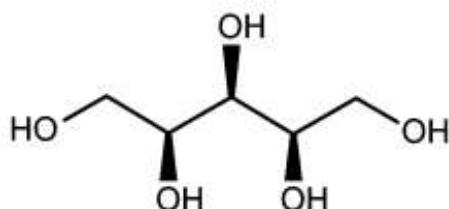
### 2) Artificial (synthetic) sweeteners

Artificial sweeteners are additives in drugs, food, or other preparations that give food a sweet taste with a high enough sweet intensity but no

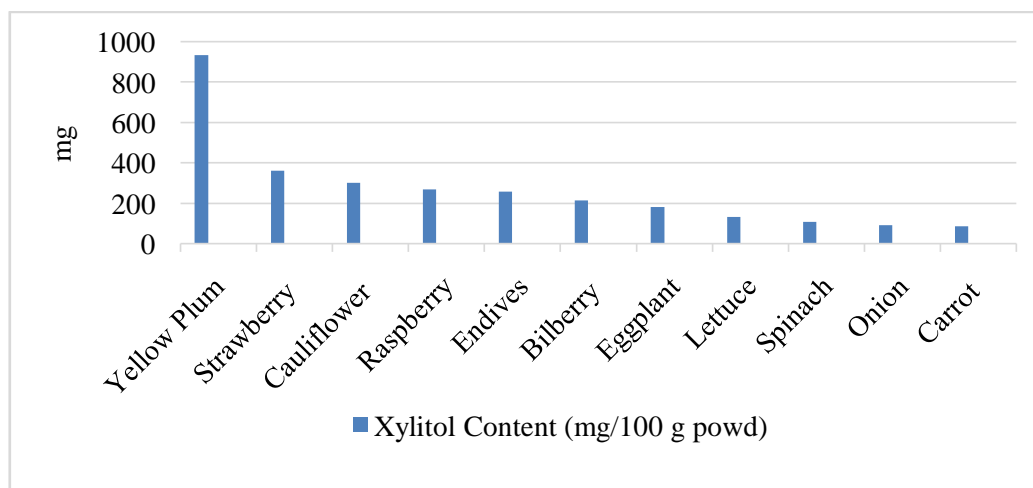
nutritional value. Artificial sweeteners are referred to as sugar substitutes, alternative sweeteners, or non-sugar sweeteners that can be used to replace sugar in foods and beverages. They can be divided into two broad groups namely nutritional sweeteners (add some energy value (calories) to food) and non-nutritive sweeteners (add no energy value to food).

## II. XYLITOL

Xylitol is a sugar alcohol (or polyol) that has been used as a food additive and sweetening agent since the 1960s. The following is the chemical structure of xylitol.



## CHEMICAL STRUCTURE OF XYLITOL



## SOURCE OF XYLITOL

The human body produces 5 to 15 g of xylitol per day during the normal period of carbohydrate metabolism in the liver. Xylitol can be made from a variety of natural plant sources containing the polysaccharide xylan polymer xylose. In industry, the most commonly used raw materials are hemicellulose sources, such as wood chips and corn cobs (both sustainable methods are used). These materials contain 20–35% xylan which is easily converted into xylose (wood sugar) through the hydrolysis process. Xylose is further converted

to xylitol through catalytic hydrogenation (reduction). This is followed by a separation and purification step which ultimately results in high purity xylitol crystals [7].

### a. Organoleptic Properties of Xylitol

Xylitol is the sweetest of all polyols, being the only polyol that exhibits a sweetness intensity equivalent to that of sucrose. Xylitol is as sweet as sucrose at a solid 10% concentration and is reported to be 20% sweeter than sucrose at a 20%

concentration. Xylitol also exhibits a sweetness intensity profile very similar to that of sucrose [7].

#### **b. Physical and Chemical Properties**

Xylitol absorbs energy from the environment as it dissolves, causing a decrease in the ambient temperature so that when xylitol dissolves in the mouth, there will be a pleasant cooling effect. The perceived cooling effect of any polyol is the result of a combination of its negative heat from solution and solubility, as solubility is a major factor in the onset and perception of this effect. Xylitol will give a mint taste with a refreshingly cool sensation immediately after consumption [7].

The absence of a reducing group in the structure of xylitol means that in common with other polyol sweeteners, it can be considered a non-reactive compound because it does not contain a reducing group, it will not undergo the Maillard reaction. The boiling point of xylitol is 216°C, and caramelization of xylitol will only occur if it is heated to a temperature close to the boiling point for a few minutes. Therefore, in applications requiring non-enzymatic caramelization or browning, the addition of a small amount of reducing sugar or coloring is required. The stability of xylitol is not affected by pH, and therefore can be used across a wide pH range [7].

The solubility of xylitol in other solvents varies from only slightly soluble (eg ether in 0.4 g/100 g solution) to very soluble (eg methanol in 6.0 g/100 g solution). Xylitol is only slightly soluble in ethanol (1.2 g/100 g solution). As with aqueous solutions, solubility increases at high temperatures, for example, free xylitol is soluble in ethanol and methanol at 50°C (14.0 and 16.0 g/100 g solution, respectively) [7].

#### **c. Uses of Xylitol**

Xylitol is beneficial in dental protection, weight control, glycemic control, and antimicrobial effects [7].

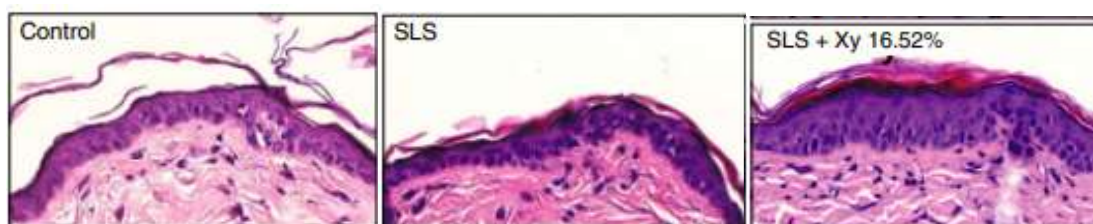
- Oral health care. Apart from being a substitute for sugar, xylitol consumption is closely related to dental and oral health care. These studies reveal that xylitol does not promote the various processes that lead to dental plaque formation, caries development, and tooth decay.
- Glycemic control. Xylitol is derived from simple carbohydrate precursors and contributes

to a glycemic or caloric effect which may in part be due to its partial digestion.

- Lipid metabolism, regulation of lipid synthesis, breakdown, or storage affects circulating lipid levels. Xylitol has been shown to have a positive impact on lipid metabolism, regulation, and circulating levels in subjects with multiple metabolic disorders or diseases.
- Weight management. Maintaining a healthy weight is important for overall health and can help in preventing and controlling many adverse chronic metabolic disorders. Unhealthy eating habits and sedentary lifestyles are major contributors to being overweight or obese, which can increase the risk of developing several serious health problems, including cardiovascular disease, hypertension, and metabolic syndrome.
- As a sweetener, xylitol has a sweeter taste than all other polyols with almost the same sweetness as sucrose. Xylitol can also be used in combination with other polyols and high-intensity sweeteners to produce a unique sweet taste compared to sucrose.

#### **d. Xylitol Applications in the Pharmaceutical**

The high use of xylitol in various fields refers to its varying effectiveness at a certain level so that market demand also increases. It is known that the demand for xylitol is more than 125,000 per year with a selling price of 4.5-5.5\$ per kilo purchased by pharmaceutical companies<sup>[8]</sup>. Xylitol at concentrations of 8.26% and 16.52% can be added to cosmetic products because it has anti-inflammatory and anti-irritant functions by restoring Transepidermal Water Loss (TEWL) to normal levels so that the skin is hydrated again. In this study, animal skin was induced by 5% Sodium Lauryl Sulfate (SLS) because of its irritating effect and could increase TEWL so that the skin becomes drier. This can happen because of the action of polyols that can bind water so as to keep the skin moist. The use of a combination of 5% xylitol and 5% glycerol can also be an option to restore the moisture of the culture<sup>[9]</sup>. Xylitol can prevent the increase in lymphocytes due to irritating agents at lower concentrations than glycerol to achieve the same effect. From the following figure, it can be seen that xylitol with the concentration below can restore a healthy epidermal layer<sup>[10]</sup>.



SKIN'S PHOTOMICROGRAPHS

**Effect of Additional of Xylitol in Pharmaceutical Formulation**

Until now, xylitol is still widely used in the manufacture of chewing gum, mouthwash, toothpaste, and several types of tablet products as a

sweetener in each formula. Most mouthwash products with certain active ingredients are intended to prevent dental plaque because they contain antibacterial ingredients.

Type of Preparations	Formulation	Effect of xylitol	Xylitol content	Reference
Mouthwash	Pineapple Peel Extract, Glycerin, Benzoic Acid, Xylitol, Oleum, Aquadest	The combination of xylitol and glycerin can provide a sweet taste that masks the taste of pineapple peel extract chelation, xylitol as plaque prevention, and noncariogenic	10%	11
Chewy candy	Velvet sour powder, Xylitol, Stevia, Corn syrup, water	The addition of xylitol at a concentration of 5.5%-6% can increase the viscosity of the chewy candy	5,5-6,0%	12
Chewable tablets	Pineapple peel dry extract, Xylitol, Aspartame, Gelatine, Talk-Mg Stearate	The addition of xylitol concentration increases the hygroscopicity of the material so that it affects the flow properties and angle of repose of the granules.	43%	13
Oral disintegrating tablet	Salbutamol sulfate, F-Melt, Xylitol effervescent, citric acid, Tartaric acid, NaBic, Stearic Acid	Xylitol can increase tablet hardness, the combination of F-Melt and xylitol will improve texture and taste.	17,67%	14



- The use of xylitol 10% as a sweetener with a combination of glycerin can provide a sweet taste and cover the taste of chelation in mouthwash preparations containing the active ingredient of pineapple peel extract. The addition of xylitol in the preparation also did not affect the color of the pineapple peel extract mouthwash [11].
- The formulation developed by Samakradhamrongthai and Jannu in 2021[12] showed that the addition of xylitol at a concentration of 5.5%-6% can increase water activity than stevia and corn syrup in chewy candy preparations, this is because xylitol can be a good humectant in the preparation so that The addition of polyols in the preparation can maintain the softness and elasticity of the chewy candy preparation texture in the longer term. The addition of xylitol and stevia can also add value to the taste, aroma with good elasticity compared to using corn syrup.
- Several types of tablet products are also made using xylitol as a sweetener additive. In the study of Ropiqa et al., in 2020[13], chewable tablet products were made using wet granulation with a combination of xylitol and aspartame (284: 40) for formula I, (292: 32) for formula II, and (300: 24). The results of the evaluation of the granules showed that the flow time was longer and the angle was greater when the xylitol concentration was higher, this happened because xylitol showed hygroscopic properties so it affected the flow properties and angle of repose of the granules. Scanning Electron Microscopy (SEM) test results show xylitol and sorbitol particles where sorbitol has a more rounded and symmetrical size than xylitol so that the flow properties of sorbitol will be better than xylitol [15]. In the evaluation of tablets, catch-up tablets will increase with the concentration of xylitol, but in the study, catch-up tablets were still within the acceptable range. The tablet hardness can be caused by the nature

of xylitol as a binder that forms crystals upon increasing compression. Humidity is an important parameter in tablet compression where xylitol compression will be better at low humidity at 20%RH and 40%RH [15].

- The oral formulation of disintegrating effervescent tablets was made by Saputra et al., in 2019[14]. The concentration of xylitol as a sweetener used varied from 15% (30 mg/200 mg) to 18% (36 mg/200 mg) with the optimum formula being F-Melt 146.00 mg, xylitol 35.33 mg, effervescent 13.65 mg. Based on his research, xylitol can increase tablet hardness, but if it is made in effervescent dosage form, it will reduce hardness and accelerate disintegration time. Meanwhile, if F-melt is combined with xylitol, it will improve the texture and taste.
- Various innovations in pharmaceutical preparations, including drugs and food, continue to be carried out in the pharmaceutical world to obtain safe, quality, and efficacious pharmaceutical preparations, especially for patients with diabetes mellitus, it is necessary to regulate lifestyle including food management to control patients' blood sugar [16]. The following is a table of pharmaceutical preparations in the form of foods containing xylitol and their effects on several aspects of the preparation such as moisture, hardness, viscosity, and sensory or organoleptic properties of the preparation.

#### Mechanism Of Xylitol As a Sweetener For Diabetic Patients

Xylitol is a safe sweetener for diabetics because it has a lower calorific value than sucrose (2.4 kcal/g vs 4.0 kcal/g) and a fairly low glycemic index value. Several studies have been conducted to determine the mechanism of action of xylitol against diabetes both in vitro, ex vivo, and in vivo.

Reference	Mechanism	dosage
17	Xylitol increases glucose uptake in muscles at certain doses without insulin. Significantly, xylitol in a single oral dose can delay gastric emptying thereby inhibiting the absorption of glucose in the intestine by inhibiting the main carbohydrate digestive enzymes	2,5-40%

18	Xylitol has a potential anti-oxidative effect that can prevent pancreatic cell damage	10%
19	Induces a slowing of gastric emptying rate, stimulates the release of the satiety hormone	7 g, 17 g, dan 25 g
20	Induces hormone release and slows gastric emptying	50 g/300 ml air
21	Pancreatic islet and beta cell regeneration	10%
22	Slows gastric emptying	10%

In vitro it has been shown that there is a significant inhibition by xylitol at a dose of 2.5-40% of the enzymes -amylase and -glucosidase<sup>(17)</sup> that affect the decrease in blood sugar levels because it can space the digestion of carbohydrates and their absorption process in the intestine. Tests of 10% xylitol and 10% sucrose respectively on healthy mice showed that mice on a 10% xylitol diet did not experience an increase in appetite and weight gain compared to sucrose<sup>(22)</sup>. These two things are related to each other where if the gastric emptying time is relatively long, the body does not give a signal for food intake so that bodyweight does not increase. In addition, xylitol can also delay gastric emptying.

Other studies have shown that xylitol acts as an antioxidant because it can donate and reduce electron compounds<sup>(18)</sup>. Xylitol has an antihyperglycemic effect if taken for a long time in diabetics<sup>(19)</sup>. Rahman and Islam's research in 2014<sup>21</sup> confirmed that compared to doses of 2.5% and 5%, 10% xylitol dose showed more significant activity against cell repair in diabetic agents-induced rats, large islet size, and increased beta-cell count. the pancreas is the parameter of improvement.

#### Xylitol Glycemic Index

As a sweetener that is widely used in various pharmaceutical and non-pharmaceutical preparations, xylitol has a lower glycemic index value than sucrose. Based on the test results of total sugar in ice cream containing sucrose, inulin, xylitol, and erythritol, the results showed that the sugar content of ice cream containing sucrose was much higher than xylitol, erythritol, and inulin. When viewed from the glycemic index value of each sweetener, the highest value for sucrose was 51.358, followed by xylitol 20.954, erythritol 12.852, and inulin 10.656. The glycemic index value of xylitol is 2x lower than that of sucrose<sup>(23)</sup>. Based on this information, if the use of xylitol

can be maximized in various preparations, especially food or medicine, it will provide many good food choices for diabetic patients and healthy consumers will maintain their health from high sugar foods or drugs.

#### Side Effect Of Xylitol Consumption

Research by Wölnerhanssen et al., in 2016<sup>20</sup> showed that 50 grams of xylitol given to subjects had the same side effects as 75 grams of erythritol, namely bloating and diarrhea. The side effects of 20% xylitol also show the same conditions<sup>(21)</sup> Because up to 50% of xylitol is digested in the small intestine and the rest is fermented in the large intestine, a high increase in xylitol dosage will refer to an increase in osmotic pressure in the large intestine so that provides a laxative effect. Based on the research of Wölnerhanssen et al., in 2020<sup>19</sup>, administration of xylitol at levels of 7 g, 17 g, and 35 g did not show the effect of abdominal pain, diarrhea, vomiting, nausea, or flatulence.

### III. CONCLUSIONS

Xylitol has many uses in the pharmaceutical field, especially for diabetics.

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