CURRENT DEVELOPMENTS IN SUGAR ALCOHOLS: CHEMISTRY, NUTRITION, AND HEALTH CONCERNS OF SORBITOL, XYLITOL, GLYCEROL, ARABITOL, INOSITOL, MALTITOL, AND LACTITOL

***Awuchi, Chinaza Godswill**[1,2] and **Echeta, Chinelo Kate**[2]

[1]School of Engineering and Applied Sciences, Kampala International University, Kampala, Uganda.
[2]Department of Food Science & Tech, Federal university of Technology Owerri, Imo State, Nigeria.

Abstract

The research discussed the current developments in the chemistry, nutrition, and medical and health concerns of sugar alcohols, particularly sorbitol, xylitol, glycerol, arabitol, inositol, maltitol, and lactitol. Sugar alcohols (also called glycitols, polyols, polyhydric alcohols, polyalcohols, or alditols) are organic compounds, typically derived from sugars, containing one hydroxyl group attached to each carbon atom. Sugar alcohols are widely used as thickeners and sweeteners in the food industry. In commercial foods, sugar alcohols are commonly used in place of sucrose, usually in combination with high-intensity artificial sweeteners, in order to offset their low sweetness. Sorbitol is a sugar substitute, and is about 60% as sweet as sucrose (table sugar). Inositol is half as sweetness as sucrose, and is made naturally in humans from glucose. Glycerol is also widely used as a sweetener in the food industry and as a humectant in pharmaceutical formulations. Xylitol naturally occur in small amounts in plums, strawberries, pumpkin, and cauliflower; and can be produced industrially from lignocellulosic biomass from which xylan is extracted. Arabitol can be formed by reduction of either lyxose or arabinose. Lactitol is used as a laxative, and also as a replacement in bulk sweetener for low calorie foods with roughly 40% of the sugar sweetness. The high sweetness of maltitol allows its solitaire use without mixing with other sweeteners. Like other sugar alcohols, foodstuffs containing sorbitol may cause gastrointestinal distress. Sorbitol acts as laxative by drawing water into large intestine, stimulating bowel movements. Inositol is used in managing preterm babies who are at a risk of (or have) infant respiratory distress syndrome. Glycerol may pose very low toxicity when consumed. At high doses, xylitol and other polyols can cause gastrointestinal discomfort, including irritable bowel syndrome, flatulence, and diarrhea. Arabitol is associated with ribose-5-phosphate isomerase deficiency and Alzheimer's disease. Like other sugar alcohols, lactitol may cause diarrhea, cramping, and flatulence in some individuals who consume it.

Keywords: Sugar alcohols, Chemistry, Nutrition, Health concerns, Biochemistry

1. Introduction

Sugar alcohols (also known as polyhydric alcohols, polyalcohols, glycitols, or alditols) are organic compounds, normally derived from sugars, containing one –OH (hydroxyl group) attached to every carbon atom. They (Sugar alcohols) are white, water-soluble solids which can naturally occur or be industrially produced by the hydrogenation of sugars. They are classified as polyols because they contain multiple –OH groups. In the food industry, sugar alcohols are widely used as sweeteners and thickeners. In commercial food products, sugar alcohols are often used in place of sucrose (table sugar), usually together with high-intensity artificial sweeteners, so as to offset their low sweetness. Sorbitol and xylitol are popular sugar alcohols in commercial foods (Hubert *et al.*, 2012).

People always take advantage of nature benefits. Recently, in the later years of the 20^{th} century, the food industry recorded huge progress. This was mainly due to the developments in biochemical studies, the change in lifestyle of the population, the increase in the consumer awareness regarding food products (Małgorzata, 2015), and the increasing demand for low (or zero) calorie foods. The quality and health benefits of foods depend mainly on nutrients composition and also presence of foreign substances like food additives. The presence of foreign substances in foods can be allowed or tolerated only when their levels are harmless or safe. The prevalence of obesity and diabetes encouraged the demand and growth of the artificial sweetener industry. More and more individuals are trying to either lose or maintain weight. Consequently, artificial sweeteners are now used in almost all food products (Małgorzata, 2015) as substitutes to sugars, such as sucrose, fructose, etc., which have high calories. The two main types of sweeteners are nutritive and artificial sweeteners. The latter does not offer calories and does not influence blood glucose (Małgorzata, 2015). However, some nutritive sweeteners such as sugar alcohols have lower blood glucose response and could be metabolized without insulin regulation (Małgorzata, 2015).

In terms of chemical structure, Sugar alcohols have the general formula $HOCH_2(CHOH)_nCH_2OH$. In contrast, in terms of chemical structures, sugars have two fewer hydrogen atoms; for instance $HOCH_2(CHOH)_{n-1}C(O)CH_2OH$ or $HOCH_2(CHOH)_nCHO$. The sugar alcohols differ in their chain length. Most sugar alcohols have six- or five-carbon chains, because they are derived from hexoses (six-carbon sugars) and pentoses (five-carbon sugars), respectively. Some have lesser or more carbon chains. Each carbon has one –OH group attached to it. They are further differentiated by the stereochemistry and relative orientation of these –OH groups. Unlike sugars that tend to be rings, sugar alcohols do not exist as rings. However, they can be dehydrated to form cyclic ethers, e.g. dehydration of sorbitol to isosorbide.

The sugar alcohols normally found in foods are xylitol, isomalt, hydrogenated starch hydrolysates, sorbitol, mannitol (Awuchi, 2017), lactitol, among others. Sugar alcohols are detected in plant products such as berries and fruits. The carbohydrates in these plant products are altered through a chemical process (Awuchi, 2017). These sugar substitutes provide rather fewer calories than sucrose, mainly because they are not absorbed properly and may have laxative effect to some extent. Many supposed "dietetic" foods that are labeled and branded "no sugar added" or "sugar free" in fact contain sugar alcohols as substitute. Individuals with diabetes erroneously think that foods labeled as "no sugar added" or "sugar free" will have no impact on their blood glucose (Awuchi, 2017). Foods containing these sugar alcohols are required to have their carbohydrate contents and calorie value accounted for in one's overall meal plan, as carbohydrate raises blood glucose levels (Awuchi, 2017). Since many individuals

typically *overeat* "no sugar added" or "sugar free" foods, there may be significant elevation in their blood glucose.

Mannitol is no more obtained from natural sources; presently, mannitol and sorbitol are obtained by the hydrogenation of sugars, with Raney nickel catalysts (Hubert *et al.*, 2012). The conversion of mannose and glucose to mannitol and sorbitol, respectively, is given as shown:

$$HOCH_2CH(OH)CH(OH)CH(OH)CH(OH)CHO + H_2 \rightarrow HOCH_2CH(OH)CH(OH)CH(OH)CH(OH)CHHOH$$

Over one million tons of sorbitol are made in this way each year. Xylitol and lactitol are similarly obtained. Erythritol can be obtained by the fermentation of sucrose and glucose.

Sugar alcohols have been reported not to contribute to tooth decay as earlier claimed; on the contrary, xylitol deters tooth decay (Bradshaw and Marsh, 1994; Honkala *et al.*, 2014). Sugar alcohols are absorbed at 50 percent of the rate of absorption of sugars, resulting in less effect on the levels of blood sugar as measured by comparing and equaling their effects to sucrose using glycemic index (Sue and Barbara, 2011; Paula and Ian, 2004). The unabsorbed sugar alcohols can cause bloating and diarrhea owing to their osmotic effects, if consumed in sufficient quantities. However, like several other incompletely digestible substances, the overconsumption of sugar alcohols may lead to bloating, flatulence, and diarrhea as they are not absorbed entirely in the small intestine. Some people experience such symptoms in a single-serving amount. With continued use, most individuals develop some tolerance degree to sugar alcohols and may no longer experience these symptoms as they used to.

1.1. Sugar alcohols as food additives

Polyols (sugar alcohols) are naturally present in small quantities in fruits and in some kinds of mushrooms or vegetables, and, also, they are regulated as either generally accepted as safe or food additives (Małgorzata, 2015). Food additives are substances or compounds intentionally added to foods with the aim of performing some technological functions such as giving color, sweetening or to assist in preservation. Table 1shows the relative sweetness and energy of the most commonly used sugar alcohols. Regardless of the variance in food energy of sugar alcohols, the EU labeling requirements ascribe a blanket value of 2.4 kilocalories per gram to all sugar alcohols.

Table 1: Properties of sugar alcohols

Name	Relative sweetness (%)[a]	Food energy (kcal/g)[b]	Relative food energy (%)[b]	Glycemic index[c]	Maximum non-laxative dose (g/kg body weight)	Dental acidity[d]
Arabitol	70	0.2	5.0	?	?	?
Glycerol	60	4.3	108	3	?	?
Erythritol	60–80	0.21	5.3	0	0.66–1.0+	None
HSHs	40–90	3.0	75	35	?	?
Lactitol	30–40	2.0	50	5–6	0.34	Minor
Isomalt	45–65	2.0	50	2–9	0.3	?
Maltitol	90	2.1	53	35–52	0.3	Minor
Sorbitol	40–70	2.6	65	9	0.17–0.24	Minor
Mannitol	40–70	1.6	40	0	0.3	Minor
Xylitol	100	2.4	60	12–13	0.3–0.42	None

[a] = Sucrose is 100%. [b] = Carbohydrates, inclusive of sugars like sucrose, glucose, and fructose, are ~4.0 kcal per g and 100 percent. [c] = Glucose is 100 and sucrose is 60–68%. [d] = Sugars, like glucose, fructose, and sucrose, are high. **References: (**Karl, 2017; Mäkinen, 2016; Kathleen and Marjorie, 2009; Kay and Malcolm, 2012; Lyn, 2011**)**

1.2. General characteristics of sugar alcohols

Sugar alcohols are not biochemically metabolized by oral bacteria in the mouth, and so they do not make any contribution to tooth decay (Bradshaw and Marsh, 1994; Honkala *et al.*, 2014). They do not caramelize or brown when heated.

Sugar alcohols, as a group, have little less food energy than sucrose. The flavor of sugar alcohols is similar to sucrose, and can be used to mask the unsavory and unpleasant aftertastes of many high-intensity sweeteners.

Along with their sweetness, some sugar alcohols produce a perceptible cooling sensation in the walls of the mouth when highly concentrated, for example in sugar-free chewing gum or hard candy. This happens, for instance, with the crystalline phase of mannitol, lactitol,maltitol, sorbitol, erythritol, and xylitol. The cooling sensation is caused by the dissolution of the sugar alcohols, in an endothermic reaction (heat-absorbing), (Hubert *et al.,* 2012) one with strong heat of solution (Cammenga *et al.,* 1996).

1.3. Absorption of sugar alcohols from the small intestine

Sugar alcohols are commonly absorbed incompletely into the blood stream from small intestine which, in general, results to a smaller change in blood glucose level than table sugar (sucrose). This biochemical property makes them popular sweeteners among diabetic individuals, people on low-carbohydrate diets, and anyone intending to lose weight. As an exception, erythritol is absorbed in the small intestine and then excreted unchanged via urine, so it does not contribute to calories despite the fact that it is rather sweet (Hubert *et al.,* 2012).

1.4. Common sugar alcohols

- Ethylene glycol (2-carbon)
- Glycerol(3-carbon)
- Erythritol (4-carbon)
- Threitol (4-carbon)
- Ribitol (5-carbon)
- Arabitol (5-carbon)
- Xylitol (5-carbon)
- Mannitol (6-carbon)
- Sorbitol (6-carbon)
- Iditol (6-carbon)
- Inositol (6-carbon; a cyclic sugar alcohol)
- Galactitol (6-carbon)
- Fucitol (6-carbon)
- Volemitol (7-carbon)
- Maltitol (12-carbon)
- Lactitol (12-carbon)
- Isomalt (12-carbon)
- Maltotriitol (18-carbon)
- Maltotetraitol (24-carbon)
- Polyglycitol

Both monosaccharides and disaccharides can form sugar alcohols; nevertheless, sugar alcohols derived from disaccharides (e.g. lactitol and maltitol) are not completely hydrogenated as only one aldehyde group can be available for reduction.

2. Chemistry, Nutrition, and Health Concerns of some sugar alcohols

2.1. Sorbitol

Sorbitol (also known as glucitol), a sugar alcohol with a sweet taste, is metabolized slowly in the human body. It can be obtained by glucose reduction, which transforms the converted –CHO (aldehyde group) to a $-C(OH)H_2$ group. Sorbitol can be made from potato starch, and can also be found in nature, e.g. in apples, pears, prunes and peaches (Teo *et al.,* 2006). Sorbitol-6-phosphate 2-dehydrogenase converts sorbitol to fructose. Sorbitol is isomer of mannitol, another type of sugar alcohol; both differ only in the hydroxyl group orientation on carbon 2 (Kearsley and Deis, 2006). While similar, both sugar alcohols have different sources in nature, uses, and melting points.

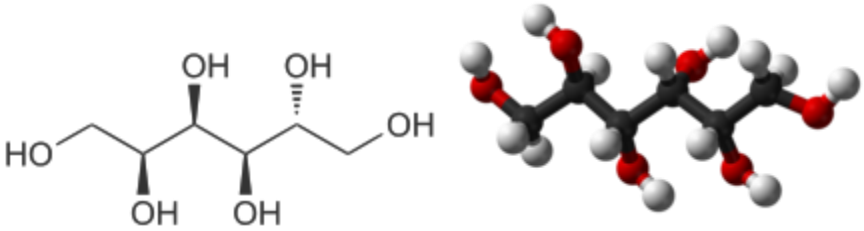
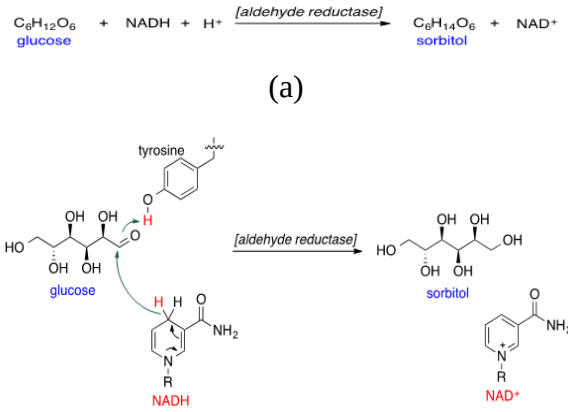


Figure 1: Sorbitol

2.1.1. Synthesis of sorbitol



(a)

(b)

Figure 2: Synthesis of sorbitol

The mechanism involves a residue of tyrosine in the active site of the aldehyde reductase. The hydrogen atom (H) on NADH is transferred to electrophilic aldehyde carbon atom; the electrons on the double bond of the aldehyde carbon-oxygen are transferred to the oxygen which grabs the proton on the side chain of tyrosine to form hydroxyl group. The major role of aldehyde reductase tyrosine phenol group is mainly to serve as general acid to offer proton to reduced aldehyde oxygen on glucose.

Sorbitol may be synthesized by glucose reduction reaction in which the chemically transformed aldehyde functional group is converted into a hydroxyl functional group. The reaction needs NADH and is catalyzed by the enzyme aldose reductase. The first step of polyol pathway of glucose metabolism is glucose reduction, and is implicated in multiple diabetic complications (Awuchi, 2017).

In a normal human body, where glucose level is in the normal range, glucose reduction is not the major pathway for glucose metabolism. However, in diabetic patients with high blood glucose level, up to 1/3 of their glucose level could go through the pathway of glucose reduction. This consumes NADH and eventually results to cell damage. Also, sorbitol may be synthesized by catalytic hydrogenation of d-glucose to yield d-sorbitol (Srinivasan and Gundekari, 2017; Awuchi, 2017). This reaction yields 100% d-sorbitol when d-glucose reacts with hydrogen in water for 1 hour at 120^{o}C, under 150001.5 Torr.

2.1.2. Uses of sorbitol

2.1.2.1. Sweetener

Sorbitol is used as a sugar substitute. When used in food, it has the E number and INS number 420. Sorbitol is about 60 percent as sweet as sucrose (table sugar) (Awuchi, 2017). Sorbitol is considered a nutritive sweetener because it offers dietary energy: 2.6 kcal/g (11 kJ/g) versus the average 4 kcal/g (17 kJ/g) for carbohydrates. It is commonly used in diet foods (including ice cream and diet drinks), sugar-free chewing gum, mints, and cough syrups (Campbell, 2011). Most bacteria cannot utilize sorbitol for energy, nevertheless it can be fermented slowly in the mouth by *Streptococcus mutans*, bacterium that contributes to tooth decay. In contrast, some other sugar alcohols such as xylitol and isomalt are considered non-acidogenic (Hayes, 2001; Nicolas *et al.*, 2011). Also, it naturally occurs in several stone fruits and berries from the trees of the genus *Sorbus* (Nelson, 2005).

2.1.2.2. Medical applications of sorbitol

Laxative

Like other sugar alcohols, foodstuffs containing sorbitol can result to gastrointestinal distress. Sorbitol could be used as laxative when consumed orally or taken as an enema. Sorbitol acts as laxative by drawing water into large intestine, stimulating bowel movements. Also, sorbitol has been reported safe for use and consumption by the elderly, though not without the advice of a doctor (Lederle, 1995). Sorbitol is found in many dried fruits and can contribute to the laxative effect of prunes (Stacewicz-Sapuntzakis *et al.*, 2001). Sorbitol was first discovered in fresh juice of *Sorbus aucuparia* (mountain ash) berries in 1872 (Panda, 2011). Also, it is found in the fruits of dates, peaches, apricots, apples, plums, pears, and cherries.

Other medical applications

Sorbitol is used in culture media of bacteria to distinguish the pathogenic *Escherichia coli* (*E. coli*) O157:H7 from many other strains of *Escherichia coli*, because it is often not able to ferment sorbitol, unlike 93% of known strains of *E. coli*.

Hyperkalaemia (elevated blood potassium) treatment uses sorbitol and ion-exchange resin sodium polystyrene sulfonate (trademark Kayexalate) (Rugolotto *et al.*, 2007). The resin exchanges ions of sodium for potassium ions in bowel, while sorbitol assists in eliminating it. In 2010, the United States FDA gave warning on the increased risk for gastrointestinal necrosis with this combination.

Also, sorbitol is used in the manufacture of capsules of soft gel to store single dose of liquid medicines.

2.1.2.3. Health care, food, and cosmetic uses of sorbitol

Beyond the use of sorbitol as sugar substitute in reduced-sugar food, sorbitol is also used as humectant in low-moisture foods (such as fruit preserves and peanut butter) and cookies (Awuchi, 2017). It is valuable in baking because it functions as a plasticizer, and slows down process of staling.

Sorbitol is used often in modern cosmetics as a thickener and humectant. It is also used in toothpaste and mouthwash. Due to its high refractive index, some transparent gels are made with sorbitol alone.

Sorbitol is used as cryoprotectant additive (mixed with sodium polyphosphates and sucrose) in the manufacturing of surimi, a delicious processed fish paste (Medina and Garrote, 2002). Also, in some cigarettes, it is used as a humectant.

2.1.2.4. Miscellaneous uses of sorbitol

A mixture of potassium nitrate and sorbitol has found success as amateur solid rocket fuel (Richard, 2015). Sorbitol is recognized as potential key chemical intermediate (Metzger, 2006) for fuel production from biomass resources. The carbohydrate fractions in biomass, like cellulose, undergo successive hydrolysis and hydrogenation in presence of some metal catalysts to produce sorbitol (Shrotri *et al.,* 2012). Complete sorbitol reduction opens the way to alkanes, like hexane, to be used as biofuel. The hydrogen needed for this reaction can be made by the aqueous phase catalytic reforming of sorbitol (Tanksale *et al.,* 2010).

$$19\ C_6H_{14}O_6 \rightarrow 13\ C_6H_{14} + 36\ CO_2 + 42\ H_2O$$

The chemical reaction above is exothermic. Exactly 1.5 moles of sorbitol generate roughly 1 mole of hexane. When the hydrogen is co-fed, no CO_2 (carbon dioxide) yield. Sorbitol based polyols are used in production of polyurethane foams for the construction industry. Also, sorbitol is added after yeasts electroporationin transformation protocols, allowing cells to recover through raising the medium osmolarity.

2.1.3. Medical importance of sorbitol

The first enzyme in sorbitol-aldose reductase pathway is aldose reductase (Nishikawa *et al.,* 2000) which is responsible for reduction of glucose to sorbitol, and galactose reduction to galactitol. Too much sorbitol trapped incells of retina, cells of the lens, and the cells of Schwann which myelinate peripheral nerves, is a common result of prolonged hyperglycemia which accompanies poorly diabetes control. It can damage these cells, resulting to retinopathy, cataracts and the peripheral neuropathy, respectively. The aldose reductase inhibitors (substances that slow or prevent the action of the aldose reductase) are presently being studied as a way to prevent these complications or at least delay there occurrence. Sorbitol is fermented in the colon, producing short-chain fatty acids, which have benefits to the overall colon health (Awuchi, 2017).

2.1.4. Overdose effects of sorbitol

Ingesting large quantities of sorbitol may lead to abdominal pain, mild to severe diarrhea, and flatulence. Habitual sorbitol intake of over 20g (0.7 oz) per day as sugar-free gum causes severe diarrhea, leading to unintentional weight loss or even necessitating hospitalization (Kathleen, 2008). In earlier studies, a dose of 25grams of sorbitol, consumed through the day, had a laxative effect in 5% of individuals. Due to the large molecular weight of sorbitol, after large quantities of sorbitol are consumed, only small quantity of sorbitol is absorbed in small intestine; most of the sorbitol go into the colon, with resulting gastrointestinal effects.

2.1.5. Adverse medical effects of sorbitol

Individuals with untreated celiac disease frequently present sorbitol malabsorption, due to the small bowel damage. The malabsorption of sorbitol is a main cause for persisting symptoms in patients on a gluten-free diet already. The sorbitol hydrogen breath test is suggested as a tool to spot celiac disease due to strict correlation between intestinal lesions and cut-off value. Nevertheless, it is not yet recommended as diagnostic tool in clinical practice, although it can be indicated for research purposes (Montalto *et al.,* 2013).

It is well-known that sorbitol added to sodium polystyrene sulfonate (SPS, which is used in hyperkalemia treatment) can cause complications in the gastrointestinal tract, including

bleeding, ischemic colitis, perforated colonic ulcers, and colonic necrosis, especially in patients with uremia. The risk factors for damage induced by sorbitol include hypovolemia, postoperative setting, immune suppression, peripheral vascular disease, and hypotension after hemodialysis. SPS-sorbitol should as a result be used carefully in hyperkalemia management (Mohamad *et al.*, 2010).

2.2. Inositol (*myo*-inositol)

Inositol, precisely called *myo*-inositol, is a carbocyclic sugar alcohol that is abundant in brain and many other mammalian tissues, participates in osmoregulation, and mediates transduction of cell signal in response to a range of hormones, growth factors, and neurotransmitters (Parthasarathy *et al.*, 2006). It is a sugar alcohol that has half the sweetness of sucrose. In humans, *myo*-inositolis naturally made from glucose. A human kidney produces approximately 2g per day. Also, other tissues synthesize it. The highest concentration of inositol is in the brain where it plays a significant role making some steroid hormones and other neurotransmitters bind to their receptors (Croze and Soulage, 2013). Within the last 10 years, *myo*-inositol gained relevance in the management of PCOS because of its efficacy, worldwide availability, and safety profile (Gateva *et al.*, 2018).

Figure 3: inositol

myo-Inositol plays a vital role as the structural basis for many secondary messengers in the eukaryotic cells, the several inositol phosphates. Additionally, inositol serves as an essential constituent of the structural lipids PI (phosphatidylinositol) and its numerous phosphates, the PIP (phosphatidylinositol phosphate) lipids.

Inositol or its associated lipids and phosphates are found in various foods, fruits in particular, especially oranges and cantaloupe. In plant, the hexaphosphate of inositol, phytic acid and its salts, the phytates, act as the stores of phosphate in seed, for instance in beans and nuts. Also, phytic acid occurs in cereals with high content of bran. However, phytate is not directly bioavailable to humans through diet, as it is indigestible; some techniques for food preparation partly break down phytates to alter this. However, inositol in form of glycerophospholipids, as in some plant-derived substances like lecithins, is absorbed well and also relatively bioavailable.

myo-Inositol (phosphatefree) was once regarded a member of the Bvitamins, known as Vitamin B_8 in this context. However, as it is synthesized from glucoseby the human body, it is not essential nutrient (Reynolds, 1993).

2.2.1. Isomers and structure of inositol (*myo*-inositol)

The isomer of *myo*-inositol is a meso compound, and therefore optically inactive, as it has a plane of symmetry. Consequently, *meso*-inositol is obsolete name for this compound. In addition to *myo*-inositol, other naturally occurring stereoisomers of inositol are *scyllo*-, D-*chiro*-, *muco*-,and *neo*-inositol, though they occur in insignificant quantities in nature (Majumder and Biswas, 2006). The other likely isomers are L-*chiro*-,*epi*-, *allo*-, and *cis*-

inositol. As their names signify, D- and L- *chiro* inositol are the only pair of enantiomers of inositol, but they are each other's enantiomers, not of *myo*-inositol (Majumder and Biswas, 2006).

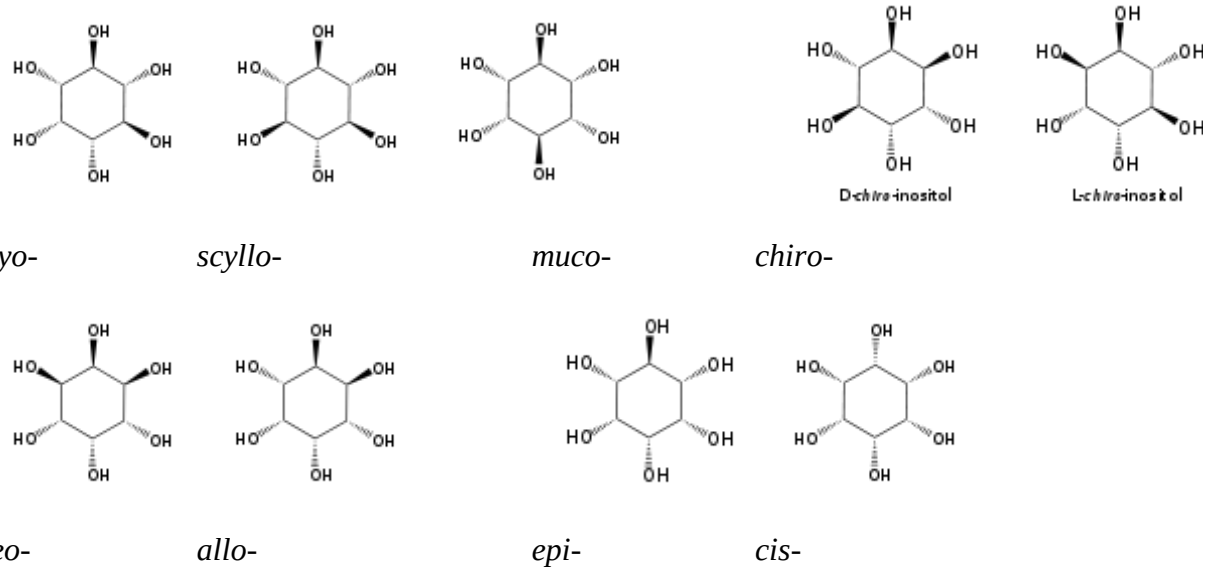


Figure 4: Isomers and structure of inositol (*myo*-inositol)

In its greatest stable conformation, the *myo*-inositol isomer adopts the chair conformation, which causes the movement of the maximum number of hydroxyls (-OH) to the equatorial positions, where they are clearly farthest apart from one another. In this conformation, the natural and regular *myo* isomer has structure in which five out of the six -OH(the first, third, fourth, fifth, sixth) are equatorial, while the second -OHis axial (Brady *et al.*, 2005).

2.2.2. Biosynthesis of inositol

In two steps, *myo*-Inositol is synthesized from glucose 6-phosphate (G6P). First, G6P is isomerized by an enzyme of inositol-3-phosphate synthase (ISYNA1, for example) to *myo*-inositol 1-phosphate, which is further dephosphorylated by an enzyme of inositol monophosphatase (IMPA1 for example) to yield free *myo*-inositol. Most inositol in humans is synthesized in the kidneys, which is followed by testicles, typically in a few grams per day (Parthasarathy *et al.*, 2006). *Myo*-inositol is changed to D-*chiro*-inositol, at the peripheral level, by a specific epimerase. The epimerase activity is insulin dependent. It is worthy of note that only a small amount of *myo*-inositol is transformed into D-*chiro*-inositol, and, also, the conversion is irreversible (Carlomagno *et al.*, 2011).

Inositol, phosphatidylinositol as well as some of their mono- and polyphosphates act as secondary messengers in many intracellular signal transduction pathways. Also, they are involved in many biological processes, including:

- Cytoskeleton assembly
- Nerve guidance (epsin)
- Insulin signal transduction (Larner, 2002)
- Intracellular calcium (Ca^{2+}) concentration control (Gerasimenko *et al.*, 2006)
- Breakdown of fats
- Cell membrane potential maintenance (Kukuljan *et al.*, 1997)

- Gene expression (Shen *et al.,* 2003)

In one significant pathways family, phosphatidylinositol 4,5-bisphosphate (PIP_2) remains (is) stored in cellular membranes till it is released by any of several signaling proteins and changed into numerous secondary messengers, for instance inositol triphosphate and diacylglycerol.

2.2.3. Phytic acid in plants

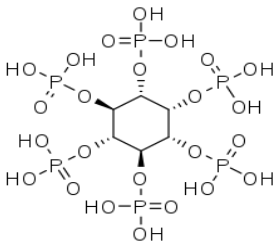


Figure 5: Phytic acid (or inositol hexaphosphate)

Inositol hexaphosphate (IP6), also called phytic acid, is the main storage form of phosphorus in several plant tissues, especially seed and bran. Inositol and phosphorus in phytate form are not bioavailable in general to non-ruminant animals because the non-ruminant animals lack the digestive enzyme phytase needed to remove the phosphate groups. Conversely, ruminants readily digest phytate due to the phytase produced by rumen microorganisms (Klopfenstein *et al.,* 2002). Moreover, phytic acid also chelates essential minerals such as calcium, zinc, magnesium, and iron, making them unabsorbable, preventing their bioavailability, and contributing to mineral deficiencies in individuals whose diets highly rely on seeds and bran for their mineral consumption, such as occurs in developing countries (Hurrell, 2003). Phytic acid is an anti-nutrient. Inositol triphosphate (IP3), tetra- (IP4), and penta- (IP5) are also called "phytates".

2.2.4. Use of inositol in the manufacture of explosives

At the meeting of the American Chemical Society in 1936, Edward Bartow, a professor of the University of Iowa, presented commercially viable and possible means of extracting large quantities of inositol from the phytic acid present naturally in waste corn. As a likely use for the chemical, Edward suggested inositol nitrate as a rather more stable alternative to nitroglycerin. Inositol nitrate is used currently to gelatinize nitrocellulose, hence can be found in some solid rocket propellants and modern explosives (Ledgard, 2007).

2.2.5. Use of inositol as a cutting agent

Inositol is used as a cutting agent or an adulterant for many illegal drugs, such as methamphetamine, cocaine, and sometimes heroin, possibly because of its powdery texture, solubility, or reduced sweetness (50%) compared to sugars. Also, inositol is used as a substitute film prop for cocaine in filmmaking (Golianopoulos, 2012).

2.2.6. Counter to road salt

The exposure of plants to increasing concentrations of road salt leads to the plant cells becoming dysfunctional and undergoing apoptosis, resulting to inhibited growth. Pretreatment with inositol could reverse these effects (Chatterjee and Majumder, 2010; Theerakulp and Gunnula, 2012).

2.2.7. Research and clinical applications

Large doses of inositol have been evaluated for depression treatment, but evidence is sufficient to determine whether the effectiveness of the treatment (Taylor *et al.,* 2004). Inositol is also effective in management of preterm babies who are at a risk of (or have) infant respiratory distress syndrome (RDS) (Howlett *et al.,* 2015). It is worthy to note that *myo*-inositol result is efficient in prevention of the neural tube defects, particularly when combined with folic acid (Cavalli and Ronda, 2017).

Inositol is considered a safe, benign, and effective treatment for the polycystic ovary syndrome (PCOS). The mechanism works by increasing the sensitivity of insulin, which helps to improve ovarian function and reduce hyperandrogenism (Monastra *et al.,* 2017). It is also reported to reduce the risk of metabolic diseases in individuals with PCOS (Nordio and Proietti, 2012). Additionally, it plays role as FSH second messenger. It (myo-inositol) is effective in menstrual cycle regularization and in restoring the ratio of FSH/LH (Unfer *et al.,* 2012). The role of *myo*-inositol as FSH second messenger results to a correct maturation of ovarian follicle and subsequently to a higher oocyte quality. Enhancing the oocyte quality in women with or without PCOS, *myo*-inositol could be considered a likely approach for increasing the possibility of success in assisted reproductive technologies (Ciotta *et al.,* 2011; Papaleo *et al.,* 2009). Contrarily, D-*chiro*-inositol may impair oocyte quality in dose-dependent manner (Isabella and Raffone, 2012). The high level of DCI appears to be related to elevated levels of insulin retrieved in approximately 70% of PCOS women (Moghetti, 2016). With regard to this, insulin stimulates the irreversible transformation of *myo*-inositol to D-*chiro*-inositol leading to a drastic *myo*-inositol reduction. Depletion of *myo*-inositol results to particularly damaging at the ovarian follicles level because it is involved in FSH signaling which is impaired by the depletion of*myo*-inositol. Recent evidence indicates a faster improvement of the hormonal and metabolic parameters when these two isomers of inositol are administered in their required physiological ratio. The plasmatic ratio of D-*chiro*-inositol and *myo*-inositol in healthy subjects is1:40 of D-*chiro*-inositol and *myo*-inositol respectively (Facchinetti *et al.,* 2015). The use of the1:40 ratio indicates the same efficacy of *myo*-inositol only but in a shorter time period. Additionally, the physiological ratios do not impair oocyte quality (Colazingari *et al*., 2013).

The use of inositols in PCOS (polycystic ovary syndrome) is gradually gaining more relevance and an efficiency greater than 70% with strong safety profile is reported. In contrast, approximately 30% of patients can result as inositol-resistant (Kamenov *et al.,* 2015). New evidence regarding the polycystic ovary syndrome, aetiopathogenesis, in fact, explains an alteration, not in the species alone but also in the amount of each strain characterizing the normal GI flora. This alteration can result to a chronic low grade of malabsorption and inflammation (González, 2012). A possible solution can be represented by the *myo*-inositol and α-lactalbumincombination. This combination indicates synergic effects in increasing myo-inositol absorption (Monastra *et al.,* 2018). Recently, a study reported that the combination of *myo*-inositol and α-lactalbumin increases *myo*-inositol plasmatic content in patients of inositol-resistant with a relative improvement of the hormonal and metabolic parameters (Oliva *et al.,* 2018).

2.2.8. Nutritional sources of inositol

myo-Inositol is naturally present in many foods, though food composition tables do not regularly distinguish between phytate, the unavailable form in grains, and lecithin, the bioavailable form. Foods with the highest *myo*-inositol concentrations (its compounds

inclusive) are fruits, beans, nuts, and grains. Beans, grains, and nuts, however, contain large quantities of phytate.

2.3. Glycerol (propane-1,2,3-triol)

Glycerol, a.k.a glycerin or glycerine, is a simple polyol compound. It is an odorless, colorless, sweet-tasting, non-toxic, and viscous liquid. The glycerol backbone is in those lipids called glycerides. Due to its antimicrobial and antiviral properties glycerol is extensively used in FDA permitted burn and wound treatments. Also, it is widely used as humectant in pharmaceutical formulations and as a sweetener in the food industry. Due to the presence of three hydroxyl (-OH) groups, glycerolis hygroscopic nature and is miscible with water (Christoph *et al.,* 2006).

Though achiral, glycerol is prochiral in relation to the reactions of the one of the two primary alcohols (-CH_2OH). Thus, in substituted derivatives, stereospecific numbering tags "sn-" prefix to the molecule before the stem name of that molecule (Alfieri *et al.,* 2017).

2.3.1. Production of glycerol (glycerine)

Generally, glycerol is obtained from animal and plant sources where it occurs in esters of glycerol with long-chain carboxylic acids (i.e. triglycerides). The transesterification, saponification, or hydrolysis of these triglycerides produces glycerol and the fatty acid derivative. Triglycerides can also be saponified with sodium hydroxide (NaOH) to yield glycerol and fatty sodium salt or its soap.

Typical plant sources of glycerol are soybeans and palm. Tallow derived from animal is another source of glycerol (glycerine). Approximately 950,000 tons each year are produced in Europe and the US; 350,000 tons of glycerol per year were produced in the US alone from 2000 to 2004 (Nilles, 2005). The directive of the EU 2003/30/EC set requirement that 5.75 percent of petroleum fuels will be replaced with biofuel sources in all member states by 2010. A projection in 2006 estimated by 2020, production would increase six times more than the demand, creating an excess of glycerol (Christoph *et al.,* 2006).

Crude glycerol from hydrolysis of triglycerides could be purified by the treatment with alkali to remove unreacted glycerol esters, ion exchange to remove salts, and activated carbon to remove organic impurities. High purity glycerol (> 99.5%) can be obtained by multi-step distillation; due to its high boiling point (290 °C), vacuum is necessary (Christoph *et al.,* 2006).

Glycerol from triglycerides is manufactured on a large scale, however, the crude product is of varied quality, with low selling price of 2 – 5 U.S. cents per kg in 2011 (Pei *et al*., 2016). It can be purified, though the process is expensive. Many glycerol is burned for energy, although its heat value is low (Sims, 2011).

2.3.2. Synthetic glycerol

Although usually not economical, glycerol can be made by numerous routes from propylene. The process of epichlorohydrin is the most important: the process involves propylene chlorination to give allyl chloride, which is then oxidized with hypochlorite to dichlorohydrins. The dichlorohydrins reacts with a strong base to yield epichlorohydrin. The epichlorohydrin is, at this point, hydrolyzed to give glycerol. The chlorine-free processes from propylene are the synthesis of glycerol from propylene oxide and acrolein (Christoph *et al.,* 2006).

Due to the large-scale manufacture of biodiesel from fats, in which glycerol is a waste product, market for glycerol is down. Thus, synthetic processes are not cost-effective. Due to

oversupply, efforts are made to convert glycerol to the synthetic precursors, such as epichlorohydrin and acrolein (Yu, 2014).

2.3.3. Applications and uses of glycerol

2.3.3.1. Application and use of glycerol in food industry

In food and beverage products, glycerol is used as a humectant, sweetener, and solvent, and may also help food preservation. Also, it is used as filler in low-fat foods (e.g., cookies) commercially prepared, and as a thickener in liqueurs. Water andglycerol are used to preserve some types of plant leaves (Gouin, 1994). As a sugar substitute, glycerol has roughly 27 kcal per teaspoon (sugar has 20kcal per teaspoon) and is 60%as sweet as sucrose. It does not cause dental carries. Glycerol does not feed nor nourish the bacteria that form plaques and cause tooth decay and dental cavities. Glycerol E number, as a food additive, is labeled as E422. Glycerol is added to icing (frosting) to inhibit it from setting very hard.

The Academy of Nutrition and Dietetics (AND) of the U.S. categorized glycerol as a carbohydrate. Glycerol has a caloric density very similar to sucrose, but different pathway for metabolism in the body and lower glycemic index. Some dietary advocates recognize glycerol as a sweetener well-suited with low-carbohydrate diets. The USFDA categorization of carbohydrate includes all the caloric macronutrients except protein and fat. Glycerol is also recommended as additive when using the artificial sweeteners such aserythritol and xylitol which have a cooling effect, due to its warming and heating effects in the mouth, when the cooling effect is not needed.

2.3.3.2. Medical, pharmaceutical and personal care uses and applications

Glycerin is mildly antiviral and antimicrobial and is a US FDA approved treatment for many wounds. A Red Cross report stated that an 85% solution of Glycerin indicates antiviral and bactericidal effects, and the wounds treated with Glycerin indicate reduced inflammation after approximately 2 hours (120 minutes). Due to this attribute it is widely used in wound care products, inclusive of Glycerin based Hydrogel sheets for injuries, burns and other wound care. Glycerin is approved for all kinds of wound care excluding third degree burns. It is also used to package the donor skin used in skin grafts. No topical treatment is approved for third degree burns, and therefore this limitation is not only exclusive to Glycerin.

Xerosis and ichthyosis have been relieved by topical use glycerin (Ichthyosis, 2013; Mark *et al.,* 2017). It is found in hair care products, soaps, elixirs and expectorants, toothpaste, mouthwashes, allergen immunotherapies, cough syrups, skin care products, water-based personal lubricants, and shaving cream. In solid dose forms like tablets, glycerol (glycerine) is used as an agent for holding tablet. For the consumption by human, glycerol is classified by the FDA among the sugar alcohols as caloric macronutrient. Also, glycerol is used in blood banking for preservation of red blood cells before to freezing.

Glycerol is used in medical, personal care, and pharmaceutical preparations, often for improving smoothness, as a humectant, and for providing lubrication.

Glycerol is a constituent of glycerin soap. Some essential oils are added for fragrance. Soap of this kind is used by individuals with sensitive, easily irritated skin as it prevents the dryness of skin with its moisturizing properties. The soap draws moisture up through layers of the skin and prevents or slows excessive drying and evaporation.

Glycerol functions as a laxative, when taken rectally, by irritating anal mucosa and prompting a hyperosmotic effect, causing colon expansion by drawing water into the colon to induce

peristalsis leading to evacuation (National Cancer Institute, 2011). It may be undilutedly administered either as a small-volume (2 to 10 ml) enema or as a suppository. Alternatively, it can be administered in a diluted solution, e.g., 5 percent, as a high volume enema (Bertani *et al.,* 2011).

Taken orally (usually mixed with fruit juice to lessen its sweet taste), glycerol may cause a rapid, temporary decline in the eye internal pressure. This may be useful for initial emergency treatment of severe elevation of eye pressure.

Glycerol has also been integrated as a constituent of formulations of bio-ink in the field of bioprinting (Atala *et al.,* 2016). The glycerol content functions to add viscosity to the bio-ink without the addition of large carbohydrate, protein, or glycoprotein molecules.

2.3.3.3. Uses and applications in botanical extractions

When used in tincture method extractions, especially as a 10 percent solution, glycerol prevents the precipitating of tannins in plants ethanol extracts (tinctures). It is also used as alcohol-free alternative to ethanol as solvent in preparation of herbal extractions. When used in a standard tincture methodology, it is less extractive. Also, alcohol-based tinctures can have the alcohol removed and replaced using glycerol for its preservation properties. In a scientific sense, such products are not alcohol-free, as glycerol contains three hydroxyl (-OH) groups. Manufacturers of fluid extract often extract herbs using hot water before the addition of glycerol to produce glycerites.

When used as a "true" primary alcohol-free botanical extraction solvent in methodologies based on non-tincture, glycerol has shown to possess high degree of extractive flexibility for the botanicals including the removal of numerous complex compounds and components, with an extractive power that can contend and rival that of water–alcohol solutions and alcohol itself. That glycerol has such high extractive power makes the assumption that it is used with dynamic methodologies as contrasting to standard passive "tincturing" methodologies which are better suited to alcohol. Also, glycerol possesses the inherent property of not denaturing a botanical's constituents or rendering it inert (as alcohols – i.e. methyl (wood) alcohol, ethyl (grain) alcohol, etc., do). Glycerol is a stable agent for preserving botanical extracts that, when used in right concentrations in a solvent base extraction, does not allow reduction-oxidation or inverting of a finished extract's components, even over many years. Both ethanol and glycerol are viable preserving agents. Ethanol is bactericidal in its action, and glycerol is bacteriostatic in its action (Leffingwell and Lesser, 1945).

2.3.3.4. Use as electronic cigarette liquid

Glycerin, together with propylene glycol, is a common constituent of e-liquid, a solution utilized with electronic cigarettes (electronic vaporizers). This glycerol is heated with atomizer (a heating coil usually made of Kanthal wire), generating the aerosol that carries nicotine to the user (Dasgupta and Amitava, 2014).

2.3.3.5. Anti-freezing uses and applications of glycerol

Like propylene glycol and ethylene glycol, glycerol is a non-ionic kosmotrope which forms strong hydrogen bonds with the molecules of water, contending with water-water hydrogen bonds. The interaction disrupts ice formation. The minimum freezing point temperature is around −38 °C (−36 °F) corresponding to 70 percent glycerol in water.

Historically, glycerol was utilized as an anti-freeze for applications in automotive industries before its replacement by ethylene glycol. Ethylene glycol has a lower freezing point. Whilst the minimum freezing point of glycerol-water mixture is higher than the mixture of ethylene

glycol-water, glycerol is not toxic and is currently being re-examined for use in the automotive applications (Hudgens *et al.,* 2007).

In the research laboratory, glycerol is a common constituent of solvents used for enzymatic reagents stored in temperatures below 0 °C because of the freezing temperature depression. It is also utilized as a cryoprotectant where glycerol is dissolved in water to lessen damage by the ice crystals to laboratory organisms which are stored in frozen solution, such as bacteria, mammalian embryos, and nematodes.

2.3.3.6. Use of glycerol as chemical intermediate

Glycerol is used for the production of nitroglycerin, which is an important ingredient of numerous explosives such as gelignite, dynamite, and propellants such as cordite. The reliance on soap-production to supply co-product glycerol led to difficulty to increase production to meet up with wartime demand. Therefore, synthetic glycerol processes were the priorities of national defense in days leading up to the Second World War (WWII). Nitroglycerin, also called glyceryl trinitrate (GTN) is usually used for relieving *angina pectoris*, taken as an aerosol spray or in the form of sub-lingual tablets. An oxidation of glycerol gives mesoxalic acid (Rosaria and Mario 2003).

2.3.3.7. Use of glycerol for vibration damping

Glycerol is used as the fill for pressure gauge to damp vibration. External vibrations, from pumps, compressors, engines, etc., produce harmonic vibrations within the Bourdon gauges that can make the needle to move in excess, giving inaccurate readings. The swinging of the needle excessively can also damage internal gears and other components, causing premature wear. When poured into a gauge to replace air space, glycerol reduces the harmonic vibrations which are transmitted to the needle, thereby increasing the reliability and lifetime of the gauge (Majumdar, 2006).

2.3.3.8. Niche uses of glycerol

Film industry: Glycerol is used in the film industry when filming scenes and actions involving water to stop the areas from drying out very quickly. Glycerine is used— in combination with water (in a proportion of 1:99)—to make a smooth smoky environment. The glycerine-water solution is vaporized and then pushed into the room with a ventilating equipment.

Ultrasonic couplant: Sometimes glycerol can be used as a replacement for water in the ultrasonic testing, as it has favorably higher acoustic impedance (2.42Mrayl) compared to water (1.483Mrayl), while being non-toxic, non-corrosive, relatively safe, and relatively low cost.

Bubble Mixture: Glycerol is added to mixture of bubble for blowing soap bubbles. Glycerol creates longer-lasting bubbles by reducing the evaporation of water.

Internal combustion fuel: Glycerol is used to power diesel generators providing electricity for FIA Formula E series of the electric race cars.

2.3.4. Research on uses of glycerol

Research has been conducted to manufacture value-added products from glycerol gotten from biodiesel production (Johnson and Taconi, 2007). Examples (apart from combustion of waster glycerol):

- Glycerine acetate is potential fuel additive.
- Hydrogen gas production
- Conversion to propylene glycol

- Conversion to acrolein
- Conversion to epichlorohydrin; raw material for epoxy resins
- Conversion to ethanol

2.3.5. Glycerol metabolism

Glycerol is a precursor and backbone for the synthesis of triacylglycerols (triglycerides) and of phospholipids in adipose tissue and the liver. When the body makes use of stored fat as an energy source, fatty acids and glycerol are released into the bloodstream. The circulating glycerol does not, in any way, glycate proteins as do fructose or glucose, and does not result to the formation of the advanced glycation endproducts (AGEs). In a number of organisms, the glycerol constituent can directly enter the glycolysis pathway and, thus, produce energy for the cellular metabolism or, potentially, undergo gluconeogenesis and be converted to glucose.

Before glycerol can enter the glycolysis or gluconeogenesis pathway, depending on the physiological conditions, it must first be converted to their intermediate glyceraldehyde 3-phosphate.

The enzyme glycerol kinase is mainly present in the kidneys and liver, but also in other tissues of the body, including muscle and brain (Jenkins and Hajra, 1976). In the adipose tissues, glycerol 3-phosphate is obtained from the dihydroxyacetone phosphate (DHAP) with enzyme glycerol-3-phosphate dehydrogenase.

It is worthy to note that glycerol has a very low toxicity when consumed; its LD_{50} oral dose for rats has been reported to be 12600 mg/kg, while for mice is 8700 mg/kg.

2.3.6. Historical occurrences of contamination with diethylene glycol

On 4 May 2007, the US FDA advised all makers of medicines in the US to test all the batches of glycerol for toxic diethylene glycol (U.S. Food and Drug Administration, 2007). This came after an occurrence of hundreds of reported fatal poisonings in Panama caused by a falsified import customs declaration by the Panamanian import/export firm, the Aduanas Javier de Gracia Express, S.A. Cheaper diethylene glycol was relabeled as the more expensive glycerol (Walt, 2007).

2.4. Xylitol ((2*R*,3*R*,4*S*)-Pentane-1,2,3,4,5-pentol)

Xylitol is a sugar alcohol frequently used as a sugar substitute in many applications. Xylitol is classified as a polyalcohol or sugar alcohol (precisely an alditol). Xylitol has the chemical formula $CH_2OH(CHOH)_3CH_2OH$. It is a white or colorless solid soluble in water. Use of xylitol-containing manufactured products can promote better dental health, but there is no much evidence to support whether it prevents cavities (Riley *et al*, 2015). When used as food additive within the EU, xylitol has an E number E967 (European Association of Polyol Producers, 2019).

2.4.1. Structure, production, and occurrence of xylitol

Xylitol occurs naturally in small amounts in pumpkin, plums, strawberries, and cauliflower; animals and humans make trace amounts during carbohydrates metabolism (Ur-Rehman *et al.*, 2015). Unlike many sugar alcohols, xylitol is achiral (Wrolstad, 2012). Most isomers of pentane-1,2,3,4,5-pentol are chiral, but xylitol is achiral and has a plane of symmetry.

The industrial production of xylitol starts with the biomass of lignocellulose from which xylan is extracted; the raw biomass materials include softwoods, hardwoods, and agricultural waste from processing wheat, rice, or maize. The xylan polymers can be hydrolyzed/converted into xylose, which is then catalytically hydrogenated into xylitol. This conversion transforms the aldehyde sugar (xylose) into the primary alcohol, xylitol. The impurities are then removed (Ur-Rehman *et al.,* 2015). The processing is usually done using standard industrial methods, such as industrial fermentation involving bacteria, mold, or yeast;particularly *Candida tropicalis*, are common, but not thoroughly efficient (Ur-Rehman *et al.,* 2015; Jain and Mulay, 2014).

2.4.2. Uses of xylitol

Xylitol is used often as a sugar substitute in industrial and most traditional manufactured products, such as dietary supplements, drugs, confections, chewing gum, and toothpaste, but is not used a common household sweetener (Riley *et al,* 2015). Sucrose (table sugar), honey, etc., are commonly used household sweeteners. Xylitol has insignificant effects on blood sugar level as it is metabolized freely of insulin. More slowly absorbed than sugar, xylitol supplies 40 percent fewer calories than table sugar (sucrose). It is approved to be used as a food additive in the US. The rationing of sugar during the World War II led to a heightened interest in sugar substitutes, as a result interest in xylitol and other sugar alcohols became intense, leading to their categorization, characterization, and manufacturing (Hicks, 2010) at industrial scale.

2.4.3. Food properties

Xylitol is almost as sweetness as sucrose, but has more sweetness than similar compounds such as sorbitol and mannitol (Ur-Rehman *et al.,* 2015). Its glycemic index is 7 (very low compared to 100 for glucose) (Foster-Powell *et al.,* 2002). As xylitol and other polyols are stable when heated, they do not caramelize as sugars do, and also they lower the freezing point of mixtures and formulations in which they are used (Burgos *et al.,* 2016).

No health risk exists for normal consumption levels. Due to the adverse laxative effects that high doses of polyols (sugar alcohols) have on the digestive system, xylitol is banned from use in soft drinks in the EU. Also, due to a report in 1985, by the European Union Scientific Committee on Food, asserting that ingesting 50 g of xylitolper day can cause diarrhea, all tabletop sweeteners containing xylitol are required by order to display the warning of a possible diarrhea due to their consumption. Chewing gum containing xylitol is allowed (EFSA, 2008).

2.4.4. Health effects of xylitol

Dental care

People apparently get little or no cavities when they chew gums sweetened with xylitol (or similar sugar alcohols such as sorbitol) compared to when they chew gums sweetened with sugar (sucrose) (Mickenautsch and Yengopal, 2012; Mickenautsch and Yengopal, 2012). As of 2015, clinical trials evaluating whether only xylitol or its combination with other agents could prevent cavities found poor evidence to allow generalizations, though when children who have permanent teeth utilize fluoride toothpaste with xylitol, they can get fewer cavities compared to when they use fluoride toothpaste without it (Riley *et al*, 2015).

In 2008, EFSA evaluated the literature on xylitol, and concluded that xylitol chewing gum decreases the risks of cavities in children (EFSA, 2008; Söderling, 2009). The claim required

rephrasing because xylitol chewing gum is not regarded as a medicine, therefore cannot be claimed to decrease the risk of a disease (EFSA, 2008). EFSA approved a claim in 2011 which stated that substituting sugar with xylitol and other similar sweeteners may maintain tooth mineralization compared with sugar-containing foods (EFSA, 2011).

Preventing ear aches

As of 2016, based on studies conducted on children who are either in school or in daycare in Finland, xylitol, administered in a syrup or chewing gum, may have moderate effect in preventing the occurrence of ear aches in healthy children; however, it is unclear whether it can help in preventing ear infections in children who have a respiratory infection or who are prone to them (Azarpazhooh *et al.,* 2016). Although, in 2011, EFSA evaluated the claim, and concluded that evidence was not enough to support the claim that gum sweetened with xylitol could prevent ear aches (EFSA, 2011). However, this claim may have been countered, although with little evidence. More research and studies are required to establish a generally accepted scientific-based opinion.

Diabetes management

In 2011, EFSA approved a marketing claim stating that foods or beverages containing xylitol and (or) similar sugar substitutes cause lower blood glucose level and lower insulin responses compared with sugar-containing foods or drinks (EFSA, 2011).

Weight management

Eating processed foods having xylitol as a non-nutritive sweetener in place of sugar may be useful to help the management of body weight. Xylitol and most other sugar alcohols have little or no glycemic index compared to sugar.

2.4.5. Adverse effects

Humans

There is no known xylitol toxicity in humans. At high doses, usually beyond the recommended consumption levels, xylitol and other sugar alcohols cause gastrointestinal discomfort, including diarrhea, flatulence, irritable bowel syndrome; some individuals have these effects at lower doses (Mäkinen, 2016). Xylitol has a lower threshold of laxation than some other sugar alcohols but is more tolerated easily than sorbitol and mannitol.

Dogs

In dogs, xylitol, in quantities greater than 100 milligram per kilogram body weight, generates a rapid, dose-reliant insulin release that can cause hypoglycemia, which may be life-threatening (Gwaltney-Brant, 2018; Dunayer and Gwaltney-Brant, 2006). Low blood sugar may result in a loss of coordination, collapse, seizures, and depression in dogs as rapidly as 30 minutes following ingestion (Dunayer, 2004). Intake of xylitol doses greater than 500 to 1000 mg/kg body weight has been associated with potentially deadly liver failure in dogs (Dunayer, 2006). Xylitol is used in relatively much lower doses, in ingredients of two additives of commercial veterinary drinking-water, marketed to freshen the breath of pets or prevent plaque.

2.4.6. Metabolism

Xylitol has 10 kJ/mol (2.4 kcal/g) of food energy according to the United States and the EU food labeling regulations (Food and Agriculture Organization of the United Nations,

2017). Real value differs a bit from this value due to many metabolic related factors. About 50 percent of xylitol consumed is unabsorbed by the human intestines. Instead, 50–75 percent of this quantity is fermented to short-chain organic acids and gases by the gut bacteria, which can cause flatulence. The remaining unabsorbed xylitol is excreted without changing mostly through feces. Less than 2 g of xylitol in every 100 g consumed is excreted through the urine (Livesey, 2003).

About 50 percent of xylitol is absorbed through intestines. It is primarily metabolized by the liver. In humans, the main metabolic pathway is: in cytoplasm, nonspecific NAD-dependent dehydrogenase (i.e. polyol dehydrogenase) converts xylitol to D-xylulose. A Specific xylulokinase phosphorylates the D-xylulose to D-xylulose-5-phosphate. This then enters the pentose phosphate pathway (the hexose monophosphate shunt) for further processing (Livesey, 2003).

2.5. Arabitol (or arabinitol)((2*R*,4*R*)-Pentane-1,2,3,4,5-pentol)

Arabitol, also called arabinitol, is a sugar alcohol (a polyol). It can be produced by the reduction of either lyxose or arabinose. Some organic acid tests often check for D-arabitol presence, which may show the overgrowth of intestinal microorganisms such as *Candida albicans* or other species of yeast/fungus. D-Arabitol is a polyol. A polyol is any sugar alcohol linked to pentose phosphate pathway (PPP), also called the hexose monophosphate shunt. Polyols are classified according to the number of carbon atoms. They (polyols) occur in body fluids. Patient with peripheral neuropathy and leukoencephalopathy has been indicated to be suffering from the deficiency of ribose-5-phosphate isomerase (RPI), a defect in PPP. In this defect and disorder, highly elevated concentrations of the five carbon polyols such as D-arabitol are detected in body fluids. Additionally, the deficiency of transaldolase, another defect in the PPP, was diagnosed in a patient with mostly liver problems among others. The patient had increased polyols concentrations, mostly D-arabitol. The pathophysiological role of polyols, so far, is relatively not known. It is believed that the metabolic end-product in humans is D-arabitol. The strong polyols brain-CSF-plasma gradient in the patient with deficiency of RPI suggested a primary disorder in metabolism. The mechanisms of neuronal and brain damage in deficiency of RPI remain to be well established. A neurotoxic effect due to the polyols accumulation may play a part. D-Arabitol is a product of enzyme D-arabinitol 4-dehydrogenase in the pathway of pentose and glucuronate interconversion (Klusmann *et al*., 2005). D-Arabitol has also been identified as a fungal metabolite, the urinary D-arabinitol is a marker for infection by Candida fungal species or invasive candidiasis (Hui *et al*., 2004; Christensson *et al*., 1999). It can also be a metabolite in Debaryomyces, Zygosaccharomyces, and Pichia.

L-arabinitol is an L-enantiomer of arabinitol, which has a role as a metabolite of humans, a mouse metabolite, and a *Saccharomyces cerevisiae* metabolite. It is an enantiomer of D-arabinitol.

2.5.1. Biochemistry of arabitol

L-Arabitol, also called L-lyxitol or L-arabinitol, is a member of the compounds known as sugar alcohols, which are hydrogenated forms of carbohydrates in which the carbonyl group (ketone or aldehyde reducing sugar) is reduced to a secondary or primary hydroxyl group (US National Library of Medicine, 2019). L-Arabitol is water soluble and is a very weakly acid. L-Arabitol can be found in many food items such as European chestnut, sweet potato, deerberry, and moth bean, which makes it a potential biomarker for consumption of these foods. L-Arabitol can be

detected in most biofluids, including cerebrospinal fluid (CSF), saliva, blood, and urine. L-Arabitol is present in all living things, ranging from bacteria to humans.

2.5.2. Health effects of arabitol

L-arabitol is found to be connected with Alzheimer's disease and the deficiency of ribose-5-phosphate isomerase, which is inborn error of metabolism. Normally, L-Arabitol can be made by the reduction of either lyxose or arabinose. L-Arabitol has been stated in pentosuric acidemia (US National Library of Medicine, 2019). L-Arabinosinuia has been reported in a patient, presented at 16 months of age with facial dysmorphism and delayed motor development. Recently, congenital liver cirrhosis has been reported in a patient with highly elevated urine and plasma levels of arabitol due to the deficiency of transaldolase.

Table 2: Chemical and Physical Properties of arabitol (arabinitol)

Property Name	Property Value
Molecular Weight	152.15 g/mol
XLogP3	-2.5
Hydrogen Bond Acceptor Count	5
Hydrogen Bond Donor Count	5
Rotatable Bond Count	4
Monoisotopic Mass	152.068473 g/mol
Exact Mass	152.068473 g/mol
Topological Polar Surface Area	101 A^2
Formal Charge	0
Complexity	76.1
Heavy Atom Count	10
Isotope Atom Count	0
Undefined Atom Stereocenter Count	0
Defined Atom Stereocenter Count	2
Defined Bond Stereocenter Count	0
Covalently-Bonded Unit Count	1
Undefined Bond Stereocenter Count	0
Compound Is Canonicalized	Yes

2.6. Lactitol

Lactitol is a sugar alcohol often used as a substitute bulk sweetener for foods low in calorie, with about 40% as sweetness as sugar. Also, it is medically used as a laxative.

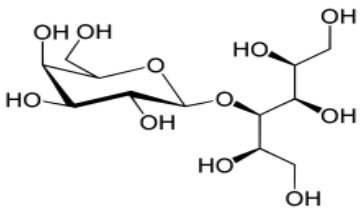


Figure 6: Lactitol

2.6.1. Applications of lactitol

Lactitol is used in a range of low fat foods or low energy foods. Its high stability makes it commonly used for baking. Lactitol is used in cookies (biscuits), chocolate, ice cream, and sugar-free candies. Lactitol also promotes the colon health as a prebiotic. A prebiotic is a

substance in food that is difficult to digest and promotes the growth of beneficial intestinal microorganisms. Due to poor absorption, lactitol only gives 2.4 kcal/g (9 kJ/g), compared to 4 kcal/g(17 kJ/g) for typical saccharides (carbohydrates). Hence, lactitol is about 60 percent as caloric as typical saccharides. It (lactitol) is listed as an excipient in various prescription drugs, like Adderall. Lactitol is a laxative and also used to treat or prevent constipation, for example, under the brand name Importal. Combination of lactitol with Ispaghula husk is apermitted combination for idiopathic constipation as laxative and is used to also treat or prevent constipation.

2.6.2. Safety and health concerns of lactitol

Lactitol, erythritol, maltitol, sorbitol, xylitol, and mannitol are all sugar alcohols. The US FDA categorizes sugar alcohols as GRAS (generally recognized as safe). They are approved for use as food additives, and are accepted and recognized as not causing increases in blood glucose and not contributing to tooth decay. Lactitol is also permitted for use in foods in many countries round the world.

Like many other sugar alcohols, lactitol causes diarrhea, cramping, and flatulence in some people who consume it. The reason is due to humans lack a suitable enzyme beta-galactosidase in the upper GI tract, and a majority of consumed lactitol reaches the large intestine (Grimble *et al.*, 1988), where it then made fermentable to gut microorganisms (prebiotic) and can draw water into the gut through osmosis. Those with health conditions ought to consult their dietician or GP prior to consumption.

2.7. Maltitol

Maltitol is a sugar alcohol usually used as sugar substitute. It is 75 to 90% as sweet as sucrose (table sugar) and also has nearly identical properties of sucrose, with the exception of browning. It is used to substitute table sugar as it is half as caloric as sugar, has a somewhat insignificant effect on blood glucose, and does not promote tooth decay. In chemical terms, maltitol is identified as 4-O-α-glucopyranosyl-D-sorbitol. Maltitol is used in commercial products (Igwe *et al*., 2018) under the trade names such as Lesys, SweetPearl, and Maltisweet.

2.7.1. Production of maltitol

Maltitol is a disaccharide made by the hydrogenation of maltose obtained from the hydrolysis of starch. A hydrogenated starch hydrolysate, maltitol syrup, is produced by the hydrogenation of corn syrup, a carbohydrates mixture produced from the starchhydrolysis. The product contains between 50% to 80% maltitol by weight. The remaining percent is mainly sorbitol, with a small amount of other sugar-related substances.

2.7.2. Uses of maltitol

The high sweetness of maltitol allows its use without being mixed with other nutritive or non-nutritive sweeteners. Maltitol exhibits positive heat of solution, a negligible cooling effect, in comparing with other sugar alcohols, and also is very similar to the subtle cooling effects of sucrose (Field and Simon, 2007). It is used in the manufacturing of candies, particularly sugar-free hard candies, chewing gum, ice cream, chocolates, and baked goods. Maltitol is used as an excipient in the pharmaceutical industry, where it is used as low-calorie sweetener. The similarity of maltitol to sucrose allows its use in syrups with the benefit that crystallization (which can cause sticking of bottle caps) is less likely. Also, maltitol may be used as a humectant, as a plasticizer in gelatin capsules, and as an emollient.

2.7.3. Nutritional information on maltitol

Maltitol provides 2 to 3 kcal/g (Franz *et al.,* 2002). Maltitol is mostly unaffected by the digestive enzymes in human, and is fermented by intestinal bacteria, particularly in the large intestine, with approximately 15% of ingested maltitol seeming unchanged in the feces (Oku *et al.,* 1991).

2.7.4. Chemical properties

In its crystallized form, maltitol measures the same (bulk) as sucrose, and also caramelizes and browns in a manner too similar to that of sucrose following liquifying by intense heat exposure. The crystallized form dissolves readily in warm liquids at 48.9 °C (120 °F) and above; the powdered form is more desirable if either cold liquids or room temperature is used. Owing to its sucrose-like structure, it is easy to produce maltitol and make it available (commercially) in crystallized, powdered, and syrup forms.

Maltitol is not metabolized by the oral bacteria, thus it does not cause tooth decay. Maltitol is somewhat absorbed more slowly than sucrose, which makes it rather more suitable for individuals with diabetes than table sugar (sucrose). The food energy value of maltitol is 8.8 kJ/g (2.1 kcal/g); (sucrose is 3.9 kcal/g (16.2 kJ/g)).

2.7.5. Effects of maltitol on digestion

Like other sugar alcohols (with likely exception of erythritol), maltitol poses a laxative effect, usually causing diarrhea when consumed above about 90 g per day (Ruskoné-Fourmestraux *et al.,* 2003). Doses of around 40 g may cause flatulence and mild borborygmus (Mäkinen, 2016).

2.7.6. Warnings by government of some countries on the effects of maltitol

In the European Union and countries such as Australia, Canada, Norway, Mexico and New Zealand, maltitol carries a mandatory warning such as "Excessive consumption may have a laxative effect." In the United States, it is a generally recognized as safe (GRAS) substance, with a recommendation of a warning about its laxative potential when consumed at levels above 100 grams per day.

3. Conclusion

Sugar alcohols, also known as polyalcohols, alditols, glycitols, or polyhydric alcohols, are organic compounds, commonly derived from sugars, with one hydroxyl (–OH) group attached to every carbon atom. Sugar alcohols are widely used in the food industry as sweeteners and thickeners. In commercial foods and beverages, sugar alcohols are usually used in place of sucrose, often combined with artificial sweeteners of high-intensity, in order to address their low sweetness. Sugar alcohols are absorbed at average of 50% of the rate of sugars absorption, resulting in less effect on blood sugar level as measured by comparing their effects to sucrose with the use of the glycemic index. Polyols are present naturally in smaller amounts in fruits and in some kinds of mushrooms or vegetables, and, also, they are regulated as either generally recognized food additives or as safe. Sugar alcohols, as a group, have marginally less food energy than sucrose (sugar). Their flavor is also similar to that of sucrose, and they could be used to mask the unsavory and unpleasant aftertastes of some sweeteners of high intensity. Sugar alcohols are often absorbed incompletely into the blood stream from small intestine which usually results in a lesser change in blood glucose compared to sucrose.

This property makes them common sweeteners among diabetics and individuals on diets with low carbohydrate. Sorbitol is a sugar substitute, and is about 60% as sweet as sucrose (table sugar). Inositol has half the sweetness of sucrose, and is made naturally in humans from glucose. Glycerol is also widely used as a sweetener in the food industry and as a humectant in pharmaceutical formulations. As a sugar substitute, glycerol has approximately 27 kilocalories per teaspoon (sugar has 20) and is 60% as sweet as sucrose. Glycerol is a precursor for triacylglycerols synthesis and of phospholipids in the liver and adipose tissue. Xylitol is naturally occurring in small quantities in plums, pumpkin, strawberries, and cauliflower; and can be produced industrially from lignocellulosic biomass from which xylan is extracted. Humans and animals make trace amounts of xylitol during metabolism of carbohydrates. Arabitol (or arabinitol) is a sugar alcohol. Arabitol can be formed by reduction of either lyxose or arabinose. Lactitol is a sugar alcohol often used as a replacement bulk sweetener for low calorie foods with approximately 40% of the sweetness of sugar. It is used medically as a laxative. Maltitol's high sweetness allows it to be used without being mixed with other sweeteners. Like other sugar alcohols, foods containing sorbitol can cause gastrointestinal distress. Sorbitol can be used as laxative when taken as an enema or orally. Sorbitol works as laxative by drawing water into the large intestine, thereby stimulating bowel movements. Sorbitol has been noted to be safe for use by the elderly, although it is not recommended without the advice of a doctor. Hyperkalaemia treatment (elevated blood potassium) makes use of sorbitol and ion-exchange resin sodium polystyrene sulfonate (with the tradename Kayexalate). Inositol is effective in managing preterm babies who have or are at a risk of infant respiratory distress syndrome (RDS). Glycerol has very low toxicity when ingested. Xylitol has no known toxicity in humans. At high doses, other polyols including, xylitol, cause discomfort of gastrointestinal tract, including flatulence, diarrhea, and irritable bowel syndrome; some people have these adverse effects at lower doses. A patient with leukoencephalopathy and peripheral neuropathy has been identified as suffering from ribose-5-phosphate isomerase (RPI) deficiency, a defect in the PPP. In this disorder, highly elevated concentrations of the C5 polyols such as D-arabitol are found in body fluids. In addition, transaldolase deficiency, another defect in the PPP, has been diagnosed in a patient with mainly liver problems among others. This patient had increased concentrations of polyols, mainly D-arabitol. L-arabitol is found to be connected with Alzheimer's disease and the deficiency of ribose-5-phosphate isomerase, which is an inborn error of metabolism. Like other sugar alcohols, lactitol can cause cramping, diarrhea, and flatulence in some people who consume it. Maltitol has a laxative effect, resulting to diarrhea when comsumed above 90 g per day.

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