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The Fate of Aldose Reductase Inhibition and Sorbitol Dehydrogenase Activation

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Abstract

Diabetic complications are the unavoidable ailment in hyperglycaemic condition. The polyol pathway mediated adverse effects of hyperglycemia are responsible for development of severe health ailments. Aldose reductase and sorbitol dehydrogenase are the important cytosolic enzymes involved in polyol pathway. In diabetic state, owing to higher glucose flux generates bulk amount of intracellular sorbitol through the polyol pathway. The intracellular accumulation of sorbitol is proved to be deleterious to tissue microenvironment that leads to development of secondary complications of diabetes. The reduction of sorbitol level in the tissue is therapeutically important in the management of polyol mediated diabetic complications. A variety of structurally diverse Aldose Reductase Inhibitors (ARIs) have been developed for inhibiting the generation of sorbitol, some are in clinical practice but majority of the newly synthesized molecules failed in clinical trial studies and thus not approved by FDA. On the other hand, Sorbitol dehydrogenase, the second enzyme of polyol pathway has a role of metabolizing harmful sorbitol to fructose is least focused as a therapeutic target. In this review an alternative strategy is proposed for minimizing the tissue sorbitol level that may be useful for the management of diabetes and its related complications. This review will provide an overview of importance of sorbitol dehydrogenase activation over the aldose reductase inhibition. Furthermore, in future it may find applications in the design and development of activators of sorbitol dehydrogenase.

Keywords: Diabetic complication; Polyol pathway; Aldose reductase; Sorbitol dehydrogenase; ARI's

Introduction

Diabetes Mellitus (DM) is a complex metabolic syndrome characterised by elevation of blood glucose level beyond its glucose tolerance threshold. The condition arises as a result of defects in insulin secretion, action or a combination of both that results into long-lasting hyperglycemia [1]. World Health Organization (WHO report 2015) highlighted diabetes as the leading cause of mortality (1.6 million deaths in 2015) and ranking seventh position among the top ten causes of deaths in the world [2]. The incidence of diabetes is more in undeveloped and developing countries like India: a capital of diabetes and put a serious concern to the health care professionals [3]. The International Diabetes Federation (IDF 2016) reported 415 million people have diabetes and it may affect over 640 million people in 2040. A plethora of studies evidenced that the degree and duration of hyperglycemic state is the basis for development of secondary complications of diabetes [4]. The most inevitable complications of DM include both microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (cardiovascular disease) that affecting many organs of the body [5].

So far many attempts have been taken for mitigating the DM and its associated complications; but none of them demonstrated effective repercussion to treat DM completely. The currently available therapeutic drugs for diabetes mellitus includes glucose lowering agents like insulin, biguanides, sulphonylureas, glinides, thiazolidinediones, alpha-glucosidases inhibitors, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 agonists etc [6,7]. Moreover, tightly controlled diet and increased physical activities improves the blood glucose level considerably. But at present, even with the finest therapeutic prophylaxis available for the management of DM, it is practically impossible for a diabetic individual to keep up normal glycemia at all times throughout the life [8]. Therefore, novel, effective and safe strategies is needed to nullify the threatening effects of hyperglycemia. In this regards the research thrust continues across the world; in search of new agents and targets to develop long term effective antidiabetic drugs that eventually reduces the diabetes risks and its associated complications.

In this review we mainly focus the polyol pathway and its associated diabetes complications. Moreover, the structural details of polyols enzymes, its inhibitors and future therapeutic prospective is highlighted that have applications in the management of diabetes complications.

The polyol pathway

The polyol pathway is the alternative to the glycolysis and pentose phosphate pathways which contributes very small portion of carbohydrate metabolism. The schematic showing in Figure 1 illustrates the complete polyol pathway that converting intracellular glucose into fructose via sorbitol within the cell. Under the normal glycemic condition, the polyol enzymes function as general housekeeping enzymes, but in case of diabetic state these enzymes activated exponentially that result into increased glucose flux to this

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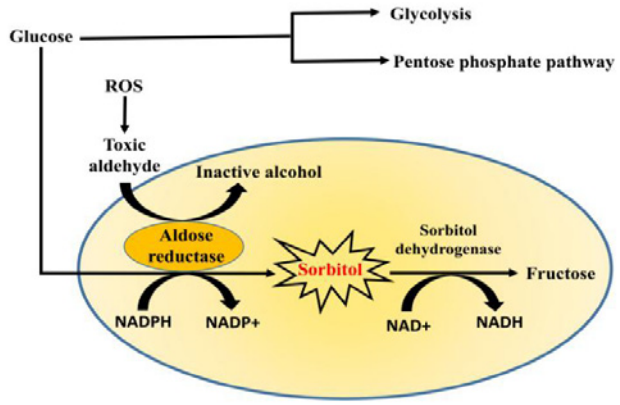


Figure 1: Schematic representation of polyol pathway showing the intracellular conversion of glucose into fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase also involved in the reduction of toxic aldehyde generated by Reactive Oxygen Species (ROS) to less toxic inactive alcohol.

pathway [9].

Polyol pathway is a two steps reaction pathway aggravated in response to hyperglycemic condition. It is accomplished through a series of two different cytoplasmic enzymes [4]. The first enzyme in this pathway is Aldose Reductase (AR) that reduces glucose into sorbitol by using NADPH as cofactor. The second enzyme is NAD^+ dependant Sorbitol Dehydrogenase (SDH) that converts sorbitol into fructose[8]. Under the normal glucose homeostasis this pathway metabolise only 3% of glucose whereas in the diabetic state it crossed over 30%. The overwhelming body of literature described that hyperactivity of polyol pathway is an important and plausible contributor in the diabetic complications. By considering its potent involvement in the diabetic complications; inhibition or the pathway deviation is the foremost alternative solution in the management of diabetes and its related complications.

Aldose Reductase (AR)

The enzyme aldose reductase (AR; EC 1.1.1.21) belongs to the aldo-keto reductase superfamily. It is a small monomeric protein composed of 315 amino acid units with a molecular weight of ~35,900 Daltons [10]. Crystallographic data revealed that this enzyme molecule contains (β/α) structural framework comprising eight α helices circumjacent to the eight parallel β sheets; making a large hydrophobic active site at the c terminal ends of β barrel (Figure 2a) [10-12]. The active site is approximately 10.84 A° deep forming a large binding cleft to accommodate both prosthetic group and substrates (or inhibitors). Structural analysis of active site portrayed that; the tryptophan amino acid located at 111 positions in the polypeptide chain divide catalytic site into the two major sub pockets [13]. The pocket first is termed as anion binding pocket because it has intrinsic binding affinity towards the anionic heads of ligands. The anion binding pocket is composed of Y48, L77, H110, SN (159-160), Q183, Y209 and I260 residues that enable binding site for both the substrate and NADPH [11,13-15]. The cofactor NADPH resides at the bottom of the active site in an extended confirmation, with the nicotinamide moiety of the NADPH forming a part of active site[12]. On the other hand the second pocket (Specificity Pocket) is formed by the residues PTGF (112-115), F122, A299, L300, C303 and YPFHE (309-313) including W111; an amino acid that split the blinding cleft into two sub-pockets by forming separating wall [11,13-15]. Various studies demonstrated that upon binding of specific ligand in the active site of AR induces structural modulation in the active site and open up the specificity pocket [16,17]. The knowledge of induced fit adaptation of AR by ligands binding at specificity pocket plays the important role in the designing of structure based AR inhibitors [14].

The commencement of enzymatic reaction takes place once the substrate is attached in the binding cleft of holoenzyme. The reaction is carried out by the donation of hydride ion from carbon C4 of NADPH to the carbonyl carbon of aldehyde resulting into negatively charged intermediate molecules [18]. These intermediate molecules get protonated from neighbouring acidic amino acid residue of the enzymes and forms corresponding reaction products [18,19]. The catalytic process of AR follows the ordered bi-bi mechanism with cofactor (NADPH) binding first then binding of aldehyde followed by release of alcohol and at the last oxidised $NADP^+$ [20].

Sorbitol dehydrogenase (SDH)

The enzyme sorbitol dehydrogenase (SDH, EC 1.1.1.14) is the translational product of a gene SORD, which is located on chromosome 15 in humans. It is the member of superfamily of medium chain reductase/dehydrogenase and requires NAD^+ as a cofactor for enzymatic activity [21]. The X-ray crystallographic studies of human SDH showed that, it consist of four identical subunits with a 354-356 amino acid residues having a molecular weight of 38,000–40,000 Daltons of each monomer [22]. The mammalian SDH contains a deep cleft which is formed between the two β barrel domains in each subunit. The active site is located at the bottom of the cleft facing the surface of the tetramer. The tetrameric SDH facilitates binding of NAD^+ in the grooves of all four subunits identically and also one catalytic Zinc (Zn) atom per subunit of the enzyme (Figure 2b) [22,23]. The catalytic action of SDH also follows the ordered bi-bi mechanism, wherein, the binding of cofactor (NAD^+) subsequently leads to binding of substrates followed by removal of products and finally the cofactor from the enzyme [21]. The enzymatic reaction of SDH involves oxidation of C2 carbon of the sorbitol by the coenzyme

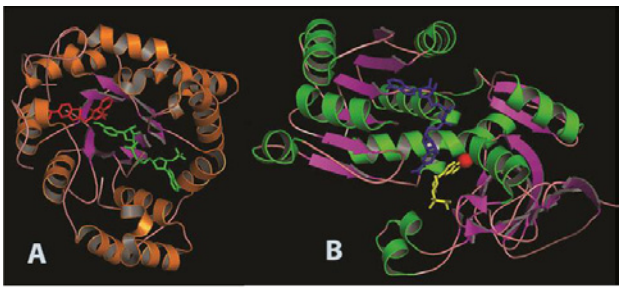


Figure 2: A) A structure of human Aldose Reductase (AR) showing the β/α barrel motif with a bound molecule of NADPH and AR inhibitors zopalrestat. The active site is located centrally surrounded by eight β barrel (magenta) sheets and eight α helices (orange). The nicotinamaide moiety (Green stick) forming the parts of active site. The zopalrestat (red stick) bounded in the binding cleft of AR holoenzyme. **B)** A monomeric structure of tetrameric human Sorbitol Dehydrogenase (SDH) with bound NAD, inhibitor and a Zink (Zn) atom. The active site is located between the two β barrel (magenta) domains in the bottom of cleft facing towards the surface of tetramer. The structure depicted in this Figure 2 A) is the bound cofactors: NAD^+ (blue sticks), SDH inhibitor (Yellow stick) and the catalytic zinc atom (red sphere).

NAD^+ leading to formation of keto group and subsequently conversion into fructose and NAD(H) [23].

Pathophysiological consequences of polyol pathway

The polyol pathway was first identified by Hers (1956) in the seminal vesicles [24]. Soon after its discovery, van Heyningern (1959) observed excess amount of sorbitol accumulated in lens fiber cell of diabetic rat [25,26]. On the contrary, there is no physiologically significant quantity of detectable sorbitol present in the normal cells. The accumulation of high level of polyol is due to the increased AR activity [25]. This observation suggests that, sorbitol is the key player in the development of diabetic complications. Studies carried out by Varma et al. found similar observations that support van Heyningen investigations/conclusions. Furthermore, they experimentally demonstrated, inhibition of AR by flavonoids prevented diabetic cataract and improved progression of disease [27].

The vast body of literatures explains about the tissue damaging effect of sorbitol. The major cells and tissue affected by polyols are retina, lens, kidney, nerve and heart [28]. The pathomechanism of tissue damage by sorbitol is because of the increased osmotic stress that leads to cell membrane rupture and leakage of cellular contents. Moreover the cofactor; NADPH and NAD^+ of AR and SDH respectively expended during the enzymatic reaction that bring about its inadequacy needed to keep the redox homeostasis [11,29,30]. In certain tissues, the activity of glutathione reductase (an anti-oxidative enzymes) get paralysed as a result of excess utilization of NADPH by AR and creates the scarcity of NADPH for glutathione reactivity [25,31]. This probably induces intracellular oxidative stress and consequently leads to cellular damage. Besides this, hyperglycemia activates certain cascade of reactions like superoxide production, Advanaced Glycation Endproducts (AGEs), protein kinase C pathway, hexosamine pathway flux that will further add some hurdle to the cellular microenvironment [30,32].

For example, in diabetic retinopathy a microvascular complications affecting the retinal capillary mural cells in a patients suffering from diabetes mellitus. A plenty of literatures describing polyol pathway is the one of the proposed mechanism of diabetic retinopathy [33]. Studies cited that sugar alcohol accumulation associated with destruction of microvasculature of the retina, swelling of the blood vessels and leakage of cellular fluid, growing of new vessels, thickening of basement membranes and loss of pericytes that ultimately lead to the detachment of the retina [34,35]. While in case of diabetic cataract, owing to AR activation sorbitol accumulates in the lens epithelial cells. The hydrophilic nature of sorbitol making it impermeable for passing through the hydrophobic cell membrane and thus creates a osmotic stress that leads to cellular damage and ultimately the diabetic cataract [36,37]. A lot of research studies accumulating in scientific community describing the pathophysiological role of AR and its associated macro and micro vascular complications. Despite the remarkable research in this area, there is no pertinent treatment modality exists for the management of diabetic associated complications and needs more attention in this field.

Structural requirements of aldose reductase inhibitors (ARI): Efficacy and Inadequacy

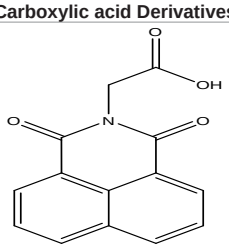
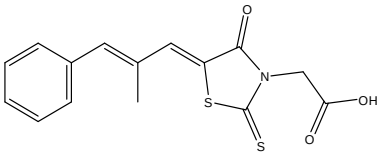
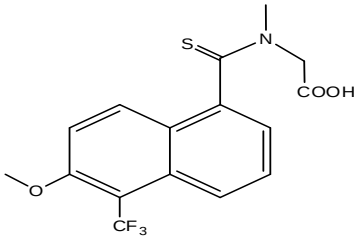
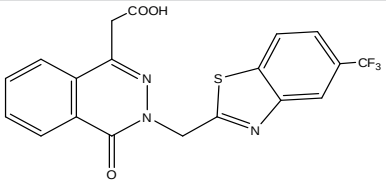
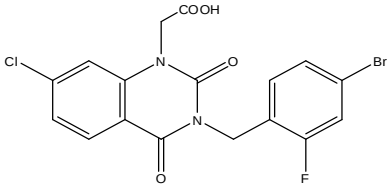
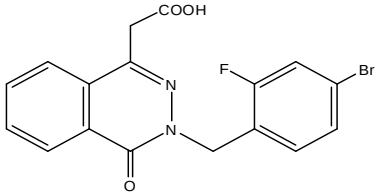
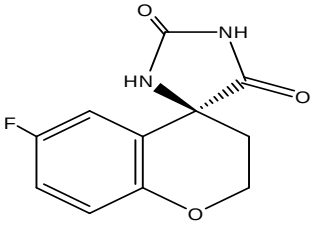
The significance of AR in various diabetic pathologies leads to developments of variety of Aldose Reductase Inhibitors (ARIs). Initial studies on AR inhibition reveals that at least one carboxylic group along with a aliphatic moiety either in ring form or in a chain must be present in the structure for the effective AR inhibitory activity [38]. The experimental study carried out by Jedziniak et. al. (1971) proved that Tetramethylene Glutaric acid (TMG); a dicarboxylic acid demonstrated 68% of lens aldose reductase inhibition [38]. Since then, a range of structurally diverse ARI's (Table 1) were developed to date and still research continues in this field for design and development of potential AR inhibitors. Alrestin is a class of compound developed in 1973 for the treatment of diabetic neuropathy. It was the first ARI undergone for human clinical trials studies [39].

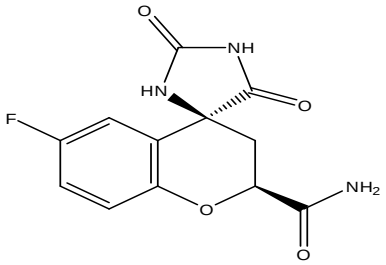
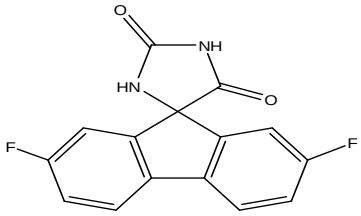
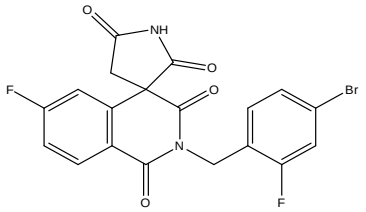
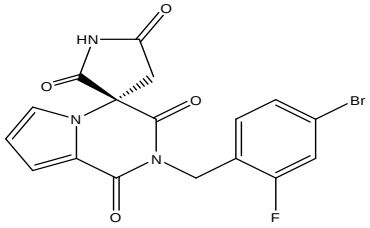
Based on the structural and functional group present, the ARI's are categorised into two major classes as acetic acids derivatives and cyclic imide derivatives. Recently the polyphenols are the new class of inhibitors included in this category [40,41]. The carboxylic acid derivatives are the most important and largest class of ARI and possess acetic acid as a structural backbone. The major inhibitors developed in this category include Epalrestat, Tolrestat, Zenarestat, Ponalrestat, Fidarestat, Zopalrestat etc. Whereas the second class of ARI is the spirohydantoin derivatives possesses cyclic imide structure as a backbone. This class of ARIs involves Sorbinil, Imirestat, Minalrestat Renirestat etc [40,42]. Only drug approved is the Eplarestat that is marketed in some Asian countries like Japan, China and India [40]. Besides the potential in vitro AR inhibitory activity, most of the ARIs were failed in clinical trials studies and thus not approved by FDA (Table 1).

The reviews of literatures suggest that the efficacy of most of the AR Inhibitors (ARIs) has been disappointing in clinical trials [43]. The extensive body of literature exist that emphasizing on the discrepant results of ARIs in clinical vs. preclinical studies [44]. Major factors associated with failure of these ARIs are the poor pharmacokinetic properties, lack of efficacy or they exerted adverse side effects [8,44-46]. The x ray crystallographic studies of AR-inhibitors complex revealed that ARIs (both carboxylic acid and cyclic imide type) occupies in the same binding cleft of anionic pocket of AR [47]. Indeed the cyclic imide derivatives are more potent in inhibiting the aldose reductase than carboxylic acid ARI *in vivo*. The subtle difference in potency between these two classes of ARIs is due to the difference between their pka values [48]. The carboxylic acid containing inhibitors has low pka values so causes ionization at physiological pH and therefore difficult to pass through cell membrane easily. On the other hand cyclic imide type of ARI has high pka values thus it fairly ionized at physiological pH and therefore easily diffuse through cell membrane and reach to target proteins [45,47,48].

The other side of investigations assumed that selectivity of ARIs is an important parameter to inhibit the target enzymes potentially. A good quality of inhibitors must possess highest selectivity that interacts only with the target enzyme and not with the other biomolecules [15]. Aldehyde reductase (EC 1.1.1.2) a member of aldo keto reductase suferfamily shares 65% sequence identity with aldose reductase[49]. The structural and functional similarities between the active site of these two enzymes making it a good competitor for binding of ARIs in the binding pocket of both the enzymes as these enzymes catalyzes NADPH dependant reduction of molecules [49,50]. Sorbinil an inhibitor specially designed for inhibition of aldose reductase

Table 1: Status of clinical trials involving ARI.

Sr. No	ARIs (Carboxylic acid Derivatives)	Originator	Clinical Trial status	Risk/ Side Effects/ Complications	Remark
1.	 **Alrestatin**	Ayerst Pharmaceuticals	Failed in early stage of clinical trial	First ARI undergone for Clinical trials. Development was terminated due to low quality trials and hepatotoxicity.	Discontinued in Late 1980
2.	 **Epalrestat**	Ono Pharmaceuticals	Approved in Japan, China and India	Non-competitive reversible inhibitors	Marketed
3.	 **Tolrestat**	Wyeth-Ayerst's	Failed In Phase III clinical trial	Severe liver toxicity and death	Discontinued in 1997
4.	 **Zopalrestat**	Pfizer	Failed in Phase III clinical trial	Withdrawn for Neuropathy Non competative	Discontinued in 1999
5.	 **Zenarestat**	Fujisawa Pharmaceuticals	Failed In Phase III clinical trial	Renal toxicity	Discontinued in 2001
6.	 **Ponalrestat**	Zeneca	Failed in Phase III clinical trial	Withdrawn because of Lack of Efficacy	Discontinued in 2002
ARIs Cyclic Imide Derivatives (Spirohydantoins)					
7.	 **Sorbinil**	Pfizer	Phase III	Hypersensitivity reaction	Discontinued in 1985

8.	 **Fidarestat**	Sanwa Kagaku Kenkyusho Co., Ltd	Phase III clinical trial	Adverse events occurred in approximately 5% of patients in both treatment groups	2006 Discontinued in 2006 - Phase-II/III for Diabetic neuropathies in Europe & USA
9.	 **Imirestat**	Alcon	Phase III clinical trial	Toxicity	Discontinued in 2002
10.	 **Minalrestat**	Wyeth	Phase III clinical trial	Liver Toxicity	Discontinued in 2002
11.	 **Ranirestat**	Dainippon Sumitomo Pharma	Phase III Clinical Trial	Still in Clinical Phase III in Japan, no adversities reported.	Discontinued in Canada, Belgium, Estonia, Hungary, India, USA, United Kingdom

inhibits the activity of aldehyde reductase with similar potency [16]. Presumably the aldehyde reductase has detoxification role and serves to eliminate the reactive aldehyde and dicarbonyls compounds in most of the tissue [51]. The unnecessarily inhibition of aldehyde reductse activity by ARI affecting the detoxification functions of this enzyme and thus creates a severe side effects. So designing a novel and highly specific enzyme inhibitors is a major task in ARI preparations.

A recent effort has been expended to discover the specificity and selectivity of aldose reductase over the aldehyde reductase enzyme. The data from various literatures suggest that the c terminal loop of adehyde reductase determine the selectivity and specificity of substrate and/or inhibitors [52]. So understanding the difference between the catalytic mechanism and the residues involved in the catalysis of aldose reductase and aldehyde reductase are most important aspect to design enzyme inhibitors [8].

Toxicity of ARIs is another ambiguity for their clinical use. As after the long term use it showed the adverse effects. Sorbinil demonstrating potent inhibitory activity in vitro and in animal model were withdrawn because it causes hypersensitivity reactions [53]. In similar way tolarestat and zenarestat were also withdrawn due to the liver and renal toxicity respectively [54]. So designing an effective inhibitors one must keep in the mind that, it must possess a higher activity with least toxicity to human.

Increased sorbitol dehydrogenase activity: a novel prospective

As the metabolic activity of sorbitol dehydrogenase in polyol pathway is slower than the AR that leads to generations of harmful metabolite sorbitol [3]. The vast body of literatures described that the accumulation of polyols is detrimental to tissue; since generation of sorbitol creates the osmotic and oxidative stress to cellular microenvironment. Most of the attempts have been done on targeting aldose reductase by designing variety of AR inhibitors. *In vitro* and animal model studies were successful by using these ARIs but in the human use it is still a major challenge. On the other hand, the second enzyme of this pathway has a role of metabolising generated harmful sorbitol to fructose is least focused. The unfavourable effects of sorbitol accumulation may be reduced either by inhibiting the synthesis of excess sorbitol by ARI or by metabolically converting harmful sorbitol into fructose through SDH activation [55]. The agent who increase the SDH reactivity have been playing beneficial role in minimizing the sorbitol. Lindstad et al. (1994) demonstrated that haloalcohol and detergent activate the SDH action. The proposed mechanism of activation of SDH is the formation of enzyme-NADH-

inhibitor ternary complexes, which dissociate more rapidly than the usual rate-determining enzyme-NADH dissociation [56]. The other study revealed that conserved lysine residue (K 294) involved in the cofactor binding have been shown to play role in SDH activation [55].

A discourse on activating sorbitol dehydrogenase as a therapeutic strategy is a debatable issue in the current state of the art, since some group of researcher thought that fructose generated through polyol pathway will enter into glycation [57]. The study carried out by Jeffery et al. (1983) documented the bypass routes of glucose flux and unravels the enzymatic and intermolecular relationship in glucose metabolism [58]. The scheme represented in the paper showed that the polyol pathway further extended by the two additional enzyme hexokinase and fructokinase that metabolize fructose into fructose-6-phosphate and fructose-1-phosphate respectively. These intermediate products then tend to enter into either glycolysis or lipogenesis [58]. In the view of this hypothesis; finding of SDH activators or raise the metabolic activity of it is helpful in reducing the negative effects of sorbitol [55].

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