Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 9s, https://carcinogenesis.com/

Sagacious Aldose Reductase Inhibition for Treatment of Metabolic Disorders

Deepshikha Patel, Shom Prakash Kushwaha*, Syed Misbahul Hasan

Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh, 226026, India,

E-mail: shompk@iul.ac.in , E-mail: drxdeepshikhapatel@gmail.com, E-mail: deanphar@iul.ac.in

ABSTRACT

Aldose reductase inhibitors (ARIs) belong to a group of medications designed to target to manage metabolic disorders, including diabetic neuropathy, diabetic cardiomyopathy, and inflammatory complications. These inhibitors block the polyol pathway, a metabolic route responsible for glucose breakdown, which, when over activated, contributes to diabetes related complications. The most prevalent chronic endocrine disease is diabetes mellitus, whose incidence is steadily increasing worldwide. The health is significantly impacted by it, and it is currently among the leading causes of death. Aldose reductase (AR), a key player in the development of problems from diabetes, has been connected in numerous studies to the polyol pathway. One promising therapeutic approach involves thiazolidinedione derivatives, which feature a heterocyclic ring system with a pharmacophore scaffold widely recognized in medicinal chemistry. Initially developed as antidiabetic agents, these compounds act as specific ligands of Peroxisome Proliferator-Activated Receptors (PPARs). Extensive research has uncovered their diverse biological activities and broad therapeutic potential.

Keywords: *Thiazolidinedione, Aldose reductase, Inhibitors, Pharmacophore, Metabolic disorders.*

How to Cite: Deepshikha Patel, Shom Prakash Kushwaha*, Syed Misbahul Hasan, (2025) Sagacious Aldose Reductase Inhibition for Treatment of Metabolic Disorders, *Journal of Carcinogenesis*, *Vol.24, No.9s*, 410-418.

1. INTRODUCTION

A family of drugs known as ARIs, or aldose reductase inhibitors, are designed to prevent the buildup of fructose and sorbitol in tissues by blocking the enzyme aldose reductase. This approach lowers the chance of developing diabetes sequelae, including neuropathy, nephropathy, and retinopathy. These inhibitors function by preventing aldose reductase, a crucial polyol cycle enzyme, from becoming abnormally active during hyperglycemia. ARIs are therefore regarded as a potentially effective treatment strategy for controlling or possibly curing diabetic problems, especially diabetic neuropathy, retinopathy, and nephropathy.[1] Diabetes mellitus, one of the most prevalent endocrine metabolic diseases, has a substantial effect on patients' health, life expectancy, and quality of life in addition to the healthcare system. [2] The disease, which results in insufficient insulin synthesis, is often caused by degenerative changes in pancreatic β cells. Chronic hyperglycemia brought on by impaired insulin production in type 2 diabetes results in long-lasting metabolic abnormalities. [3] As stated by the WHO, globally, diabetes ranks as the tenth most common cause of death, and its prevalence is alarmingly increasing. Type 2 diabetes is one of the four main forms of the disease., affects almost 90% of adults, highlighting the critical need for effective treatment strategies. As per WHO reports, diabetes has become the 9th leading cause of millions of deaths worldwide. [4] There is mounting proof that the biology and consequences of diabetes are significantly influenced by oxidative stress. Cell damage and the advancement of disease are caused by an excess of reactive oxygen species (ROS) and a malfunction in the body's natural antioxidant defense system. This emphasizes the significance of treatments that combat oxidative stress in addition to controlling blood glucose levels.

One promising class of therapeutic agents is thiazolidinedione; a group of heterocyclic compounds originally developed as antidiabetic agents and peroxisome proliferator-activated receptor (PPAR) ligands. As diabetes is becoming more prevalent, a great deal of research is being done on its effects, with an emphasis on how crucial it is to efficiently control blood sugar levels to prevent the disease from worsening. Vascular injury, myo-inositol depletion, polyol route activation, regarding glycation that is not enzymatic, are the fundamental processes of neuropathy caused by diabetes, and they all lead to nerve deterioration. Its global prevalence is rising by 10.2%, thus it will affect 578 million by 2030 and 700 million by 2045. [5] Apart from that, there is increasing evidence that confirms the crucial free radicals' part in diabetes mellitus etiology [6] and the problems that come with it. Its pathogenesis is also associated with oxidative stress, which is brought on by a reduction in the body's enzymatic and non-enzymatic antioxidant system as well as an excess of reactive oxygen species (ROS). Dyslipidemia, the primary risk factor for cardiovascular illnesses, is frequently linked to diabetes. Therefore, diabetic individuals often have higher blood triglyceride and cholesterol levels.[7]

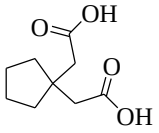
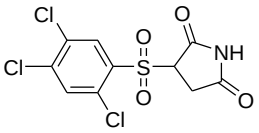
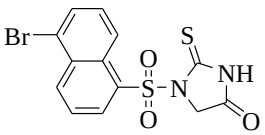
Assessments of insulin levels, glycated hemoglobin (HbA1c), insulin sensitivity, glucose tolerance, and pancreatic β-cell activity are now among the many advanced diabetes diagnostic techniques. The Federation of International Diabetes Federation (IDF) estimates that 537 million people globally have 2021 diabetes. It has been estimated that the number of cases will increase dramatically, reaching 643 million by 2030 and 783 million by 2045[8] and alter the quality of life. Diabetes's promote the formation of free radicals and their development beyond the capacity of the body's antioxidant defenses to scavenge them, which leads to both macrovascular and microvascular dysfunction. [9] Along with abnormalities associated with the aforementioned parameters, diabetic patients frequently develop diabetic cardiomyopathy, diabetic nephropathy, and diabetic retinopathy (DN). Damage to the nerves that begins in the toes and progresses to other parts of the body is called neuropathy.[10] That usually starts in the toes and progressively moves throughout the body. The four main categories of DN are focal, proximal, autonomic, and peripheral neuropathy. Each variety has Among the riskiest side effects of diabetes is diabetic neuropathy (DN), which causes nerve loss unique symptoms, such as cardiovascular problems, digestive problems, heart difficulties, stomach troubles, and numbness.[11] Including increased nonenzymatic glycation, polyol pathway activation, and myoinositol depletion, are all important factors in the development of diabetic nerve damage.[12]

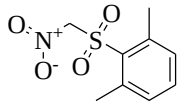
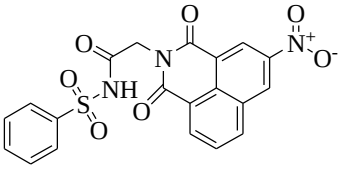
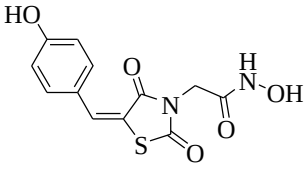
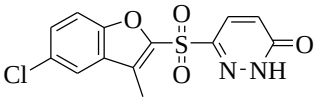
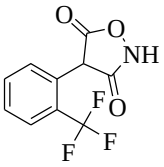
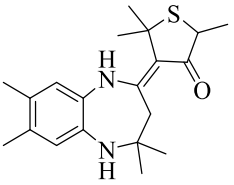
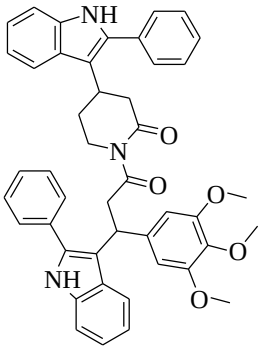
Current diabetes treatments primarily rely on oral hypoglycemic agents, many of which have adverse side effects. This has driven interest in natural, plant-derived therapies with antioxidant properties as potential alternatives. Since ancient times, herbal remedies have played a significant role in traditional healthcare, and their potential to offer safe and effective treatments for diabetes and its related consequences is starting to be recognized by modern medicine. [13]

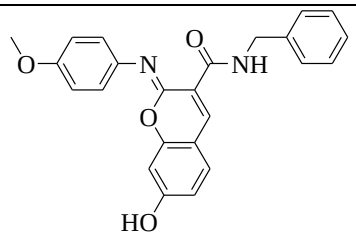
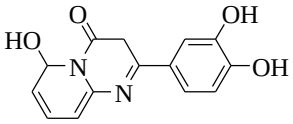
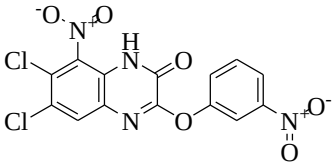
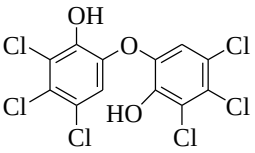
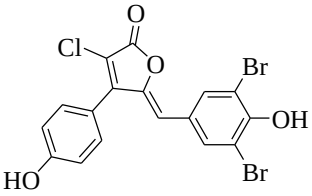
2. ALDOSE REDUCTASE

Aldose reductase (AR) is an enzyme that belongs to the aldo-keto reductase superfamily, which is a broader family, is essential to the polyol pathway that facilitates the digestion of glucose. The molecular weight of this cytoplasmic enzyme is 36 kDa., is structurally similar to triose phosphate isomerase, with 10 α-helical segments encircling an inner β-pleated sheet barrel. It is composed of 315 amino acids and is devoid of structural carbohydrates, lipids, and metal ions. The top of the β/α barrel is where the NADPH cofactor is located., the pyrophosphate group is situated across the barrel's lip, and the nicotinamide ring extends downward through the middle. The active region of the enzyme is contained in this barrel, along with hydrophobic residues, A "anion well" that contains the nicotinamide ring of NADPH or NADP+, and significant residues like Tyr48 and His110. Aldose reductase is mainly responsible for catalyzing the first step in the polyol pathway, which is the conversion of glucose to sorbitol. [14-15] years old Using NADPH, the enzyme transforms the C1 aldehyde group in glucose into an alcohol in this step. Concurrently transporting a proton from Tyr48 via His110. A slow conformational shift can cause oxidized NADP+ to dissociate[16] after the reaction's conclusion, when the newly formed alcohol is released. Although several ARIs have been developed (Table 1), only a limited number of small molecule AR inhibitors (ARIs) are presently undergoing clinical studies. Among these, phenolic derivatives, cyclic imides, and acetic acid derivatives are notable structural groups.[17]

Table1. Derivatives of Aldose Reductase Inhibitors

Derivatives	Chemical Structure	Ref.
Carboxylic acid derivative		[18]
Hydantoin		[19]
		[20]

Nitromethane		[21]
Sulfonamidederivatives		[22]
Thiazolidinedione		[23]
Benzofuran		[24]
Isoxazolidinedione		[25]
Benzodiazepine		[26]
Piplartine		[27]

Carboxamides		[28]
Pyridopyrimidinone		[29]
Quinaxolinone		[30]
Diphenylether		[31]
Ascidianbutenolide		[32]

The Pathway of Aldose Reductase Inhibitors

The polyol pathway's part in problems from diabetes. The polyol route is a reversible metabolic process that uses enzymes to convert glucose to sorbitol, which is then transformed into fructose.

Two essential enzymes primarily regulate this pathway: Aldose Reductase (AR)

This enzyme aids in the NADPH is used as a cofactor in the conversion of glucose to sorbitol. SDH, or sorbitol dehydrogenase: This enzyme uses NAD^+ as a cofactor to help oxidize sorbitol into fructose. In physiological circumstances, cellular glucose undergoes predominant metabolism via glycolysis and the Krebs cycle, yielding energy and essential cellular components. Osmotic stress is caused by accumulated sorbitol, whereas oxidative stress is exacerbated by disturbances the ratio of NADPH to $NADP^+$ and NAD^+ depletion. It is evident from This means that several metabolic parameters can be altered by the activation of AR in the polyol pathway.[33-34]

Aldose reductase inhibitor (ARIs) for Management of Diabetes Mellitus

Aldose reductase inhibitors (ARIs) function by competitively inhibiting aldose reductase activity. Key points about the pathway of an aldose reductase inhibitor: Target enzyme: Aldose reductase, Metabolic pathway affected: Polyol pathway, Mechanism of action: By inhibiting aldose reductase, the inhibitor prevents the sorbitol conversion from glucose. Normal glucose metabolism: In typical circumstances, the glycolysis pathway, It serves as the primary source of energy production, metabolizes the bulk of glucose.

High glucose and polyol pathway activation:

Sorbitolaccumulation and cell damage: The buildup of sorbitol inside cells disrupts osmotic balance, causing cell swelling and damage, especially in tissues with low membrane.

Role of aldose reductase inhibitor: By blocking aldose reductase, aldose reductase inhibitors (ARIs) prevent glucose from converting to sorbitol, reducing the harmful effects of polyol pathway activation and permeability to sorbitol.

Clinical applications: The primary purpose of aldose reductase inhibitor research is to treat diabetic problems, where Retinopathy, neuropathy, and nephropathy rely on the polyol pathway being activated. The current theory regarding the pathway's involvement.[35]

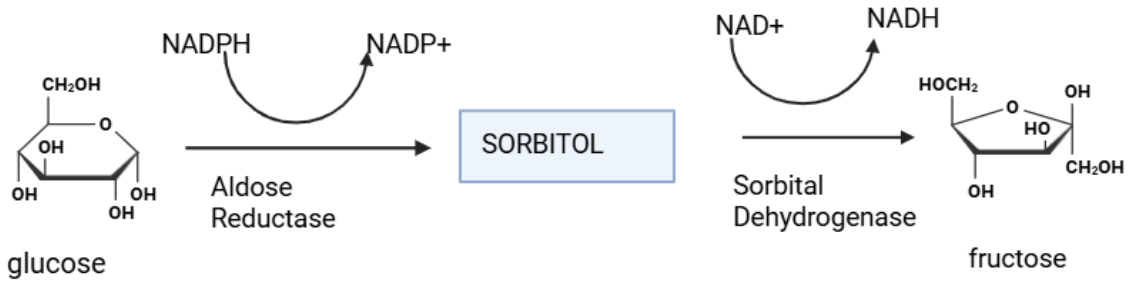


Figure 1. Aldose reductase catalyzes the NADPH

Normally, the primary mechanism that converts glucose into ATP and energy is glycolysis. However, different metabolic pathways are triggered to deal with the excess when glucose levels are too high. The glycation, alpha-ketoaldehyde, and sorbitol (polyol) pathways. [36] Sorbitol dehydrogenase transforms sorbitol into fructose in the second step. adding a hydrogen atom to NAD+, with the result being NADH. [37] Reversing this response is feasible. The sorbitol pathway not only helps in glucose metabolism but also influences, NADPH and SNAD+ are used to maintain the redox balance, which are critical for cellular homeostasis (Figure 1). However, oxidative damage and osmotic imbalance brought on by excessive activation of this system under hyperglycemic settings lead to diabetic complications.

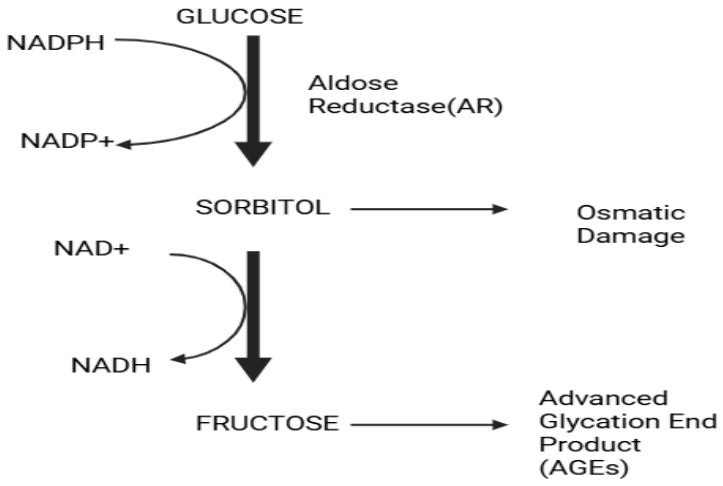


Figure 2. The Polyol Pathway

Hyperglycemia has been connected in numerous studies to the genesis of microvascular sequelae of diabetes, such as retinopathy, nephropathy, neuropathy, and cognitive disorders.[38]

Aldose reductase inhibitors:
A Possible Target for Diabetic Management Complications The polyol pathway (Figure 2) is closely linked to the pathophysiology of diabetics because sorbitol builds up intracellularly as a result of elevated aldose reductase (AR) activity. Due to its high hydrophilia and limited diffusion across cell membranes, sorbitol builds up and causes osmotic stress, which can lead to diseases such diabetic retinopathy, neuropathy, and nephropathy.[39] Aldose reductase inhibitor (ARIs) offer a promising therapeutic approach by blocking AR activity , thereby: Reducing sorbitol accumulation, alleviating osmotic stress. Preventing oxidative damage caused by excessive polyol pathway activation. Mitigating diabetic complications by preserving cellular redox balance.

Physiological Significance
The majority of diabetic tissues contain the cytosolic enzyme AR, which has a broad substrate specificity. Many diabetic tissues include AR, an enzyme with broad substrate selectivity that is cytosolic. Its main job is to catalyze the conversion

of glucose to sorbitol. [40-41]

Physiological Roles of Aldose reductase: Osmoregulation in the Kidneys
Sorbitol, a biological osmolyte, helps balance extracellular sodium chloride andfluctuatesin response to urine osmolality, suggesting AR's osmoregulatory role in renal homeostasis.

Energy Source for Sperm Cells: The polyol route in seminal vesicles transforms glucose into fructose, which powers sperm movement.

Neurotransmitter and Hormone Metabolism: AR, along with aldehyde reductase, facilitates the reduction of aldehydes producedduring serotonin and catecholamine metabolism. It also aids in the breakdown of is corticosteroids, intermediates in corticosteroid hormone catabolism.

Lipid Peroxidation and Glycation: AR possesses reductase activity for isocaproaldehyde, a byproduct of the metabolism of cholesterol, and 17α-hydroxyprogesterone. It aids in cellular detoxification by lowering acrolein, a carcinogenic consequence of lipid peroxidation, and 3-deoxyglucosone, a non-enzymatic glycation intermediate.

Potential Role in Detoxification: AR may serve in a variety of tissues as an extra-hepatic detoxifying enzyme. Studies on AR knockout models suggest that AR inhibition prevents the reduction of toxic aldehydes, potentially mitigating oxidative stress-related damage. These diverse functions highlight AR's critical role in cellular metabolism, while its involvement in diabetes related complications makes it a significant therapeutic target for intervention.

Active Sites of Aldose Reductase
The "specificity pocket" is a more flexible hydrophobic portion of the live AR website, in contrast, the " binding pocket of anion" is a more durable area. The active site residue Tyr48 contributes protons to a hydrogen bonding network, whereas His110 regulates substrate orientation. Aldose reductase's (AR) β/α barrel structure contains the enzyme's active site. Several key amino acid residues contribute to its catalytic function- 1) Tyr48: Serves as a donor of protons in a network of hydrogen bonds. 2) His110: Assists in positioning substrates inside the pocket of the active site. 3) Cys298: Controls inhibitor sensitivity and catalytic activity. 4) Lys79: Helps bind nucleotides. 5) There are two separate areas on the active site: a) An inflexible pocket for binding anion. b) A hydrophobic specificity pocket that is flexible.

NADPH cofactor
The conformation of the region between Gly-213 and Ser-226 changes depending on whether NADPH is present. The area is in a closed conformation when NADPH is present, and it is in an open conformation when it is not.

Role of AR Inhibition in Diabetes Management
Prolonged hyperglycemia in diabetes leads to both reversible and irreversible damage, affecting: Peripheral nerves and blood vessels, which can lead to problems such as cataracts, retinopathy, neuropathy, nephropathy, and vasculopathy. Elevated chances of blindness, amputations, heart attacks, strokes, kidney failure, and atherosclerosis. Since the polyol pathway, which breaks down excess glucose in hyperglycemic circumstances, depends on the enzyme aldose reductase (AR), inhibiting AR is still a promising technique to prevent diabetes complications.

Several natural compounds have been identified as AR inhibitors, including, Phytochemicals: Quercetin, kaempferol, ellagic acid. Other natural sources Vegetables and Fruits Indian gooseberry, orange, lemon, and spinach. Curry leaves, cumin seeds, fennel seeds, curry leaves, cinnamon are examples of herbs and spices. Other: Litchen and other Furthermore, synthesized forms of luteolin, a flavonoid mostly present in leaves.[42-43]

Synthetic Inhibitors of Aldose Reductase
Thiadiazine Derivatives: These derivatives have bulky hydrophobic groups at the C7 position.
Spirobenzopyran Derivatives: The potency and affinity of these compounds against the target enzyme, ARL2, have been produced and assessed.

Quinoxalinones: These compounds have been designed and synthesized to be potent and multifunctional. Additionally, Luteolin, a flavonoid predominantly found in leaves, and its synthetic derivatives have demonstrated potential as AR inhibitors.Other notable ARIs include Alrestatin, Benurestat, Epalrestat, Fidarestat, Imirestat, Lidorestat, Minalrestat, Ponalrestat, Ranirestat, and Risarestat.

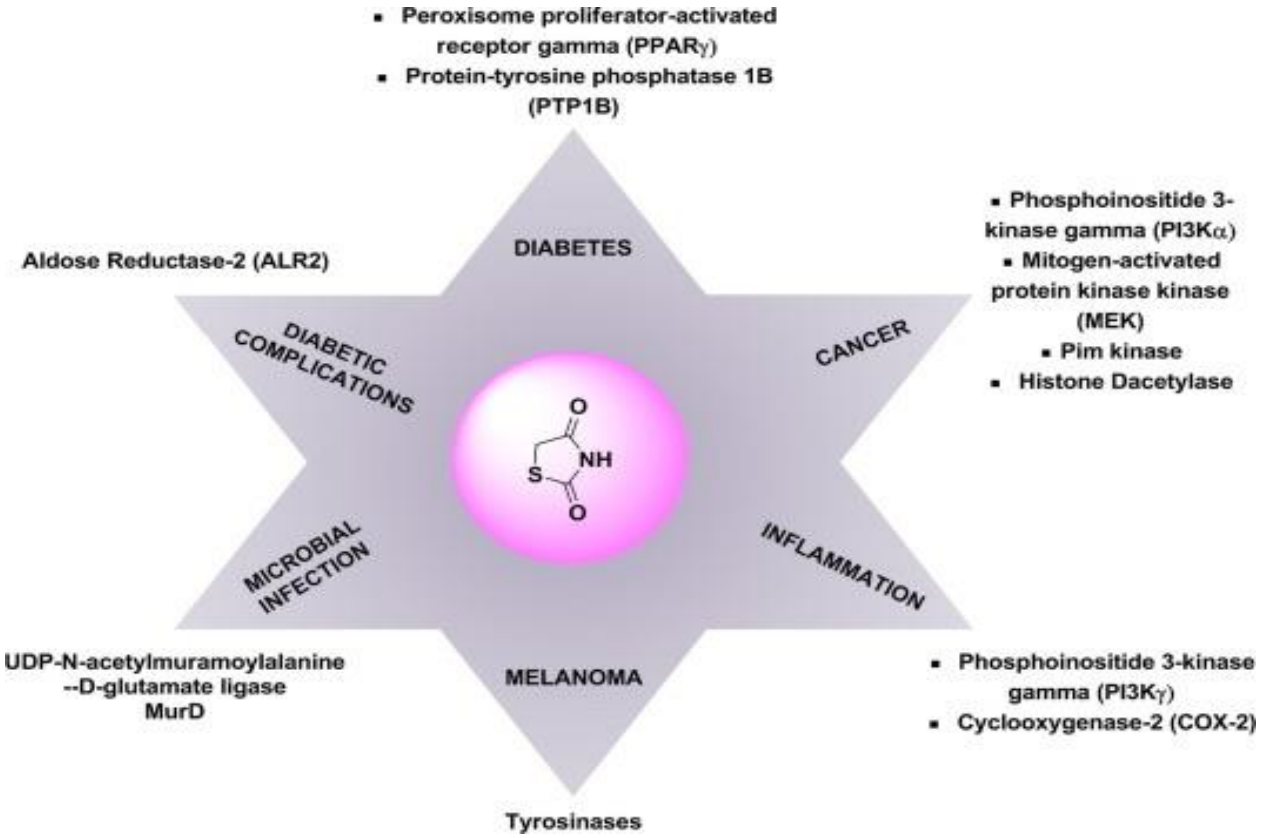


Figure 3. Pharmacological Spectrum of Thiazolidinedione

Molecular Properties of Thiazolidinediones

Antidiabetic compounds featuring a TZD scaffold have been synthesized and characterized. Global reactivity analysis and frontier molecular orbitals (FMOs) indicate that intramolecular charge transfer between the benzodioxole and thiazolidine-2,4-dione moieties takes place in two ways. Strong electrophilicity is highlighted by molecular electrostatic potential (MEP) mapping, which could improve binding to receptor protein's polar active sites. Molecular docking tests revealed high binding affinities against Peroxisome proliferator-activated receptor gamma (PPAR-γ) and α-amylase, suggesting that these kinases may have a regulatory role. Future prospective aldose reductase inhibitors are likely to focus on developing highly selective, potent compounds with improved pharmacokinetic profiles, potentially targeting (Figure. 3) not only diabetic complications like neuropathy but also other conditions related to oxidative stress, with a focus on natural product-derived molecules and utilizing advanced drug design strategies like computational modeling and molecular docking to identify novel scaffolds with better efficacy and safety profiles.[44-45]

Key Aspects of Future Aldose Reductase Inhibitors

1) Enhanced selectivity: Overcoming the current limitation of non-selective inhibition by designing molecules that specifically target aldose reductase without affecting other related enzymes, leading to potentially reduced side effects. 2) **Multifunctional activity:** Incorporating antioxidant or anti-inflammatory properties alongside aldose reductase inhibition to address the complex pathology of diabetic complications. 3) **Natural product-based leads:** Further exploration of plant extracts and compounds with known aldose reductase inhibitory activity, potentially leading to novel drug candidates with favorable safety profiles. 4) **Computational Drug Design:** Utilizing advanced molecular docking and simulation techniques to identify novel chemical scaffolds with high binding affinity to the aldose reductase enzyme. 5) **Potential therapeutic applications beyond diabetes:** The kidney, the eye and the tissues that comprise the myelin sheath-all of which are commonly linked to problems from diabetes-also contain the enzyme.[46] The polyol pathway may be responsible for as much as 33% of the total glucose consumption in certain tissues. Aldose reductase has long been thought to be the cause of diabetes problems involving multiple organs, and diabetics frequently have increased glucose concentrations. Even while some aldose reductase inhibitors, like Epalrestat, are commercially accessible in a number of countries, almost all of the therapeutic candidates that have been researched have failed. Alrestatin, Epalrestat, Exisulind, Imirestat, Zopolrestat, Tolrestat, Zenarestat, Caficrestat, Fidarestat, Govorestat, Ranirestat, Ponalrestat, Risarestat, and Sorbinil are further reductase inhibitors.[47] This included their synthetic routes, stereochemistry, suggested mechanism of action, mode of binding interactions, and SAR and QSAR studies.[48] Thiazolidinedione is a common heterocyclic pharmacophore with a wide range of pharmacological properties and a great deal of structural modification potential

Conversely, peripheral insulin resistance causes decreased insulin sensitivity to skeletal muscle, liver, and adipose tissues,

which leads to Type II diabetes, which is seen in most patients. [49] In vitro α-glucosidase inhibitory effects of thiazolidinedione derivatives were investigated.,Additionally, docking studies were conducted to examine the binding mode and important interactions with α-glucosidase's amino acid residues.[50] The main aim is to reduce insulin resistance [51] which will manage/treat type 2 diabetes. [52-56]

3. CONCLUSION

The use of safe and efficient aldose reductase inhibitors (ARIs) in the future may be essential in reducing the severity of inflammatory and multi-disease disorders including cancer and cardiovascular diseases, hence tackling important global health issues. These issues fall into two categories: Macrovascular and microvascular. More potent ARIs have been created as a result of improvements in our understanding of the structure of the enzyme. The characterization of a recently synthesized thiazolidinedione molecule showed that the benzodioxole and thiazolidine-2,4-dione regions undergo intramolecular charge transfer. Strong electrophilicity was revealed by molecular electrostatic potential (MEP) studies, which improved interactions with the polar active site of the receptor. PPAR-γ and α-amylase kinases could be efficiently regulated by these drugs, according to molecular docking simulations. When compared to acarbose and other inhibitors, compounds 5, 6, and 11 showed the highest efficacy in in vitro α-amylase inhibition experiments. Some aldose reductase inhibitors, including Epalrestat, are currently marketed in China, India, and Japan for the treatment of diabetes, while others, such Sorbinil and Ranirestat, have progressed to late-stage clinical studies. Recent pharmaceutical advancements have introduced water-soluble salts of ARIs, such as Zopolrestat, for improved treatment efficacy. ARIs have also shown promise as safe anti-inflammatory agents. The dearth of efficient therapeutics for problems associated with diabetes highlights the need for novel approaches to drug creation and improvements to current treatments. Aldose reductase (ALR2) is still a major therapeutic target for upcoming medication development because of the intricate pathophysiology of diabetes problems.

ACKNOWLEDGEMENTS

Authors sincerely thank Integral University, Lucknow, Uttar Pradesh, for providing the necessary facilities. The authors also express their sincere gratitude to the Dean, Research and Development, for support (Manuscript communication number: IU/R&D/2025-MCN0003659).

REFERENCES

[1] Chalk C, Benstead TJ, Moore F. Cochrane Database Syst Rev. 2007;(4):CD004572.
[2] World Health Organization. Diabetes – Fact Sheet. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes.
[3] Rorsman P, Ashcroft FM. Physiol Rev. 2018;98(1):117–214.
[4] Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi JA. J Epidemiol Glob Health. 2020;10(1):107–111.
[5] Saeedi P, Petersohn I, Salpea P, Malanda B, et al. Diabetes Res Clin Pract. 2019;157:107843.
[6] Mazumder PM, Rathinavelusamy P, Sasmal D. Asian Pac J Trop Dis. 2012;2(Suppl 2):S969–S979.
[7] Adlak P, Sagar R, Kori ML. Int J Pharm Sci Drug Res. 2022;14(5):631–638.
[8] Kumari P, Kohal R, Gupta BGD, Verma SK. Journal of Molecular Structure. 2024; 1318(1):139207.
[9] Adlak P, Sagar R, Kori ML. Int J Life Sci Pharma Res. 2023;13(1):87–97.
[10] Callaghan BC, Little AA, Feldman EL and Hughes RAC, Cochrane Database Syst. Rev. 2012 Jun 13;2012(6):CD007543.
[11] Grover M, Behl T, et al. Curr Drug Targets. 2020;21(8):806–818.
[12] Zychowska M, Rojewska E, Przewlocka B and Mika J. Pharmacol. Rep. 2013;65(6):1601-10.
[13] Modak M, Dixit P, Londhe J, Ghaskadbi S, Paul A, Devasagayam TPA. J Clin Biochem Nutr. 2007;40(3):163–173.
[14] Jez JM, Penning TM. Chem Biol Interact. 2001;130–132:499–525.
[15] Yabe-Nishimura C. Pharmacol Rev. 1998;50(1):21–33.
[16] Oates PJ. Curr Drug Targets. 2008;9(1):14–36.
[17] Ramunno A, Maccari R, Ottanà R, Vigorita MG. Eur J Med Chem. 2012;51:216–228.
[18] Mylari BL, Larson ER, Beyer TA, Zembrowski WJ, Aldinger CE, Dee MF, Siegel TW, Singleton DH. J. Med. Chem. 1991; 34(1):108-22.
[19] Hasler H, Kaufmann F, Pirson W, Schneider F. Eur. J. Med. Chem. 1987; 22(6):559-67.
[20] Malamas MS, Sestanj K, Millen J. Eur. J. Med. Chem. 1991; 26(4):369-74.
[21] Ward WH, Cook PN, Mirrlees DJ, Brittain DR, Preston J, Carey F, et al. Biochem. Pharmacol. 1991; 42(11):2115-23.
[22] Donkor IO, Klein GM, Broderick TL, Khanna KK. Eur J Med Chem. 1998;33(1):15–22.
[23] Maccari R, Ottanà R, Amato G, Monforte F, Vigorita MG. Bioorg Med Chem. 2008;16:5840–5848.

[24] Mylari BL, Armento SJ, Beebe DA, Conn EL, Coutcher JB, Dina MS, et al. J. Med. Chem. 2005, 48(20):6326–39
[25] Richon AB, Maragoudakis ME and Wasvary JS. J. Med. Chem. 1982; 25(6):745-47.
[26] Pozarentzi M, Geronikaki A, Hadjipavlou-Litina D, Kamoutsis C, et al. Tetrahedron. 2009;65:7741–7751.
[27] Rao VR, Muthyala MK, Purohit MG. Eur J Med Chem. 2012;57:344–351.
[28] Endo S, Okamoto T, Shimizu Y, et al. Bioorg Med Chem. 2013;21:6378–6387.
[29] La Motta C, Sartini S, Mugnaini L, Simorini F, Taliani S, Salerno S, et al. J Med Chem. 2007;50(20):4917–4927.
[30] Hussain S, Kumar D, Kaur H, Rana AC. Bioorg Med Chem Lett. 2014;24:2086–2091.
[31] De la Fuente JA, Manzanaro F, Martín MJ, Cuevas C. J Med Chem. 2003;46(24):5208–5221.
[32] Manzanaro F, Crews P, Rodríguez J, Cuevas C, De la Fuente JA. J Nat Prod. 2006;69(10):1485–1490.
[33] Brownlee M. Diabetes. 2005;54(6):1615–1625.
[34] Brownlee M. Nature. 2001;414(6865):813–820.
[35] Yapar G, Gül S, Akpınar C, Kılıç D. Bioorg Chem. 2021;117:105473.
[36] Feng B, Ruiz M, Chakrabarti S. Can J Physiol Pharmacol. 2013;91(3):213–219.
[37] Kawanami D, Matoba K, Utsunomiya K. Histol Histopathol. 2016;31(10):1059–1067.
[38] Umegaki H, Hayashi T, Nomura H, Yanagawa M, Nonogaki Z, Nakshima H, Kuzuya M. Geriatr. Gerontol. Int. 2013; 13(1):28-34.
[39] Zhu C, In: Diabetes Mellitus-Insights and Perspectives. In Tech Rijeka.2013; 17-46.
[40] Chung SS, Chung SK. Curr Drug Targets. 2005;6(4):475–486.
[41] Borhani DW, Harter TM, Petrash JM. J Biol Chem. 1992;267(34):24841–24847.
[42] Sebastian J, Curr Drug Discov Technol. 2016;13(3):152-163.
[43] Chadha N, Silakari O, Jain N, Silakari P. Bioorg Med Chem. 2015;23(13):2953–2974.
[44] Bansal G, Chhabra G, Sharma N. Adv Res. 2020;23:163–172.
[45] Skljarevski V, Malik RA. In: Clinical Diagnosis of Diabetic Neuropathy. Totowa (NJ): Humana Press; 2007. p. 275–290.
[46] Schrijvers BF, De Vriese AS, Flyvbjerg A. Endocr Rev. 2004;25(6):971–1003.
[47] Schemmel KE, Padiyara RS, D'Souza JJ. J Diabetes Complications. 2010;24(5):354–360.
[48] Verma SK, Thareja S. In: Rahman AU, ed. Stud Nat Prod Chem. 2020;65:381–429.
[49] Siddiqui Z, Khan MI, Akhtar BJ, Ahmad M. J Diabetes Metab. 2022; 13(6):939.
[50] Dahiya L, Singh R, Kumar S, et al. J Biomol Struct Dyn. 2023;43(2):997–1011.
[51] Shakya P, Singh K. Int J Pharm Sci Res. 2010;1(11):153–160.
[52] Khan MM, Sonkar GK, Alam R, Mehrotra S, Khan MS, Kumar A, et al. J Family Med Prim Care. 2017;6(2):366–73.
[53] Ahmad S, Siddiqui Z, Rehman S, Khan MY, Khan H, Khanum S, et al. Curr Vasc Pharmacol. 2017;15(4):352–64.
[54] Nabi R, Ahmad S, Saeed M, Alouffi S. Curr Pharm Des. 2019;25(30):3208–24.
[55] Ahmad S, Akhtar S, Kamal MA, Farooqui A. Curr Diabetes Rev. 2025;21(10):31–49.
[56] Surajo B, Khan Z, Shadab M, Khan N, Sada M, Ahmad M, et al. Int J Basic Clin Pharmacol. 2024;13(6):849–54.