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Updates on Aldose Reductase Inhibitors for Management of Diabetic Complications and Non-diabetic Diseases

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V. Lather

Abstract: Diabetes mellitus occurrence has been associated to the modification of the physiological levels of glucose and is often accompanied by several long-term complications, namely neuropathy, nephropathy, retinopathy, cataract, and cardiovascular. Aldose reductase (AR) is an enzyme of aldo-keto reductase super-family that catalyzes the conversion of glucose to sorbitol in the polyol pathway of glucose metabolism. In this context, aldose reductase inhibitors (ARIs) have received much attention worldwide. Decreased sorbitol flux through polyol pathway by ARIs could be an emerging target for the management of major complications of diabetes. The present review article describes a brief overview of the role of aldose reductase in the diabetic complications, advances achieved on ARIs and their potential use in the treatment and management of the major diabetic complications such as cataract, retinopathy, neuropathy, nephropathy and cardiovascular. The ARIs developed vary structurally, and representative structural classes of ARIs include i) carboxylic acid derivatives (such as Epalrestat, Alrestatin, Zopalrestat, Zenarestat, Ponalrestat, Lidorestat, and Tolrestat), ii) spirohydantoins and related cyclic amides (such as Sorbinil, Minalrestat, and Fidarestat), and iii) phenolic derivatives (related to Benzopyran-4-one and Chalcone). Among these inhibitors, Epalrestat is the only commercially available inhibitor till date. In addition, some other ARIs such as Sorbinil and Ranirestat had been advanced into late stage of clinical trials and found to be safe for human use. The role of various natural ARIs in management of diabetic complications will be discussed**.** Adapting ARIs could prevent sepsis complications, prevent angiogenesis, ameliorate mild or asymptomatic diabetic cardiovascular autonomic neuropathy and appear to be a promising strategy for the treatment of endotoxemia and other ROS-induced inflammatory diseases. The role of ARIs in non-diabetic diseases will also be discussed.

Keywords: Aldose reductase, Aldose reductase inhibitors, Cataract, Diabetes, Nephropathy, Neuropathy, Polyol pathway, Retinopathy, Sepsis complications.

INTRODUCTION

Diabetes mellitus or simply diabetes is a group of metabolic disorders resulting from lack of insulin, insulin resistance, or both leading to chronic hyperglycemia with impaired carbohydrate, fat and protein metabolism [1, 2]. Diabetes mellitus occurrence has been linked to the modification of the physiological levels of glucose [3]. According to etiological classification, diabetes is of four types; two major types are Type 1 and Type 2. Type 1 diabetes (T1D), also known as insulin dependent diabetes mellitus or juvenile-onset diabetes, comprising approximately 5-10% of all diabetic cases, results from destruction of the β-cells in the pancreas, leading to absolute insulin deficiency. T1D may be autoimmune mediated or idiopathic.

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Type 2 diabetes (T2D) also known as non-insulin dependent diabetes mellitus or adult-onset diabetes, is characterized by resistance of tissues towards insulin action. The majority of people with diabetes have T2D; accounting for about 90% of all the cases of DM [1, 4, 5]. According to the most recent estimates of International Diabetes Federation's (IDF), 382 million patients had diabetes in 2013, and the number of patients with diabetes may increase beyond 592 million by the year 2035. Diabetes mellitus is one of the leading causes of death across the globe, particularly in the developing world. Diabetes caused 5.1 million deaths in 2013, and every six seconds a person dies from diabetes. The latest figures from IDF Diabetes Atlas indicated diabetes as a major hurdle in the global development. Diabetes has become a global health burden, and has gained prime public health importance because of the complications associated with it [6-10]. The basic effect of defects in insulin secretion or insulin action is the impairment in uptake and utilization of glucose by the cells of the body, leading to increase in the

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concentration of blood glucose, and increased metabolism of fats and proteins. The symptoms of diabetes include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis [11-14].

Acute metabolic diabetic complications associated with mortality include ketoacidosis from exceptionally high blood glucose concentrations and coma due to low blood glucose. The diabetic complications are grouped under microvascular complications (diabetic neuropathy, nephropathy, retinopathy, and cataracts) and macrovascular complications (disorders of cardiovascular system and cerebrovascular system leading to myocardial infarction and strokes respectively). Diabetic neuropathy is an abnormal and decreased responsiveness, usually in a stocking-glove distribution starting with the feet later often fingers and hands. Patients with neuropathy are at considerably higher risk for developing foot ulceration. Diabetic nephropathy is the damage to the kidney, which can lead to chronic renal failure, eventually requiring dialysis. Diabetic retinopathy is the damage to retina which involves swelling of macula along with growth of low quality retinal blood vessels leading to severe vision loss or blindness. These diabetic complications occur due to chronic hyperglycemia, which causes damage to blood vessels and peripheral nerves [15-20]. A number of mechanisms had been proposed for the diabetic complications. First mechanism includes increased activity of the polyol pathway resulting in the increased accumulation of sorbitol in cells leading to increased osmotic stress on cells which damages proteins by means of oxidative reactions, and is then concerned mainly with microvascular complications. Second mechanism includes increased formation of advanced glycation end products (AGEs) which activates non-enzymatic glycosylation of proteins and lipids, resulting in dysfunctional behaviors of related proteins. These modified circulating proteins can then bind to AGE receptors and activate them, thereby causing the production of inflammatory cytokines and growth factors, which in turn cause vascular complications. The third mechanism includes hyperglycemia-induced increased synthesis of diacylglycerol which causes activation of protein kinase C (PKC) isoforms which induces pathological changes in growth factor expression. The fourth mechanism includes changed metabolism of excess glucose though hexosamine pathway leading to subsequent altered enzymatic proteins by N-acetylglucosamine as well as abnormal enzyme behaviors resulting in pathogenesis of diabetic complications. Finally, the fifth mechanism had been recently proposed in which a hyperglycemia-induced impairment of antioxidant defense such as the overproduction of reactive oxygen species (ROS) readily initiates inflammation responses. ROS are produced by a number of factors including oxidative phosphorylation, nicotinamide adenine dinucleotide phosphate oxidase (NADPH), xanthine oxidase, the uncoupling of lipoxygenases, and cytochrome P450 monooxygenases diminish antioxidant defenses, making the target cells more vulnerable to oxidative stress leading to altered structure and functioning of cell through oxidation of lipids, proteins and DNA [20-24]. Among these mechanisms, the polyol pathway was first discovered and in fact is generally accepted to be the mechanism of prime importance in the pathogenesis of diabetic complications. Aldose reductase (AR), the first and rate-controlling enzyme in the polyol pathway has been a potential target for drug design. In this context, the inhibition of AR has been an attractive approach to the treatment and management of diabetic complications. AR is involved in the transformation of glucose into sorbitol which has been implicated in the pathogenesis of the secondary diabetic complications, such as cataractogenesis, retinopathy, neuropathy, nephropathy, and cardiovascular. AR also catalyzes reduction of a variety of aldehydes and their glutathione conjugates. Further, AR also plays an essential role in inflammatory disorders including atherosclerosis, sepsis, asthma, uveitis, and ovarian cancer [25-34].

The present review article has been planned in a way to give a brief overview of the role of AR in the diabetic complications, advances achieved on ARIs and their potential use in the treatment and management of the major diabetic complications such as cataract, retinopathy, neuropathy and nephropathy.

ALDOSE REDUCTASE (AR)

Biology of AR

Aldose Reductase (EC 1.1.1.21, AKR1B1, and ALD2) is a member of the aldo-keto reductase super-family of proteins that catalyzes the first and rate-limiting step of the polyol pathway of glucose metabolism. It is a 36 kDa cytoplasmic enzyme with a triose phosphate isomerase structural motif that contains 10 peripheral α-helical segments surrounding an inner barrel of β-pleated sheet segments. The protein structure is composed of 315 amino acid residues. The NADPH cofactor is situated at the top of the β/α barrel, with the nicotinamide ring projecting down in the center of the barrel and pyrophosphate spanning the barrel lip. The protein has no structural carbohydrate, lipid or metal ion. The catalytic active site, located within the barrel structure, is formed by an assortment of hydrophobic residues and an "anion well" which includes the nicotinamide ring of NADPH or $NADP^+$ along with key residues Tyr48 and His110. AR is a small monomeric protein that is primarily known for reducing glucose to sorbitol, the very first step of polyol pathway [35-39]. In the conversion of aldehyde substrate to alcohol product, AR uses NADPH to catalyze the reaction. Chemical reduction of the C_1 aldehydic carbon of the substrate is accomplished by concerted transfer of the pro-R-hydride (H) from the C_4 carbon of the NADPH nicotinamide ring to the reface of the planar carbonyl group of the substrate, with a proton concurrently being transferred from Tyr48 via His110 to the substrate. The product is then released followed by a slow conformational change to dissociate the now-oxidized nucleotide, $NADP^+$ [25].

Physiological Significance of AR

AR is a cytosolic enzyme present in most of the tissues affected in diabetes and displays broad substrate specificity (Fig. **2**). AR catalyzes the NADPH-dependent reduction of glucose to sorbitol, the first step in polyol pathway of glucose metabolism. Sorbitol is one of the biological osmolytes that balance the osmotic pressure of extracellular sodium chloride, fluctuating in accordance with urine osmolality. As a result AR plays an osmoregulatory role in

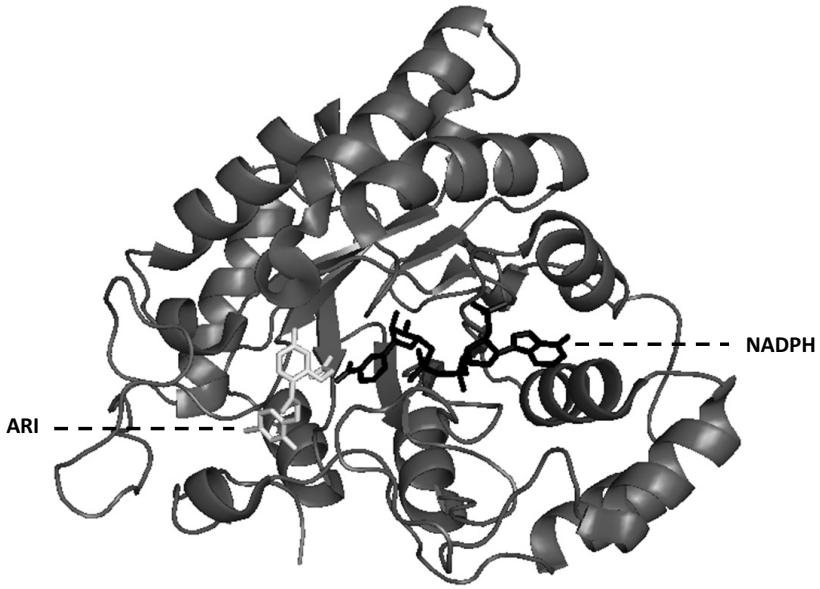


Fig. (1). Crystal structure of AR. As shown in the cartoon structure, human AR is bound to a nicotinamide-adenine dinucleotide phosphate (NADPH shown in black colour) cofactor and an inhibitor (ARI shown in grey colour) molecule (PDB entry: 1US0).

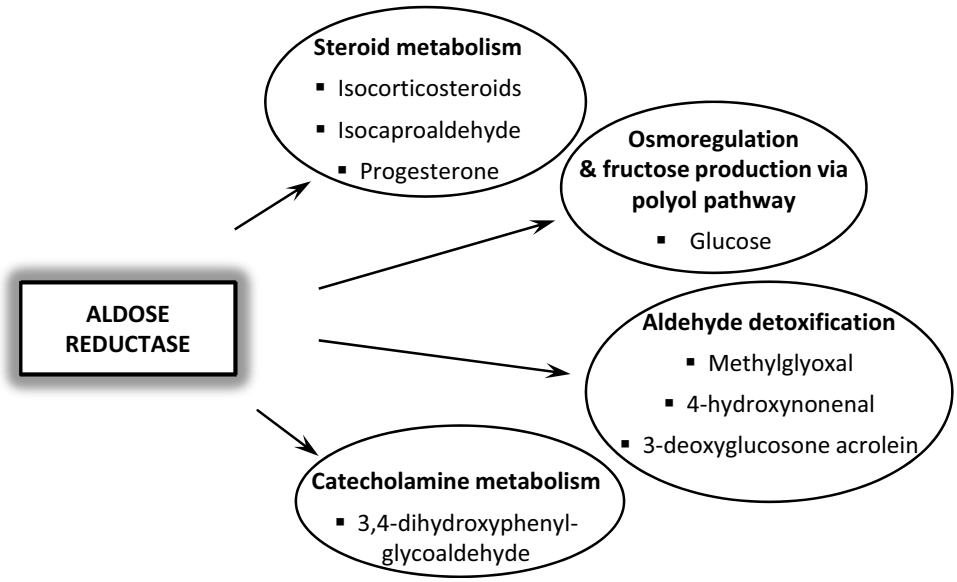


Fig. (2). Physiological significance and major substrates of AR. The major physiological roles played by the enzyme AR include osmoregulatory role in kidneys, aldehyde detoxification, fructose production in the sperms for energy needs, and metabolism of steroids and catecholamines.

the renal homeostasis. Glucose is converted to fructose via polyol pathway in the seminal vesicles to act as source of energy source in sperms. AR and aldehyde reductase, both catalyze the reduction of aldehydes produced by the metabolism of the catecholamines and serotonin in the biological systems. These two enzymes catalyze the reduction of isocorticosteroids (intermediates in the catabolism of the corticosteroid hormones). AR displayed the reductase activity for 17α-hydroxyprogesterone and isocaproaldehyde (a product of metabolism of cholesterol). AR also catalyzes the reduction of 3-deoxyglucosone (non-enzymatic glycation intermediate), acrolein (a highly reactive mutagen produced through lipid peroxidation). The enzyme may also act as extra-hepatic detoxification enzyme in various tissues [30, 39-48]. AR knockout prevented reduction of toxic aldehydes [36].

Role of AR in diabetic complications (Polyol Pathway)

The polyol pathway is usually a two-step metabolic process through which glucose is reduced to sorbitol, which is further converted to fructose (Fig. **3**). The polyol pathway consists of two enzymes. The first enzyme AR with its co-factor NADPH catalyzes the reduction of glucose to sorbitol, and the second enzyme, sorbitol dehydrogenase (SDH), with its co-factor NAD^+, oxidizes sorbitol to fructose. Normally, the cellular glucose is metabolized through the glycolysis pathway and then the Krebs cycle to produce the building

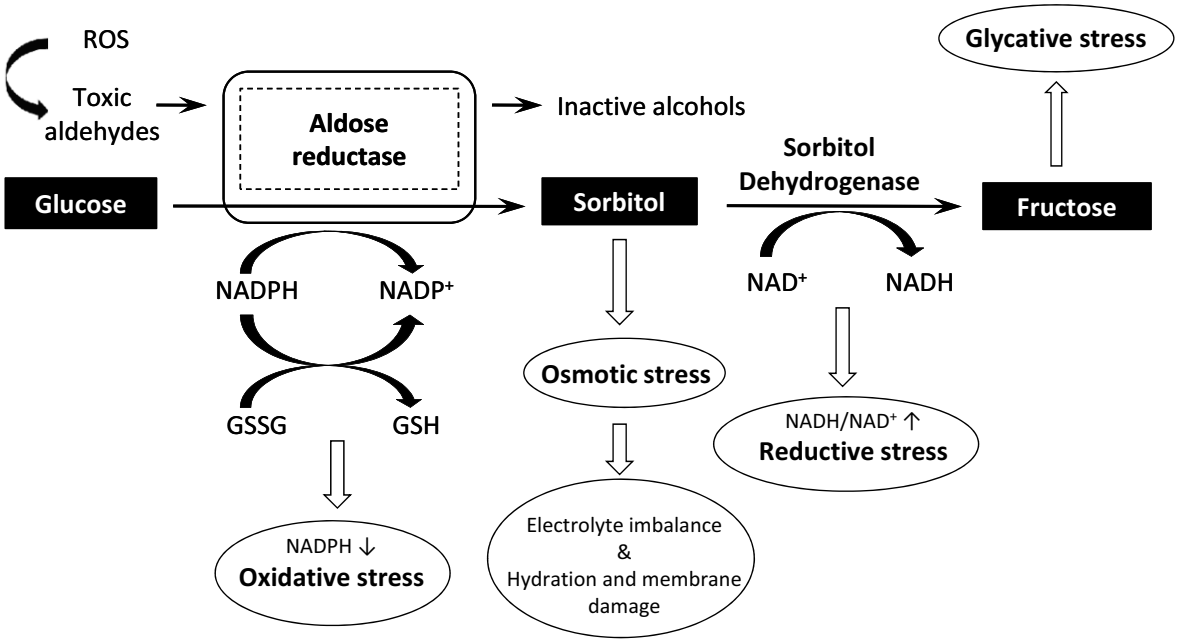


Fig. (3). Role of AR in diabetic complications. Polyol pathway and various pathogenic factors involved in diabetic complications are shown in the Figure 3. Increased accumulation of sorbitol through polyol pathway may lead to osmotic stress which causes electrolyte imbalance, hydration and membrane damage. Decreased levels of NADPH may lead to oxidative stress and increased NADH/NAD^+ ratio may lead to reductive stress causing pseudohypoxia resulting in cell damage. Also the phosphorylation of fructose may lead to formation of AGEs and subsequent binding of AGEs with their receptors may lead to production of ROS.

blocks and energy for cells. In case of hyperglycemia, higher glucose concentration stimulates AR resulting in metabolism of glucose by activated polyol pathway. AR reduces reactive oxygen species (ROS)-generated toxic aldehydes to inactive alcohols, but in case of high cellular glucose levels, AR also reduces that glucose to sorbitol, which is later oxidized to fructose. In the process of reducing high intracellular glucose to sorbitol, AR consumes the cofactor NADPH (an important co-factor involved in production of an important antioxidant, glutathione (GSH), resulting in decreased GSH levels). Osmotic stress due to accumulation of extra sorbitol and oxidative stress due to decrease in NADPH/$NADP^+$ ratio and reduced NAD^+ are the major causes of various complications of diabetes (Fig. **3**) [24]. Therefore, under hyperglycemia, AR activity reduces the cellular antioxidant capacity. Sorbitol is a strong hydrophilic and polyhydroxy alcohol and therefore does not diffuse readily through cell membranes and accumulates in cells resulting in osmotic stress which eventually leads to the development of diabetic complications. Thus, it can be seen that the activation of AR in the polyol pathway can lead to the alteration of various metabolic factors, particularly the generation of ROS which cause oxidative stress and which can be regarded as the initial and the main factor that provoked diabetic complications [21, 24, 39, 49-52].

AR as a Potential Target for Treatment and Prevention of Diabetic Complications

The polyol pathway appears to be a compelling mechanism of diabetic complications because growing evidences had been reported for an involvement of the abnormally activated polyol pathway in the pathogenesis of diabetic complications. Increased production of sorbitol catalyzed by AR in polyol pathway accumulates in cells and is difficult to diffuse through the cell membranes, which increases osmotic stress to cells leading to the development of diabetic complications. The accumulation of sorbitol throught increased activity of AR in lens, retina, and sciatic nerves result in retinopathy, neuropathy, and nephropathy, respectively. The polyol pathway can be targeted by inhibiting the enzyme AR resulting in the reversal of the osmotic stress caused by increased activation of polyol pathway. Thus, reduction of the polyol pathway by AR inhibitors could be a potential therapeutic opening in the treatment and prevention of diabetic complications. Numerous AR inhibitors have been advanced as drug candidates for the treatment and prevention of diabetic complications [24-26, 39, 48, 49, 53-55].

ALDOSE REDUCTASE INHIBITORS

Number of small molecule AR inhibitors (ARIs) were synthesized, and a very few molecules are in clinical trials**.** Among these, representative structural classes include: acetic acid derivatives, cyclic imides, and phenolic derivatives [56]. At the beginning of research on AR properties, it was reported that the enzyme is sensitive to organic anions, particularly to long-chain fatty acids, leading to the development of first ARI 3,3-tetramethyleneglutaric acid (TMG), for the prevention of diabetes-induced cataracts [57]. Since then, the more potent ARIs were developed. In 1973, an orally active ARI, alrestatin (AY-22,284) was developed which was 10 fold more potent than TMG for the prevention

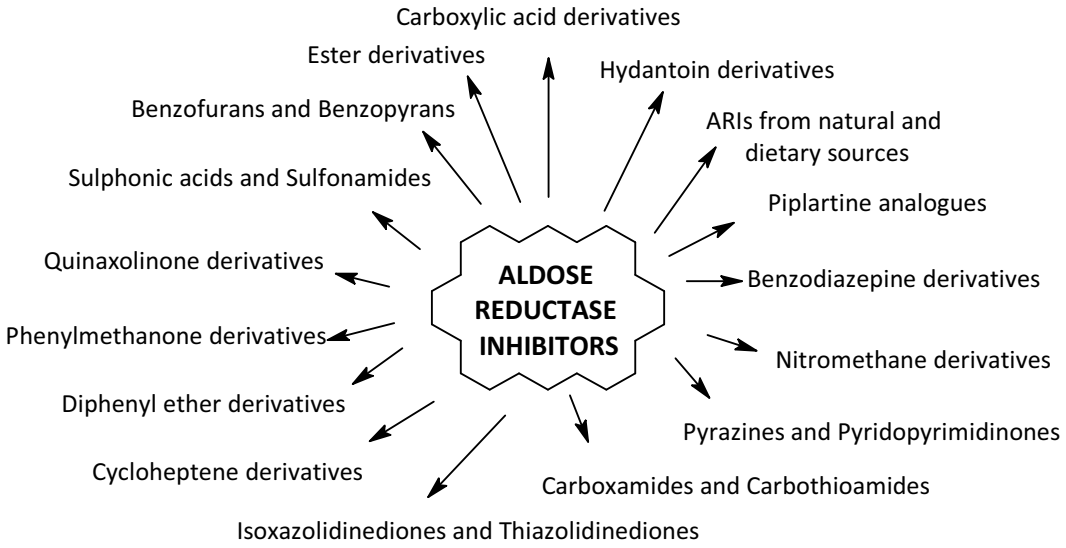
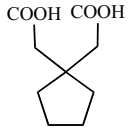
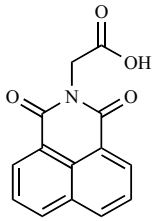


Fig. (4). Various classes of ARIs. A wide diversity was reported in the chemical structure of the small molecule ARIs.

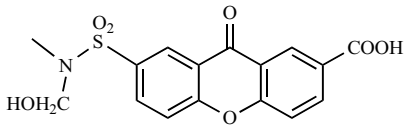
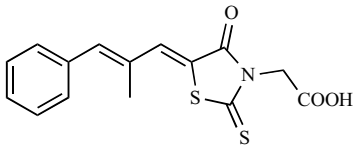
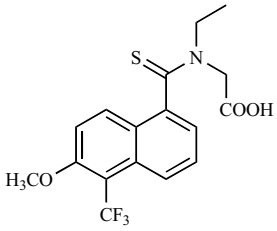
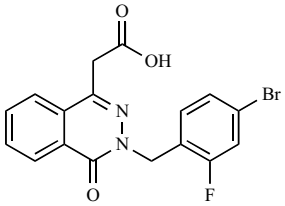
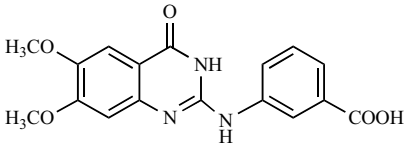
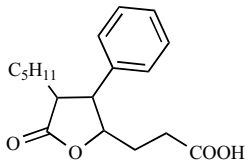
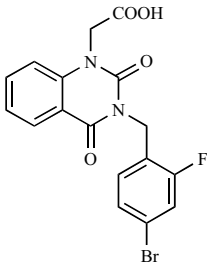
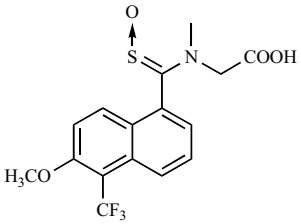
of cataracts and in 1981 the first clinical trials of alrestatin in patients with diabetic neuropathy were reported [58]. There has been a considerable effort to develop small molecules useful for inhibition over the past decades and a number of potent ARIs have been developed. Several of these ARIs have proven effective in the *in vitro* studies and some have been advanced to late phase of clinical trials. Specially, epalrestat (a carboxylic acid derivative) was commercially available in Japan for years and recently permitted for marketing in China and India. A variety of synthetic small molecules as well as natural compounds were reported to inhibit AR. A wide diversity (Fig. **4**) in the chemical structure of the ARIs developed has been reported, although carboxylic acid derivatives are the most important and the largest class of ARIs due to structural feature of carboxylate anion group which may fit well in the active site of AR. It was evident from the X-ray co-crystal structures with Fidarestat and Minalrestat that the hydantoin and succinimide moieties of the inhibitors interacted with the anion-binding site located between the nicotinamide ring of the coenzyme and active site residues Tyr48, His110, and Trp111 [59].

Table **1** summarises various classes of ARIs along with the chemical name ands chemical structure of lead compounds.

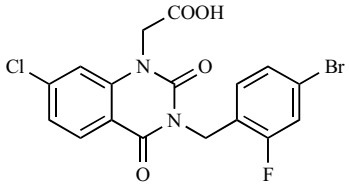
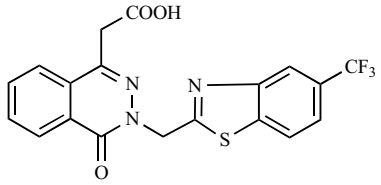
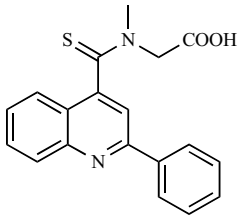
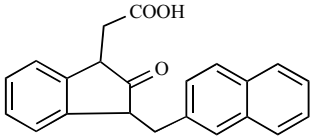
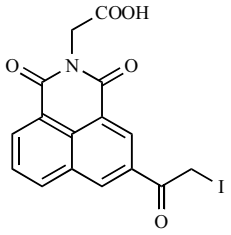
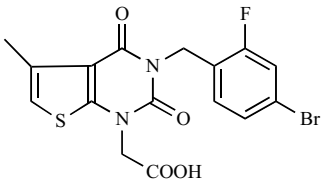
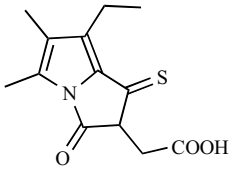
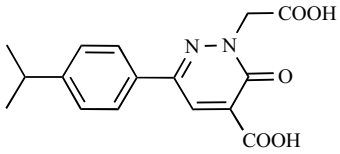
Table 1. Aldose reductase inhibitors (ARIs) from various chemical classes reported in recent literature.

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
Carboxylic acid derivatives			
3,3-tetramethyleneglutaric acid		▪ TMG (First decent ARI) ▪ 68% inhibition of enzyme at 0.1 mM concentration	[57]
(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetic acid (**Alrestatin**)		▪ First ARI with oral bioavailability to undergo clinical trials but development was terminated due to low quality trials and hepatotoxicity	[58]

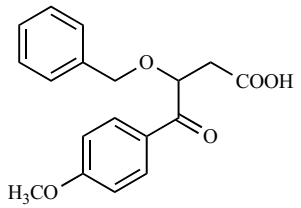
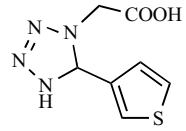
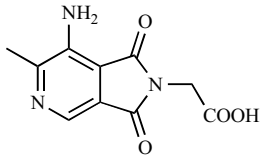
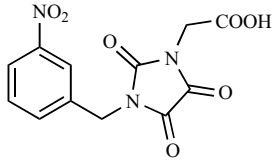
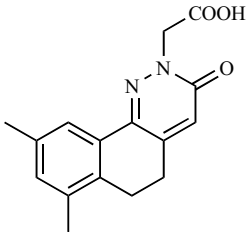
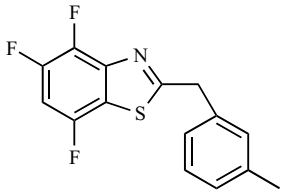
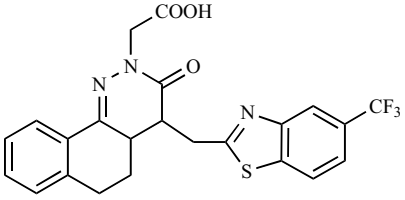
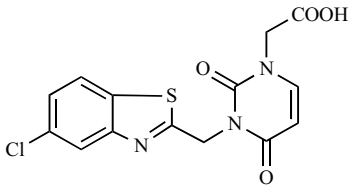
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
7-((hydroxymethyl)(methyl) sulfamoyl)-9-oxo-9H-xanthene-2-carboxylic acid		▪ Assayed for *in vitro* inhibition of AR isolated from rabbit lens ▪ 83% inhibition of AR at a concentration of 10^{-6} M	[60]
2-(5-(2-methyl-3-phenylallylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid (**Epalrestat**)		▪ Significantly reduced he sorbitol content of sciatic nerve and red blood cells ▪ 150 mg/day for 12 weeks improved diabetic neuropathy	[61, 62]
2-(N-ethyl-2-methoxy-1-(trifluoromethyl)naphthalene-5-carbothioamido)acetic acid		▪ A strong ARI and potential drug for the treatment of diabetic complications ▪ IC_{50} value of 3.5×10^{-8} M for inhibition of AR ▪ Approved to several markets but withdrawn due to severe liver toxicity	[63]
2-(3-(4-bromo-2-fluorobenzyl)-4-oxo-3,4-dihydrophthalazin-1-yl)acetic acid		▪ Partially inhibit AR with IC_{50} value of 2×10^{-8} M for human lens ▪ Prevented the development of cataracts in diabetic rats at low doses	[64]
3-(6,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-ylamino)benzoic acid		▪ Inhibit crude AR obtained from rat lens with IC_{50} value of 34μM ▪ Less potent than alrestatin	[65]
3-(5-oxo-4-pentyl-3-phenyl-tetrahydrofuran-2-yl)propanoic acid		▪ Potent ARI with IC_{50} value of 5×10^{-8} M ▪ Carboxyl group was necessary for activity	[66]
2-(3-(4-bromo-2-fluorobenzyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)acetic acid		▪ 94% inhibition of the enzyme AR at 10^{-5} M concentration ▪ Protected 88% of animals from development of cataract after 23 days treatment	[67]
N-((6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl)thioxomethyl)- N-methylglycine S-oxide		▪ S-oxide metabolite of tolrestat ▪ 93% inhibition of the enzyme AR at 10^{-5} M concentration	[68]

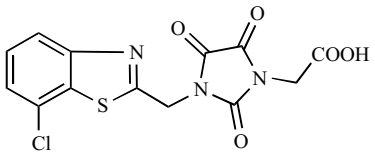
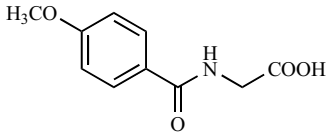
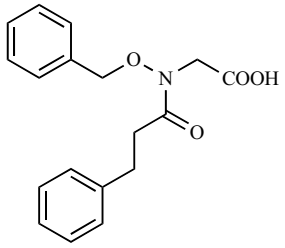
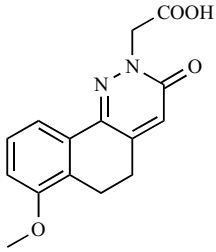
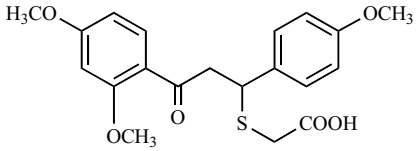
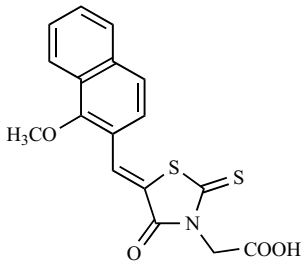
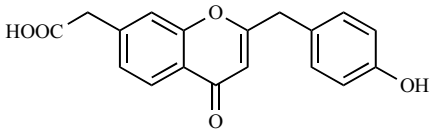
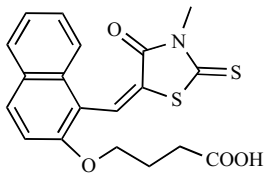
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
2-(3-(4-bromo-2-fluorobenzyl)-7-chloro-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)acetic acid (**Zenarestat**)		▪ IC_{50} value of 3.6 nM (rat sciatic nerve) and 4.4 nM (rat lens) for AR inhibition ▪ Delayed cataract formation ▪ Decreased sorbitol levels in human erythrocytes, rat lens, and rat sciatic nerve	[69]
2-(4-oxo-3-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-3,4-dihydrophthalazin-1-yl)acetic acid (**Zopalrestat**)		▪ Potent ARI with IC_{50} value of 3.1×10^{-9} M for inhibition of AR ▪ Well absorbed in diabetic patients and highly favorable plasma half-life	[70]
2-(N-methyl-2-phenylquinoline-4-carbothioamido)acetic acid		▪ 91% inhibition of enzyme AR at 10^{-7} M concentration ▪ Ester derivatives were found to be inactive	[71]
2-(3-(naphthalen-2-ylmethyl)-2-oxo-2,3-dihydro-1H-inden-1-yl)acetic acid		▪ IC_{50} value of 0.12 µM for AR inhibition ▪ Poor pharmacokinetics	[72]
(5-(iodoacetyl)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetic acid		▪ Selective and irreversible inhibitor of rat lens AR ▪ IC_{50} value of 0.40 µM for AR inhibition	[73]
2-(3-(4-bromo-2-fluorobenzyl)-5-methyl-2,4-dioxo-3,4-dihydrothieno[2,3-d]pyrimidin-1(2H)-yl)acetic acid		▪ Selective inhibitor of rat lens AR ▪ IC_{50} value of 1.5×10^{-8} M for AR inhibition	[74]
2-(7-ethyl-5,6-dimethyl-3-oxo-1-thioxo-2,3-dihydro-1H-pyrrolizin-2-yl)acetic acid		▪ Potent orally active ARI ▪ IC_{50} value of 23×10^{-8} M for AR inhibition	[75]
2-(carboxymethyl)-6-(4-isopropylphenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid		▪ AR inhibitory as well as anti-oxidant activity ▪ IC_{50} value of 0.95×10^{-5} M for AR inhibition ▪ Inhibited lipid peroxidation with IC_{50} (1.87×10^{-3} M)	[76]

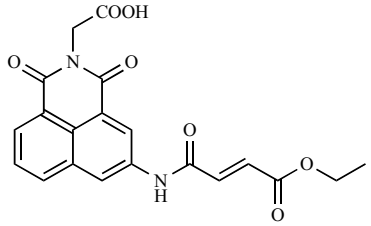
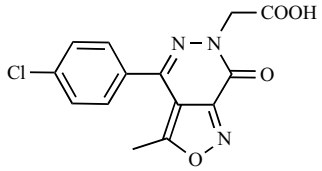
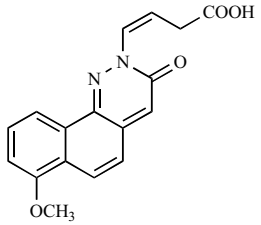
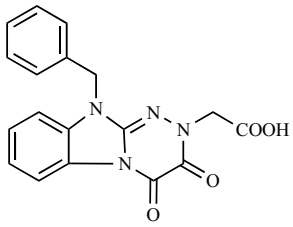
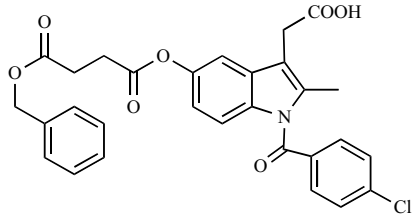
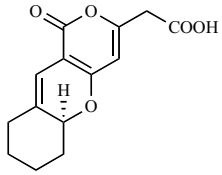
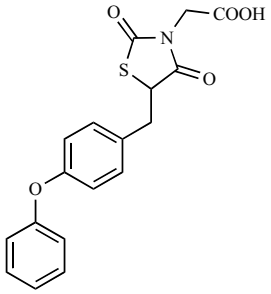
(Table 1) Contd…..

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
3-(benzyloxy)-4-(4-methoxyphenyl)-4-oxobutanoic acid		▪ 89% inhibition of the enzyme AR at 50 µM concentration ▪ IC_{50} value of 3.5 µM for AR inhibition	[77]
(5-(thiophen-3-yl)-4,5-dihydro-1H-tetrazol-1-yl)acetic acid		▪ Potent ARI ▪ Erythrocyte sorbitol content was significantly reduced	[78]
(7-amino-6-methyl-1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)acetic acid		▪ 100% inhibition of AR ▪ IC_{50} value of 1.4 µM for AR inhibition	[79]
(3-(3-nitrobenzyl)-2,4,5-trioxoimidazolidin-1-yl)acetic acid		▪ Highly selective activity for inhibition of AR compared to aldehyde reductase ▪ Selected for clinical trials	[80]
(7,9-dimethyl-3-oxo-5,6-dihydrobenzo[h]cinnolin-2(3H)-yl)acetic acid		▪ Non-competitive type selective ARI ▪ IC_{50} value of 6 µM for AR inhibition	[81]
4,5,7-trifluoro-2-(3-methylbenzyl)-1,3-benzothiazole		▪ Compounds with less complex structures were orally active ARIs ▪ IC_{50} value of 6.6 nM for AR inhibition	[82]
2-(3-oxo-4-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-4,4a,5,6-tetrahydrobenzo[h]cinnolin-2(3H)-yl)acetic acid		▪ Designed using structure based drug design ▪ IC_{50} value of 0.15µM for AR inhibition	[83]
2-(3-((5-chlorobenzo[d]thiazol-2-yl)methyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetic acid		▪ Selectively inhibited AR without significantly inhibiting aldehyde reductase	[84]

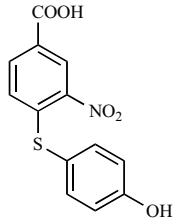
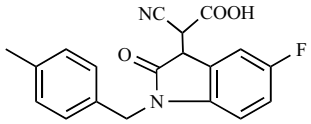
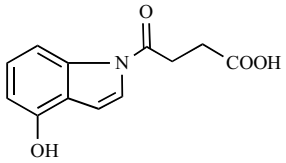
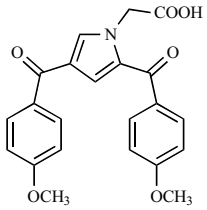
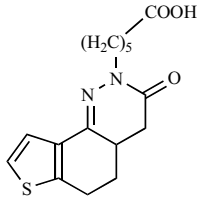
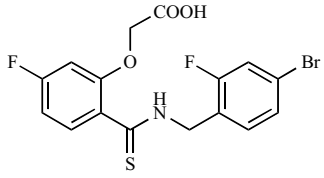
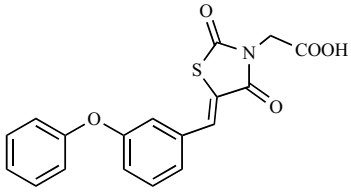
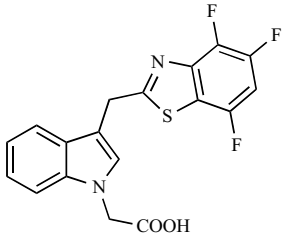
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
(3-((7-chloro-1,3-benzothiazol-2-yl)methyl)-2,4,5-trioxoimidazolidin-1-yl)acetic acid		▪ Selective ARI with 83% enzyme inhibition at 10^{-7} M concentration ▪ IC_{50} value of 1.2×10^{-8} M for AR inhibition	[85]
((4-methoxybenzoyl)amino)acetic acid		▪ Weak inhibitor of AR ▪ 1/100 activity compared to the activity of sorbinil	[86]
((benzyloxy)(3-phenylpropanoyl)amino)acetic acid		▪ Selective ARI ▪ IC_{50} value of 14 µM for AR inhibition (versus 2 µM for sorbinil)	[87]
(7-methoxy-3-oxo-5,6-dihydrobenzo[h]cinnolin-2(3H)-yl)acetic acid		▪ Designed based on free energy perturbation calculations ▪ IC_{50} value of 6.7 µM for AR inhibition	[88]
((3-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-oxopropyl)sulfanyl)acetic acid		▪ Selective ARI ▪ IC_{50} value of 6.43 µM for AR inhibition	[89]
(5-((1-methoxynaphthalen-2-yl)methylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid		▪ Selective ARI for bovine lens ▪ IC_{50} value of 9 nM for AR inhibition (similar to that of epalrestat)	[90]
(2-(4-hydroxybenzyl)-4-oxo-4H-chromen-7-yl)acetic acid		▪ Showed anti-oxidant as well as ARI activity ▪ IC_{50} value of 1.30 µM for AR inhibition	[91]
4-((1-(-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl)naphthalen-2-yl)oxy)butanoic acid		▪ *In vitro* IC_{50} value of 700 nM for AR inhibition, and 34.6% *in vivo* inhibition of AR ▪ Good oral absorption and efficient tissue penetration power	[92]

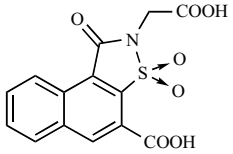
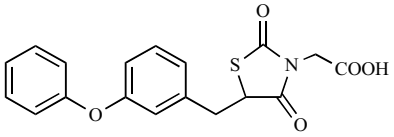
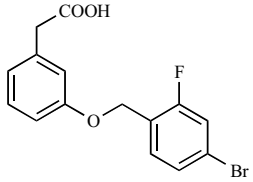
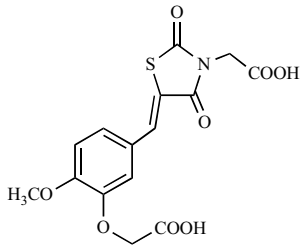
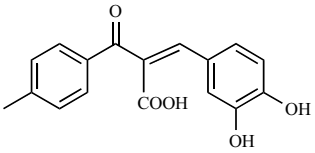
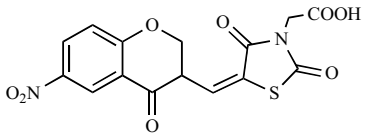
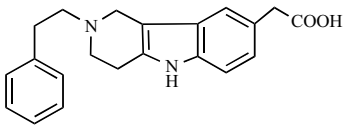
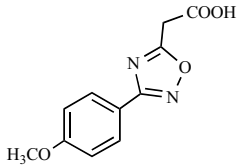
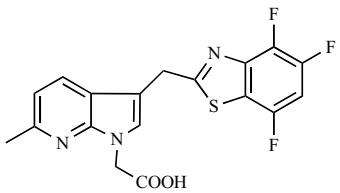
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
(5-((-4-ethoxy-4-oxobut-2-enoyl)amino)-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetic acid		▪ Selective inhibitor of rat lens AR versus rat kidney AR ▪ IC_{50} value of 0.1 µM for AR inhibition	[93]
(4-(4-chlorophenyl)-3-methyl-7-oxo[1,2]oxazolo[3,4-d]pyridazin-6(7H)-yl)acetic acid		▪ Designed using molecular modeling studies ▪ IC50 value of 3.72 µM for AR inhibition	[94]
4-(7-methoxy-3-oxobenzo[h]cinnolin-2(3H)-yl)but-3-enoic acid		▪ Potency range from that of sorbinil (standard) to very weakly active compounds ▪ IC_{50} value of 3.90 µM for AR inhibition	[95]
(10-benzyl-3,4-dioxo-3,4-dihydro[1,2,4]triazino[4,3-a]benzimidazol-2(10H)-yl)acetic acid		▪ Potent ARI with IC_{50} value of 0.36 µM for AR inhibition ▪ Effective in preventing cataract formation in rats (as eye drops)	[96]
2-(5-(4-(benzyloxy)-4-oxobutanoyloxy)-1-(4-chlorobenzoyl)-2-methyl-1H-indol-3-yl)acetic acid		▪ Designed using protein structure based approach ▪ Potent ARI with IC_{50} value of 0.21 µM for AR inhibition	[97]
(S)-2-(1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-3-yl)acetic acid		▪ Potent ARI with IC_{50} value of 2 nM for AR inhibition ▪ 80% reduction in the polyol accumulation in lens epithelial cells at 10 µM concentration	[98]
2-(5-(4-phenoxybenzyl)-2,4-dioxothiazolidin-3-yl)acetic acid		▪ Very potent ARI with IC_{50} value of 0.13 µM for AR inhibition	[99]

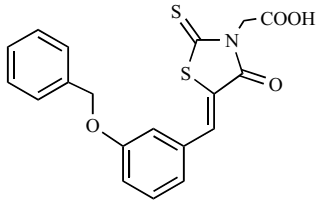
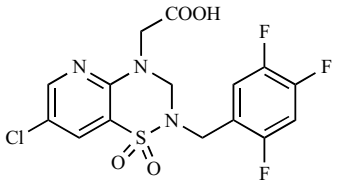
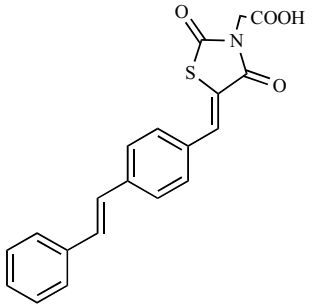
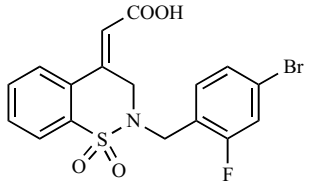
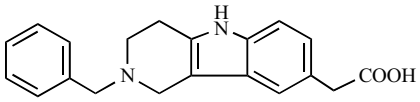
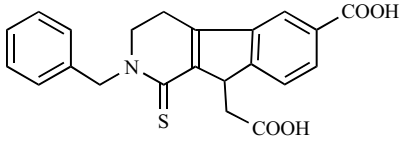
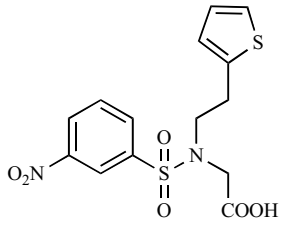
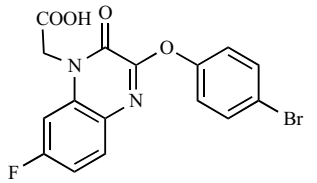
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
4-(4-hydroxyphenylthio)-3-nitrobenzoic acid		▪ Potent ARI designed by means of docking and database screening ▪ IC_{50} value of 0.99 µM for AR inhibition	[100]
Cyano(5-fluoro-1-(4-methylbenzyl)-2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid		▪ Very potent ARI designed using docking study ▪ IC_{50} value of 0.075 µM for AR inhibition	[101]
4-(4-hydroxy-1H-indol-1-yl)-4-oxobutanoic acid		▪ Designed using docking and 3-D QSAR studies of phenethylamine derivatives ▪ IC_{50} value of 7.4 µM for AR inhibition	[102]
(2,4-bis(4-methoxybenzoyl)-1H-pyrrol-1-yl)acetic acid		▪ Showed ARI as well as anti-oxidant activity ▪ Potency comparable to that of epalrestat (standard)	[103]
6-(3-oxo-4,4a,5,6-tetrahydrothieno[2,3-h]cinnolin-2(3H)-yl)hexanoic acid		▪ Potent pig lens ARI ▪ IC_{50} value of 7.6 µM for AR inhibition	[104]
(2-((4-bromo-2-fluorobenzyl)carbamothioyl)-5-fluorophenoxy)acetic acid		▪ Highly potent and selective ARI ▪ IC_{50} value of 30 nM for AR inhibition ▪ Significantly lowered nerve sorbitol levels	[105]
(2,4-dioxo-5-(3-phenoxybenzylidene)-1,3-thiazolidin-3-yl)acetic acid		▪ Designed using molecular modeling ▪ IC_{50} value of 0.13 µM for AR inhibition	[106]
(3-((4,5,7-trifluoro-1,3-benzothiazol-2-yl)methyl)-1H-indol-1-yl)acetic acid		▪ Selective ARI ▪ IC_{50} value of 5.0 nM for AR inhibition ▪ Significantly lowered nerve and lens sorbitol	[107]

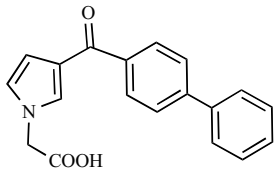
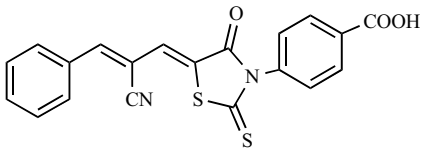
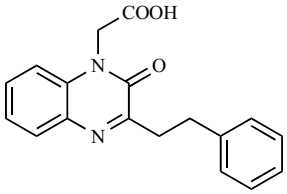
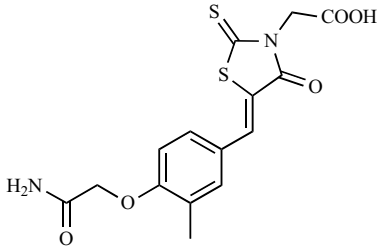
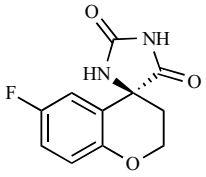
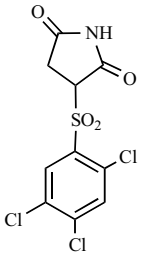
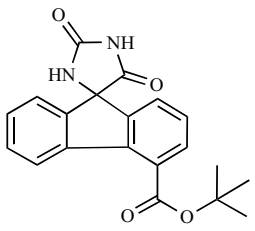
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
Naphtho[1,2-d]isothiazole Acetic Acid Derivative		▪ Selective and potent lens ARI ▪ IC_{50} value of 0.14 µM for AR inhibition ▪ Significantly prevented cataract formation	[108]
(2,4-dioxo-5-(3-phenoxybenzyl)-1,3-thiazolidin-3-yl)acetic acid		▪ Selective and potent bovine lens ARI ▪ IC_{50} value of 1.01 µM for AR inhibition	[109]
(3-((4-bromo-2-fluorobenzyl)oxy)phenyl)acetic acid		▪ Evaluated using spectrophotometric assay for AR inhibition activity ▪ IC_{50} value of 20.9 µM for AR inhibition	[110]
(5-(3-(carboxymethoxy)-4-methoxybenzylidene)-2,4-dioxo-1,3-thiazolidin-3-yl)acetic acid		▪ Selective ARI designed using molecular modeling simulations ▪ IC_{50} value of 0.20 µM for AR inhibition	[111]
3-(3,4-dihydroxyphenyl)-2-(4-methylbenzoyl)prop-2-enoic acid		▪ Selective rat lens ARI ▪ IC_{50} value of 0.49 µM for AR inhibition	[112]
(5-((6-nitro-4-oxo-3,4-dihydro-2H-chromen-3-yl)methylidene)-2,4-dioxo-1,3-thiazolidin-3-yl)acetic acid		▪ Selective rat kidney ARI ▪ Assayed using *in vitro* spectrophotometric assay ▪ IC_{50} value of 0.261 µM for AR inhibition ▪ Prevented cataract formation	[113]
(2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl)acetic acid		▪ Selective inhibitor of rat lens AR ▪ IC_{50} value of 16.7 µM for AR inhibition	[114]
(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)acetic acid		▪ Potent ARI with IC_{50} value of 0.27 µM for AR inhibition ▪ Significantly prevented cataract development	[115]
(6-methyl-3-((4,5,7-trifluoro-1,3-benzothiazol-2-yl)methyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid		▪ Highly potent and selective ARI ▪ IC_{50} value of 8 nM for AR inhibition and IC_{50} value of >100000 nM for inhibition of aldehyde reductase	[116]

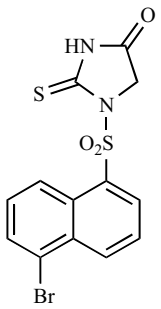
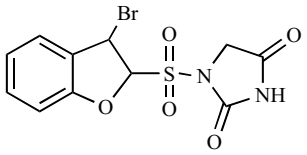
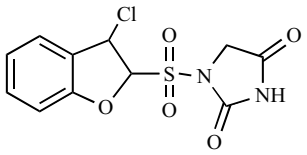
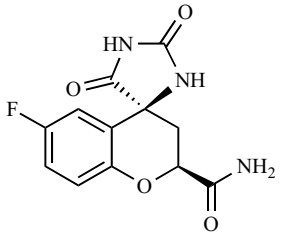
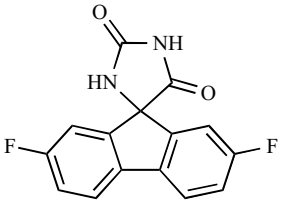
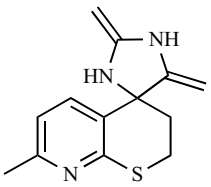
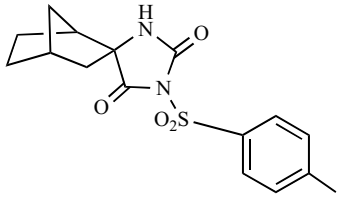
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
(5-(3-(benzyloxy)benzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid		▪ Potent ARI with IC_{50} value of 0.11 μM for AR inhibition ▪ Potency was similar to that of epalrestat	[117]
(7-chloro-1,1-dioxido-2-(2,4,5-trifluorobenzyl)-2,3-dihydro-4H-pyrido[2,3-e][1,2,4]thiadiazin-4-yl)acetic acid		▪ Highly selective and potent ARI with IC_{50} value of 0.038 μM for AR inhibition	[118]
(2,4-dioxo-5-((2-phenylethenyl)benzylidene)-1,3-thiazolidin-3-yl)acetic acid		▪ Potent ARI with IC_{50} value of 0.27 μM for AR inhibition ▪ Potency was similar to that of epalrestat	[119]
(2-(4-bromo-2-fluorobenzyl)-1,1-dioxido-2,3-dihydro-4H-1,2-benzothiazin-4-ylidene)acetic acid		▪ Selective and potent ARI with IC_{50} value of 0.11 μM for AR inhibition ▪ Saturated carboxylic acid derivatives showed greater binding affinity with enzyme	[120]
(2-benzyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl)acetic acid		▪ ARI as well as anti-oxidant with zwitter-ion structure ▪ IC_{50} value of 18.02 μM for AR inhibition	[121]
2-benzyl-9-(carboxymethyl)-1-thioxo-2,3,4,9-tetrahydro-1H-indeno[2,1-c]pyridine-6-carboxylic acid		▪ Highly selective ARI ▪ Showed strong AR inhibitory effects with IC_{50} value of 0.17 μM	[122]
(((3-nitrophenyl)sulfonyl)(2-(thiophen-2-yl)ethyl)amino}acetic acid		▪ Selective and potent ARI with IC_{50} value of 0.431 μM for AR inhibition	[123]
(3-(4-bromophenoxy)-7-fluoro-2-oxoquinoxalin-1(2H)-yl)acetic acid		▪ Potent and selective ARI with IC_{50} value of 11.4 nM for AR inhibition ▪ Regioselective method of synthesis	[124]

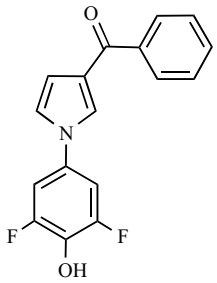
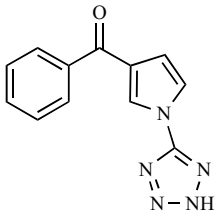
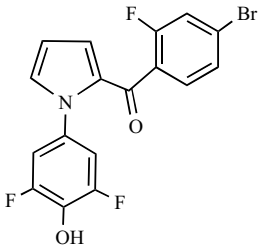
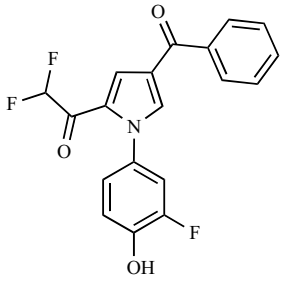
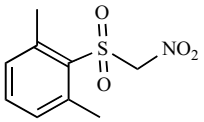
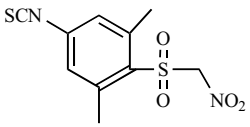
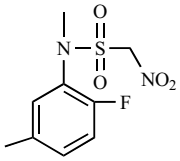
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
(3-(biphenyl-4-ylcarbonyl)-1H-pyrrol-1-yl)acetic acid		▪ Potent and selective ARI with IC_{50} value of 0.334 µM for AR inhibition	[125]
4-(5-(2-cyano-3-phenylprop-2-en-1-ylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)benzoic acid		▪ Epalrestat analogues developed using Baylis-Hillman adducts ▪ IC_{50} value of 0.22 µM for AR inhibition	[126]
(2-oxo-3-(2-phenylethyl)quinoxalin-1(2H)-yl)acetic acid		▪ Selective and potent ARI with IC_{50} value of 0.143 µM for AR inhibition	[127]
(5-(4-(2-amino-2-oxoethoxy)-3-methylbenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid		▪ Potent and selective ARI with IC_{50} value of 0.11 µM for AR inhibition ▪ Target diabetic complications as well as inflammation	[127]
Hydantoin (or spirohydantoin) derivatives and their analogs			
(4S)-6-fluoro-2,3-dihydro-2'H,5'H-spiro(chromene-4,4'-imidazolidine)-2',5'-dione (**Sorbinil**)		▪ Highly potent and selective inhibitor of calf lens AR with IC_{50} value of 5×10^{-7} M for AR inhibition ▪ Orally effective at a dose of 0.25 mg/kg, and produced 85% inhibition of sorbitol accumulation	[56, 129]
3-((2,4,5-trichlorophenyl)sulfonyl)pyrrolidine-2,5-dione (**TriCl-PSH**)		▪ Potent ARI with IC_{50} value of 0.28×10^{-6} M for AR inhibition ▪ Inhibited sorbitol accumulation in the sciatic nerve completely and in lens more than 92%	[130]
Spiro-(4-(tert-butoxycarbonyl)-9H-9,4'-imidazolidine)-2',5'-dione		▪ Potent ARI with pIC_{50} value of 7.4 for AR inhibition ▪ Reduced the sorbitol concentration in nerve and lens to 20-25%	[131]

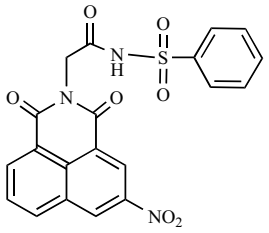
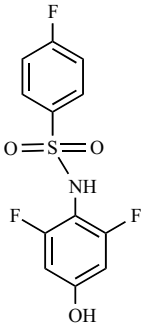
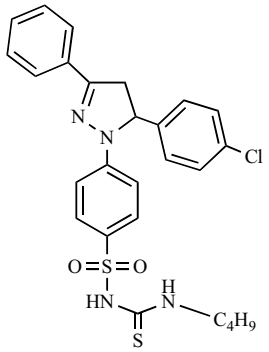
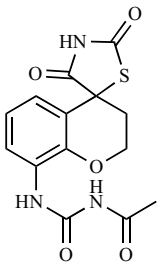
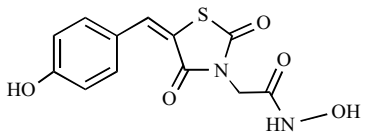
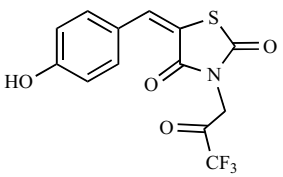
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
1-((5-bromonaphthalen-1-yl)sulfonyl)-2-thioxoimidazolidin-4-one		▪ 67% inhibition of AR *in vitro* at 10^{-5} M concentration ▪ Showed results comparable to that of tolrestat	[132]
1-((3-bromo-2,3-dihydro-1-benzofuran-2-yl)sulfonyl)imidazolidine-2,4-dione		▪ M16209 (Potent ARI) ▪ Effective in prevention of galactosemic cataracts	[133]
1-((3-chloro-2,3-dihydro-1-benzofuran-2-yl)sulfonyl)imidazolidine-2,4-dione		▪ M16287 (Potent ARI) ▪ Prevented accumulation of sorbitol in rat tissues	[133]
(2S,4S)-6-fluoro-2',5'-dioxo-2,3-dihydrospiro(chromene-4,4'-imidazolidine)-2-carboxamide (**Fifarestat**)		▪ SNK-860 ▪ Potent ARI with IC_{50} value of 18 nM ▪ Useful in diabetic neuropathy	[134, 135]
2,5-Difluorospiro(fluoren-9,4'-imidazolidine)-2',5'-dione (**Imirestat**)		▪ Potent ARI with IC_{50} value of 0.064×10^{-6} M for AR inhibition	[136]
7'-methyl-2,5-dimethylidene-2',3'-dihydrospiro(imidazolidine-4,4'-thiopyrano[2,3-b]pyridine)		▪ Selective and potent ARI with IC_{50} value of 0.94 µM for AR inhibition ▪ Highly effective in preventing cataract	[137]
1'-((4-methylphenyl)sulfonyl)-2'H,5'H-spiro(bicyclo[2.2.1]heptane-2,4'-imidazolidine)-2',5'-dione		▪ Highly potent and selective ARI with IC_{50} value of 1.8 µM for AR inhibition	[138]

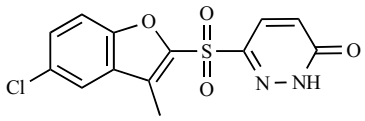
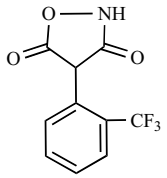
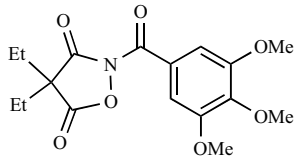
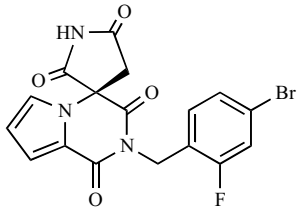
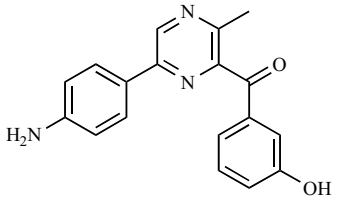
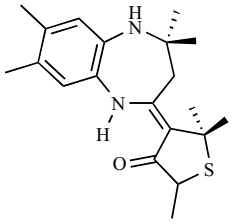
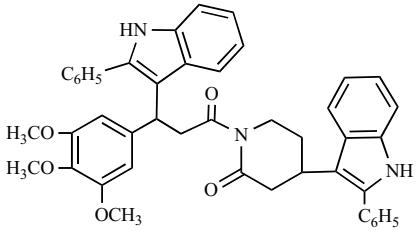
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
Phenylmethanone derivatives			
(1-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrol-3-yl)phenylmethanone		▪ Synthesized as a bioisoster of a known acetic acid derivative ARI ▪ 5 times more potent as compared to the parent compound	[139]
Phenyl(1-(2H-tetrazol-5-yl)-1H-pyrrol-3-yl)methanone		▪ Selective ARI aimed at long term diabetic complications ▪ IC_{50} value of 18.0×10^{-4} M for AR inhibition	[140]
(4-bromo-2-fluorophenyl)(1-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrol-2-yl)methanone		▪ Highly potent and selective ARI with IC_{50} value of 0.11 µM for AR inhibition	[141]
1-(4-benzoyl-1-(3-fluoro-4-hydroxyphenyl)-1H-pyrrol-2-yl)-2,2-difluoroethanone		▪ Selective submicromolar ARI with IC50 value of 0.443 µM for AR inhibition ▪ Potentially favorable membrane permeation (rat jejunum)	[142]
Nitromethane derivatives			
1,3-dimethyl-2-((nitromethyl)sulfonyl)benzene		▪ Non-competitive inhibitor of AR with IC_{50} value of 0.23 µM for AR inhibition ▪ Reported to associate with an allosteric site on enzyme	[143]
5-isothiocyanato-1,3-dimethyl-2-((nitromethyl)sulfonyl)benzene		▪ Almost complete irreversible inhibitor of recombinant rat lens AR ▪ Selective ARI with IC_{50} value of 0.13 µM for AR inhibition	[144]
N-(2-fluoro-5-methylphenyl)-N-methyl-1-nitromethanesulfonamide		▪ Non-competitive inhibitor of AR ▪ IC_{50} value of 0.35 µM for AR inhibition	[145]

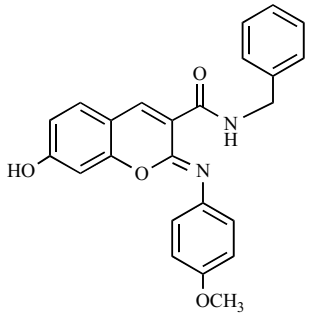
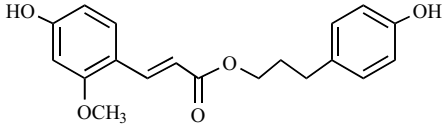
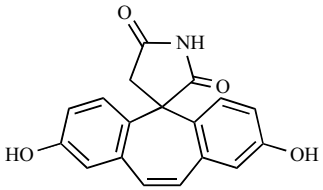
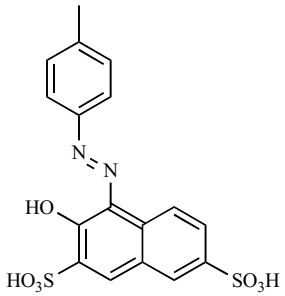
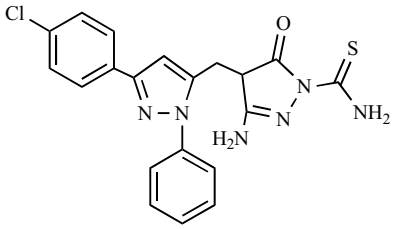
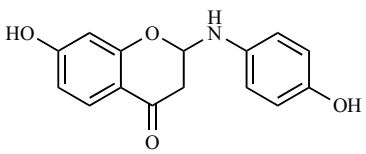
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
Sulfonamide derivatives			
2-(5-nitro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-N-(phenylsulfonyl)acetamide		▪ Selective inhibitors of rat kidney AR with IC_{50} value of 2.4 mM for AR inhibition ▪ Useful in diabetic nephropathy	[146]
N-(2,6-difluoro-4-hydroxyphenyl)-4-fluorobenzenesulfonamide		▪ Highly potent anti-oxidant and selective ARI ▪ IC_{50} value of 14.1 µM for AR inhibition	[147]
1-butyl-3-(4-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)phenylsulfonyl)thiourea		▪ Showed anti-hyperglycemic (anti-diabetic) as well as ARI activity ▪ Potent ARI with IC_{50} value of 0.0175 µM for AR inhibition	[148]
Thiazolidinedione derivatives			
N-((2',4'-dioxo-2,3-dihydrospiro(chromene-4,5'-[1,3]thiazolidin)-8-yl)carbamoyl)acetamide		▪ Potent inhibitor of AR with IC_{50} value of 0.01 µM for AR inhibition ▪ Showed beneficial effects in galactosemic rats	[149]
N-hydroxy-2-(5-(4-hydroxybenzylidene)-2,4-dioxo-1,3-thiazolidin-3-yl)acetamide		▪ Designed using induced fir docking ▪ Potent ARI with IC_{50} value of 1.79 µM for AR inhibition	[150]
5-(4-hydroxybenzylidene)-3-(3,3,3-trifluoro-2-oxopropyl)-1,3-thiazolidine-2,4-dione		▪ Potent and selective inhibitor of AR with IC_{50} value of 3.0 µM for AR inhibition	[151]

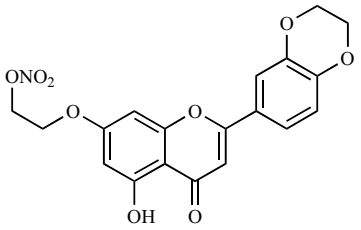
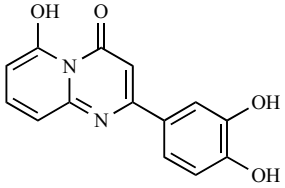
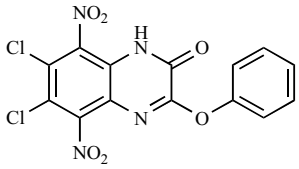
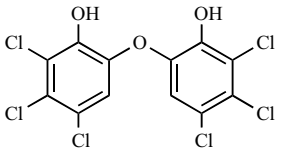
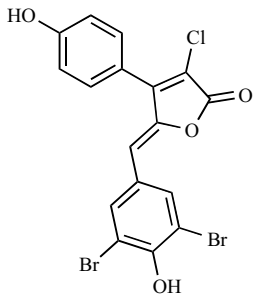
(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
Benzofuran derivatives			
6-(5-chloro-3-methylbenzofuran-2-ylsulfonyl)pyridazin-3(2H)-one		▪ Orally active ARI ▪ Well absorbed orally (98%) ▪ Long plasma half-life ($t_{1/2}$ of 26±3 h)	[152, 153]
Isoxazolidinedione derivatives			
4-(2-(trifluoromethyl)phenyl)isoxazolidine-3,5-dione		▪ Active at a concentration of 50 µM ▪ 80% inhibition of lens AR	[154]
4,4-diethyl-2-(3,4,5-trimethoxybenzoyl)isoxazolidine-3,5-dione		▪ Potent inhibitor of rat lens AR ▪ IC_{50} value of 1.85×10^{-8} M for AR inhibition	[155]
Pyrazine derivatives			
(R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4- tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (**Ranirestat**)		▪ Potent ARI with IC_{50} value of 1.5×10^{-8} M for AR inhibition ▪ (-)-isomer 10 times more potent than (+)-isomer	[156]
(6-(4-aminophenyl)-3-methylpyrazin-2-yl)(3-hydroxyphenyl)methanone		▪ Mixed type inhibitor of AR ▪ IC_{50} value of 0.91 µM for AR inhibition	[157]
Benzodiazepine derivatives			
2,5,5-trimethyl-4-(4,4,7,8-tetramethyl-4,5-dihydro-1H-benzo[b][1,4]diazepin-2(3H)-ylidene)-dihydrothiophen-3(2H)-one		▪ 88% inhibition of the AR enzyme at a concentration of 0.01 mM	[158]
Piplartine derivatives			
4-(2-phenyl-1H-indol-3-yl)-1-(3-(2-phenyl-1H-indol-3-yl)-3-(3,4,5-trimethoxyphenyl)propanoyl)piperidin-2-one		▪ Synthesized using Michael Addition reaction ▪ Potent ARI with IC_{50} value of 4 µM for AR inhibition	[159]

(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
Carboxamides derivatives			
N-benzyl-7-hydroxy-2-(4-methoxyphenylimino)-2H-chromene-3-carboxamide		▪ Selective ARI with competitive inhibition of the enzyme ▪ IC_{50} value of 4.7 nM for AR inhibition ▪ Useful for the treatment of cancer	[160]
Ester derivatives			
3-(4-hydroxyphenyl)propyl-3-(4-hydroxy-2-methoxyphenyl)acrylate		▪ Potent ARI with IC_{50} value of 4.7 nM for AR inhibition ▪ Significantly suppressed farnesal metabolism	[161]
Cycloheptene derivatives			
Spiro(2,8-dihydroxy-5H-dibenzo[a, d]cycloheptene-5,3′-pyrrolidine)-2′,5′-dione		▪ Potent and selective inhibitor of AR ▪ IC_{50} value of 3.0 µM for AR inhibition	[162]
Sulphonic acid derivatives			
3-hydroxy-4-(p-tolyldiazenyl)naphthalene-2,7-disulfonic acid		▪ Designed using molecular docking analysis of structures of more than 127000 organic compounds ▪ IC_{50} value of 0.58 µM for AR inhibition	[163]
Carbothioamide derivatives			
3-amino-4-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-5-yl)methyl)-5-oxo-4,5-dihydropyrazole-1-carbothioamide		▪ Selective inhibitor of goat lens AR ▪ Synthesized using one-pot eco-friendly method ▪ IC_{50} value of 6.30 µM for AR inhibition	[164]
Benzopyran-4-one derivatives			
7-hydroxy-2-[(4-hydroxyphenyl)amino]-2,3-dihydro-4H-chromen-4-one		▪ Potent ARI with IC_{50} value of 9.8 µM for AR inhibition	[165]

(Table 1) Contd….

IUPAC/Brand name (if any)	Structure of the lead compound	Remarks	Ref.
2-((2-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-hydroxy-4-oxo-4H-chromen-7-yl)oxy)ethyl nitrate		▪ Selective ARI ▪ IC_{50} value of 0.099 µM for AR inhibition	[166]
Pyridopyrimidinone derivatives			
2-(3,4-dihydroxyphenyl)-6-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one		▪ Potent ARI as well as anti-oxidant ▪ IC_{50} value of 0.10 µM for AR inhibition	[167]
Quinaxolinone derivatives			
6,7-dichloro-5,8-dinitro-3-phenoxyquinoxalin-2(1H)-one		▪ Potent and selective ARI with IC_{50} value of 1.54 µM for AR inhibition	[168]
Diphenyl ether derivatives			
2,2'-oxybis(4,5,6-trichlorophenol)		▪ Synthesized from a marine natural product ▪ IC_{50} value of 0.24 µM for AR inhibition	[169]
Ascidian butenolide derivative			
(5Z)-3-chloro-5-(3,5-dibromo-4-hydroxybenzylidene)-4-(4-hydroxyphenyl)furan-2(5H)-one (**Rubrolide L**)		▪ A marine butenolide isolated from the ascidians *Ritterella rubra* and *Synoicum blochmanni* ▪ Potent inhibitor of human AR with IC50 value of 0.8 µM for AR inhibition	[170, 171]

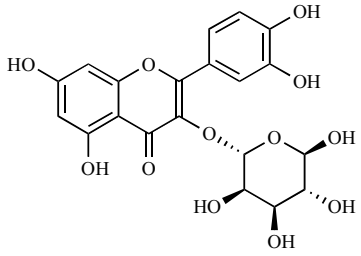
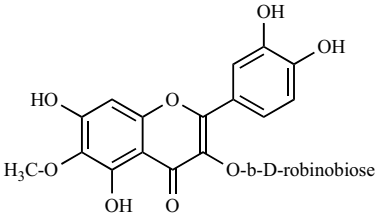
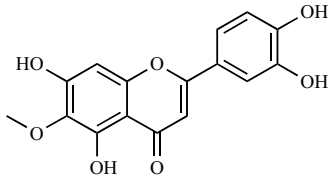
ARIs DERIVED FROM NATURAL/PLANT SOURCES

Various natural substances with AR inhibitory activity were reported for their role in management of diabetic complications. Variety of structurally diverse compounds has been identified as potent ARIs from natural sources such as terrestrial, marine and microorganisms. ARIs obtained from natural sources include flavonoids and vitamin C, a series of alkaloids including nandazurine, aporphine, benzylisoquinoline, papaverine, berberine, palmatine, coptisine, and jateorrhizine [172-174]. Some dietary sources were studied for ARI activity and prominent inhibitory activity was found in spinach (*Spinaceae oleracea*), cumin (*Cuminum cyminum*), fennel (*Foeniculum vulgare*), lemon (*Citrus lemon*), basil (*Ocimum sanctum*), black pepper (*Piper nigrum*), fenugreek (*Trigonella foenumgraceum*), bitter gourd (*Momordica charantia*), orange (*Citrus sinensis aurantium*), curry leaves (*Murraya koenigii*), cinnamon (*Cinamomum zeylencium*), ajwain (*Trachyspermum ammi*), and gauva (*Psidium guajava*) with IC_{50} values raning from 0.10 to 0.70 mg/mL for inhibition of rat lens AR [175]. Many plant extracts were reported as potent inhibitors of AR including aqueous and alcoholic extracts of *Azadirachta indica*, *Curcuma longa*, *Ocimum sanctum*, *Withania somnifera*, *Embelica officinalis*, *Gymnema sylvestre*, *Aralia*

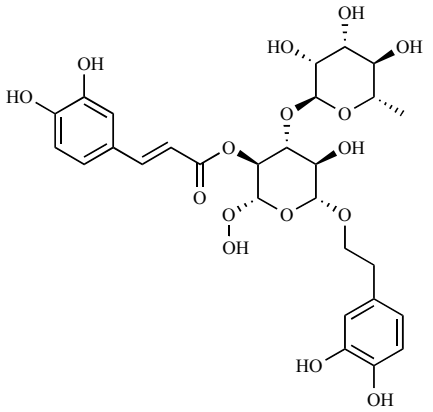
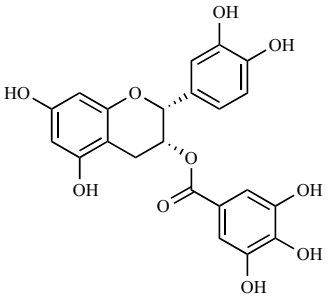
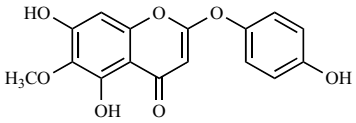
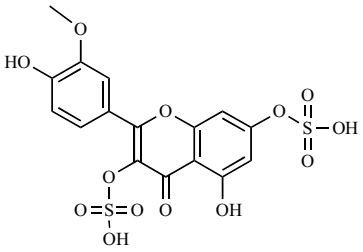
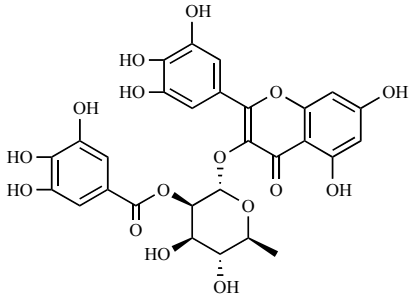
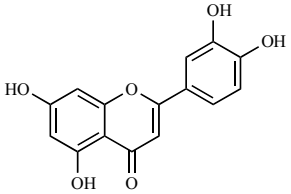
elata, *Hybanthus enneaspermus*, *Cinamomum zeylencium*, *Citrus lemon*, *Cuminum cyminum*, *Foeniculum vulgare*, *Momordica charantia*, *Artemisia apiacea*, *Cassia fistula*, *Biophytum sensitivum*, *Adhatoda vasica*, *Ocimum sanctum*, *Psoralea corylifolia*, *Tinospora cordifolia*, *Flemingia lineata*, *Murraya koenigii*, *Ocimum sanctum*, *Piper nigrum*, *Psidium guajava*, *Spinaceae oleracea*, *Trachyspermum ammi*, and *Trigonella foenumgraceum* [176]. A molecule with both AR inhibitory activity and antioxidative properties could be more effective than a compound with either ARI or antioxidant property alone. Many plants with AR inhibitory activity were reported for to be used for the treatment of diabetic complications [177]. Indobine and indobinine isolated from *Rauvolfia serpentina* were found to be potent inhibitors of AR [178]. Alcoholic extracts of *Ceasalpinia digyna* Rottler and, *Alangium lamarckii* Thwaits plant exhibited significant inhibitory effects on AR in the rat lens *in vitro* [179]. Ether and methanol extracts of *Gentiana lutea* roots showed significant inhibitory activities against both rat lens and human ALR2 and inhibited sorbitol accumulation in human erythrocytes in a dose-dependent manner under high glucose conditions. Molecular docking studies revealed that a secoiridoid glycoside, amarogentin, may be a potential inhibitor of ALR2 [180]. β-glucogallin isolated from the gooseberry fruit was reported as selective as well as relatively potent ARI (IC_{50} value of 17 μM) *in vitro*, and significantly prevented sorbitol accumulation [181]. Four different types of marine natural compounds containing a heterocyclic system, and at least two phenolic groups were isolated from tunicates and were found to inhibit human AR [182]. Magnesium lithospermate B isolated from the Oriental herbal remedy, *Salvia miltiorrhizae* is a new generation antioxidant as well as ARI. In this context, researchers found that magnesium lithospermate B activated the NQO1 via the Nrf2-ARE pathway, which plays an important role in inhibition of the major molecular mechanisms that lead to vascular damage and the proliferation and migration of vascular smooth muscle cells. Magnesium lithospermate B treatment can block four consequences of endothelial cell exposure to hyperglycaemia (increase in AGE formation, increase in oxidative stress, and increase in hexosamine pathway and reduction in vascular function). Magnesium lithospermate B has potent antifibrotic effect in TAA-treated cirrhotic rats, and inhibited fibrogenic responses in HSCs, thereby suggest that magnesium lithospermate B has potential as a novel therapy for hepatic fibrosis [183-186]. Recently, many phytoconstituents isolated from well known medicinal plants such as *Chrysanthemum indicum*, *Chrysanthemum morifolium*, *Prunus mume*, *Myrcia multiflora*, *Centella asiatica*, *Salacia reticulata*, *Salacia oblonga*, and *Salacia chinensis* were reported as potent inhibitors of the enzyme AR [187].

Phytoconstituents along with the chemical structure with significant AR inhibitory activity obtained from plant/natural sources are summarized in Table **2**. These phytoconstituents belong to a variety of chemical classes including flavonoids and other phenolic compounds, terpenoids, alkaloids, coumarins, and tannins [176-177, 187-189].

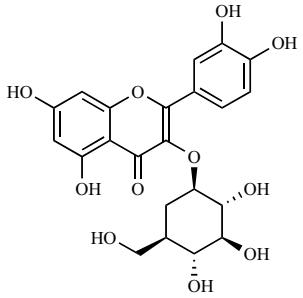
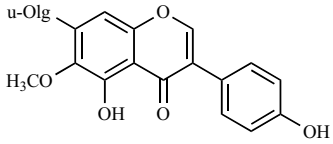
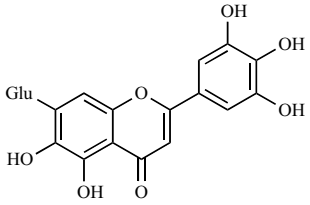
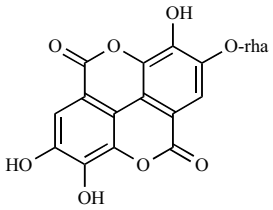
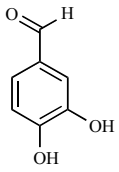
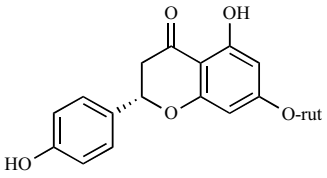
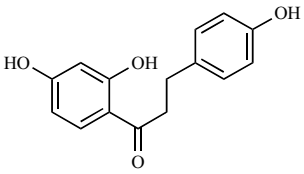
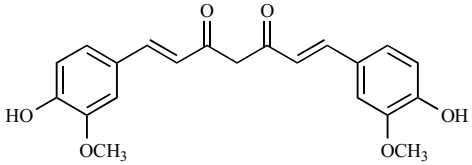
Table 2. Phytoconstituents with most potent AR inhibitory activity obtained from plant/natural sources.

Compound Name	Compound Structure	Remarks	Ref.
Flavonoids and other phenolic compounds			
Quercitrin		▪ Potent noncompetitive type ARI from flavonoids category ▪ Effectively blocked polyol accumulation in intact rat lenses	[190]
Patuletin-3-O-β-D-robinoside		▪ Potent ARI isolated from *Brickella arguta* ▪ 86% inhibition of AR at 10^{-5} M concentration	[191]
Nepetin		▪ Isolated from *Eupatorium ballotaefolium* ▪ AR inhibitory activity similar to that of quercitrin	[192]

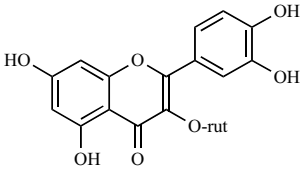
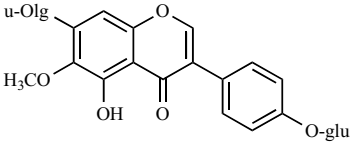
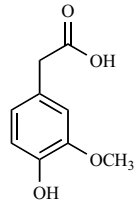
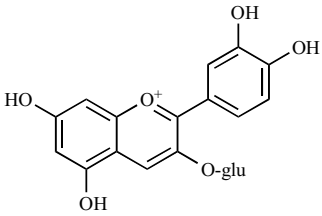
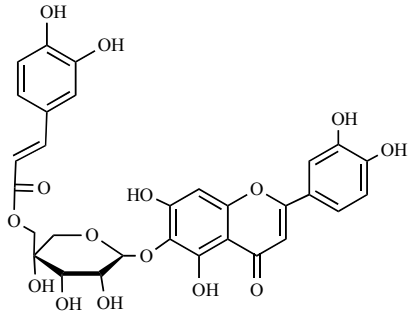
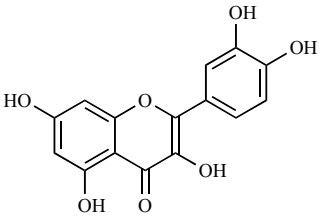
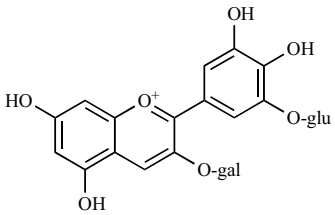
(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Acetoside		▪ A potent ARI isolated from *Monochasma savatierii* ▪ More potent ARI than baicalein (pevisouly known ARI) with IC_{50} value of 3.90×10^{-7} M compared to IC_{50} value of 9.80×10^{-7} M for baicalein	[193]
Epicatechin gallate		▪ Isolated from hot-water extract of green tea ▪ A potent ARI with IC_{50} value of 38 µmol/L for AR inhibitory activity	[194]
Capillarisin		▪ Potent bovine rat lens ARI isolated from an ethyl acetate extract of *Artemisiae Capillari* ▪ IC_{50} value of 0.22 µM	[195]
Isorhamnetin-3,7-disulfate		▪ Potent ARI isolated from *Polygonum hydropiper* ▪ Selective inhibitor of AR with IC_{50} value of 1.8 µM compared to aldehyde reductase	[196]
Desmanthin-1		▪ Potent inhibitor of AR and α-glucosidase obtained from leaves of *Myrcia multiflora* ▪ Selective inhibitor of AR with IC_{50} value of 8.2×10^{-8} M	[197]
Luteolin		▪ Potent and selective ARI isolated from methanolic extract of *Chrysanthemum indicum flowers* ▪ IC_{50} value of 0.45 µM	[198, 199]

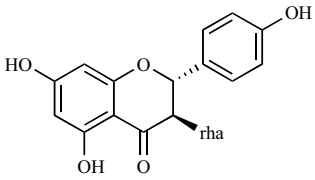
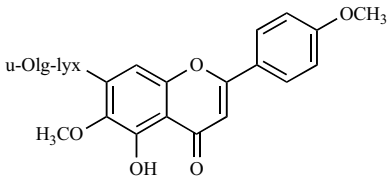
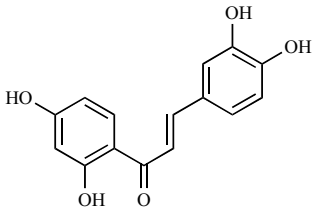
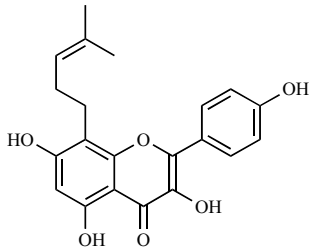
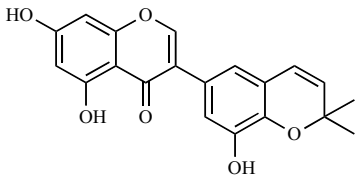
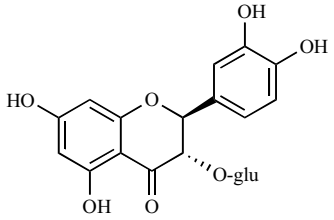
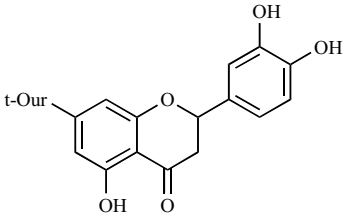
(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Isoquercitrin		▪ Isolated from tea leaves (English tea) ▪ Potent inhibitor of AR with IC_{50} value was 10^{-6} M for AR inhibition ▪ Significantly inhibited sorbitol accumulation	[200]
Tectoridin		▪ Potent ARI isolated from from methanolic extract of *Belamcanda chinensis* rhizomes along with IC_{50} value of 1.08×10^{-6} M	[201]
Isoaffinetin		▪ Potent lens ARI isolated from *Manilkara indica* ▪ Selectively inhibited rat lens AR with no activity against aldehyde reductase	[202]
4-(α-rhamnopyranosyl)ellagic acid		▪ Potent ARI isolated from *Myrciaria dubia* leaves ▪ IC_{50} value of 4.1×10^{-8} M for inhibition of human recombinant AR	[203]
Protocatechualdehyde		▪ Potent rat lens ARI isolated from fruiting bodies of *Ganoderma applanatum* ▪ IC_{50} value of 0.7 µg/mL	[204]
Naringin		▪ 69% AR inhibition in streptozotocin induced diabetic rats ▪ Significantly reduced blood glucose of diabetic rats	[205]
Davidigenin		▪ Isolated from seeds of *Aremisia dracunculus* ▪ A potent ARI with IC_{50} value of of 12.70 µM	[206]
Curcumin		▪ Isolated from *Curcuma longa* ▪ Potent ARI with IC_{50} value of 6.8 µM for AR inhibition	[207-208]

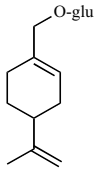
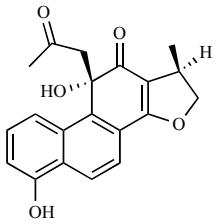
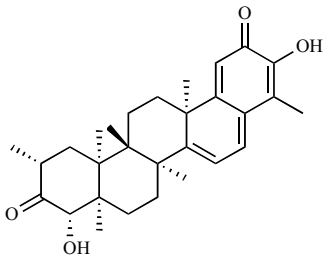
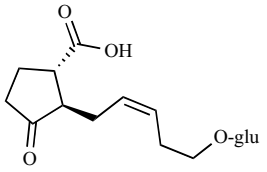
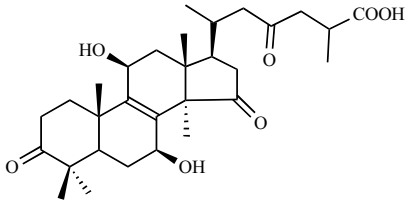
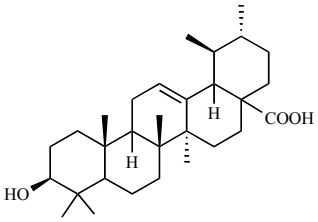
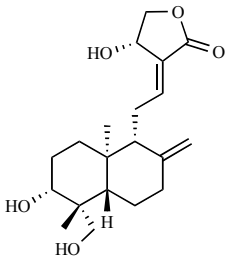
(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Rutin		▪ Isolated from *Nelumbo nucifera* leaves ▪ Potent lens ARI with IC_{50} value of 2.49 µM	[209]
Tectoridin 4′-O-β-D-glucoside		▪ Isolated from *Viola hondoensis* ▪ Potent rat lens ARI with IC_{50} value of 0.54 µM	[210]
2-(4-hydroxy-3-methoxyphenyl)ethanoic acid		▪ Isolated from *Zingiber officinale* ▪ Good inhibitor of recombinant human AR with IC_{50} value of 18.5 µM for AR inhibition	[211]
Cyanidin-3-glucoside		▪ Isolated from pigmented rices (*Oryza sativa*) ▪ Potent ARI with IC_{50} value of 8.7 µg/mL	[212]
Luteolin 6-C-(6"-O-trans-caffeoylglucoside)		▪ Isolated from *Phyllostachys nigra* ▪ Showed antioxidative as well as AR and AGEs inhibitory effects ▪ IC_{50} value of 0.0134 µM for AR inhibition	[213]
Quercetin		▪ Isolated from finger millet (*Eleusine coracana*) ▪ Potent lens ARI with IC_{50} value of 14.8 nM ▪ Effectively inhibited cataract formation	[214]
Delphinidin-3-O- β-galactopyranoside-3′-O-β-glucopyranoside		▪ Isolated from fruit extract of *Litchi chinensis* ▪ Potent rat lens ARI with IC_{50} value of 0.23 µg/mL for AR inhibition	[215]

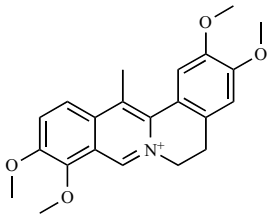
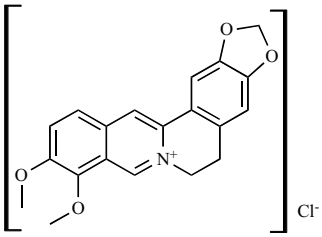
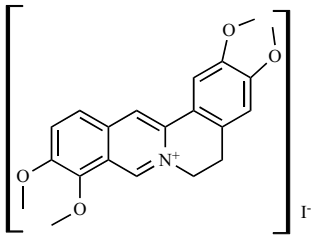
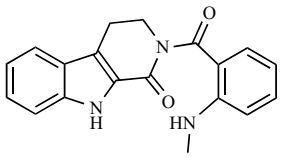
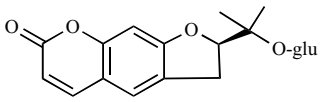
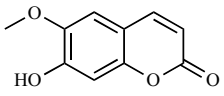
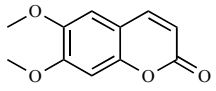
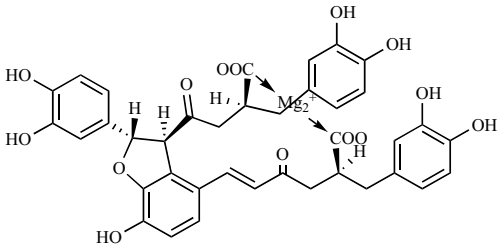
(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Engeletin		▪ Isolated from leaves of *Stelechocarpus cauliflorus* ▪ IC_{50} value of 1.16 µM	[216]
Kakkalide		▪ Isolated from ethyl acetate extract of *Viola hondoensis* ▪ Potent rat lens ARI with IC_{50} value of 0.3 µg/mL	[217]
Butein		▪ Potent ARI isolated from *Rhus verniciflua* with IC_{50} value of 0.5 µM ▪ Also displayed antioxidant as well as AGE inhibitory activity	[218]
Desmethylanhydroicaritin		▪ Isolated from *Sophora flavescens* ▪ Potent ARI with IC_{50} value of 0.95 µM for inhibition of rat lens AR	[219]
Semilicoisoflavone B		▪ Isolated from *Glycyrrhiza uralensis* roots ▪ Potent ARI with IC_{50} values of 1.8 µM for inhibition of rat lens AR	[220]
Glucodistylin		▪ Noncompetitive ARI isolated from *Quercus acutissima* ▪ IC_{50} value of 7.2 µM ▪ Inhibited sorbitol accumulation by 48.84% at 50 µM	[221]
Luteolin 7-rutinoside		▪ Isolated from methanolic extracts of *Artemisia montana* by repeated column chromatography ▪ Potent ARI with IC_{50} value of 0.55 µM for inhibition of rat lens AR	[222]

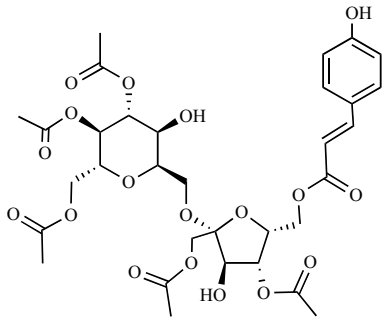
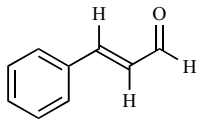
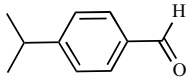
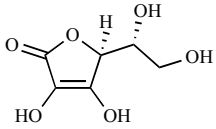
(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Terpenoids and related compounds			
Perilloside A		▪ Isolated from leaves of *Perilla frutescens* ▪ Competitive inhibitor of rat lens AR with respect to glyceraldehyde	[223]
Danshenol A		▪ Isolated from methanolic extract of *Salvia miltiorhiza* ▪ IC_{50} value of 0.10 µg/mL for inhibition of rat lens AR	[224]
Tingenin B		▪ Isolated from methanolic extract of Salacia chinensis stems ▪ Potent ARI with IC_{50} value 7 µM for inhibition of rat lens AR	[225]
12-hydroxyjasmonic acid 12-O-β-glucopyranoside		▪ Isolated from *Origanum vulgare* ▪ 77% inhibition of rat lens AR at 100 µM concentration	[226]
Ganoderic acid Df		▪ Isolated from fruiting body of *Ganoderma lucidum* ▪ Potent ARI with IC_{50} value of 22.8 µM	[227]
Urosolic acid		▪ Isolated from *Ocimum gratissimum* ▪ Potent ARI with IC_{50} value of 14.47 µM for rat lens AR inhibition	[228]
Andrographolide		▪ Potent rat lens ARI isolated from methanolic extract of *Andrographis paniculata* ▪ Significantly decreased galactitol accumulation *in vivo*	[229]

(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Alkaloids and related compounds			
Dehydrocorydaline		▪ Isolated from methanolic extract of *Corydalis turtschaninovii* tubers ▪ 44.5% inhibition of lens AR	[230]
Berberine chloride		▪ Isolated from Coptis japonica ▪ IC_{50} value of 13.98 µM for inhibition of rat lens AR	[231]
Palmatine iodide		▪ Isolated from Coptis japonica ▪ IC_{50} value of 13.45 µM for inhibition of rat lens AR	[231]
Rhetsinine		▪ Potent ARI isolated from hot water extract of *Evodia rutaecarpa* ▪ IC_{50} value of 24.1 µM	[232]
Coumarin derivatives			
Nodakenin		▪ Isolated from *Angelica gigas* roots ▪ IC_{50} value of 7.33 µM for inhibition of rat lens AR	[233]
Scopoletin		▪ Isolated from *Angelica gigas* stems ▪ IC_{50} value of 2.59 µM for inhibition of rat lens AR *in vitro*	[234]
Scoparone		▪ Isolated from *Artemisia montana* ▪ IC_{50} value of 44.30 µM for inhibition of rat lens AR	[222]
Miscellaneous			
Magnesium lithospermate B		▪ Isolated from oriental herbal remedy (*Salvia miltiorrhizae*) ▪ Signifiacnly useful in the treatment of hepatic fibrosis	[183-186]

(Table 2) Contd….

Compound Name	Compound Structure	Remarks	Ref.
Prunose I		▪ Isolated from methanolic extract of *Prunus mume* fresh flowers ▪ Potent rat lens ARI with IC_{50} value of 58 µM ▪ Also inhibited thrombin induced platelet aggregation	[235]
trans-Cinnamaldehyde		▪ Isolated from *Cinnamomum cassia* bark ▪ IC_{50} value of 3 µg/mL for AR inhibition	[236]
Cuminaldehyde		▪ Rat lens ARI isolated from *Cuminum cyminum* ▪ IC_{50} value of 0.80 M	[237]
Vitamin C		▪ Treatment with 100 mg for 58 days resulted in normalized levels of sorbitol	[238]

ROLE OF ARIs IN THE TREATMENT OF DIABETIC COMPLICATIONS

AR along with importance as detoxification of harmful aldehydes, renal osmoregulation and as energy provider in sperms was first found to be involved in the pathogenesis of diabetic complications [239]. Major diabetic complications include cataract, retinopathy, neuropathy, and nephropathy. ARIs appear to be an emerging treatment option for the management of the diabetic complications according to the study results from experiments *in vitro*, in animal models, and clinical trials [26].

Diabetic Cataract

Cataract is considered a major cause of blindness in diabetic patients worldwide and covers around 42% of overall visual impairment. Cataract is mainly responsible for almost 80% blindness in India [240]. It had been reported that diabetic complications such as diebetic cataract resulted in blindness in diabetic patients. It was reported in literature that sorbitol accumulation in the cells results in the formation of lens cataracts due to hyperosmotic effect. In case of lens, formation of sorbitol is more and fast than its conversion to fructose by SDH. Also due to the polar nature sorbitol is difficult to remove from cells. This results in the osmotic vhanges leading to cataract formation. It was evidenced from the animal studies that accumulation of sorbitol in lens resulted damage to lens fibers, leading to formation of lens opacities. These results led to the formation of osmotic hypothesis about formation of cataracts explaining that osmotic changes due to increased sorbitol accumulation due to action of AR resulted in the swelling of lens leading to formation of cataracts. In addition, osmotic changes due to accumulation of polyols in lens lead to cataract formation due to stimulation of apoptosis of lens epithelial cells [241-244]. Thus, inhibition of the enzyme AR (polyol pathway) is an emerging target for the prevention and treatment of diabetic cataracts.

Administration of plant flavonids, such as quercitrin or the isoflavone genistein to diabetic rats, have delayed dietary galactose-induced or diabetic cataract formation by the decrease in the accumulation of sorbitol [245-247]. Examples of natural products with known AR inhibitory activity useful in the prevention or treatment of diabetic cataracts are extracts from plants like *Ocimum sanctum, Withania somnifera, Curcuma longa, Azadirachta indica, Enicostemma hyssopifolium, Gymnema sylvestre, Eclipta alba, Tinospora cordifolia, Hybanthus enneaspermus, Houttuynia cordata, Tinospora cordifolia, Phyllanthus emblica, Embelica officinalis, Adhatoda vasica, Allium cepa, Angelica dahurica, Cassia fistula, Citrus aurantium, Cochlospermum religiosum, Emilia sonchifolia, Erigeron annuus, Ginkgo biloba, Momordica charantia, Moringa oleifera, Origanum vulgare, Pterocarpus marsupium, Silybum marianum, Trigonella foenum-graecum, and Vitex negundo* [248-254]. Diabecon (an Indian herbal drug used for diabetes) was reported as potent inhibitor of rat lens AR with an IC_{50} value of 10 µM. The anti-cataract effect was mainly due to *Gymnema sylvestre*, one of the constituent herbs of Diabecon [255].

The first ARI to undergo actual early-stage drug development for diabetic cataract was alrestatin (AY-22284) by Ayerst Pharmaceuticals, was effective in reducing the swelling of diabetic lenses in glucose medium. Oral administration of AY-22284 resulted in singnificantly reduced accumulation of sorbitol in the lenses and sciatic nerves of galactosemic rats and rats with streptozotocin-induced diabetes leading to suppression of cataract formation [256, 257]. Sorbinil, a potent ARI, effectively blocked the progression of a galactose-induced cataract when treated topically in one eye. Sorbinil treated eye remained clear during the experiment and and untreated eye developed cataracts during the experiment. In addition treatment of diabetic rats with sorbinil resulted in prevention of cataract formation during the experiment [258-260]. In ranirestat (a pyrazine derivative ARI) treated diabetic rats, no lens opacity was observed in the lens of streptozotocin-diabetic rats. Ranirestat significantly prevented development of cataract formation in diabetic rat lens [261, 262]. Treatment of control and streptozotocin-diabetic rats with fidarestat (an ARI) resulted in prevention of diabetic cataract formation and counteracted retinal nitrosative stress, and poly(ADP-ribose) polymerase activation, as well as glial activation [263]. In dogs the topically applied ARI kinostat has been shown to reverse the development of sugar cataracts in dogs fed a diet high in galactose [264]. Two new potent ARIs, AL-1567 and AL-1576; when administered orally once per day to 3-week diabetic rats for a period of eight days, successfully prevented the development of cataract formation [265]. Ponalrestat (a potent rat lens ARI) administration (at a dose of 25 mg per kg per day) to diabetic rats resulted in complete prevention of cataract formation [64]. The oral administration of zenarestat (a potent rat lens ARI) to diabetic rats resulted in delayed cataract formation and admixture of 0.028% zenarestat with diet completely inhibited the cataract formation [69]. Treatment of diabetic rats with GP-1447 (an ARI) resulted in significant prevention of cataract formation via decrease in sorbitol levels in lens [266]. Ellagic acid a bioflavonoid present in many dietary sources significantly delayed diabetic cataract formation in rats by inhibition of AR [267]. Quercitrin gallate showed potential inhibitory activity against rat lens AR and significantly reduced the cataract formation [268].

Diabetic Retinopathy

Diabetic retinopathy is the most frequently occurring microvascular complication of DM and is a leading cause of blindness in the developed and developing countries. In Europe and the U.S. alone, the WHO (World Health Organization) has estimated that diabetic retinopathy accounts for approximately 15-17% of total blindness. According to study on more than 20,000 participants with diabetes, 34.6% had diabetic retinopathy among individuals with diabetes [269-271]. The main features of diabetic retinopathy are retinal lesions and abnormalities that indicate vascular damage and death or dysfunction of the neural retina [270]. AR is implicated with diabetic retinopathy through numerous mechanisms including activation of nuclear factor kB, monocyte chemotactic protein-1 (MCP-1) which contributes to the formation of diabetic epiretinal membranes, increased oxidative stress, upregulation of retinal vascular endothelial growth factor (VEGF), and activation of poly(ADP-ribose)polymerase (PARP). These alterations in vascular permeability and oxidative stress can be prevented by the use of ARIs [272].

A two fold thickening of capillary basement membranes of rat retinas resulting from dietary galactose was prevented by ARI sorbinil. It was reported that sorbinil played an important role in the stabilization of the blood-retinal barrier in early diabetic retinopathy of non-insulin-dependent diabetic patients (250 mg once a day oral administration of sorbinil). Sorbinil treatment of galactose-fed rat model had prevented the retinal microangiopathies of the galactose-fed rat model of diabetic retinopathy. Galactose-fed, sorbinil-treated rats, at 24 months, had no intraretinal microvascular abnormalities [273-275]. According to the results from phase III trial research in Japan, Zenarestat developed as an eye drop formulation was specifically effective for the treatment of diabetic retinopathy [276]. Treatment of insulinized streptozotocin-induced diabetic rats with ARI-809 improved protected the retina from abnormalities that occur in diabetes [277]. Fidarestat was reported to prevent retinal oxidative stress and overexpression of VEGF in diabetic rats. Oral administration of fidarestat diminished accumulation of leukocytes prevalence rate of microaneurysms, basement membrane thickness, and decreased number of pericytes, reduced polyol pathway and oxidative stress leading to prevention of diabetic retinopathy [278-280]. Treatment with M79175 resulted in dose-dependent protection against pericyte degeneration and subsequent microaneurysms formation associated with early diabetic retinopathy in galactose-fed dogs [281-283]. A diabetic-like thickening of retinal capillary basement membranes induced in rats fed for 207 consecutive days a diet containing 50% galactose was prevented by the addition to the diet of tolrestat. However, clinical trials of ARIs had little therapeutic success in diabetic retinopathy [284-285].

Among the various ARIs from natural sources, some plants like *Ocimum sanctum, Tinospora cordifolia, Azardiracta indica, Ganoderma lucidum* were found to be effective in diabetic retinopathy. Combined therapy of streptozotocin induced diabetic albino male rats with *Ocimum sanctum* (Tulsi) and Vitamin E for 16 weeks was effective in diabetic retinopathy and vision was improved. The diabetic retinopathy in the animals was reversed significantly. *Tinospora cordifolia* showed safe and significant efficacy in the treatment of diabetic retinopathy in streptozotocin induced diabetic rats due to its anti-hyperglycemic, angiogenic, anti-inflammatory and antioxidant actions. *Ganoderma lucidum* spores were effective in the treatment of diabetic retinopathy by increasing the capability of diabetic rats against oxidation and reduce damage of retina from oxidation [286-288].

Diabetic Neuropathy

Diabetic neuropathy is the most common neuropathy in developed nations. Diabetic neuropathy is the most common and incapacitating long-term complication of both types of diabetes which results in discomfort, illness and sensory and motor deficits in the limbs, and is also an important reason

for development of foot ulcers. The prevalence of diabetic neuropathy was estimated to be about 8% in newly diagnosed patients and more than 50% in patients with old disease. Hyperglycemia plays an important role in the pathogenesis of diabetic neuropathy through activation of AR resulting in increased sorbitol levels leading to cellular injury and reduced myo-ionositol in the peripheral nerves and thereby leading to reduced activity of Na^+/K^+-ATPase, which is necessary for nerve conduction [289-293].

Among the various ARIs obtained from natural sources, some compounds like quercetin, rutin, baicalein, chlorogenic acid, epigallocatechin-gallate, ellagic acid, naringin, puerarin, curcumin, baicalin, and eugenol were reported to be effective in painful diabetic neuropathy [175]. Quercetin (a bioflavonoid) produced a marked increase in tail-flick latencies in both diabetic and non-diabetic mice indicating an antinociceptive activity pointing towards its potential to mitigate diabetic neuropathic pain. Rutin (a glycoside of a flavonoid) produced a protective effect against diabetic neuropathy via its metal chelating property. The flavonoid baicalein (5,6,7-trihydroxyflavone), a potent ARI counteracted diabetes-associated p38 mitogen-activated protein kinase phosphorylation, oxidative-nitrosative stress, and activation of lipoxygenase, but had no effect on sorbitol accumulation. Chlorogenic acid (a natural organic phenolic compound) was found to show antihyperalgesic activity in diabetic neuropathic pain owing to its antioxidant and anti-inflammatory effects. The chronic oral treatment of streptozotocin-induced diabetic rats with a potent ARI epigallocatechin-gallate (found in green tea) improved diabetic neuropathy due to the inhibition of oxidative stress. Ellagic acid, a potent phenolic ARI produced neuroprotective effects against oxidative damage in diabetic neuropathy models due to its antioxidant property. Naringin (a flavanone glycoside) an ARI along with antioxidant property produced neuroprotective effect in painful diabetes induced neuropathy. Puerarin (an isoflavonoid) was efficient in the treatment of diabetic peripheral neuropathy due to dilation of blood vessels, improved microcirculation and decreased blood thickness leading to increased conductive function of the nerves. Curcumin showed significant antihyperalgesic activity in streptozotocin induced diabetic mice pointing towards its potential in the treatment of diabetic neuropathic pain. Treatment of diabetic rats with baicalin resulted in increased nerve conduction velocity and prevention of diabetic neuropathy development through direct inhibition of AR. Eugenol (found in clove oil) improved diabetic vascular and nerve function in streptozotocin-induced diabetic rats. PMI-5011 (an ethanolic extract of *Artemisia dracunculus*) was found useful in the treatment of diabetic neuropathy by decreasing lipoxygenase activation and oxidative stress. Administration of fenugreek seed powder (*Trigonella foenum*) to diabetic rats showed the preventive effects in diabetic neuropathy. Although these plants products or plants were effective in the treatment of diabetic neuropathy, and are potent inhibitors of AR but it is not necessary that the effect was due to inhibition of AR [177, 294-306].

Epalrestat (ONO-2235) is the only ARI that is approved in Japan, India and China for the symptomatic treatment and management of diabetic neuropathy [26]. In a 3-year, multi-centre, clinical study, the long term administration of epalrestat significantly delayed the development of diabetic neuropathy and improved the associated symptoms of the disease, without any severe adverse effects [307]. On the basis of data form six clinical trials, it was reported that administration of epalrestat in a dose of 50 mg (three times daily) improved motor and sensory nerve conduction velocity and subjective neuropathy symptoms along with minor side effects [308]. Epalrestat was reported to inhibit the worsening of diabetic peripheral neuropathy [309]. In a clinical study of 2190 patients with diabetic neuropathy for 3-12 months; epalrestat was reported to improve the subjective symptoms in 75% patients with minor side effects in 2.5% patients [310]. It was reported in a study that epalrestat showed better efficacy in the patients with good glycemic control and less severe diabetic complications for the prevention and treatment of diabetic neuropathy. Later it was reported in a long-term clinical study that the prevention of the diabetic neuropathy by epalrestat was dependent on the severity of the diabetic neuropathy [311-312]. In a study on 220 patients with diabetic neuropathy, treatment of diabetic neuropathy with combination of epalrestat and methylcobalamin resulted in faster and better relief from synptoms of diabetic neuropathy [313]. Tolrestat (AY-27773) a potent inhibitor of enzyme AR was approved for the treatment of diabetic complications including diabetic neuropathy in several countries, but it was discontinued due to severe liver toxicity [26]. In a study, treatment of diabetic patients with fidarestat (SNK-860) considerably stabilized the increased levels of sorbitol in erythrocytes without any major side effect. Administration of fidarestat to 279 patients with diabetic neuropathy for 52 weeks resulted in improvement of subjective symptoms of diabetic neuropathy without any major adverse effect [314-316]. Treatment of diabetic neuropathic rats with fidarestat for 10 weeks resulted in normalization of the increased levels of sorbitol and fructose and reduced number of 8-hydroxy-2'-deoxyguanosine-positive cells in dorsal root ganglion neurons [317]. Administration of ranirestat (AS-3201, under development by Dainippon Sumitomo Pharma Co Ltd) for 60 weeks (at a dose 20 mg per day) in patients with diabetic sensorimotor polyneuropathy improved motor nerve conduction velocity and vibration perception thresholds [318, 319]. Ranirestat is an uncompetitive and reversible inhibitor of AR. Oral administration of ranirestat in the sciatic nerve and lens of streptozotocin-induced diabetic rats reduced sorbitol levels. It was reported that repeated oral administration of ranirestat significantly reduced sorbitol levels in rats with diabetic sensorimotor polyneuropathy [2]. In a study on 549 patients ranirestat was well tolerated without any major adverse effects. Ranirestat has completed two Phase III clinical trials for the treatment of diabetic complications [320-321]. Zenarestat is a potent ARI with IC_{50} value of 3.6 nM, significantly reduced the sorbitol level in rat sciatic nerve [69]. In a randomized clinical trial conducted in patients with mild to moderate diabetic peripheral polyneuropathy for 52 weeks, zenarestat significantly reversed the progression of diabetic neuropathy [322]. In a study of the effects of zenarestat on diabetic peripheral neuropathy in an animal model of type 2 diabetic

rats, it was found that treatment with zenarestat (at a dose of 32 mg/kg) improved nerve dysfunctions in diabetic rats, along with normalization of nerve sorbitol levels [323]. Administration of zenarestat to streptozotocin-induced diabetic rats (at a dose of 32 mg/kg) normalized the increased sorbitol levels (40% inhibition of sorbitol accumulation) and considerably improved the nerve blood flow and minimal F-wave latency [324]. Zenarestat was reported to significantly restore or inhibit the alteration of endoneurial blood flow in streptozotocin-induced diabetic rats caused by an impairment of nitric oxide function [325]. It was reported that treatment of streptozotocin-induced diabetic rats with zenarestat for thirteen months reversed the morphological abnormalities of the dorsal root ganglia in diabetic somatosensory neuropathy [326]. Sorbinil was reported to have a significant beneficial effect in the treatment of diabetic neuropathy in a clinical study on 37 patients without any side-effects [327]. Treatment of diabetic rats with sorbinil prevented and reversed accumulation of sorbitol and normalized depletion of nerve myo-inositol in the sciatic nerve [328]. However, no beneficial effect of Sorbinil was reported on either the clinical manifestation or on the neurophysiological measurements made in diabetic neuropathic diabetic patients over 12 months of treatment [329]. Later it was reported that the early clinical signs and symptoms of diabetic neuropathy were not altered by sorbinil treatment in 497 insulin-dependent diabetic patients but improved nerve conduction velocity [330]. It was reported that administration of sorbinil as dietary supplement in rats with streptozotocin induced diabetic rats resulted in improvement of sorbitol accumulation, normalization of myo-inositol depletion and decrease in the turnover of monoesterified phosphate groups in phosphatidylinositol-4,5-bisphosphate [331]. It was reported that treatment with adequate doses of sorbinil is an effective approach for the reversal of early diabetic neuropathy. Treatment with sorbinil restored nerve concentrations of GSH and ascorbate (two major non-enzymatic antioxidants), and completely blocked diabetes-induced lipid peroxidation [330]. Treatment with sorbinil was effective in the prevention of neural dysfunction in diabetes and significantly improved the diabetes-induced impairment of acetylcholine-mediated vasodilation of epineurial vessels of the sciatic nerve. This therapy was effective in prevention of the appropriate metabolic disorders associated with either activation of the polyol pathway or increased non-enzymatic glycation [332]. Later it was reported that treatment with sorbinil resulted in the significant inhibition of polyol pathway which improved vascular and C-fiber functions leading to restoration of pressure-induced vasodilation. Thus, sorbinil was effective in inhibition of ulcers [333, 334].

Diabetic Nephropathy

Diabetic nephropathy or diabetic kidney disease is the major reason behind the occurrence of chronic renal disorder, and affects approximately 40% of patients with T1D and T2D. It is a progressive disorder that results in kidney failure. Diabetic neuropathy had been defined as increased excretion of proteins in urine and it increased the risk of mortality due to cardiovascular disorders. It was reported that excretion of albumin in urine predicts the development of diabetic neuropathy due to elevated glomerular filtration rates and higher blood pressures [335-337]. As the number of patients with diabese is expected to increase; resulting in prevalence of diabetic nephropathy leading to significant heavy burden on medical, social and economic systems worldwide mainly in the developing nations [338]. It was reported that increased Ar activity resulted in increased production of ROS and increased production of metabolites that lead to hyperglycemia-induced cellular impairment [29, 339]. Conversion of glucose to sorbitol by AR and then conversion of sorbitol to fructose by SDH results in oxidative stress and activation of PKC. Sorbitol may interfere with the uptake and metabolism of myo-inositol. The flux of glucose through the polyol pathway leads to increased production of AGEs, which produce oxidative stress [340]. It was reported that the inhibition of the AR enzyme was beneficial in the treatment of diabetic neuropathy, by a variety of ARIs [338].

Many phytoconstituents reported as potent ARIs were showed significant potential in the treatment of diabetic neuropathy. Among these compounds quercetin, myricetin, rosmarinic acid (isolated from *Origanum vulgare*), nepetrin and nepetin (isolated from *Rosmarinus officinalis*), isoquircetrin (isolated from *Polygonun hydropiper*), astilbin (isolated from the leaves of *Englhardtia chrysolepis* and *Smilax china*), luteolin (isolated from *Chrysanthemum indicum*), catechins (isolated from green tea), (-)-epigallocatechin 3-O-gallate, mangiferin (isolated from *Salacia chinensis*), naringin, curcumin, apocynin (an isoflavonoid isolated from *Belamcanda chinensis*), ellagic acid (isolated from *Myrciaria dubia*), caffeic acid (isolated from *Origanum vulgare*), ferulic acid (isolated from *Eleusine coracana*), Butein (isolated from bark of *Rhus verniciflua*), Berberine (isolated from *Coptis japonica*) and various phytoconstituents in rhizome of *Zingiber officinalis* were reported to show protective and prophylactic role on the diabetic nephropathy mainly by reducing the oxidative stress and due to their anti-inflammatory properties in various animal models [175, 177]. Berberine is a plant alkaloid with anti-diabetic action. The antioxidant and AR inhibitory activities of berberine may be useful in alleviating diabetic nephropathy [341].

Tolrestat was reported to normalize the functional changes of glomerular hyper-filtration, mesangial cell hypo-contractility, and increased glomerular permeability to albumin due to diabetic nephropathy in diabetic rat indicating potential role of ARIs in the treatment of diabetic kidney disease [342]. Epalrestat prevented renal hypofunction and mesangial expansion in diabetic rats without influencing the levels of blood glucose in streptozotocin-induced diabetic rats. In a clinical trial on type 2 diabetic patients with micro-albuminuria to expose the long-term effect of epalrestat on the development of incipient diabetic nephropathy showed that treatment with epalrestat (150 mg/day) for 5 years resulted in significantly prevented increased urinary albumin excretion suggesting the potential benefits of ARIs in preventing the development of diabetic nephropathy in patients with T2D [343-344].

ROLE OF ARIs IN THE TREATMENT OF NON-DIABETIC DISEASES

Cancer

The increased expression of the enzyme AR was reported in the cancer cells which suggested that the overexpression of AR may lead to resistance of cancer chemotherapy by inactivating some of the anticancer drugs like anthracycline, daunorubicin and doxorubicin [33, 239, 345, 346]. In this context, inhibition of AR increased the sensitivity of HeLa cell to anticancer agents through increased stimulation of extracellular signal-regulated kinases. These results suggested that the cancer treatment with anticancer agents in conjunction with ARIs resulted in improved effectiveness of anticancer agents [347]. Sorbinil prevented fibroblast growth factor-induced and platelet-derived growth factor-induced up-regulation of prostaglandin E2 (PGE2) synthesis in human colon cancer cells. It was reported that AR is an essential mediator of growth factor-induced up-regulation of COX-2, PGE2, and growth of Caco-2 cells, indicating that inhibition of AR may be a novel therapeutic approach in preventing the progression of colon cancer [348, 349]. AR appears to activate the signaling pathways and regulate the expression of genes essential to the survival or growth of cancer cells and adhesion molecules [350]. Recently, it was reported that, inhibition of AR prevented colon cancer cell viability by modulating microRNA-21 mediated expression of programmed cell death [351]. Results of another study showed that AR inhibition could be an emerging approach for the treatment of colon cancer as AR regulated cancer cell adhesion, invasion and migration [352]. AR inhibition was reported to inhibit the development of colon cancer by restoring phosphatase and tensin homolog [353]. In view of above, the inhibition of AR may be an emerging therapeutic target for the treatment of cancer.

Cardiovascular and Myocardial Disorders

Cardiovascular disorder is a major cause of morbidity and mortality in patients with diabetes mellitus. Increased activity of AR was reported in the mediation of various cardiovascular disorders such as cardiac hypertrophy, cardiac ischemia, angiopathy, cardiomyopathy, hypertension, restenosis, atherosclerosis, and endothelial dysfunction via activation of the polyol pathway [354]. Researchers showed that cardiomyocyte overexpression of human AR play a key role in the pathogenesis of cardiac dysfunction. These studies indicate that AR inhibition can be an emerging therapeutic approach for the treatment of ischemia and some forms of heart failure [355]. Results showed that ischemia increases activity of myocardial AR due to activation by nitric oxide. AR inhibition increased glycolysis and glucose oxidation. AR inhibited heart function, when subjected to ischemia/reperfusion, exhibited less ischemic injury and was associated with lower lactate/pyruvate ratios (a measure of cytosolic $NADH/NAD^+$), greater tissue content of adenosine triphosphate, and improved cardiac function. These findings indicate that AR is a component of ischemic injury and pharmacological inhibitors of AR were a novel adjunctive approach for protecting ischemic hearts [356]. Blockade of AR-dependent pathways plays an important role in disturbing cycles of cellular perturbation and tissue damage in cardiovascular disease [357]. Results from various researchers also showed that ARIs could be potential therapeutic agents for prevention of angiogenesis [358]. Blockade of polyol pathway through inhibition of AR was also reported as an emerging approach for the prevention and treatment of diabetic cardiovascular autonomic neuropathy [359].

Inflammatory Disorders

AR inhibition resulted in the suppression of the genes responsible for production of nitric oxide, overexpression of iNOS mRNA, prevented apoptosis, activation of caspase-3, p38-MAPK, c-Jun N-terminal kinase (JNK), NF-kappaB, and AP1 [360]. Inhibition of AR can be regarded as an emerging approach for the treatment of endotoxemia, sepsis and other ROS-induced inflammatory diseases [361-362]. Systemic inflammation and widespread organ injury during uncontrolled bacterial infections lead to sepsis. Recent studies indicate that targeting polyol pathway enzyme AR could be an emerging target for treatment of sepsis complications. In animal models of endotoxemia and polymicrobial sepsis, ARIs have shown promising results to control overproduction of inflammatory cytokines and chemokines which propagate systemic inflammatory response and tissue damage. These results suggest that AR inhibitors could act as novel anti-inflammatory agents [363]. AR plays a major role in the pathogenesis of a number of inflammatory disorders such as atherosclerosis, sepsis, asthma, uveitis, and colon cancer. As many ARIs had completed up to phase-III clinical trials for the treatment of diabetic complications, they may act as safe anti-inflammatory agents [364]. Recently AR inhibition was reported as an emerging target for prevention of allergic reactions due to their inhibitory effects on generation of pro-inflammatory cytokines and chemokines [365]. Airway inflammation due to allergic response to ragweed pollen extract, which subsequently activates oxidative stress-induced expression of inflammatory cytokines, could be prevented by ARIs [366]. ARIs such as tolrestat, imirestat and quercetin demonstrated efficacy in preventing loss of alveolar bone due to periodontitis in both diabetics and non-diabetics, suggesting a role for the sorbitol pathway and the potential for ARIs to reduce inflammatory responses [367].

Kidney Failure

AR has an impact on transforming growth factor (TGF) β1-induced synthesis of a high-molecular weight glycoprotein called fibronectin and type IV collagen in the mesangial cells under normoglycemia via activation of various protein kinases. Sorbinil or zopolrestat were reported to decrease the activation of these protein kinases. Under normal glucose concentration ALR2 produces extracellular matrix (ECM) components in the mesangial cells which might play a role in pathogenesis of nondiabetic glomerulosclerosis by deposition and obliteration of glomerular capillaries. The increased ALR2 activity in such cases may affect the peritoneal membrane from the vascular side in patients undergoing peritoneal dialysis which may decrease ultrafiltration process [368, 369]. Increase in the AGE-RAGE axis has been demonstrated in renal failure, both in animal models and in

humans [370]. It was reported that AR levels were increased in patients with chronic renal failure, suggesting that AR inhibition could be useful for the treatment of kidney failure [371].

Ovarian Disorders

Galactose is an important energy-providing nutrient and plays a major role in the biosynthesis of many macromolecules in the body. Accumulation of galactose and its metabolites in the mammalian ovary may damage ovary in case of abnormally high levels of AR. Galacticol is not easily metabolized and its intracellular accumulation results in damage to ovary as a result of osmotic changes and decrease in GSH levels. At this point, it must be noted that the affinity of ALR2 for galactose is relatively low, and high intracellular concentrations of galactose are required as in galactosemia. Inhibitors of AR were reported to block the damage due to galactose in animal models by decreasing galactitol concentration. They have been found to prevent ovarian dysfunction in rats fed with high galactose diet [372, 373].

Psychological Disorders

Based on the finding that peripheral neuropathy is a risk factor for depression in diabetes, it was speculated that there may be a connection between psychological disorders and increased sorbitol flux through polyol pathway. Actually, increased sorbitol levels in the cerebrospinal fluid (CSF) of patients with psychological disorders were reported. CSF sorbitol levels in patients with psychological disorders were significantly higher than controls [374, 375]. In another study, high sorbitol concentration in brains from non diabetic patients with psychological disorders was reported [376]. The reported data suggest a disturbance of brain glucose metabolism in psychological disorders and inhibition of AR may be an emerging approach for the management of psychological disorders [239].

CONCLUSION AND PERSPECTIVES

Diabetes is a group of metabolic disorders resulting from lack of insulin, insulin resistance, or both leading to chronic hyperglycemia, which has become global health burden because of the complications associated with it. The diabetic complications are grouped under "microvascular complications" (due to damage to small blood vessels which include neuropathy, cataract, nephropathy, and retinopathy) and "macrovascular complications" (due to damage to the arteries which include accelerated cardiovascular disease resulting in myocardial infarction and cerebrovascular disease manifesting as strokes). Diabetic Complications, affecting both small and large blood vessels, occur in the majority of individuals with type 1 and type 2 diabetes. The polyol pathway is of prime importance in the pathogenesis of diabetic complications including diabetic cataract, retinopathy, neuropathy, and nephropathy. Some of the major clues about the structure of enzyme resulted in the development of new effective ARIs. Several structurally varied chemical classes including carboxylic acid derivatives and cyclic imides have been explored as ARIs and are being used in number of diseased conditions like inflammation, asthma, uveitis, cancers and number of diabetic complications. The aldose reductase inhibitor, Epalrestat is marketed in Japan, China and India for the treatment of diabetic complications. In addition, some other ARIs such as Sorbinil and Ranirestat had been advanced into late stage of clinical trials. An excess of AR is found in different human cancers, such as liver, colon, breast, and cervical cancer. Alkaloids based ARIs that contain isoquinoline/bis(isoquinoline) and related ring structures may be used to manage diabetic complications and may substitute for the chemically synthesized ARIs. More recently, Mylari reported pharmaceutically acceptable water soluble salts of ARIs, 2-(8-oxo-7-((5-trifluromethyl)-1H-benzo[d]imidazol-2-yl)methyl)7,8-dihydropyrazin[2,3-d]pyridazin-5-yl)acetic acid and [4-oxo-(5-trifluoromethyl-benzothaiazol-2-ylmethyl)-3,4-dihydro-phthalazin-1-yl]-acetic acid (also known as zopolrestat), their pharmaceutical compositions and methods of treating diabetic complications in mammals comprising administering to mammals these salt and compositions [377]. ARIs are also reported as safe anti-inflammatory drugs. Although careful control of glycemia and blood pressure have stabilized the level of morbidity and mortality associated with diabetes in most developed nations but less strict management in developing nations due to resource issues may result in a greater incidence of vascular complications. Experts are of opinion that future use of safe and effective ARIs in down-regulating major multi-diseases and inflammatory pathologies such as cancer and cardiovascular diseases could relieve some of the major health concerns worldwide. ARIs use in nondiabetic complications needs to be further explored. A case study demonstrates that including patent documents in the routine monitoring of newly disclosed knowledge could significantly alert researchers about emerging drug candidates for the treatment of diabetic complications earlier than reports in the peer review literature [378].

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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