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A Review on Aldose Reductase Inhibitors: Chemistry and Pharmacological Activity

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Abstract: The activity of oxidoreductase aldose reductase increases with glucose concentration during diabetes in the glomerulus, peripheral nerves, and tissues that are not insulin sensitive. Aldose reductase initiates the polyol pathway by converting glucose to sorbitol. Thus produced sorbitol is unable to diffuse through cell membranes and thus starts accumulating and causing osmotic damage, which causes conditions like retinopathy and neuropathy, diabetic cataract, asthma, and COPD as aldose reductase also inhibits the respiratory epithelium's development of goblet cells. This article discusses aldose reductase inhibitors of natural and synthetic origin. Along with that, all the known dietary, sulfated, synthetic, and natural flavonoids or their aldose reductase inhibitory activity will be discussed in the later sections. The basic structural requirements for a compound to behave as an aldose reductase inhibitor are also being mentioned.

Keywords: aldose reductase; aldose reductase inhibitors; semi-synthetic inhibitors; aldose reductase differential inhibitors; phytopharmaceuticals; synthetic inhibitors; flavonoids; sulfated flavonoids.

1. Introduction

Aldose reductase is a multifunctional enzyme that reduces aldehydes. A range of aldehydes and carbonyls, including monosaccharides, are reduced by this cytosolic NADPH-dependent oxidoreductase. Under diabetic conditions, the first step in the polyol pathway of glucose metabolism is the conversion of glucose into sorbitol by aldose reductase, which is then converted to fructose.

All of the target tissues for diabetes complications include AR. These tissues consist of the lens, kidney, vascular endothelium, pericytes in the retinal capillary walls, and peripheral nerve. Diabetes mellitus is brought on by changes in physiological glucose levels and frequently coexists with a number of long-term consequences, including neuropathy, nephropathy, retinopathy, cataracts, and cardiovascular disease [1]. Aldose reductase inhibitors inhibit the polyol pathway's rate-limiting enzyme, which is activated in hyperglycemic conditions; it also inhibits or reduces secondary complications induced by diabetes [2]. For this reason, the study of aldose reductase inhibitors is necessary. In spite of so many ARI, only one compound is presently being used clinically, i.e., epalrestat. In the near future, ARI Fidarestat is anticipated to join the list of medications approved by the US FDA [2]. This article will discuss all the natural, semi-synthetic, or synthetic compounds that have a potent aldose reductase inhibitory potential.

2. Aldose Reductase Inhibitors of Natural Origin

The use of traditional herbal medicines could be easily acceptable and affordable to poor populations as they are currently consumed in emerging nations. Many aqueous or organic extracts of various plant parts (Table 1) have been identified and trademarked for their ability to inhibit aldose reductase. Mostly, the mixtures of polyphenolic compounds are claimed to possess aldose reductase inhibitory activity. The chemical structure odf compounds has been shown in Figures 1-4.

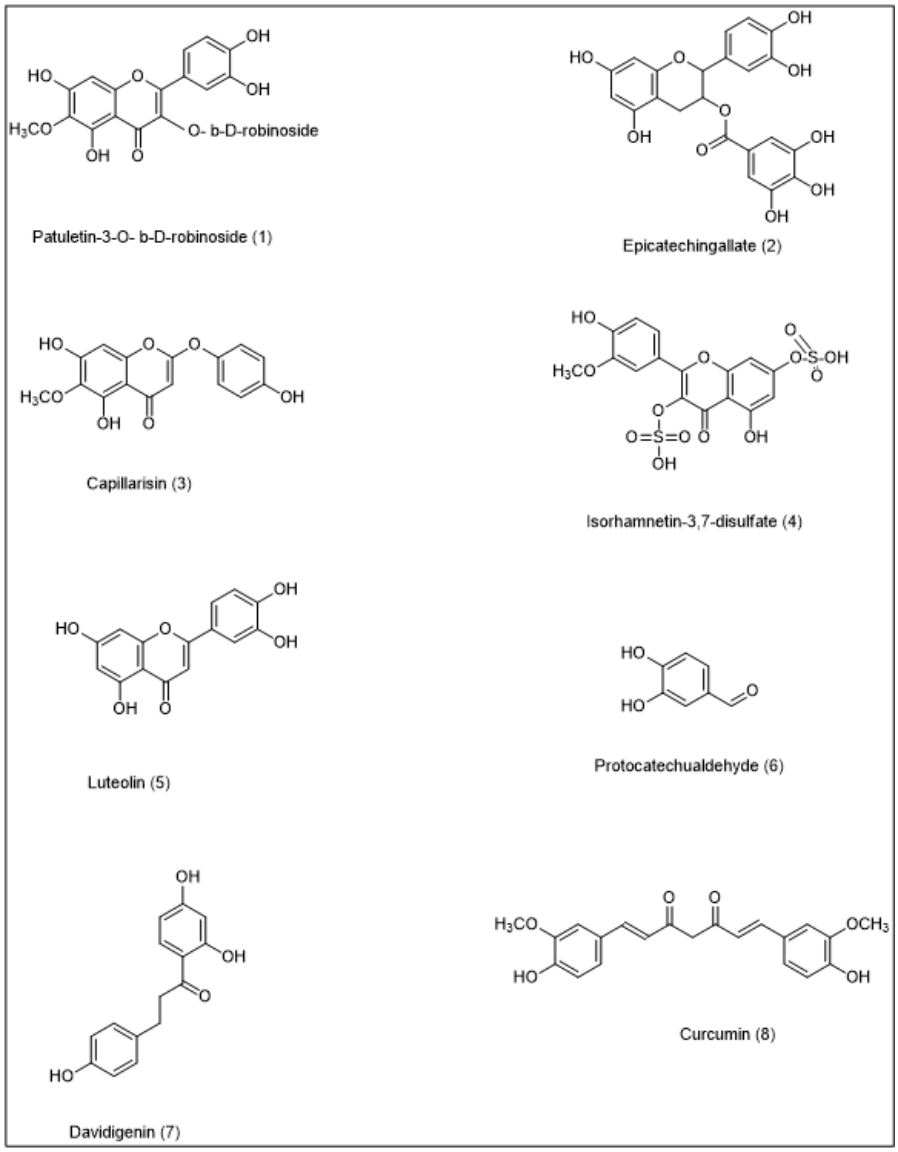

Figure 1. Structures of aldose reductase inhibitors of natural origin.

Table 1. Contains aldose reductase inhibitors of natural origin.

Plant Name	Description	References
Brickella *arguta*	Obtaining Patuletin-3-O- β-D-robinobioside (1) from B. *arguta* is found to have 86% inhibition of aldose reductase at a concentration of 10^{-5} M.	[3]
Camellia *sinensis*	Epicatechin gallate (2) (natural phenolic compound) obtained from green tea C. *sinensis* is found to have IC_{50} = 38 µM	[4]
Artemisiae *capillaries*	Capillarisin (3) obtained from A. *capillaris* is found to have IC_{50} =0.22 µM	[4]
Polygonum *hydropiper*	Isorhamnetin-3,7-disulfate (4) obtained from P. *hydropiper* is found to have IC_{50} =1.8 µM	[4]
Chrysanthemum *indicum*	Luteolin (5) obtained from C. *indicum* is found to have IC_{50} =0.45 µM	[4]

Plant Name	Description	References
Ganoderma *applanatum*	Protocatechualdehyde (6) obtained from G. *applanatum* is found to have IC_{50} =0.7 µM	[4]
Artemisia *dracunculus*	Davidigenin (7) obtained from A. *dracunculus* is found to have IC_{50} =12.70 µM	[4]
Curcuma *longa*	Curcumin (8) obtained from C.*longa* is found to have IC_{50} =6.8 µM	[4]
Zingiber *officinale*	Z. *officinale* provided the 2-(4-Hydroxy-3-methoxyphenyl)ethanoic acid (9) is found to have IC_{50} =18.5 µM	[4]
Eleusine *coracana*	Quercetin (10) obtained from E. *Coracana* is found to have IC_{50} =14.8 nM	[4]
Rhus *verniciflua*	Butein (11) obtained from R. *verniciflua* is found to have IC_{50} =0.5 µM	[4]
Sophora *flavescens*	Desmethylanhydroicaritin (12) obtained from S. *flavescens* is found to have IC_{50} =0.95 µM	[4]
Glycyrrhiza *uralensis*	Semilicoisoflavone B (13) obtained from G.*auralensis* is found to have IC_{50} =1.8 µM	[4]
Eupatorium *ballotaefolium*	Nepetin (14) isolated from E. *ballota folium* is found to have a similar aldose reductase inhibiting effect as quercitrin.	[5]
Monochasma *savatierii*	A powerful inhibitor of aldose reductase acetonide (15) is isolated from M. *savatierii* with IC_{50} Value = 3.90 X 10^{-7} M.	[6]
Cuminum *cyminum*	Cuminaldehyde (16) isolated from C. *cyminum* is found to have IC_{50} = 0.80 M.	[7]
Belamcanda *chinensis*	Tectoridin (17) from the methanolic extract of B. *chinensis* rhizomes, a potent aldose reductase inhibitor, can be isolated with an IC_{50} = 1.08 X 10^{-6} M.	[8]
Manilkara *indica*	Isoaffinetin (18) obtained from M.*indica* is a potent aldose reductase inhibitor that has no activity against aldehyde reductase.	[9]
Myrciaria *dubia*	4-(α-rhamnopyranosyl)ellagic acid (19) discovered in M.*dubia* leaves which have an IC_{50} value = 4.1 X 10^{-8} M.	[10]
Nelumbo *nucifera*	Rutin (20) extracted from the leaves of N.*nucifera* is found to have an IC_{50} value = 2.49 µM	[11]
Viola *hondoensis*	Tectoridin 4'-O- β-D-glucoside (21), isolated from V. *hondoensis* with an IC_{50} of 0.54 µM, is discovered to be a powerful lens aldose reductase inhibitor.	[12]
Oryza *sativa*	Cyanidin-3-glucoside (22) isolated from O.*sativa* is a potent aldose reductase inhibitor with IC_{50} = 8.7 µg/mL.	[13]
Cassia *glauca*	Shade-dried and powdered leaves extract of C.*glauca* extracted in soxhlet with methanol for 30 minutes is found to have aldose reductase inhibitory activity.	[14]
Phyllostachys *nigra*	Luteolin 6-C-(6''-O-trans-caffeoylglucoside) isolated from P. *nigra* is found to have antioxidative and aldose reductase inhibition effect with IC_{50} = 0.0134 µM.	[15]
Tridax *procumbens*, Merremia *emarginata*, Permotrema *perlatum*, and Euphorbia *prostrate*	Using UV-visible spectroscopy at 340 nm, the leaf extracts of these weedy plants were tested for their aldose reductase inhibitory capacities and shown to be effective.	[16]
Dioscorea *zingiberensis*	Diosgenin (23) found in D. *zingiberensis* is an efficient ARI with IC_{50} = 4.59X10^{-6} mol/L. Food rich in diosgenin can be recommended as dietary management for diabetic subjects.	[17]
Dendrobium *chrysotoxum*	Gigantol (24), found in D. *chrysotoxum*, has been discovered to inhibit aldose reductase and AR gene expression.	[18]
Swertia	Demethylbellidifolin extracted from genus Swertia is found to be useful in treating diabetic nephropathy by reducing kidney cell damage, with an IC_{50} of 1.29 ± 0.16 µM.	[19]
Bergenia *ciliate*, Anacyclus *pyrethrum*, Rhododendron *arboreum*, and Swertia *chirayita*	The crude ethanol extracts of Bergenia *ciliate*, Anacyclus *pyrethrum*, Rhododendron *arboretum*, and Swertia *chirayita* were found potent towards Recombinant human aldose reductase. Among all, B. *ciliate* showed a greater effect (94.74 ± 0.01%), followed by A. *pyrethrum* (89.47 ± 0.01%), R. *arboretum* (63.64 ± 0.01%) and S. *chirayita* (56.25 ± 0.01%).	[20]

Plant Name	Description	References
Araucaria *heterophylla*	The essential oil of A. *heterophylla* oleogum resin exhibits potent aldose reductase inhibitory activity with an IC_{50} = 0.133 ± 0.006 µg/mL.	[21]
Polygonatum *cyrtonema*	The phenolic compounds (1S,2R) and (1S,2S) (25) isolated from the methanol extract of P. *cyrtonema* leaves, and (26) and (27) isolated from the methanol extract of P. *cyrtonema* flowers were discovered to have a strong inhibitory effect on aldose reductase with IC_{50} = 29.05 µM, 22.38 µM, 22.16 µM, and 17.63 µM respectively.	[22, 23]

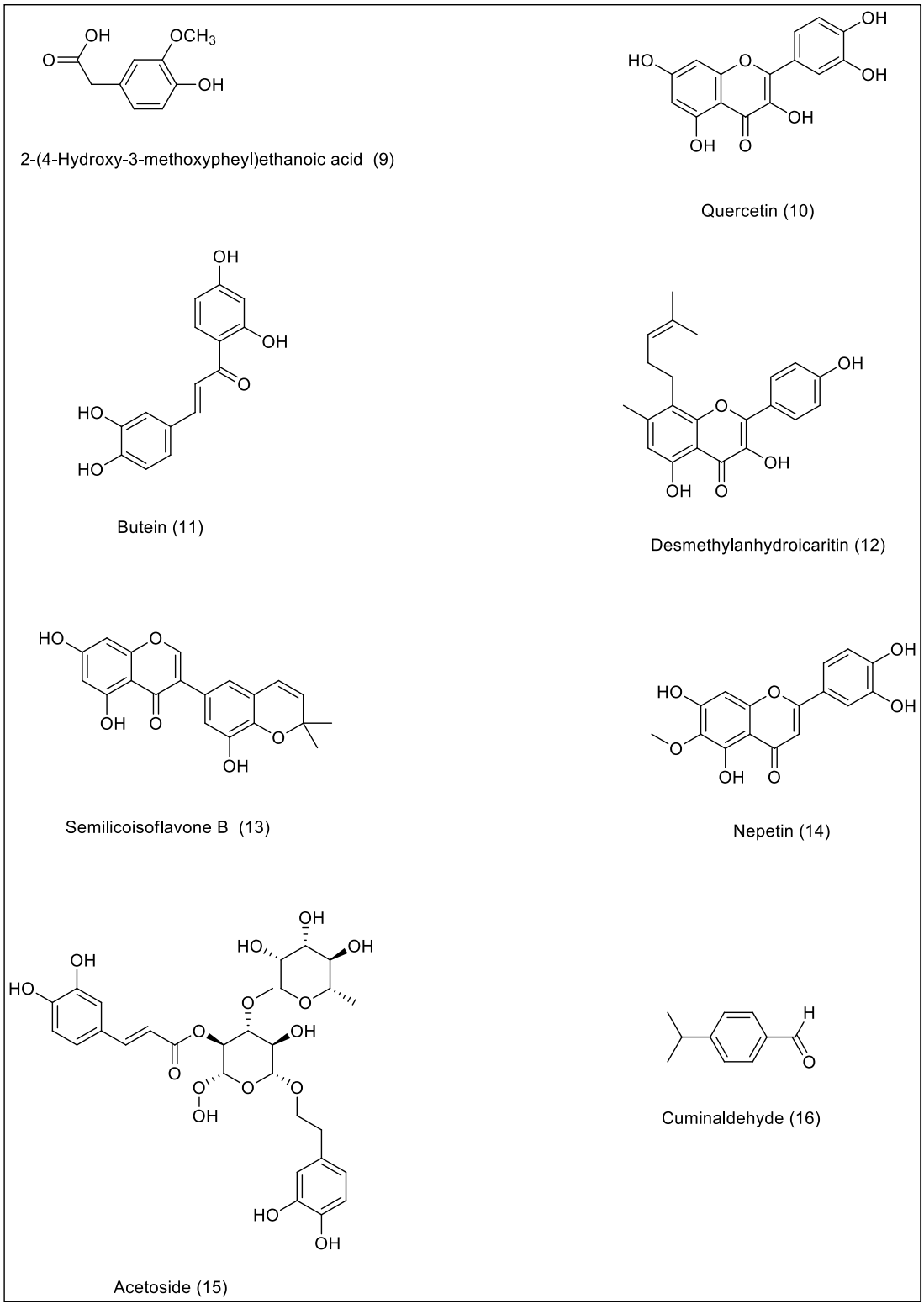

Figure 2. Structures of aldose reductase inhibitors of natural origin.

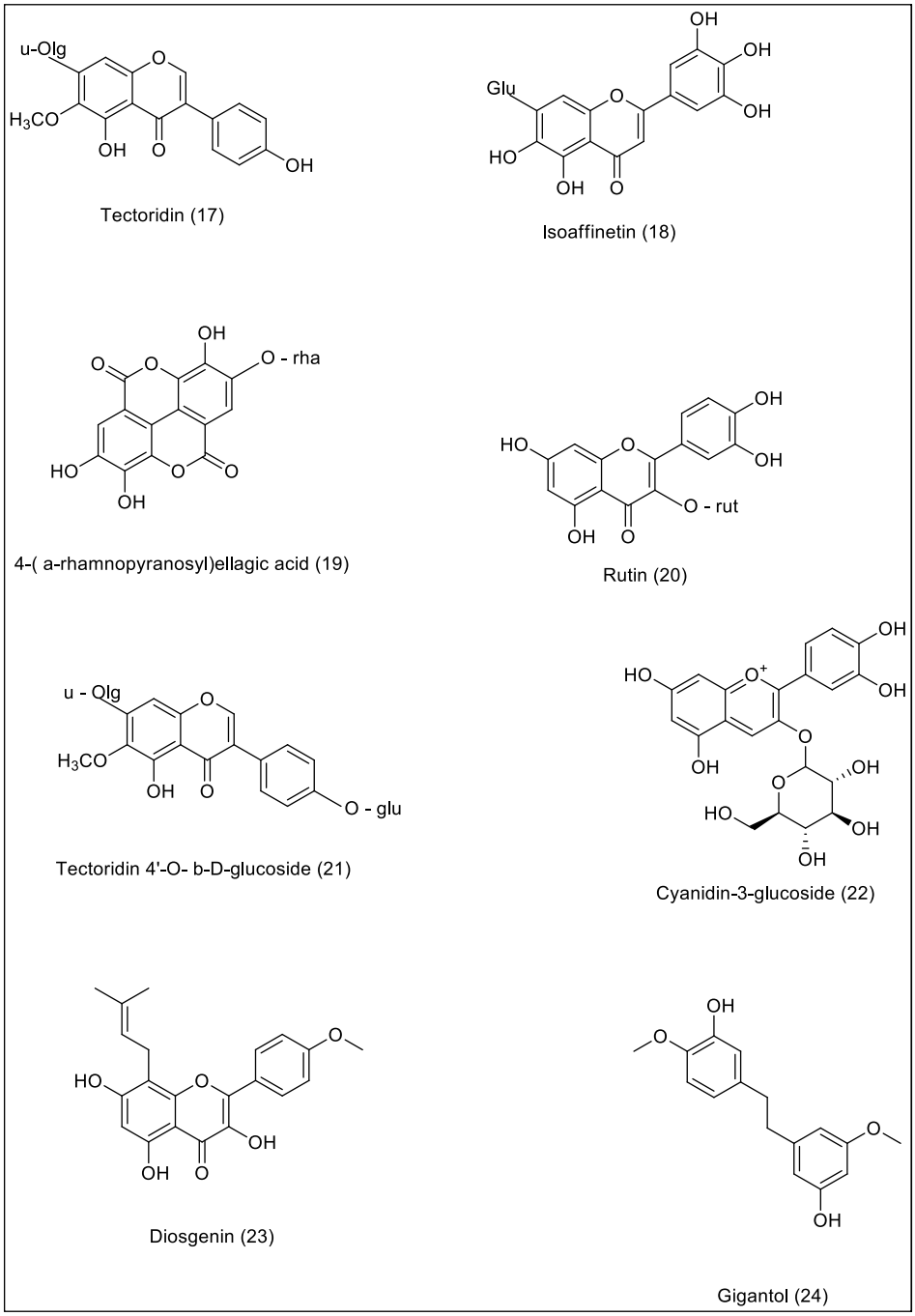

Figure 3. Structures of aldose reductase inhibitors of natural origin.

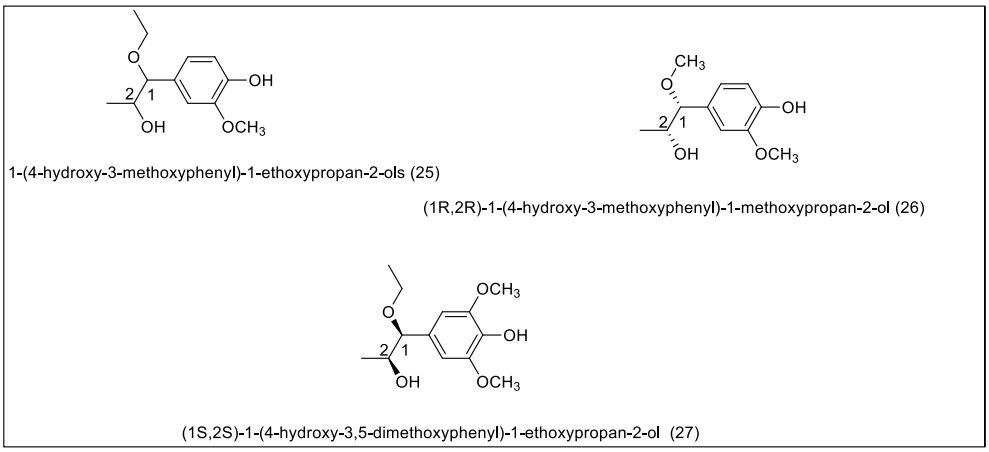

Figure 4. Structures of aldose reductase inhibitors of natural origin.

3. Aldose Reductase Inhibitors of Synthetic Origin

Zopolrestat (28), alrestatin (29), benurestat (30), epalrestat (31), fidarestat (32), lidorestat (33), minalrestat (34), ponalrestat (35), risarestat (36), sorbinil (37), tolrestat (38), zenarestat (39) [24], Bendazac lysine (40) [25], Naproxen (41) [26], Kinostat [27], and Rhodanine-3-hippuric acid derivatives [28] are the aldose reductase inhibitors of synthetic origin. (42) has been found to be over five times more potent than epalrestat (43) [29]. Quinazolinone-based rhodanine-3-acetic acids [30], Benzoxazinone-thiosemicarbazones [31], Novel 2-phenoxypyrido[3,2-b]pyrazin-3(4H) derivatives [32], quinoxalinone scaffold-based acyl sulphonamides [33] are found to possess anti-aldose reductase activity. Sulfonamides also behave as an aldose reductase inhibitor and display the IC_{50} in the range of 37.27-87.65 µM [34]. Aldose reductase inhibitory action is exhibited by the indole core when combined with a sulfonyl-linker and an acidic group, such as the phenol ring [35]. It was discovered that introducing phenolic hydroxyl to the quinoxalinone core and the C3 side chain results in a group of aldose reductase inhibitors with IC_{50} ranges of 0.059 to 6.825 µM (44) [36]. The structures of the compounds are shown in Figure 5.

Aspirin (45) also serves as an inhibitor of aldose reductase and can lessen the risk of diabetic cataract [37].

The aldose reductase inhibitory activity of calcium channel blockers such as cinnarizine, nilvadipine, amlodipine besylate, Nifedipine, isradipine, and nitrendipine is reported to have IC_{50} values in the range of 5.87-8.77 µM. Cinnarizine is discovered to be the most effective AR inhibitor out of all of these medications [38]. The analog of rhodanine (46) (TA-01) binds to aldose reductase (ALR) and interacts with it via hydrogen bonds. The development of a stable ALR rhodanine complex is the result of this interaction. As a result, it is a promising chemical that could be developed into a powerful aldose reductase inhibitor for treating long-term diabetes problems [39]. 2-[(1-(4-Hydroxyphenyl)-1*H*-tetrazol-5-yl)thio]-*N'*-(4-fluorobenzylidene)acetohydrazide, a tetrazole-hydrazone hybrid markedly known to exhibit aldose reductase inhibitory effect with an IC_{50} of 0.297 µM [40]. Acyl hydrazones derived from vanillin are found to inhibit aldose reductase with IC_{50} and K_I values in the range of 94.21 ± 2.33 to 430.00 ± 2.33 nM and 49.22 ± 3.64 to 897.20 ± 43.63 nM [41]. The bis-sulfide derivatives also exhibit strong inhibitory effects on aldose reductase with K_I values ranging from 0.53 ± 0.03 µM to 0.71± 0.05 µM [42]. With a K_I value of 61.20 ± 10.18 nM, acetic acid derivative with a quinazolin-4(3*H*)-one ring inhibits aldose reductase [43]. With an IC_{50} of 0.23 µM, 4- phenyl benzaldehyde, aldose reductase inhibitor is efficient [44]. Nifedipine, an analog of the dihydro nicotinamide with an IC_{50} value of 2.5 µM, demonstrates a significant aldose reductase inhibitory action [45]. Thiazolidine-2,4-dione hybrid (47) has been found to inhibit aldose reductase with an IC_{50} value of 0.16 µM [46]. A series of quinazolin-4(1 *H*)-one derivative have been synthesized as selective and potent aldose reductase inhibitors with IC_{50} values ranging from 0.015 to 31.497 µM [47] Figure 6. (48) Figure 7, derivatives are found to show aldose reductase inhibitory activity with IC_{50} values in the range of 40.76-8.25 µM [48]. Sulfonamides are also found to be effective against aldose reductase and have IC_{50} values in the range of 37.27-87.65 µM and K_I values in the range of 25.72 ± 6.45 to 73.56 ± 17.49 µM [49].

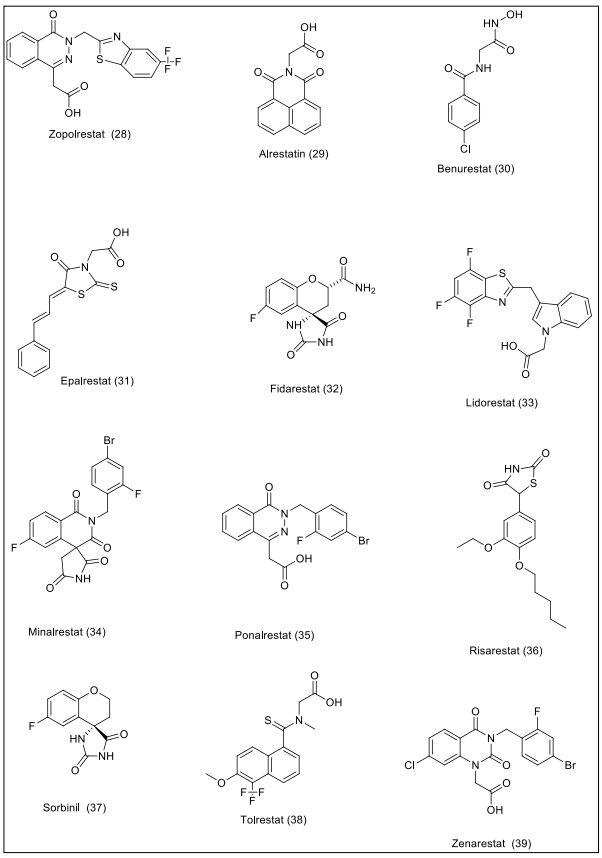

Figure 5. Structures of aldose reductase inhibitors of synthetic origin.

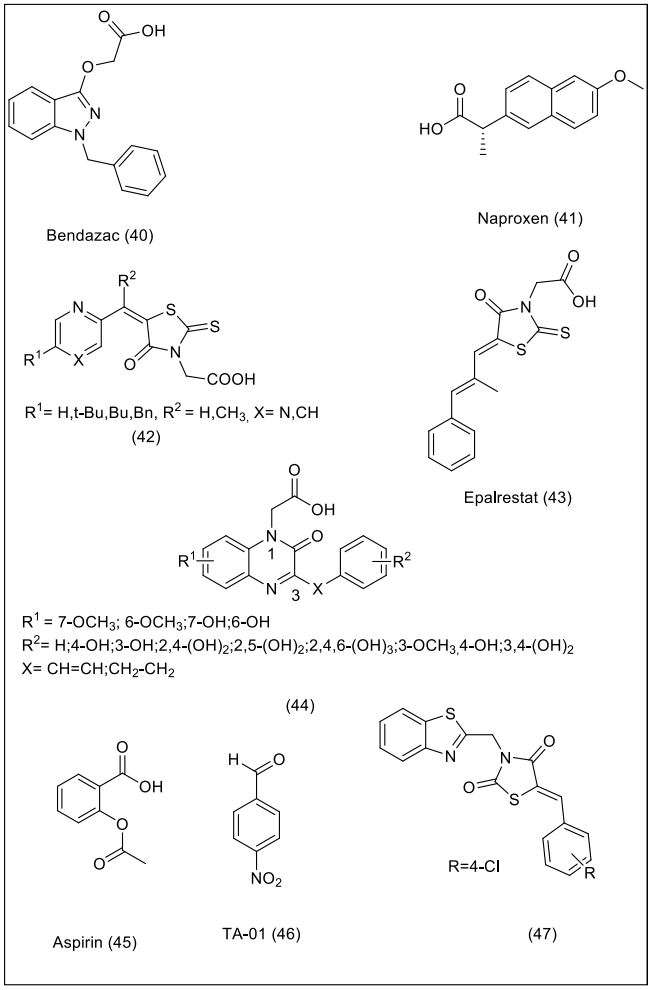

Figure 6. Structures of aldose reductase inhibitors of synthetic origin.

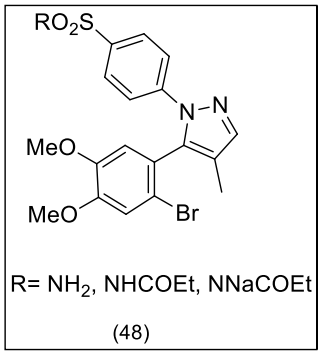

Figure 7. Structure of aldose reductase inhibitor of synthetic origin.

4. Flavonoids as Aldose Reductase Inhibitors

The multifunctional compounds known as plants produce flavonoids as their secondary metabolites. Flavonoids can effectively inhibit lens aldose reductase. Quercetin (49), quercitrin (50), and myricitrin (51) in Figure 8 are found to be more potent than other flavonoids [50]. Because of their bioactivities, flavonoids have gained interest in diagnosing, treating, and preventing disease [50]. (52), (53), ionicerin, (54), (55), and (56) are discovered to be very potent flavonoids that inhibit aldose reductase [51]. As compared to flavonols and flavanones, flavones are found to be more active, and among glycosides and aglycones, glycosides are found to be more active aldose reductase inhibitors [51].

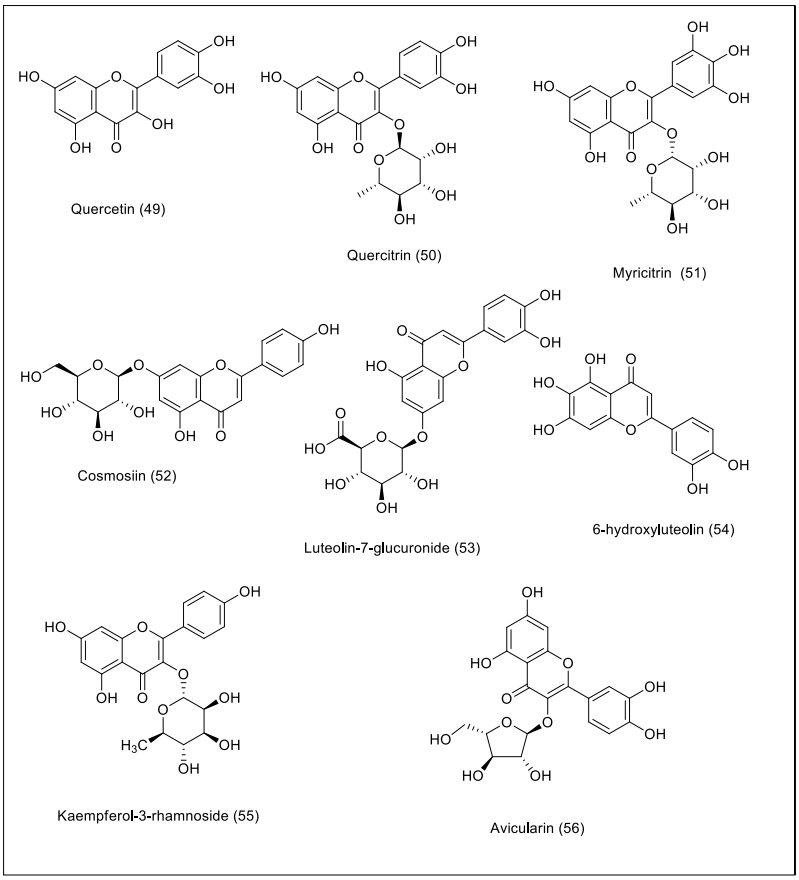

Figure 8. Structures of flavonoids showing aldose reductase inhibitory activity.

The compounds shown in Figure 9, Table 2, were examined for their in vitro inhibitory effects on commercially available human recombinant aldose reductase enzyme, and the results are as follows [52].

Table 2. Contains flavonoids and their IC_{50} values.

Compound	IC_{50} ;µM
(57)	2.05 µM
(58)	2.97 µM
(59)	15.75 µM
(60)	16.1 µM
(61)	49.5 µM
(62)	63 µM

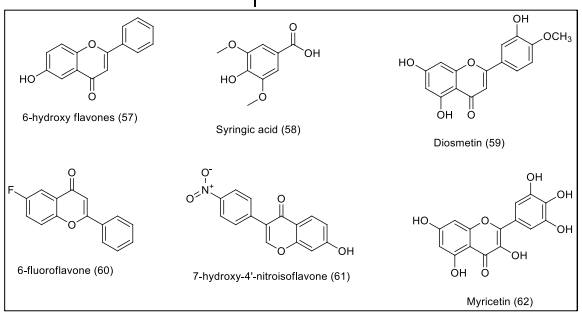

Figure 9. Structures of flavonoids showing aldose reductase inhibitory activity.

4.1. Dietary flavonoids.

4'-Methoxyflavanone (63), Hesperidin (64), Rutin (20), Formononetin (65), Naringenin (66), Diadzin, Silymarin (67), Hesperetin (68), Naringin (69), and Silibinin (70) (Figure 10) are the dietary flavonoids which can inhibit glycation and aldose reductase activity. Out of these, (63), (65), and (68) showed decreased activity, although silibinin displayed good activity despite having methoxyl groups. Out of (64), (69), and (20), (20) exhibited promising activity in all respect [53].

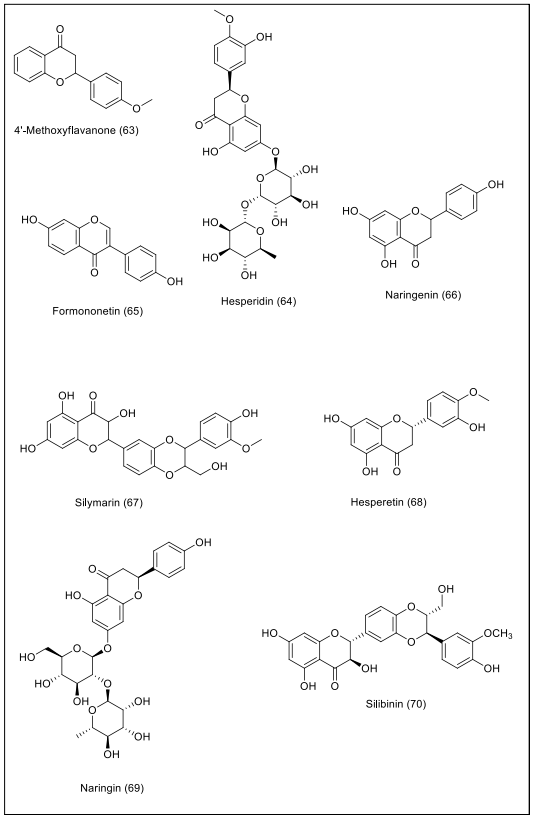

Figure 10. Structures of flavonoids showing aldose reductase inhibitory activity.

4.2. Sulphated flavonoids.

Polygonum *hydropiper*'s sulfated flavonoids have strong aldose reductase inhibitory properties. (71) Figure 11, one of the examined flavonoids from P. *hydropiper*, has the strongest aldose reductase inhibitory activity in the eye lens, making it useful for preventing cataract development [54].

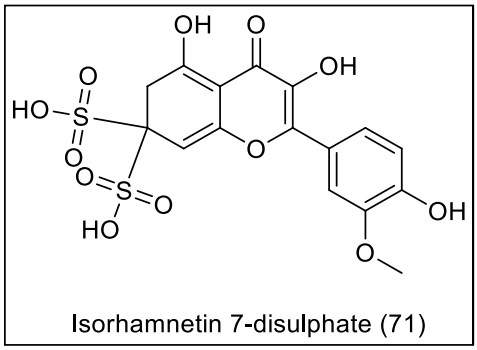

Figure 11. Structure of flavonoid showing aldose reductase inhibitory activity.

4.3. Natural flavonoids.

The compounds in Table 3, extracted from the leaves of Leea *guineense* G.Don, were tested for their aldose reductase inhibitory action and have been stated as follows [55].

Table 3. Contains compounds extracted from the leaves of Leea *guineense* and their IC_{50} values.

Compound	IC_{50} (µM)
Kaempferol	120
Quercetin	49
Quercitrin	88
Quercitrin 3'-sulphate	>>200
Quercetin 3,3'-disulphate	>>200
Quercetin 3,3',4'-trisulphate	150
Gallic acid	35
Ethyl gallate	67

Following flavonoids Table 4, obtained from the genus Sophora, are found to be effective aldose reductase inhibitors [56].

Table 4. Contains compounds extracted from the genus Sophora and their IC_{50} values.

Compound	IC_{50} (µM)
Desmethylanhydroicaritin [57]	0.95
8-lavandulylkaempferol [58]	3.80
Kurarinol [59]	2.13
Kurarinone [60]	2.99
(2S)-2'-methoxykurarinone [61]	3.77
3,7,4'-trihydroxy-5-methoxy-8-prenylflavanone [62]	3.63
Kushenol C [63]	7.74

Flavonoids obtained from Acer *okamotoanum* Table 5 are believed to have aldose reductase inhibitory activity [64].

Table 5. Contains flavonoids obtained from Acer *okamotoanum* and their IC_{50} values.

Compound	IC_{50} (µM)
Afzelin	2.61
Quercitrin	0.40
Isoquercitrin	0.63

Compound	IC_{50} (µM)
TMG	1.52

Inhibitory activity of chemical constituents obtained from the leaves of Myrcia *multiflora*. Table 6 [65].

Table 6. Contains chemical constituents obtained from the leaves of Myrcia *multiflora* and their IC_{50} values.

Compound	IC_{50}
Myrciacitrin I	3.2 x10^{-6}M
Myrciacitrin II	1.5 x10^{-5}M
Myrciacetin	1.3 x10^{-5}M
Myrciaphenone B	2.9 x10^{-5}M
Myricitrin	3.8 x10^{-6}M
Mearnsitrin	1.4 x10^{-6}M
Quercitrin	1.5 x10^{-7}M
Desmanthin -1	8.2 x10^{-8}M
Guaijaverin	1.8 x10^{-7}M
Epalrestat	7.2 x10^{-8}M

Glucopyranoside flavonoids isolated from the methanol extract of leaves of spinach (Spinacia *oleracea*) were found to exhibit aldose reductase inhibitory activity in the range of 1.5 ± 0.4 µM to 4.7 ± 0.9 µM [66].

Ellagic acid found in Jatropha *gossypifolia* L. was found to be the most promising metabolite, having an aldose reductase inhibitory potential with an IC_{50} = 12.69 and can be used for oral administration. Thus, medicines, nutritional supplements, and food containing ellagic acid can be used to manage complications of diabetes mellitus [67]. Curcumin possesses an aldose reductase inhibitory efficiency with an IC_{50} = 10 µM. Studies proved that a lowered aldose reductase activity was observed in the curcumin-fed diabetic rat lens compared to those of untreated diabetic rat lens [68].

5. Structural Requirements for Compounds to Work as Aldose Reductase Inhibitors

As discussed below, compounds should possess structural moieties to behave as an effective aldose reductase inhibitor. In the presence of (compounds 72 and 73) Figure 12, flavone modifications and flavonols exhibit strong aldose reductase inhibitory activity [69]. The inhibitory activity of aldose reductase is unaffected by the presence or absence of hydroxyl group at 5thC in flavones and flavonols moiety [69].

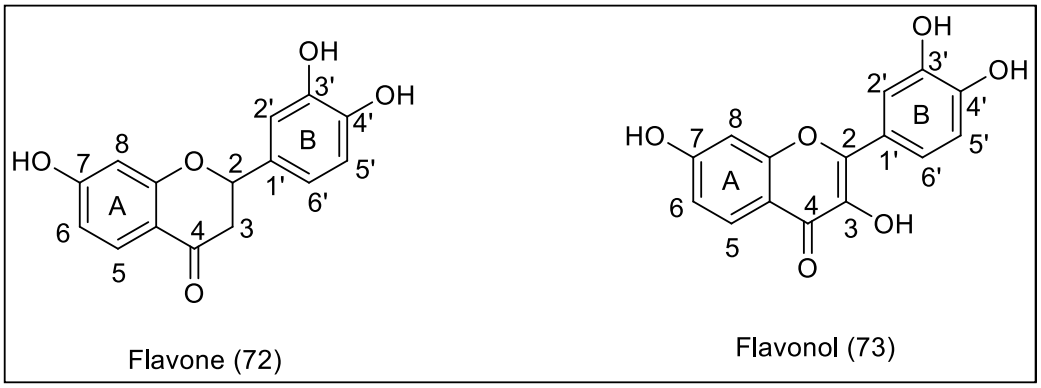

Figure 12. Structural modifications in flavones and flavonols exhibit strong aldose reductase inhibitory activity.

The presence of the hydroxyl group at 3rdC and *O*-glucosyl at 7thC decreases the aldose reductase inhibitory activity [69]. The presence of 2-3 double bonds increases the aldose reductase inhibitory activity [69]. The presence of catechol moiety at the B ring in flavones and flavonols increases aldose reductase inhibitory activity as compared to those having the pyrogallol moiety (3',4',5'-trihydroxyl moiety)[69]. Indole core exhibits higher aldose reductase inhibitory activity when combined with a sulfonyl-linker and an acidic group, such as a phenol ring [35].

6. Conclusion

A group of drugs called aldose reductase inhibitors are being researched as a means of protecting diabetics' eyes and nerves. The elimination of major pathological conditions like neuropathy, nephropathy, retinopathy, cataracts, cardiovascular disease, and angiopathy, which are related to chronic inflammation, cancer, and chronic hyperglycemia, can be facilitated by the use of aldose reductase inhibitory medicines in the pharmaceutical sectors. Thus, with just one drug, so many diseases can be cured. Aldose reductase inhibitors can be proven as a panacea for all diabetic complications. Although so many compounds with aldose reductase inhibitory activity have been discovered, there is also further scope in this field as very few aldose reductase inhibitor drugs are available in the market because of their low bioavailability or adverse effects. Hence, further research is required in this field to invent more aldose reductase drugs that overcome the above two limitations.

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Conflicts of Interest

There are no conflicts of interest.

Reference

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