Chapter - I
ALDOSE REDUCTASE INHIBITORS :
LITERATURE SURVEY
Introduction:

Diabetes mellitus is a metabolic disorder characterised by hyperglycemia arising as a consequence of relative or absolute deficiency of insulin secretion, resistance to insulin action or both. Although several pathogenic processes may be involved in the development of diabetes, the vast majority of cases fall into main categories: type - 1 diabetes and type - 2 diabetes. Type - 1 diabetes is usually due to an immune mediated distortion of pancreatic β - cells with consequent insulin deficiency and the need to replace insulin. Type - 2 diabetes, the more common type is usually due to resistance to insulin action in the setting of inadequate compensatory insulin secretory response. Insulin resistance is quite common because it arises as a consequence of obesity, a sedentary life style and ageing. The burden of diabetes in terms of complications on morbidity and mortality is enormous.

Insipite of insulin treatment most diabetic patients eventually experience the following long - term diabetic complications.

A. Neurological Complications:

Neuropathy is one of the most prevalent diabetic complication affecting 21% of diabetic patients. Diabetes may affect the autonomic sensory and motor nerves and the central nervous system, due to lower Na - K - ATPase activities, impaired sorbitol metabolism, lowered myoinositol levels and neural ischaemia etc.
B. Cardiovascular Complications:

In long-term diabetic patients, cardiomyopathy and congestive heart failure may develop as a result of the impaired left ventricular function. The function of the coronary arteries is also impaired depending upon the calcification of the arterial wall. The changes in myocardial β- adrenergic responsiveness may be responsible for the above complications.

C. Gastrointestinal Complications:

Diabetic gastroenteropathy is one of the primary autonomic syndrome related to diabetes. It is a consequence of a symptomatic dilation of the stomach and impaired gastric acid secretion in diabetic patients. Another complication is lower β- adrenergic response in almost every segment of the gastrointestinal tract.

D. Urological Complications:

Nephropathy is one of the most significant diabetic complications. Enlargement of urinary bladder, increase in the amount of urine and in the threshold urine volume necessary for triggering micturation have been reported. The excretion pattern of urinary proteins is also altered in experimental diabetes.

E. Respiratory Complications:

In Diabetes, complications related to respiratory tract have been observed in animal models. Particularly the lungs of Streptozotocin (STZ) diabetic rats show morphological and biochemical abnormalities. The tracheal smooth muscle from both types I and II diabetic rats exhibit a decrease in contractile responses to acetylcholine.
F. Ophthalmic Complications:

Diabetic patients most often suffer from cataract, retinopathy, keratopathy and thrombotic glaucoma. Diabetic eye complication is one of the major causes of blindness. It has been found that experimentally induced diabetic rats kept on high sugar diet develop cataract and suffer from related problems. A similar complications has been observed with galactose rich diet on experimentally induced diabetic animal models. Some neuronal and vascular changes have been observed in the retina of these models and may be the cause of above mentioned complications.

G. Reproductive Complications:

Male and female patients suffering from diabetes were found to have reproductive complications such as impotence, retrograde ejaculation and lower fertility.

H. Hematological and Biochemical Complications:

In both diabetic patients and animals, hematological and biochemical complications have been reported. In STZ - diabetic rats an increase in thrombin and ADP - induced platelet aggregation have been reported. Also development of non - enzymatic protein glycosylation in diabetic patients is of biochemical and hematological significance.

I. Complications related to drug metabolism:

Acute and chronic diabetes mellitus have different effects on the hepatic drug metabolism and some sex dependent changes have been observed in drug metabolism of animals.
Involvement of Polyol pathway in Diabetes:

Many theories have been proposed to explain the pathogenic mechanism leading to diabetic complications, including structural and functional alterations of tissues caused by accelerated accumulation of advanced glycation products, oxidative stress and numerous metabolic imbalances resulting directly or indirectly from chronic hyperglycemia. The involvement of polyol pathway has been implicated in the etiology of secondary complications of diabetes.

Aldose reductase (AR) is the first enzyme of the so-called polyol pathway which catalyzes the conversion of glucose to sorbitol in the presence of NADPH, which is further slowly metabolized to fructose by sorbitol dehydrogenase the second enzyme in the pathway with concurrent reduction of NAD$^+$. Since AR has low affinity for glucose, its flux through this pathway is low in most tissues under normoglycemic conditions. On the
contrary under diabetic conditions glucose concentration in blood is sufficiently high to provide a substrate for AR, in tissues such as nerve lens and retina where insulin is not necessary for transportation of glucose across the membrane. Increased glucose flux through the polyol pathway and/or accumulation of high intracellular sorbitol are likely to be involved in the etiology of late onset diabetic complications such as neuropathy, nephropathy, retinopathy and cataract.\textsuperscript{18,19}

The activation of the polyol pathway under hyperglycemic conditions, cause various metabolic imbalances in tissues that are non-insulin dependant for glucose. Accumulation of sorbitol causes hyperosmotic swelling in the ocular lens of the eye. Further, the oxidation of sorbitol catalyzed by sorbitol dehydrogenase increase the ratio of $\text{NADH} : \text{NAD}^+$, resulting in an increase in lactate: pyruvate ratio and pseudohypoxia.\textsuperscript{20}

\textbf{Role of inhibitors :}

To reduce or delay the development of late onset diabetic complications several structurally diverse aldose reductase inhibitors (ARIs) have been developed. The development of new aldose reductase inhibitors for the treatment of diabetic complications such as cataract and retinopathy has been of intense interest in the pharmaceutical community for many years. Aldose reductase inhibitors are drugs that act on the nerves exposed to high blood sugar to prevent some of the chemical imbalances that occur under hyperglycemic condition and thus protect the nerves.\textsuperscript{22} Some of them are most promising and have unique qualities that make them ideal inhibitors. The alterations in the redox state of
pyridine nucleotides (i.e. increase in NADH/NAD ratio), depleted intracellular levels of myoinositol, osmotic pressure changes in certain cells etc. can be controlled by inhibitors of aldose reductase.\textsuperscript{21}

Inhibitors of aldose reductase block the flux of glucose through polyol pathway responsible for diabetic vascular dysfunction and their role in the prevention of diabetic cataract in animals is now well established.\textsuperscript{22} Competitive inhibition of aldose reductase impedes formation of diabetic cataract due to sorbitol accumulation within the lens fibre.\textsuperscript{23}

**Aldose Reductase Inhibitors (ARIs):**

Although there exist several structurally diverse AR inhibitors synthesized chemically or isolated from plants and belong to different chemical classes they possess some common features i.e. they have common electronic and steric characteristics. The essential requirement for the inhibitory effect seems to depend on the presence of planar structure with two hydrophobic moieties (aromatic groups) and an acidic proton. The known inhibitors have been compiled under general classes on the basis of functional group present.

I. **Carboxylic Acid Derivatives:**

A variety of compounds (1 - 7) bearing carboxylic acid moiety have been tested in clinical trials on diabetic patients for more than 20 years and they still remain to be proven sufficiently effective.\textsuperscript{24} Tolerostat (1), Zopolrestat (2) and Zenerestat (3) were withdrawn from clinical trials and only epalrestat (4) is still available in the market.\textsuperscript{25}
NZ - 314 (5) increased the motor nerve conduction velocity and the sciatic nerve blood flow compared to diabetic controls in STZ induced rats. A 3 - Thiazolidine acetic acid derivative (6) and indole derivative (7) with a benzothiazole moiety have been reported to exhibit potent and selective ARI activity.26
II. Cyclic Imides & Related Compounds:

After the discovery of sorbinil (8) as potent aldose reductase inhibitor, several compounds with a spirohydantoin group or closely related skeleton have been developed and tested for ARI activity. Unfortunately in the early weeks of therapy, hypersensitivity reactions were induced by sorbinil and it is oxidatively metabolized to a potentially toxic intermediate. Nonetheless, several compounds belonging to this class of cyclic imides have entered clinical trials in the past several years.

Fidarestat (9) with high potency is awaiting approval as a drug for diabetic neuropathy. A number of compounds with 2,4-thiazolidinedione moieties were recognized as ARI agents (10-13).
III. Flavonoids:

It is well documented in literature that flavonoids particularly hydroxy chalcones, flavonols and flavones are inhibitors of aldose reductase.\textsuperscript{30} Quercetin (14) is a classical example with potent ARI activity. Yoshikawa et al.\textsuperscript{31} observed that glycosides of flavanone and flavanol present in Brazilian natural medicine reduced the level of serum glucose in sucrose loaded rats. The active components were isolated and characterised to be myricitrin (15), Meamistrin (16), quercitrin (17), desmanthin (18) and guaijaverin (19). Flavanol glycosides were shown to be more potent than flavanone glycosides myrciacitrin (20, 21) and myriciacetin (22). Also studies by Gupta et al.\textsuperscript{32} report that quercetin and myricetin (23) significantly delay the onset and progression of cataract in galactose loaded rats. Similarly, poly-hydroxy chalcones (24) have been shown to be potent inhibitors of AR in-vivo and in-vitro.\textsuperscript{33}
IV. AR Inhibitors of Natural Origin:

Yoshikawa et al.\textsuperscript{34} observed that Salacinol (25), Katalanol (26) and Mangiferin (27) present in ayurvedic traditional medicines \textit{Salacia reticulata} and \textit{S. oblonga} reduced the level of serum glucose in sucrose loaded rats, in addition the active components of \textit{Chinese Chrysanthemum indicum} flower were found to show inhibitory activity against rat lens aldose reductase.\textsuperscript{35} The active components were Kikkanol (28, 29, 30), Cis-spiroketal-enol ether polyne (31) and trans-spiroketal-enol ether polyne (32), flavone glycosides, Clovanediol (33), Caryclane 1, 9\(\beta\)-dial (34), Oplopanone (35), Luteolin (36), Acacetin 7-O-(6"-\(\alpha\)-L-rhamnopyranosyl)-\(\beta\)-D-glucopyranoside (37) and Chlorogenic acid (38). Among them flavone glycosides (36, 37) and Chlorogenic acid (38) exhibited inhibitory activity, but their activity was weaker than that of a commercially synthetic aldose reductase inhibitor epalrestat.\textsuperscript{35}
Dupriest et al.\textsuperscript{36} have reported that Spiro [ fluorine - 9, 4' - isothiazolidine ] one dioxides (39) Spiro [ fluorine - 9, 5' - isothiazolidine ] one dioxides (40) are potent inhibitors of aldose reductase.
Recently Yu et al.\textsuperscript{37} have isolated the component YUA001 (41) from alkalophilic Corynebacterium species and experimentally proved its activity on aldose reductase.

\begin{center}
\begin{tikzpicture}
  \node[draw,anchor=north west] (a) at (0,0) {\includegraphics[width=0.4\textwidth]{example.png}};
\end{tikzpicture}
\end{center}

The extract of \textit{Cinnamomum cassia} has been reported to have inhibitory effect in vitro against rat lens aldose reductase. The active components include Cinnamaldehyde (42), Cinnamyl alcohol (43), Eugenol (44) and Cinnamic acid (45). Among them Cinnamaldehyde exhibited potent inhibitory activity comparable to that of quercetin\textsuperscript{38}.

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\begin{tikzpicture}
  \node[draw,anchor=north west] (a) at (0,0) {\includegraphics[width=0.4\textwidth]{example.png}};
\end{tikzpicture}
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Tricyclic Pyrones as ARIs:

Several derivatives of the tricyclic pyrones such as HAR - 1 to HAR - 6 (46 - 51) effected normalization of polyol levels in vitro.\textsuperscript{39}

\begin{align*}
46 & \quad 47 & \quad 48 \\
49 & \quad 50 & \quad 51
\end{align*}

AR Inhibitors Based on Structure Based Drug Design / Modeling:

The discovery of 3D structure of AR has revolutionized the rational approaches for the discovery of aldose reductase inhibitors. Molecular modelling studies as well as SBDD have yielded several possible AR inhibitors but only few have been tested in clinical trials. Some of the best compounds obtained by molecular modeling and tested invitro for potency include compounds 52 - 61.
With respect to the discovery of ARI by the 3D database search, one of the first studies carried out by Petrash et al.\textsuperscript{40} yielded several aromatic aldoximes with inhibition constants in the micromolar range. Unfortunately, they were similar to known benzaldoximes with comparable inhibition constants. Recently, using ADAM and EVE programme, the 3D database of the available chemicals was searched by Iwata et al.\textsuperscript{41} and obtained 179 candidate compounds. Out of 36 compounds analyzed, 10 compounds (52 - 61) showed 40% inhibition of AR at a concentration of 15\(\mu\)g / mL. Further optimization study based in the predicted docking mode yielded compound number 61 with 20 fold increase in inhibitory activity. Structure based \textit{de novo} design and synthesis of ARIs using LEGEND program by Miyamoto et al.\textsuperscript{42} generated four lead structures with potent inhibitor activities (62, 63, 64 and 65). Hopefully advances made through such studies will reduce diabetic complications for a great number of diabetic patients.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\end{figure}
References:


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