Plants Used in the Management of Diabetic Complications

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Diabetes is a disease, which has assumed vital public health importance because of the complications associated with it. Various mechanisms including polyol pathway along with a complex integrating paradigm have been implicated in glucose-mediated complications. Though polyol pathway was established as a major mechanism, precise pathogenesis of these complications is not yet completely elucidated. Thus research focus was shifted towards key enzyme, aldose reductase in the pathway. Even though various compounds with aldose reductase inhibitory activity were synthesised, a very few compounds are under clinical use. However, studies on these compounds were always under conflicting results and an attempt has been made to review various natural substances with aldose reductase inhibitory activity and their role in management of diabetic complications.

Key words: Polyol pathway, aldose reductase, diabetes, oxidative stress

Diabetes mellitus (DM) is a chronic metabolic disorder of impaired metabolism of carbohydrates, fats and proteins, characterised by hyperglycaemia resulting from decreased utilisation of carbohydrate and excessive glycogenolysis and gluconeogenesis from amino acids and fatty acids[1]. According to recent reports, incidence of DM is about 6.4% globally affecting 285 million adults in 2010 and will increase to 7.7%, affecting 439 million adults by 2030[2]. People with DM are at higher risk of developing serious complications including heart attacks, blindness, kidney failure and neuropathy. Large prospective clinical studies show a strong relationship between glycaemia and diabetic micro vascular complications in DM[3,4].

Four molecular mechanisms are being extensively studied for their role in causing diabetic complications; increase in the flux of glucose through polyol pathway, increased intracellular formation of advanced glycation end-products (AGEs), activation of protein kinase C (PKC) and increased flux through the hexosamine pathway[5]. Among these, polyol pathway play an important role in the development of complications in DM[6]. Aldose reductase (AR), which is the first enzyme in the polyol pathway, is a cytosolic, monomeric oxidoreductase enzyme that catalyses the NADPH-dependent reduction of glucose[7]. In the polyol pathway, sorbitol is oxidised to fructose by the enzyme sorbitol dehydrogenase, with NAD^+ reduced to NADH. Hyperglycaemia-induced polyol flux leads to increase in sorbitol-induced osmotic stress, decreased Na^+/K^+-ATPase activity, an increase in cytosolic NADH/NAD^+ ratio and a decrease in cytosolic NADPH. As NADPH is required for regenerating reduced glutathione (GSH), this could induce or exacerbate intracellular oxidative stress leading to changes in respiration, membrane metabolism and oxidative resistance[8,9]. Since it is not possible to demonstrate a derived factor of aldose reductase inhibitor (ARI) activity that has more prognostic value for diabetic complications, a critical review of the literature on various ARIs from plants and their actual mechanism by which they produce a beneficial effect on progression of diabetic complications has been studied.

Even though, a large variety of compounds have been synthesised with potent *in vitro* ARI activity, very few compounds are clinically available because of undesirable side effects and poor pharmacokinetics[10]. The failure of these compounds has increased the need for search of newer molecules from natural sources. Till date numerous plant extracts and their phytoconstituents have been reported to have AR activity, but a specific review on the efficacy of these ARIs in the management of various diabetic complications has not yet been published. The

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present review aims at critical appraisal of the available literature on various ARIs from plants for their role in the management of diabetic complications.

DIABETIC NEPHROPATHY

Diabetic nephropathy or diabetic kidney disease is one of the most important complications and affects 20-30 % of patients with DM. It is a progressive condition culminating into a kidney failure. Diabetic nephropathy has been classically defined by the presence of proteinuria greater than 0.5 g/24 h. The onset of diabetic nephropathy was found to be 17 years after the diagnosis of DM[11]. The pathogenic role of AR in diabetic nephropathy is a significant increase of the enzyme in the glomerulus[12]. Hyperactivation of AR in renal cells leads to the generation of AGEs. These AGEs along with the generation of reactive oxygen species (ROS) results in the expression and activation of transcription factors like nuclear factor NF-κB and PKC, which are implicated in the pathogenesis of diabetic nephropathy (fig. 1). AGEs also contribute to the release of proinflammatory cytokines, expression of growth factors and adhesion molecules[13,14]. This data suggest that inhibition of AR in kidney contributes to the protective effect on diabetic kidney.

Flavonoids like quercetin and myricetin, which were reported to have potent ARI activity[15] were found to show protective effect as well as prophylactic role on the diabetic kidney by decreasing the oxidative stress[16,17]. In different studies, rosmarinic acid isolated from *Origanum vulgare,* nepetrin and nepetin isolated from *Rosmarinus officinalis* showed potent ARI activity. The aqueous extract of leaves of *R. officinalis* was found to alleviate the nephrotoxicity induced by CCl_4 in albino rats, which was attributed to the antioxidative activity of one or more of its constituents. However, administration of rosmarinic acid alone was reported to inhibit glomerular hypertrophy and reduce glomerulosclerosis significantly in diabetic rats[18-21].

Haraguchi *et al*.[22] investigated the ARI activity of isoquircetrin and other flavonoids isolated from *Polygonun hydropiper*. In another study by Li *et al*.,[23] isoquercetrin was found to display a strong scavenging ability for nitrite and nitric oxide (NO) and exhibited a protective effect on the kidneys of mice. Moreover, isoquercetrin can increase the superoxide dismutase or catalase activities and reduce

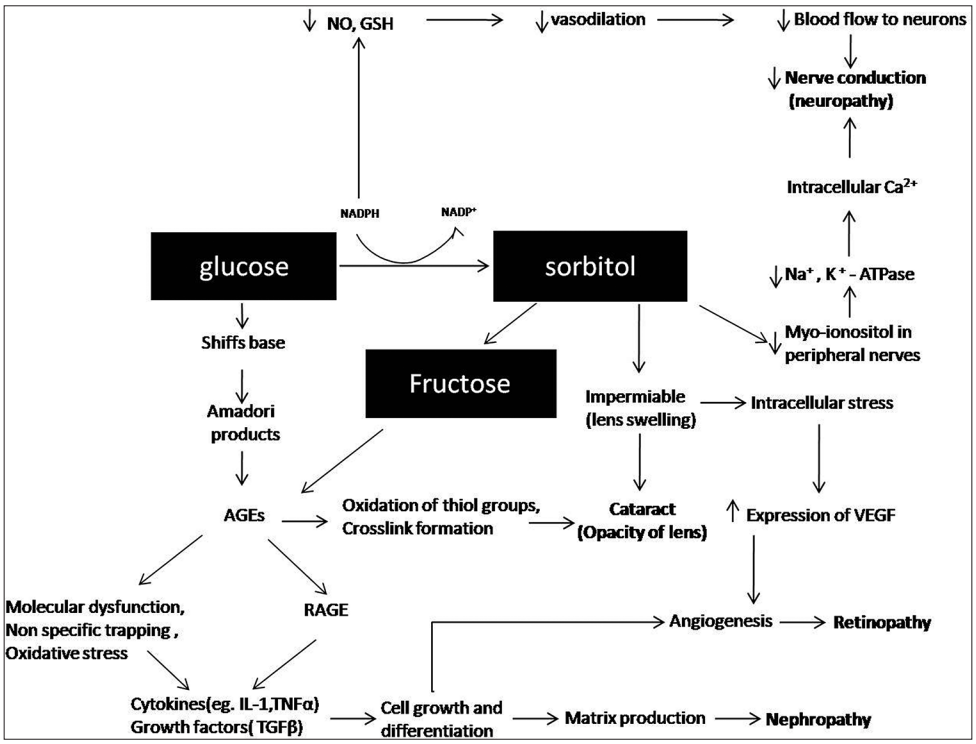

Fig. 1: Flow diagram illustrating an interplay between the polyol pathway, oxidative stress and diabetic complications.

the malondialdehyde, protein carbonyl and NO levels in the livers and kidneys of mice.

The dihydroflavonol astilbin isolated from the leaves of *Englhardtia chrysolepis* has been reported to show ARI activity, whereas astilbin isolated from the rhizome of *Smilax china* L significantly ameliorates diabetic nephropathy by reducing renal production of transforming growth factor (TGF)-β1 and connective tissue growth factor[24,25]. The ARI activity of components isolated from active fractions of *Chrysanthemum indicum* have been examined and among the tested compounds, luteolin was found to show potent ARI activity, which was found to prevent morphological destruction of kidney in diabetic rats caused by increased oxidative stress induced by polyol pathway. One of the mechanisms of the renoprotective effect of luteolin was also related to increasing heme oxygenase-1 expression and elevating antioxidant status in diabetic nephropathy[26,27].

Murata *et al*.[28] reported the inhibitory activity of various phytoconstituents isolated from green tea, which showed varying degrees of ARI effect with (-)-epigallocatechin having no activity. These catechins composing epigallocatechin, epicatechin gallate and epicatechin were found to normalise the morphological alterations in diabetic rats, indicating that catechin has renoprotective effects on diabetic nephropathy[29]. Yamabe *et al*.[30] reported the beneficial effect of (-)-epigallocatechin 3-O-gallate on diabetic nephropathy via suppressing hyperglycaemia, AGEs, their related oxidative stress and cytokine activations, and thereby altering the pathological states due to its multifocal mechanisms.

Phytochemical analysis of *Salacia chinensis* led to the isolation of mangiferin, which was found to be a potent ARI[31]. Mangiferin improved the renal function in diabetic rats, which was manifested by its decreasing effect on 24 h urinary albumin excretion. This beneficial effect was related to mangiferin's inhibitory effect on over expression of TGF-β1, AGE and extra cellular matrix accumulation, polyol pathway activation, ROS generation and mesangial cells proliferation[32].

Goodarzi *et al*.[33] investigated the ARI effect of naringin in streptozotocin (STZ)-induced diabetic rats. It was found that the inhibitory effect of naringin was comparable to that of quercetin. Besides this, naringin prevented the pathological alterations due to its insulin-sensitising, antiinflammatory, antidyslipidaemic and antioxidant activity. The mechanism for such an outcome is modulation of PPARγ, and NF-kB protein expression by naringin in kidney tissue indicating that naringin is an effective therapeutic strategy for the treatment of DM and its associated complications[34].

Curcumin, a potent inhibitor of AR, was reported to show its efficacy in diabetic nephropathy. It reverses the alterations in the activities of kidney cellular enzymes associated with DM, reverses the decrease in polyunsaturated fatty acids to saturated fatty acids ratio and ATPases activity of renal membranes, lowers nephromegaly in diabetic animals. Curcumin also acts through prevention of nuclear translocation of NF-kB, which is responsible for mesangial expansion[35-37].

Nine isoflavonoids isolated from *Belamcanda chinensis* showed varying degrees of ARI activity. Even though there are no reports on the protective effect of the plant on diabetic nephropathy, apocynin, one of the constituent of the plant with NADPH oxidase inhibitory activity was found to block the effect of increased glucose concentration to activate PKC-induced NADPH oxidase, and fibronectin secretion by peritoneal cells. Apocynin blocks the increase in PKC, O^{-2} generation and proliferation during incubation of mesangial cells with glycated albumin[38,39].

Ellagic acid isolated from *Myrciaria dubia* and caffeic acid isolated from *Origanum vulgare* were found to inhibit AR *in vitro* and was also found to significantly diminish renal activity of AR and sorbitol dehydrogenase, as well as suppressed renal AR mRNA expression along with inhibition of IL-6, IL-1β, tumour necrosis factor alpha (TNF-α) and monocyte chemoattractant protein 1 *in vivo* suggesting the combined effect of ARI and antiinflammatory activities of ellagic acid for its beneficial role in diabetic nephropathy[40,41].

Kato *et al*.[42] investigated the ARI activity of various phytoconstituents in rhizome of *Zingiber officinalis* Roscoe and was found to posses good inhibitory activity. However, the protective effect of the plant on diabetic kidney was characterised by the inhibition of structural distortions that developed by increased free radicals after a short period of hyperglycaemia. Besides this, the plant was found to protect the

kidney against the endothelial dysfunction resulting from membranous glycation[43]. Chethan *et al*.[44] reported the AR inhibiting activity of ferulic acid and other constituents isolated from Finger millet (*Eleusine coracana*) were found to show renal protective effects through improved glycemic control and renal structural changes, which are involved in the inhibition of oxidative stress, inflammation and the expression of TGF-β1 and type IV collagen[45].

Butein isolated from bark of *Rhus verniciflua* was found to be a potent inhibitor of human recombinant aldose reductase (HRAR) but the nephroprotective activity of the compound was attributed to its antioxidant ability and also the renal concentrating ability[46,47]. Berberine isolated from *Coptis japonica* was found to possess potent ARI activity, also showed the renoprotective effects, which was related to inhibition of glycosylation and improvement of antioxidation leading to upregulation of renal nephrin and podocin expressions[48,49] (Table 1).

Even though inhibition of AR plays a considerable role in the development of diabetic nephropathy, experimental studies with ARI in animal models in various studies have produced remarkably contradictory results. Treatment with tolrestat reduced the progression of urinary albumin excretion when compared with diabetic control rats, whereas other studies have failed to show this protective effect. Some studies have reported the normalisation of tissue sorbitol without much effect on urinary albumin excretion. Similarly glomerular filtration rate was found to be normalised in some studies while others have failed to show this effect on glomerular filtration rate[50]. Apart from these, various studies on ARIs have shown their efficacy in diabetic nephropathy with mechanisms that include decrease in oxidative stress-induced damage and antiinflammatory effect, which infers that even some of the potent ARIs like quercetin were found to reduce the oxidative damage that may be caused by activation of AR or by any other mechanisms. Thus, in this situation, it can be concluded that, a multiple therapy, which aims at different causative factors and various mechanisms rather than AR alone would be more beneficial in the therapy and prevention of diabetic nephropathy.

TABLE 1: PHYTOCONSTITUENTS WITH ARI PROPERTY STUDIED IN DIABETIC NEPHROPATHY

Compound	Mechanism of action	Reference
Quercetin	Reducing the oxidative stress	16
Myricetin	Reducing the oxidative stress	17
Rosmarinic acid	Reducing the oxidative stress	20
Astilbin	Inhibition of inflammatory mediators	25
Luteloin	Reducing the oxidative stress	27
Catechin	Reducing the oxidative stress	29
( )-Epigallocatechin 3-O-Gallate	Decreased AGEs induced oxidative stress, antiinflammatory property	30
Mangiferin	Decreased AGEs induced oxidative stress and antiinflammatory property	32
Naringin	Antioxidant and antiinflammatory property	34
Curcumin	Cholesterol lowering ability	36, 37
Apocynin	Decreased PKC. Decreased oxidative stress	39
Berberine	Decreased AGEs and decresed oxidative stress	49
Ellagic acid	Decreased AR, glycative and inflammatory mediators	41
Ferulic acid	Antioxidant and antiinflammatory property	45
Caffeic acid	Decreased AR, glycative and inflammatory mediators	41

AGC=Advanced glycation end-products, PKC=protein kinase C

DIABETIC NEUROPATHY

Neuropathy is a common complication of both type 1 and type 2 DM with a prevalence of about 8% in newly diagnosed individuals to 50% in patients with long standing disease. There are many different diabetic neuropathies involving different nerve types, which are mainly characterised by diffuse or focal damage to peripheral somatic or autonomic nerve fibres resulting from DM. Diabetic neuropathy can be classified into diffuse and focal neuropathies with diffuse neuropathy being more

TABLE 2: PHYTOCONSTITUENTS WITH ARI PROPERTY STUDIED IN DIABETIC NEUROPATHY

Compound	Mechanism of action	Reference
Quercetin	Central analgesic activity	53
Rutin	Metal chelating property	54
Baicalein	Antioxidative, antiinflammatory and inhibition of sorbitol pathway	55
Chlorogenic acid	Antioxidative and antiinflammatory properties	56
Epigallocatechin-gallate	Antioxidant property	57
Ellagic acid	Antioxidant property	58
Naringin	Antioxidant property	59
Curcumin	Antioxidative and antiinflammatory properties	61
Puerarin	Dilation of blood vessels (no exact mechanism)	60
Baicalin	Inhibition of AR	62
Eugenol	No mediated vasodilatation	63

AR=Aldose reductase

common, chronic and progressive, whereas focal neuropathies are less common and acute in nature. However, all these neuropathies are thought to occur from hyperglycaemia-induced damage to nerve cells and from neuronal ischemia resulting from hyperglycaemia-induced changes in the four pathways described above[51].

Increase in sorbitol concentrations by polyol pathway leads to cellular injury and decrease of *myo*-ionositol in the peripheral nerves and thereby leading to decrease in Na^+/K^+-ATPase activity, which is essential for nerve conduction[52]. Moreover, decreased NADPH results in decreased NO and reduced GSH production resulting in decreased vasodilatation and increased ROS production and oxidative damage (fig. 1). Thus ARIs are likely to contribute to the beneficial effect on development of diabetic neuropathy. A detailed review of reports on ARIs from medicinal plants showing their effect on neuropathy and their mechanism has been described (Table 2).

A potent natural ARI quercetin was found to increase nociceptive threshold indicating an antinociceptive activity of quercetin in diabetic rats[53]. However, quercetin affecting the physiological and biochemical alterations leading to diabetic neuropathy was not yet reported. Another ARI rutin was found to show a protective effect against diabetic neuropathy by its metal chelating property. It was proposed to sequester the transition metal preventing the fenton reaction, which may contribute to the development of diabetic neuropathy[54]. The protective effect of baicalein was attributed to various mechanisms like inhibition of PKC, oxidative stress and LOX pathways but does not attributed to sorbitol pathway, even though the compound was reported to be a potent ARI[55]. A phenolic ARI chlorogenic acid was found to show antihyperalgesic activity due to its antioxidant and antiinflammatory properties[56]. Similarly the beneficial effect of a potent ARI epigallocatechin-gallate against diabetic neuropathy was due to the inhibition of oxidative stress in diabetic rats[57].

Ellagic acid, which is a potent ARI along with antioxidant property, was found to show a protective effect against diabetic neuropathy by its antioxidant property. It was found to significantly decrease malondialdehyde (MDA) and nitrate levels in diabetic rats when compared with control group[58]. Likewise, a potent antioxidant, naringin with an ARI property was found to exhibit neuroprotective effect in diabetic rats by downregulation of free radical and cytokine regulated TNF-α[59]. Similarly an isoflavonoid, puerarin, was found to increase the conductive velocity of the nerves, which is due to the dilation of blood vessels leading to improvement of microcirculation and reduced blood viscosity. However, the mechanism by which these alterations occurred were yet to be studied[60]. Chronic treatment with curcumin, a potent ARI and antioxidant led to inhibition of NO and TNF-α and thereby antihyperalgesic activity in diabetic rats[61].

Baicalin was found to show a protective effect and relieve clinical symptoms of diabetic neuropathy by direct inhibition of AR in diabetic rats[62]. Similarly eugenol, a potent ARI was found to improve diabetic neuropathy by augmentation of NO and endothelium-derived hyperpolarising factor (EDHF)-mediated vasorelaxation[63].

Aremisia dracunculus, a plant with various potent ARIs, exhibited a beneficial effect of diabetic neuropathy by decreasing the sciatic nerve and spinal cord 12/15-lipoxygenase activation and oxidative nitrosative stress, but has failed to ameliorate hyperglycaemia or reduce sciatic nerve sorbitol pathway[64,65]. Likewise the curative and preventive property of trigonella in diabetic neuropathy was due to improvement in glucose intolerance, antiinflammatory and antioxidant property, even though the plant was found to possess a potent ARI activity[66,67].

Administration of a *Momordica charantia* fraction with potent ARI activity in diabetic rats led to a slight increase in myelinated fibre area. Even though, the mechanism for this beneficial effect of *M. charanti*a on the structural abnormalities of peripheral nerves in experimental DM was not established, however, the antioxidative property of the plant for the prevention of functional abnormalities in STZ-diabetic rats[68] was reported.

Apart from the above mentioned, plants such as *Olea europae*a, with no reported AR activity, was found to be effective against diabetic neuropathy and was found to attenuate thermal hyperalgesia in diabetic rats. The plant was found to show the effect by preventing the glucose-induced neuronal apoptosis[69].

DIABETIC CATARACT

Cataract is a condition where the crystalline lens of the eye loses its transparency. DM has been associated with an increase in cataract among adults[70]. Cataract in DM is mainly caused by swelling of crystalline lens due to osmotic changes caused by increased sorbitol concentration. The other mechanism is the cross linking of lens proteins due to nonenzymatic glycosylation. These glycated products generally called as AGEs readily accumulate in the lens and cause oxidation of thiol groups, cross link formation and aggregation of the crystalline proteins producing high molecular weight insoluble proteins, which are responsible for opacification[71] (fig. 1). Thus the polyol pathway plays a momentous role in the formation of cataract in DM.

Even though various classes of drugs such as antioxidants, vitamins, Nonsteroidal antiinflammatory drugs (NSAIDs) and others, have been developed, which aim to interact with the altered lens metabolism in cataract; ARIs remain to be the most studied class of drugs. The role of these drugs in the prevention of diabetic cataract is now well established and various natural and synthetic ARIs are under active research. A good number of synthetic compounds have been found to exhibit anticataract potential in different animal models and clinical trials. Never the less, even various natural compounds were found to possess good anticataract activity. Thus a brief review of various herbal ARIs and their mechanism in inhibiting the diabetic cataract has been compiled.

TABLE 3: PLANTS WITH ARI PROPERTY STUDIED IN DIABETIC CATARACT

Plant	Type of cataract	Mechanism of action	Reference
Pterocarpus marsupium	Diabetic	Antihyperglycemic affect	67
Trigonella foenum-graecum	Diabetic	Antihyperglycemic affect	67
Green tea	Diabetic	Antihyperglycemic affect	72
Adhatoda vasica	Diabetic	Inhibition of AR; antioxidant activity	73
Cassia fistula	Diabetic	Inhibition of AR;	73
Ocimum sanctum	Diabetic	Decrease in polyol accumilation	74
Silybum marianum	Diabetic	Antioxidant property	75
Hydrocotyl bonariensis	Sorbitol induced	Antioxidant property, reduced apoptosis	76
Curcuma longa	Diabetic	Inhibition of AR; antioxidant activity	77
Aralia elata	Diabetic	Inhibition of AR; antioxidant activity	80
Brickellia arguta	Diabetic	Inhibition of AR	79
Emblica officinalis	Diabetic	Inhibition of AR	78

AR=Aldose reductase

To date numerous studies were conducted to evaluate the anticataract activity of different medicinal plants and phytoconstituents. Enlisting a few of them, green tea was found to inhibit AR, glycated protein and along with its hypoglycaemic affect, it was found to show anticataract activity in diabetic rats[72]. Similarly *Adhatoda vasica* exhibited anticataract activity by inhibiting lens AR. Administration of byakangelicin to diabetic rats led to of suppression of sorbitol leading to increase in Na^+/K^+-ATPase and thereby exhibiting a protective effect on diabetic cataract. However, the mechanism was not proposed. *Trigonella foenum-graceum* and *Pterocarpus marsupium* were found to exhibit anticataract activity by means of antihyperglycaemic effect with trigonella exhibiting ARI activity, while there is no ARI activity reported for the later[67,73] (Table 3).

Cassia fistula was found to show anticataract activity by significantly inhibiting AR activity in rat lens[73]. *Ocimum sanctum* and *Silybum marianum* significantly decreased polyol accumulation and increased the GSH levels, respectively, leading to a protective effect on diabetic cataract[74,75]. Leaves extract of *Hydrocotyl bonariensis* reduced the lens protein precipitation and lens peroxidation and thereby increasing lens antioxidant status and delayed the formation of diabetic cataract. It also led to the reduction in lens apoptosis and epithelial proliferation[76]. Treatment of diabetic rats with turmeric or curcumin reversed the diabetic changes with respect to lipid peroxidation, reduced GSH. It also led to the changes in osmotic stress by modification of polyol enzymes and insolubilisation of lens proteins was also prevented[77]. Tannoid principles from *Emblica officinalis* and flavonoids from *Brickellia arguta* inhibited lens AR activity and thereby inhibited the polyol pathway induced oxidative stress leading to a protective effect on diabetic cataract in rats[78,79]. *Aralia elata* extract inhibited lens AR and along with antioxidant activity it also showed a preventive effect on cataractogenesis in xylose containing lens organ cultures and *in vivo* in STZ-induced diabetic rats[80]. Similarly flavonoids from *Emilia sochifolia* modulated lens opacification by reducing the oxidative stress in selenite-induced cataract[81].

TABLE 4: PHYTOCONSTITUENTS WITH ARI PROPERTY STUDIED IN DIABETIC CATARACT

Compound	Type of cataract	Mechanism of action	Reference
Quercetin	Diabetic	Inhibition of oxidative damage; by inhibiting lens AR	87
Myricetin	Diabetic	Inhibittion of lens AR	88
Quercitrin	Diabetic	Inhibittion of lens AR	88
Rutin	Selenite	Prevention of depletion of GSH, Inhibition of lipid peroxidation	82
Fisetin	Radiation	Decreased ROS; modulation of activation of NF-κb and MAPK	83
Ellagic acid	Selenite	Inhibition of lipid peroxidation	84
Puerarin	Diabetic	Unknown mechanism	90
Puerariafuran	Diabetic	Inhibition of AR, Inhibition of oxidative damage	89
Genistein	Diabetic	Increased expression of connexin (Cx) 43	85

ROS=Reactive oxygen species, AR=aldose reductase

Apart from the above-mentioned plants, various phytoconstituents were also found to inhibit AR with a significant protectant role in diabetic cataract[82-85]. Quercetin, which is a well-known ARI when studied in a cataract model, and its metabolite 3′-O-methyl quercetin inhibited oxidative damage in the lens[86]. Other flavonoids such as quercetrin, myricetin and puerariafuran showed the protective effect on diabetic cataract by inhibiting the lens AR[87-89]. However, puerarin was found to protect against diabetic cataract by exhibiting an anti effect on lens epithelial cells[90] (Table 4).

DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is the most common ocular complication in DM and is an important cause of preventable blindness. DR is broadly classified as nonproliferative DR involving intraretinal microvascular changes and proliferative DR involving the formation of new vessels or fibrous tissue or both on the retina. DR primarily effects the microvascular circulation of the retina. The factors leading to these changes are thickening of basement membrane of the capillary wall, increased platelet stickiness and changes in RBCs resulting in sluggish microvascular circulation and biochemical changes in the form of activation of polyol pathway resulting in tissue damage. Since the retinal ganglionic cells and endothelial cells are endowed with AR enzyme, these cells are more prone to damage caused by the activation of polyol pathway leading to DR[91] (fig. 1).

Even though a good glycaemic control seems to be the preferred option for the management of DR, knowledge and modulation of the pathways like polyol pathway through which hyperglycaemia causes diabetic complications showed promising results[92]. ARIs were able to prevent or reduce the changes in fructose fed STZ rats and normalise the retinal blood flow[93]. In contrast to the above study, a 5-year treatment with sorbinil did not show any effect on the retinal pathology in diabetic dogs[94]. In view of the contradicting results pertaining to the efficacy of ARIs in DR, a comprehensive review of the available literature on the ARIs from natural sources and their role in showing a beneficial effect in DR is essential in understanding the importance of ARIs.

Among the various ARIs from natural sources, few plants like *Ocimum sanctum, Tinospora cordifolia, Azardiracta indica, Ganoderma lucidum* were tested for their efficacy in retinopathy in various animal models. However, some plants like *Ocimum sanctum* were found to protect from DR only when given in combination with Vitamin E[95]. *Tinospora cordifolia* was found to inhibit over expression of angiogenic and inflammatory mediators and thereby prevent retinal oxidative stress exhibiting a protective effect on DR[96]. Similarly, *Ganoderma lucidum* was found to be effective in DR by enhancing the capability of antioxidation in diabetic rats and reducing the damage of retina from oxidation[97].

Phytoconstituents like baicalein, curcumin and hesperetin were effective in DR with baicalein ameliorating inflammatory process and thereby inhibiting vascular abnormality and neuronal loss in retinal tissues, whereas curcumin and hesperitin were found to decrease the levels of various mediators like vascular endothelial growth factor[98-100]. Other substances like quercetin and rosmarinic acid were found to show their effect on DR by prevention of angiogenesis, which can be related to the antioxidative properties of the compounds[101,102].

CONCLUSION

As stated earlier, many theories have been proposed and studied to explain mechanisms leading to diabetic complications, which includes glucose metabolism

through polyol pathway where AR plays a vital role and excessive oxidative stress. While ARIs are the promising targets for the treatment of diabetic complications, most of the developed ARIs show poor or only a partial amelioration and some show unacceptable toxicities[103]. This can be explained by the fact that diverse complications may not share the same and single mechanism. Since it is highly improbable for any single mechanism to explain the pathogenesis associated with diabetic complications, drugs targeted to a specific mechanism often produce unintended effects, which is one of the drawback for ARIs.

As mentioned in the above reports, various plant extracts and their phytoconstituents, which showed ARI activity, exhibited their beneficial effect on various complications. However, majority of the ARIs acted by inhibiting oxidative stress or inflammatory changes that occur during DM. As a matter of fact, polyol pathway leads to oxidative stress and inhibition of AR leads to the decrease of oxidative stress. But the protective effect of the above-mentioned ARIs in diabetic complications is due to the ARI activity, thereby decreasing the polyol pathway-induced oxidative stress and/or due to the antioxidant property of the compound. Combined with this clinical efficacy of the compounds with either ARI activity or antioxidant property alone seems to be uncertain with various reasons, which are beyond the scope of this review. Thus, a molecule with both ARI activity and antioxidative properties could be more effective than a compound with either ARI or antioxidant property alone.

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