

Natural Aldose Reductase Inhibitor: Potential Therapeutic Agent for Eye Disease

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Aldose Reductase (AR)

Aldose reductase (AR, AKR1B1) is one of the aldo-ketoreductase super family proteins first reported in 1956 by H.G. Hers [1]. AR is involved in the polyol pathway that converts glucose to sorbitol in a NADPH dependent manner [2]. Level of AR is increased in the hyperglycemic condition and is considered a risk factor for diabetic complications. In the AR polyol pathway, induction of the Reactive Oxygen Species (ROS) is observed due to the consumption of NADPH and NAD⁺, which is important for neutralizing free radicals in the cell (Figure 1). The ROS that arose from AR therefore cause disease in a variety of organs. Increasing evidence has shown that AR is implicated in the inflammatory responses in the immune cells [3-7] and in the kidney [8,9]. Additionally, AR is a major factor that causes a variety of diabetic complications in the nerve [10-14] and in the heart [15-27]. Pharmacological inhibition of AR attenuates or delays these inflammatory responses and diabetic complications; therefore providing a valuable tool for investigating pathogenesis caused by endotoxin or diabetic hyperglycemia. In this perspective article, I will review two current reported natural compounds that show inhibitory effects on AR *in vitro* and *in vivo* that may carry therapeutic benefit against eye diseases.

AR and Ocular Diseases

AR has been reported to be involved in many kinds of ocular diseases (Table 1). In the hyperglycemia condition, AR levels are increased and are highly correlated to diabetic cataract [28-33] and retinopathy [34-38]. Elevation of oxidative stress produced from the AR polyol pathway leads to lens defect and retinal cell death [39]. In the Experimental-Induced Uveitis (EIU) model, pharmacological inhibition or genetic knockout of AR prevents endotoxin-induced inflammatory responses in the eye [3,40]. On the other hand, AR also regulates inflammatory responses in retinal microglia *in vitro* [4] and *in vivo* [41]. In macrophages, AR-induced inflammatory response is mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation [5-7]. However, it is unclear if NF-κB plays the same role in retinal microglia. It will be interesting to have further research show us how NF-κB influences ocular inflammation in retinal microglia. In light of the cytotoxicity and inflammatory effects of AR, pharmacological blockade of AR polyol pathway is a potential therapy to delay or reduce the onset or progression of AR-associated complications.

Posterior Capsule Opacification (PCO), also called secondary cataract, is highly correlated with transforming growth factor beta

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(TGF-β)-induced Epithelial Mesenchymal Transition (EMT) in the lens capsule. It occurs in more than 20% of patients after 5 years of cataract removal surgery. Other than oxidative stress and inflammation, AR was recently reported to be involved in EMT in an enzyme dependent [42] and independent [43] manners. Animal study of optical administration of AR inhibitor on the lens removal model is needed to further confirm the therapeutic potential.

Natural AR Inhibitors

Herbal medicine has been widely used as a therapy for chronic diseases [44]. Among these natural products, many AR inhibitors were introduced for diabetic therapy. However, the liver and/or renal toxicity caused by these compounds, such as tolrestat and zoprest [45,46], is too high to continue onto clinical trials. Therefore, natural compounds from plants provide an opportunity for lowering the dangerous side effects. Plant-derived compounds have been used to prevent and/or cure diabetic complications for decades. For example, the indian gooseberry (*E. officinalis*), also commonly known as Amla, has been used as a traditional medicine for diabetes. Among the active components, beta-glucogallin (1-O-galloyl-β-D-glucose) was discovered from Indian gooseberry and was elucidated as an inhibitor against AR [47]. Previous studies showed that beta-glucogallin does not cause cytotoxicity and is able to inhibit endotoxin-induced inflammatory responses both *in vitro* [4] and *in vivo* [3]. Additionally, beta-glucogallin also alleviates hyperglycemia-induced cell death in Retinal Pigment Epithelial Cells (RPECs) [34].

Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) is a natural compound discovered in many plants. Many studies indicated that emodin treatment attenuates blood glucose level in diabetic animals by targeting 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) as well as regulating AKT/GSK3β and PPARγ signaling pathways [48-50]. A recent study revealed the inhibitory property of emodin against AR *in vitro* and *in vivo* [51]. In the study, oral administration of emodin attenuates AR-induced lens vacuole formation and opacity in a mouse model. In addition, molecular modeling analysis confirms the interacting residues between AR and emodin. In a recent report, Pan-Assay Interference Compounds (PAINS) are described to non-

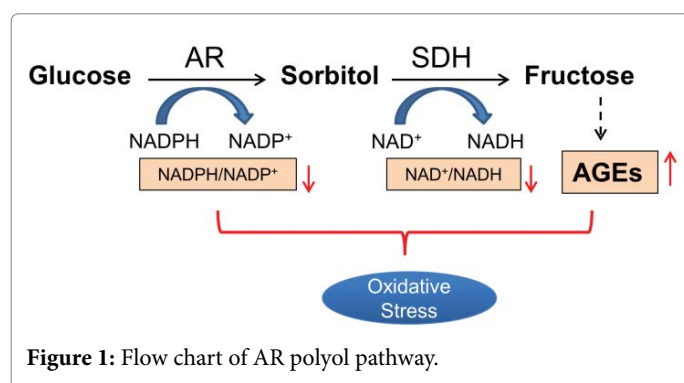
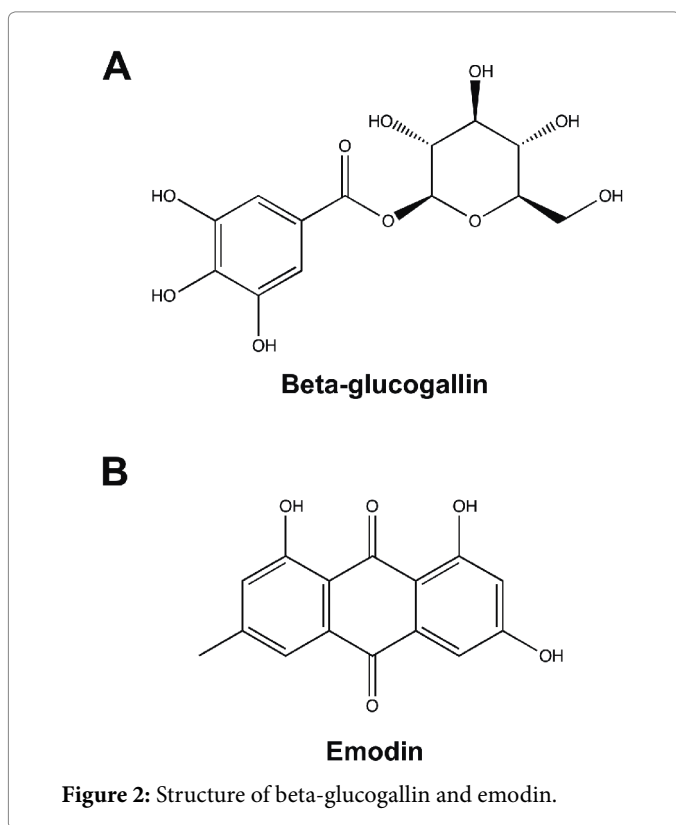


Figure 1: Flow chart of AR polyol pathway.



Role of AR in eye disease	
Organ	Associated disease
Eye	Uveitis
	Diabetic cataract
	Diabetic retinopathy
	Posterior Capsular Opacification

Table 1: Table of AR-associated eye disease.

specifically block enzymatic activity [52]. Although quinone-derived compounds like emodin might be considered as PAINS, structural elucidation indicates that emodin inhibits AR in a PAINS-independent manner [51].

In summary, beta-glucogallin and emodin were found to be potential therapeutic agents against AR-associated ocular diseases.

Conclusions and Perspectives

Although beta-glucogallin is effective *in vitro* and *in vivo*, it has been considered as one of the simplest classes of hydrolysable tannins, the gallotannins. Based on the beta-glucogallin pharmacophore, a previous study developed novel AR inhibitors carrying optimal stable linkage between the sugar moiety and the gallating while maintaining or improving potency and specificity for AR [53]. Structural comparison between beta-glucogallin and emodin was elucidated using molecular modeling and both showed interaction with the Ser302 of AR in the active dock [51]. Based on the computational prediction technique, this opens a door that could select a big amount of potential candidate compounds for AR inhibition using high throughput method. Although many studies have shown the low cytotoxicity of beta-glucogallin and emodin in animal models, further studies will be required to establish the clinical efficacy and safety of beta-glucogallin and emodin as a potential therapeutic for diabetes sourced primarily from fruits and plants.

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