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REVIEW

Therapeutic Effects of Natural Products in Diabetic Retinopathy through Aldose Reductase Inhibition

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ABSTRACT

Diabetic retinopathy (DR) is one of the most dangerous and cruel microvascular complications of diabetes, leading to visual impairment and blindness if left untreated. The development of DR is determined by complex multiple pathologic mechanisms, including oxidative stress, chronic inflammation, retinal vascular dysfunction, and retinal neuronal damage. Aldose reductase (AR) activation in the polyol pathway has been implicated to lead to excessive accumulation and production of reactive oxygen species (ROS) in several tissues (e.g., the heart, vasculature, kidney, and eye) under acute and chronic diabetic conditions. Therefore, many research scientists have extensively focused on developing synthetic AR inhibitors or finding AR inhibitors from natural products. Natural products and their bioactive compounds have been an important source of potential drugs to alleviate pathological conditions in various metabolic diseases. They are considered more effective, economical, convenient, and relatively safe. This review article aimed to focus on summarizing the therapeutic potential of natural product-based AR inhibitors for DR management. Many dietary compounds and phytochemicals have been found to be a good source of promising AR inhibitors. Their antioxidant effects can be used as a promising adjunctive treatment to conventional treatment (e.g., anti-vascular endothelial growth factor therapy) for DR management. Our comprehensive narrative review guides future research in drug discovery and development to modulate pathologic DR conditions.

Keywords: Natural Products; Diabetic Retinopathy; Aldose Reductase; Antioxidants; Reactive Oxygen Species; Phytochemicals

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1. Introduction

Diabetes mellitus is a multifactorial metabolic disorder and disease characterized by hyperglycemia (simply speaking, high glucose levels). Long-term complications of diabetes gradually develop, including diabetic neuropathy, cardiovascular disease, diabetic nephropathy, diabetic retinopathy (DR), and neurological disorders [1,2].

DR is one of the common and dangerous microvascular complications of diabetes, leading to visual impairment and blindness if left untreated. Pathologic mechanisms for DR development could occur with protein kinase C (PKC) activation, advanced glycation end products (AGEs) accumulation, and/or polyol pathway activation, further leading to oxidative stress, chronic inflammation, retinal vascular dysfunction, and retinal neuronal damage [3]. Those pathologic mechanisms have been well-presented and discussed in the previous literature [4,5].

Particularly, the polyol pathway has a two-level metabolic pathway, starting from the conversion of glucose to sorbitol through the aldose reductase (AR) activity, followed by the direct conversion of sorbitol to fructose through the sorbitol dehydrogenase activity [6]. Under the physiologic condition for glucose levels, this pathway is not extensively used. However, under the hyperglycemic condition, the polyol pathway can be highly activated. During this pathological event, production and accumulation of reactive oxygen species (ROS) via NADH oxidase, as well as dysregulation of antioxidant defense systems related to glutathione, can occur [7]. Therefore, the polyol pathway is one of the promising therapeutic signaling targets to manage DR development and progression.

Natural products have been globally used as alternative medicine for centuries [8,9]. Technological and scientific developments, such as culturing advances and analytical tools, have made natural products and their substances a valuable source of promising therapeutic agents for various metabolic diseases and disorders, including diabetes and obesity [10,11]. Natural products contain herbs, botanicals, various types of minerals, vitamins, probiotics, and/or other bioactive supplements. The current review article underscores the significance and importance of natural products and their bioactive substances to inhibit AR activity for addressing pathologic conditions in the damaged retina caused by diabetes.

2. Aldose Reductase (AR) Inhibitors from Natural Products

2.1. Quercetin

Quercetin is one of the most abundantly studied natural flavonoids detected in various fruits (such as raspberries, cranberries, tomatoes, broccoli, citrus fruits, and red grapes) and vegetables [12]. Quercetin has been proven to have strong antioxidant, anti-inflammatory, and neuroprotective effects in systemic metabolic and neurological diseases [13].

Chaudhry et al. and Varma et al. suggested that quercetin could inhibit lens AR activities [14,15]. Quercetin, quercitrin, and myricitrin are found to have more significant potentials than the widely known AR inhibitors [15].

Based on the study from Liu et al., quercetin could protect against hyperglycemia-evoked retinal damage in rats through regulation of the retina-gut axis and antioxidant nuclear factor erythroid-2-related factor 2 (NRF2) signaling pathway [16]. In fact, quercetin increases the activity of superoxide dismutase (SOD; an important enzyme playing critical roles in the defense of cells against oxidative stress/ROS) and glutathione peroxidase, and decreases various inflammatory markers. Moreover, the study by Ho et al. found that quercetin can have protective effects against lipopolysaccharide (LPS)-evoked retinal inflammatory processes in mice [17]. Although retinal protection is not directly discussed, the study from Xie et al. found that quercetin can have protective effects against diabetic peripheral neuropathy in murines (especially, rats) [18]. This therapeutic modulation is related to the reduction in ROS production levels. Finally, Chai et al. suggested that quercetin can protect against DR progression in rats through the induction of heme oxygenase-1 (HMOX-1/HO-1; one of the critical inducible enzymes responsible for the breakdown of haem) expression [19].

2.2. Berberine

Berberine is a bioactive plant compound classified as an alkaloid, which can be obtained from European barberry, goldenseal, and tree turmeric.

Liu et al. found that berberine might have inhibitory effects on AR with reducing oxidative stress levels under high glucose conditions [20]. Based on the study from Paul et al., berberine can inhibit AR and NADPH oxidase in platelets [21]. Furthermore, berberine can reduce ROS production under high glucose conditions in platelets. Its protection is also associated with Ca^{2+} release regulation. From the study of Fu et al., berberine can attenuate oxidative stress and severe inflammation in retinal Müller cells [22]. As Müller cell dysfunction can lead to DR-related pathologic changes, berberine's protective effects to those cells are significantly important. Zhai et al. demonstrated that berberine can inhibit retinal ganglion cell loss in streptozotocin (STZ)-induced diabetic rats with modulating the antioxidant system [23].

2.3. Luteolin

Luteolin is a naturally-occurring flavonoid with potential antioxidant effects and anti-inflammatory properties, derived from the *Reseda luteola* plant. Luteolin and its derivatives have been known to exert promising AR inhibitory effects [24,25].

From the study of Park et al., anti-angiogenic effects of luteolin were found on retinal neovascularization through blocking ROS production in oxygen-induced retinopathy (OIR) mice [26]. The OIR murine model has been commonly used for studying ischemic retinal diseases, such as retinopathy of prematurity (ROP) and/or proliferative DR (PDR), in that this model has neovascularization in the eye [27]. Furthermore, luteolin can inhibit vascular endothelial growth factor (VEGF)-evoked migration and formation of tubes in human retinal microvascular endothelial cells (HRMECs). Finally, from the study of Lu et al., the therapeutic effects of luteolin on retinal oxidative stress (e.g., malondialdehyde; MDA) and inflammation (e.g., IL-1beta and VEGF) were shown in STZ diabetic rats [28].

2.4. Curcumin

Curcumin is a polyphenol constituent of *Curcuma longa* [29]. Curcumin has also been found to have biological functions such as antioxidant and anti-inflammation, which can lessen pathologic conditions in DR. Moreover, accumulating evidence has shown that curcumin and its analogs have AR-inhibitory effects [30–33].

Li et al. found that curcumin could inhibit neuronal cell death in the retina of STZ-induced diabetic rats via therapeutic regulation of glutamate amounts and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activity [34]. Yang et al. also suggested therapeutic roles of curcumin on the retina in experimental diabetic rat models, which is explained by the hypoglycemic, antioxidant, VEGF-decreasing, and neuroprotective characteristics of curcumin under metabolic dysregulating conditions [35]. As curcumin bioavailability is low, combining it with piperine or other formulations is recommended to enhance its bioavailability in the body [36–38]. The increase in bioavailability of curcumin is highly considered as another interesting research topic in metabolic diseases.

2.5. Other Natural AR Inhibitors

Natural products (especially, several parts of plants) extracts contain various bioactive components for our systemic health. Targeting the bioactive components in the extract prior to separation and separating them in a target-guided protocol/methodology could enhance the screening result. Antioxidants and/or enzyme inhibitors (in this review case, AR inhibitors) in the extract could be detected using 2,2-diphenyl-1-picrylhydrazyl (simply called "DPPH") radical reaction-based DPPH-high-performance liquid chromatography (HPLC) and enzyme–ligand binding affinity-based ultrafiltration-HPLC [39,40]. Then, pH-zone-refining counter-current chromatography (CCC), upgraded from conventional and general high-speed counter-current chromatography (HSCCC), is applicable for separating ionizable target compounds productively in the extract [41,42]. This can reduce time and increase the efficiency of the extract compound collection with better targeting.

Using a series of those efficient strategies, Zuo et al. found that the root extract of *Valeriana rigida Ruiz & Pav.* (*V. rigida*) is a novel source of caffeoylquinic acids having antioxidant effects and AR inhibitory activities [40]. Based on the paper from Zuo et al., with a similar method, methyl rosmarinate, rosmarinic acid, and butyl rosmarinate in *Lepechinia meyenii* (Walp.) Epling were found to have

antioxidant and AR inhibitory properties [43]. Huang et al. found that avicularin (a bioactive flavonol) is a minor AR inhibitor in defatted seeds of *Oenothera biennis L.* using a combination of analyses and separation technologies, such as HSCCC, affinity-based ultrafiltration, and HPLC [44].

Based on the study from Julius et al., finding AR inhibitors was attempted from phytocompounds through *in vitro* and *in silico* approaches [45]. 3D structures of plant compounds with anti-diabetic properties were obtained from the PubChem database for inhibition analyses. Agnuside, as well as eupalitin-3-O-galactoside, showed inhibitory effects on human lens AR. Their inhibitory effects were further confirmed with human AR from human ARPE-19 cells.

Similarly, from the study of Gakpey et al., the *in silico* analysis was used (e.g., protein-ligand interactions) to find five natural compounds as potential inhibitors of AR: (+)-pipoxide, Naamidine A, Zinc000095485961, 1,6-di-o-p-hydroxybenzoyl-beta-d-glucopyranoside, and (−)-pipoxide [46].

From the study of Murata et al., green tea was used to obtain catechins, (−)-epicatechingallate, (−)-epicatechin, and (−)-epigallocatechingallate, and they are AR inhibitors by several instrumental analyses [47]. Balestri et al. also performed a similar study to find AR inhibitors in green tea [48]. Green tea is composed of various polyphenols, and their pharmacological properties (including the AR inhibitory activity, anti-VEGF characteristics, anti-inflammatory effect, or antioxidant effects) have been suggested to improve various diabetic conditions in the eye, which is well-discussed and presented by Boroughani et al.'s study [49].

In dietary supplements and traditional herbal medicines, a wide variety of novel compounds (including flavonoids, terpenoids, alkaloids, coumarins, tannins, and miscellaneous) possessing the inhibitory activity of AR have been well-identified, and they are listed in several research literatures [50,51]. Although further experimental investigations are highly required to clarify the bioavailability, efficacy, and safety of novel natural bioactive compounds, especially in comparison with conventional synthetic AR inhibitors, these agents may offer promising alternatives.

3. Future Direction

3.1. Co-Intervention with Hypoxia-Inducible Factor (HIF) Inhibitors

Neovascularization is the key feature of PDR [52]. Hypoxia-inducible factor (HIF)-1 has been known to play a crucial role in retinal neovascularization, as VEGF is one of the main downstream genes of the HIF-1 signaling pathway [53,54]. Under normoxia, HIF-1α is rapidly degraded and soon disappears. However, under hypoxic and oxidative stress conditions, HIF-1α is highly stabilized and activated, leading to the direct transcriptional regulation and upregulation of VEGF gene expression. Not only VEGF but also other potent angiogenic factors are increased by HIF activation. This responsive process can eventually promote pathologic angiogenesis in the eye of ischemic retinopathy, such as PDR. As neovascularization is one of the critical steps for visual impairments and vision loss, HIF targeting genetically and pharmacologically is highly required for disease intervention.

Accumulating evidence suggested that several natural products, natural product-derived bioactive compounds, or daily supplements have suppressive effects on HIF activation. Apigenin is a popular dietary flavonoid possessing anti-tumor activities and properties. Based on the study from Fang et al, apigenin might inhibit VEGF and HIF-1 expressions in ovarian cancer cells, further suppressing tube formation in vitro by endothelial cells [55]. Liu et al. also found that apigenin can inhibit VEGF expression and angiogenesis via the HIF-1 binding site [56].

Resveratrol is a compound mostly found in red grapes, possessing antioxidant properties. From the study of Lee et al., resveratrol was shown to inhibit HIF-1 and VEGF expressions in a concentration-dependent condition in human ARPE-19 cells, by promoting proteasomal degradation [57]. Furthermore, resveratrol can inhibit choroidal neovascularization in mice, which is related to wet-neovascular age-related macular degeneration. Ji et al. showed that resveratrol can protect retinal ganglion cells against retinal ischemia-reperfusion injury in murines, which is associated with glaucoma [58]. Seong et al. suggested that resveratrol can suppress VEGF secretion in ARPE-19 cells with reducing HIF-1 expression [59]. From the study of Yuan et al., resveratrol might protect against STZ-evoked

diabetic retinal ganglion cell loss through modulation of the antioxidant NRF2 and HO-1 molecular signaling pathway [60].

Vitamin B6 is one of the water-soluble vitamins naturally present and detected in a huge variety of foods. Many studies showed that changes in vitamin B6 status might be associated with the development or progression of DR [61–64]. In a mouse model of laser-evoked choroidal neovascularization mimicking wet/neovascular age-related macular degeneration, supplementation with vitamin B6 could reduce choroidal neovascularization volume, and its effect was explained by the inhibition of the HIF-1 pathway [65]. Rice bran that contains a high amount of vitamin B6 also showed HIF-1 inhibitory effects in ocular cells [65]. Taken together, AR inhibitors and HIF inhibitors might be synergistically used for DR management, and this aspect should be further studied.

3.2. Co-Intervention with Peroxisome Proliferator-Activated Receptor-Alpha (PPARα) Activators

Recently, the roles of lipid metabolism in the eye have been of great interest in DR development and progression [66,67]. Clinical and preclinical studies have shown that peroxisome proliferator-activated receptor-alpha (PPARα) can be a promising therapeutic molecular target to manage lipid metabolism under DR conditions [68–71]. Among various PPARα activators, therapeutic roles of fenofibrate have been widely examined in experimental DR models [71]. Oral administration of fenofibrate can improve lipid profiles in various tissues and activate PPARα to exert anti-inflammation and neuroprotection [71–73]. As the other protective agent, fenofibrate systemically increases fibroblast growth factor 21 (FGF21) amounts [74,75], and FGF21 can also show cytoprotective [76–80], neuroprotective [76,80], and anti-inflammatory [77–81] roles in various ocular cells, depending on the disease condition. In this regard, enhancing lipid metabolism with PPARα activators and reducing oxidative stress with AR inhibitors can be combined to show the other synergistic therapeutic effects against DR development and progression. This intriguing topic can be further considered with new preclinical experiments.

4. Conclusions

This mini-review shortly suggests that natural product-based promising AR inhibitors can be used to prevent or protect against pathologic conditions in diabetes and DR. Furthermore, a combination of AR inhibitors with chemicals that have specific characteristics (e.g., HIF inhibition or PPAR activation) may contribute to delaying or improving pathologic DR conditions more efficiently. Our comprehensive narrative review guides future research in drug discovery and development for DR management.

Author Contributions

Conceptualization, D.L. and L.V.; methodology, D.L.; validation, D.L.; formal analysis, D.L.; investigation, D.L.; resources, D.L.; data curation, D.L.; writing—original draft preparation, D.L. and L.V.; writing—review and editing, L.V.; visualization, D.L.; supervision, D.L.; project administration, D.L.; funding acquisition, D.L. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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