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REVIEW

Modulation of diabetic retinopathy pathophysiology by natural medicines through PPAR-γ-related pharmacology

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Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes and remains a major cause of preventable blindness among adults at working age. DR involves an abnormal pathology of major retinal cells, including retinal pigment epithelium, microaneurysms, inter-retinal oedema, haemorrhage, exudates (hard exudates) and intraocular neovascularization. The biochemical mechanisms associated with hyperglycaemic-induced DR are through multifactorial processes. Peroxisome proliferator-activated receptor-γ (PPAR-γ) plays an important role in the pathogenesis of DR by inhibiting diabetes-induced retinal leukostasis and leakage. Despite DR causing eventual blindness, only a few visual or ophthalmic symptoms are observed until visual loss develops. Therefore, early medical interventions and prevention are the current management strategies. Laser photocoagulation therapy is the most common treatment. However, this therapy may cause retinal damage and scarring. Herbal and traditional natural medicines may provide an alternative to prevent or delay the progression of DR. This review provides an analysis of the therapeutic potential of herbal and traditional natural medicines or their active components for the slowdown of progression of DR and their possible mechanism through the PPAR-γ pathway.

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Abbreviations
15-dPGJ$_2$, 15-deoxy-$\Delta^{12,14}$ –prostaglandin J$_2$; AGEs, advanced glycation end products; BRB, blood retinal barrier; COX-2, cyclooxygenase-2; DR, diabetic retinopathy; ICAM-1, intercellular cell adhesion molecule-1; iNOS, inducible nitric oxide synthase; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor-kappaB; PPAR-γ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; TNF-α, tumour necrosis factor; VEGF, vascular endothelial growth factor

Introduction

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes and one of the leading causes of blindness worldwide (Fong *et al.*, 2004a). The prevalence of DR increases with the duration of diabetes, and nearly all patients with type I diabetes and more than 60% with type II diabetes have some degree of retinopathy after 20 years (Fong *et al.*, 2003; 2004b; Williams *et al.*, 2004). Therefore, early detection and prevention are the current management strategies (Ciulla *et al.*, 2003). Chronic hyperglycaemia is believed to be the primary pathogenic factor for inducing damage to retinal cells (Knudsen *et al.*, 2002; Hammes, 2005; Yanagi, 2008). However, the mechanisms that lead to DR are not fully understood (West *et al.*, 2006). DR is characterized by microaneurysms, inter-retinal oedema, haemorrhages, exudates (hard exudates) and intraocular pathological neovascularization (Fong *et al.*, 2004a,b). Laser photocoagulation therapy is the most common treatment modality for DR. However, this therapy may damage neural tissue resulting in the deterioration of vision (Bloomgarden, 2007). Therefore, development of new therapeutic strategies for the treatment

of excessive retinal vasopermeability and angiogenic changes are the basis for further research focus (Garcia *et al.*, 2008).

The peroxisome proliferator-activated receptor-γ (PPAR-γ) is a ligand-inducible transcription factor that belongs to a large superfamily, comprising the nuclear receptors for steroids, thyroid hormones and retinoids (Malchiodi-Albedi *et al.*, 2008). PPAR-γ plays an important role in adipogenesis, glucose metabolism, angiogenesis and inflammation (Sarafidis and Bakris, 2006). Synthetic PPAR-γ ligands, the thiazolidinediones, including pioglitazone and rosiglitazone, improve insulin resistance in diabetic patients, and have become one of the most popular anti-diabetic drugs in developed countries (Tilg and Moschen, 2008; Tontonoz and Spiegelman, 2008; Zinn *et al.*, 2008). In addition, natural PPAR-γ ligands, such as 15-deoxy-$\Delta^{12,14}$ –prostaglandin J_2 (15-dPGJ_2) have very potent anti-inflammatory effects that also modulate cellular defence against oxidative stress (Ershov and Bazan, 2000; Straus and Glass, 2001). Moreover, there is accumulating data to show that PPAR-γ activators exert anti-inflammatory, antioxidative and anti-proliferative effects in various cells including major retinal cells (Yamagishi *et al.*, 2007; Gerry and Pascual, 2008; Giaginis *et al.*, 2008; Sulistio *et al.*, 2008; Yanagi, 2008).

Plants remain an important source of material for maintaining human health with unparallel diversity and have improved the quality of life for centuries (Li *et al.*, 2005). Moreover, medicinal plants are an abundant source of biologically active molecules that play an important role in past and modern medicine and which act as a 'stepping stone' for the discovery of novel pharmacologically active ligands (Barnett *et al.*, 2003). In recent years, numerous plant-derived ligands of PPAR-γ receptors have been identified (Huang *et al.*, 2005). However, very limited research has been undertaken on medicinal plant-derived PPAR-γ ligands in the modulation of DR-related pathophysiology. Thus, the current review is a detailed discussion summarizing the current understanding of the potential of herbal and traditional natural medicines for management and potential reversal of DR-related pathogenesis.

Diabetic retinopathy

Diabetes damages all the major cells of the retina, vascular cells (endothelial cells and pericytes; Hammes *et al.*, 1995; Mizutani *et al.*, 1996) and pigment epithelial cells (Decanini *et al.*, 2008). Basement membrane thickening, pericyte dropout and retinal capillary non-perfusion occur prior to the damage, which changes the production pattern of a number of mediators, such as growth factors, vasoactive agents, coagulation factors and adhesion molecules. These result in increased blood flow and capillary diameter, proliferation of the extracellular matrix and thickening of basal membranes, altered cell turnover (apoptosis, proliferation, hypertrophy) and procoagulant/proaggregant patterns, and finally angiogenesis with tissue remodelling. These pathological changes cause increase retinal vasopermeability and breakdown of blood retinal barrier (BRB), resulting in retinal haemorrhages, swelling, exudates and retinal detachment (Gardner *et al.*, 2000; Ciulla *et al.*, 2003; Yam and Kwok, 2007).

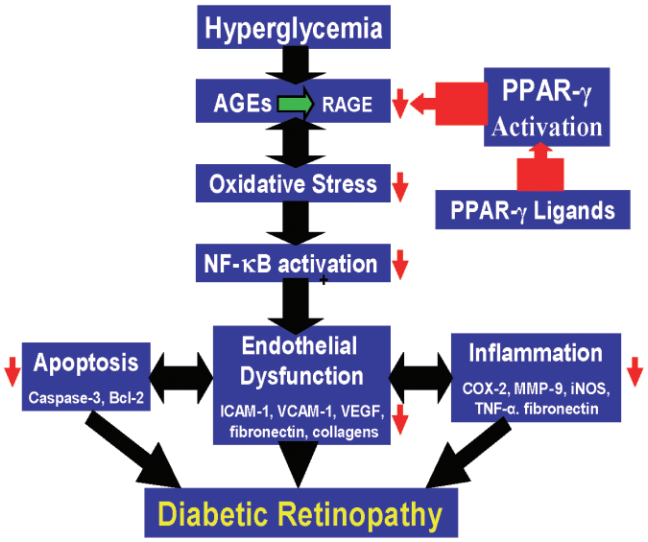

Figure 1

Pathophysiological cascades implicated in the development of diabetic retinopathy. Schematic representation showing the involvement of PPAR-γ and its receptor system in the progression of diabetic retinopathy (adapted from Yamagishi *et al.*, 2007). VCAM-1, vascular cell adhesion molecule-1.

The underlying pathophysiological mechanisms associated with hyperglycaemic-induced DR are through excessive formation of advanced glycation end products (AGEs) and production of excessive oxidative stress (Ciulla *et al.*, 2003; Abu El-Asrar *et al.*, 2009). Moreover, these biochemical mechanisms lead to a cascade of events, such as promotion of apoptosis, inflammation and angiogenesis, which induce damage to diabetic retina, leading to DR (Ciulla *et al.*, 2003; Abu El-Asrar *et al.*, 2009; Figure 1).

Advanced glycation end products (AGEs) in diabetic retinopathy

Advanced glycation end products are associated with modification of proteins or lipids that are generated from intermediate glycation products by non-enzymatic reaction of glucose with protein side chains (Schmidt *et al.*, 1994; Goh and Cooper, 2008). These intermediate glycation products undergo further condensation, dehydration or rearrangement, leading to eventual irreversible AGEs formation (Chu and Ali, 2008). AGEs formation occurs normally over time whereas an accelerated rate of AGE formation is accompanied by hyperglycaemia (Munch *et al.*, 1998).

The accumulated AGEs products are detected in the retinal blood vessel wall, responsible for mediating the pathological angiogenesis and hyper-permeability in retina. Several bodies of evidence suggest that the interaction between AGEs and their receptor activates nicotinamide adenine dinucleotide phosphate oxidase and enhances the formation of oxygen radicals, with subsequent activation and translocation of nuclear factor-kappaB (NF-κB), followed by release of pro-inflammatory cytokines and growth factors (Abu El-Asrar *et al.*, 2009). Moreover, AGEs enhance apoptosis in retinal pericytes, corneal endothelial cells, neuronal cells and renal

mesangial cells through increased oxidative stress or via induced expression of pro-apoptotic cytokines (Kasper *et al.*, 2000; Denis *et al.*, 2002; Kaji *et al.*, 2003). Indeed, AGEs induce apoptosis, angiogenesis, breakdown of BRB, and leukocyte adhesion in the retina. Thus, AGEs are detrimental to the retinal vasculature and contribute to the pathogenesis of DR (Stitt, 2001; Sato *et al.*, 2006).

Oxidative stress in diabetic retinopathy

Oxidative stress appears when there is a serious imbalance between generation of reactive oxygen species (ROS) and its clearance by antioxidant defences (Ceriello *et al.*, 2001; Brownlee, 2005). Activation of receptor for advanced glycation end products results in production of oxidative stress (conversely, glycation itself is promoted by oxidative stress), and subsequent activation of NF-κB transcription factor in microvascular endothelial cells, which is considered to be linked to endothelial dysfunction (Moore *et al.*, 2003; Vincent *et al.*, 2007). Retina, a tissue rich in polyunsaturated fatty acid, uses more oxygen and glucose oxidation than any other tissue in the body, and is very susceptible to damage (Schmidt *et al.*, 2003). Diabetic-induced oxidative stress, followed by activation of NF-κB in the retina, are early events in the pathogenesis of DR (Kowluru *et al.*, 1996; 2001; Kowluru, 2005; Obrosova and Julius, 2005). Moreover, oxidative stress has been linked to the accelerated apoptosis of retinal capillary cells and microvascular abnormalities in DR (Allen *et al.*, 2005).

Nuclear factor-kappaB in diabetic retinopathy

Nuclear factor-kappaB is a multi-protein complex which can activate many kinds of genes involved in cellular functions. Pathogenic stimuli allow NF-κB to enter the nucleus, and to bind to DNA recognition sites in regulatory regions of target genes (Schreck *et al.*, 1992; Baeuerle and Henkel, 1994; Boileau *et al.*, 2003). NF-κB is required for maximal transcription of many pro-inflammatory molecules thought to be important in the generation of inflammation, including molecules (intracellular adhesion molecule 1), critical enzymes [inducible nitric oxidase synthase, cyclooxygenase-2 (COX-2)] and a number of cytokines (interleukin-1β, tumour necrosis factor-α, IL-6) (Siebenlist *et al.*, 1994; Blackwell and Christman, 1997). The activation of NF-κB is considered a key signalling pathway by which high glucose induces apoptosis in endothelial cells (Du *et al.*, 1999). In the retina, NF-κB is localized in sub-retinal membranes and in microvessels (Hammes *et al.*, 1999) and its activation is considered responsible for the accelerated loss of pericytes observed in DR (Romeo *et al.*, 2002).

Inflammation in diabetic retinopathy

In recent years inflammation has been linked to vascular leakage in DR, at least in part (Adamis, 2002; Joussen *et al.*, 2002). Hyperglycaemia is a contributing risk factor for the development of vascular dysfunction and production of inflammatory markers (Haubner *et al.*, 2007; Tawfik *et al.*, 2009). Indeed, pro-inflammatory cytokines, chemokines and other inflammatory mediators play an important role in the pathogenesis of DR. These lead to persistent low-grade inflammation, the adhesion of leukocytes to the retinal vasculature (leukostasis), breakdown of BRB and neovascularization with subsequent sub-retinal fibrosis or disciform scarring (Carmo *et al.*, 1999; Malchiodi-Albedi *et al.*, 2008). Several inflammatory molecules are involved in the pathogenesis of DR, including tumour necrotic factor (TNF-α), fibronectin, COX-2, intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 and matrix metalloproteinase-9 (MMP-9) (Miyamoto and Ogura, 1999; Yuuki *et al.*, 2001; Joussen *et al.*, 2004).

Angiogenesis in diabetic retinopathy

Angiogenesis is defined as the growth of new vessels from pre-existing capillaries which is a complex process comprising endothelial cell proliferation, migration, extracellular proteolysis, tube formation and vessel remodelling (Beck and D'Amore, 1997). In retina, vascular endothelial growth factor (VEGF) is the major angiogenic factor for neovascularization and vascular leakage via the mitogen-activated protein kinase pathway (Miller *et al.*, 1994; Kliffen *et al.*, 1997; De Luca *et al.*, 2008). Additional pro-angiogenic factors, including MMP-9, are also required for the process of ocular neovascularization through either synergistic effects with angiogenic factor or as a stimulant for the secretion of angiogenic factors (Hollborn *et al.*, 2007). In addition, MMP-9 expression acts as a factor in increasing vascular permeability in ocular neovascularization (Herzlich *et al.*, 2008).

Apoptosis in diabetic retinopathy

Apoptosis is programmed cell death and is characterized by chromatin condensation, fragmentation and formation of apoptotic bodies that can be triggered by various signals (Nagata, 1997; Li *et al.*, 1998; Leal *et al.*, 2009). In healthy organisms apoptosis and cell proliferation are in homeostasis to maintain a physiological balance during normal embryonic development and in the cell turnover throughout life (van den Oever *et al.*, 2010; Zeng *et al.*, 2010). In contrast, retinal microvascular cells are lost selectively via apoptosis before other histopathology is detectable in diabetes (Mizutani *et al.*, 1996; Kern *et al.*, 2000; Kowluru and Odenbach, 2004). Moreover, it has been well established that apoptosis represents a final common pathway of cell loss and hence vision loss (Doonan *et al.*, 2009). Therefore, apoptosis plays an important role in the progression and pathogenesis of DR (Allen *et al.*, 2005; Leal *et al.*, 2009). As oxidative stress is closely linked to apoptosis in diabetes, oxidative stress-induced apoptotic episodes have been demonstrated by retinal abnormalities, potential visual changes and the onset of the first vascular change (Lopes de Faria *et al.*, 2001; Kowluru, 2005). Moreover, apoptotic cell death in retinal regions is a probable stimulus for the increased expression of molecules that enhance the breakdown of the BRB and lead to vascular proliferation (Henkind, 1978; Patz, 1982). Several studies have shown that retinal pigment epithelial (RPE) cells, Glial cells (Zeng *et al.*, 2009) and retinal pericytes (Leal *et al.*, 2009; Zeng *et al.*, 2010) undergo high glucose-induced apoptosis. High glucose causes activation of several proteins involved in apoptotic cell death, including members of the caspase and Bcl-2 family (Allen *et al.*, 2005).

Pathogenesis of retinal pigment epithelium in diabetic retinopathy

The RPE cells form a monolayer between the neuroretina and the choriocapillaris which are the essential component of the outer BRB that maintain physiological and structural balance within the retina (Bok, 1993; Rizzolo, 1997). The main characteristics of RPE cells are the presence of tight junctions at the apical side of their lateral molecules, which limit access of blood components to the retina. Other important functions include regulation of transport of nutrients to the photoreceptors, phagocytosis of damaged or old rod outer segments and production of growth factors (Holtkamp *et al.*, 2001). Moreover, RPE and photoreceptors are particularly susceptible to oxidative stress because of high oxygen consumption by photoreceptors (Beatty *et al.*, 2000). In response to damage caused by the hyperglycaemic condition, RPE cells migrate and proliferate, leading to a breakdown in adhesion between the RPE and the choroidal capillaries, followed by BRB breakdown compromising blood flow within the RPE layer and leading to eventual retinal oedema (Kennedy *et al.*, 1995). These cascade episodes trigger the serum components and inflammatory cells to enter the vitreous cavity and sub-retinal space, exposing the RPE cells to a variety of cytokines, pro-inflammatory mediators, extracellular matrix proteins and growth factors, causing DR (Kimoto *et al.*, 2004). Several studies have shown that the expression of angiogenic cytokines, growth factors (e.g. VEGF) and metalloproteinases (e.g. MMP-9) are produced by RPE (Grossniklaus *et al.*, 2002). Moreover, the combined effects from chronic sustained inflammation and ROS generation promote the development of RPE damage (Winkler *et al.*, 1999; SanGiovanni and Chew, 2005; de Jong, 2006). There is a strong body of evidence on the prevalence of the variety of anti-angiogenic agents, anti-inflammatory agents, antioxidants and anti-fibrogenesis present in the retinal regions for slowing down the progression of DR (Winkler *et al.*, 1999; Zhang *et al.*, 2006; Kern, 2007; Cheng *et al.*, 2008). Moreover, the discovery of biochemical mechanisms that either protect cells or promote cellular recovery from damage is important (Geiger *et al.*, 2005).

Peroxisome proliferator-activated receptor-γ and diabetic retinopathy

Peroxisome proliferator-activated receptor-γ is heterogeneously expressed in the mammalian eye, prominently present in the retinal pigmented epithelium, photoreceptor outer segments, choriocapillaries and retina (Murata *et al.*, 2000; Sarayba *et al.*, 2005; Herzlich *et al.*, 2008). Recent studies have shown that retinal expression of PPAR-γ was suppressed in experimental models of diabetes and in endothelial cells treated with high glucose (Tawfik *et al.*, 2009). Moreover, PPAR-γ ligands are potent inhibitors of corneal angiogenesis and neovascularization (Xin *et al.*, 1999; Muranaka *et al.*, 2006). Administration of 15d-PGJ_2 inhibited VEGF-stimulated angiogenesis in rat cornea (Xin *et al.*, 1999). Similarly, choroidal neovascularization was markedly reduced by intravitreous injection of troglitazone. Laser photocoagulation-induced lesions in rat and monkey eyes showed significantly less leakage in troglitazone-treated animals (Murata *et al.*, 2000). Troglitazone demonstrated that intravitreal injections significantly inhibited the percentage of lesions as well as leakage per lesion (Murata *et al.*, 2000). Increase in catalase mRNA has been shown when using known PPAR-γ agonists rosiglitazone and ciglitazone in rat brain microvascular endothelium cells, one of the cell types damaged during inflammatory responses induced by ROS generation (Girnun *et al.*, 2002). In neonatal mice, intravitreous injection of rosiglitazone or troglitazone inhibited development of new retinal vessels. In the same study, thiazolidinediones have been found to inhibit retinal endothelial cell proliferation, migration and tube formation in response to VEGF treatment (Touyz and Schiffrin, 2006). In addition, rosiglitazone inhibits both the retinal leukostasis and retinal leakage observed in experimental diabetic rats which leads to the aggravation of retinal leukostasis and retinal leakage in diabetic mice (Muranaka *et al.*, 2006). Moreover, rosiglitazone has been shown to delay the onset of DR (Shen *et al.*, 2008). These findings suggest that PPAR-γ is involved in the pathogenesis of DR (Figure 1).

Peroxisome proliferator-activated receptor-γ and AGEs

Peroxisome proliferator-activated receptor-γ ligands provide a significant prevention of AGEs-induced microvascular complications, including DR (Dolhofer-Bliesener *et al.*, 1996; Watson *et al.*, 2005). Indeed, a body of evidence has shown that PPAR-γ ligands inhibit the formation of AGEs (Rahbar *et al.*, 2000; Sobal *et al.*, 2005). The inhibitory action of PPAR-γ ligands on AGE formation may be ascribed to their antioxidative properties (Yamagishi *et al.*, 2007; Gerry and Pascual, 2008; Giaginis *et al.*, 2008; Sulistio *et al.*, 2008). In addition, activation of PPAR-γ by rosiglitazone inhibits AGE-induced inducible NO synthase expression, nitrite release, fibronectin and type IV collagen production (Chang *et al.*, 2004; Yu *et al.*, 2007). Moreover, rosiglitazone has been shown to inhibit extracellular matrix accumulation, fibronectin and type IV collagen in AGE-injected rats, and also inhibits the AGE-induced proliferation and NO production in cardiac fibroblasts (Yu *et al.*, 2007; Li *et al.*, 2008).

Peroxisome proliferator-activated receptor-γ in NF-κB, inflammatory mediators and angiogenesis

Peroxisome proliferator-activated receptor-γ plays a critical role in a variety of biological processes, including inflammation and angiogenesis, mediated through the inhibition of NF-κB (Rosen and Spiegelman, 2001; Lee *et al.*, 2006; Sung *et al.*, 2006; Kim *et al.*, 2007). In streptozotocin-induced DR, rosiglitazone was shown to inhibit both retinal leukostasis and retinal leakage by the inhibition of NF-κB activation, with consequent suppression of ICAM-1 expression (Muranaka *et al.*, 2006). In addition, one recent body of evidence has shown that the suppression of PPAR-γ in diabetic retina is associated with the activation of NF-κB target gene expression (Remels *et al.*, 2009; Tawfik *et al.*, 2009). The activation of PPAR-γ inhibits the pro-inflammatory pathways, including cytokine secretion (Uchimura *et al.*, 2001; Wong *et al.*, 2001) and inducible nitric oxide synthase (iNOS) expression (Petrova *et al.*, 1999; Reilly *et al.*, 2001) in a variety of cell lines. Indeed, PPAR-γ ligands have also been shown to

suppress the expression of iNOS, observed at both mRNA and protein levels (Ricote *et al.*, 1998b). The murine iNOS promoter contains 24 transcriptional factor-binding sites, including NF-κB transcription factor (Chang *et al.*, 2004). Inhibition of ICAM-1 expression and retinal vascular leakage in experimental diabetes has been shown by rosiglitazone, and the increase in the same parameters by depletion of the gene encoding PPAR-γ (Muranaka *et al.*, 2006). PPAR-γ ligands have also been shown to inhibit the expression of VEGF receptors and the subsequent activation of downstream signalling pathway (Xin *et al.*, 1999; Murata *et al.*, 2001). Moreover, rosiglitazone has been shown to inhibit retinal neovascularization in oxygen-induced retinopathy by a mechanism downstream from VEGF-induced angiogenesis (Murata *et al.*, 2001). In addition, it has been suggested that ICAM-1 is involved in VEGF-induced leukocyte–endothelial cell interactions and subsequent BRB breakdown in the diabetic retina (Miyahara *et al.*, 2004). COX-2 has emerged as a key regulator of inflammatory angiogenesis and its expression is induced by VEGF (Wu *et al.*, 2003; Gately and Li, 2004). Moreover, PPAR-γ activation inhibits VEGF-mediated angiogenesis through the modulation of the stimulated COX-2 expression and activity (Scoditti *et al.*, 2009).

Peroxisome proliferator-activated receptor-γ and apoptosis

Apoptosis is a complex process, involving a multitude of signalling pathways that regulate the activities of pro- and anti-apoptotic members of Bcl-2 family of proteins which play an important role in various cell types (Fehlberg *et al.*, 2003; Bonne, 2005; Fuenzalida *et al.*, 2007). Moreover, oxidative stress can induce mitochondria dysfunction, followed by cytochrome c release and subsequent activation of caspases, a group of enzymes that execute apoptosis (Danial and Korsmeyer, 2004; Lin and Beal, 2006). A recent study has shown that rosiglitazone protects against oxidative stress-induced apoptosis through up-regulation of anti-apoptotic Bcl-2 family proteins (Ren *et al.*, 2009). Moreover, rosiglitazone and PPAR-γ over-expression protect against apoptosis induced by oxygen and glucose deprivation followed by re-oxygenation and up-regulation of Bcl-2 (Wu *et al.*, 2009). In contrast, down-regulation of NF-κB activation by PPAR-γ ligands protects the cells from destruction via the apoptotic pathways (Grey *et al.*, 1999; Baker *et al.*, 2001). A screen of FDA-approved compounds identified rosiglitazone as a novel anti-apoptotic agent in retinal cells in both *in vivo* and *in vitro* (Doonan *et al.*, 2009). In addition, troglitazone has shown cytoprotective activity in apoptotic-induced ARPE-19 cells (Rodrigues *et al.*, 2010). One further study has indicated that 15d-PGJ_2 helps RPE cells to maintain mitochondrial integrity by prevention of cytochrome c release and subsequent activation of the apoptosis pathway (Garg and Chang, 2004; Chang and So, 2008).

Peroxisome proliferator-activated receptor-γ and RPE cells

A number of studies have shown that RPE might be the prime target for oxidative stress and PPAR-γ ligands modulate cellular defence against the oxidative stress (Chang *et al.*, 2008). 15-dPGJ_2 protects RPE cells from oxidative stress by elevating GSH and enhancing mitogen-activated protein kinase activation through the PPAR-γ independent pathway (Qin *et al.*, 2006). In addition, 15-dPGJ_2, independent of its PPARγ activity, protects RPE cells from oxidative injury by raising intracellular GSH levels and extending hydrogen peroxide-induced activation of JNK and p38, suggesting the possible application of the agents in preventing ocular diseases from oxidative stress (Garg and Chang, 2003; Qin *et al.*, 2006). It has also been shown that PPAR-γ ligands inhibit VEGF-induced choroidal angiogenesis, without apparent toxicity to the adjacent retina, in a laser-induced model of choroidal neovascularization (Murata *et al.*, 2000). A recent study has shown that PPAR-γ inhibits the expression of MMP-9 in response to 15-dPGJ_2, and synthetic PPAR-γ ligands by antagonizing the activities of NF-κB to decrease vascular permeability or neovascularization (Ricote *et al.*, 1998a,b; Herzlich *et al.*, 2008). Moreover, rosiglitazone inhibits the endothelial effects of VEGF (Murata *et al.*, 2000). Interestingly, synthetic PPARγ agonists, AGN195037 and rosiglitazone, have been shown to be less effective in the protection of RPE cells against hydrogen peroxide-induced injury. Hence, the cytoprotective effect of this agent has not been conclusively demonstrated (Qin *et al.*, 2006; Chang *et al.*, 2008). There is growing interest in natural products with combined anti-glycation and antioxidant properties as they may have reduced toxicity. Indeed, a number of plant-derived flavonoids with antioxidant activity (quercetin, rutin and kaempferol) have been reported to inhibit glycation (Ahmed, 2005).

Herbal and traditional medicines and diabetic retinopathy

In recent years, there has been growing attention to alternative therapies and the therapeutic use of plant-origin natural products (Li *et al.*, 2005). More than 400 traditional medicinal plants and the effective constituents derived from over 800 herbal compounds are reported to possess therapeutic potential or efficacy for the treatment of diabetes (Bailey and Day, 1989; Al-Rowais, 2002; Dey *et al.*, 2002). Herbal and traditional medicines have been globally used for diabetic complications for centuries. Moreover, it may provide an alternative to prevent or delay the progression of DR (Head, 1999). Despite modern pharmacotherapeutics and advancement in an ever changing world of biotechnology, a lack of understanding still exists on the bioactivity of these herbal medicines and related active ligands towards the modulation of DR pathogenesis (Bailey and Day, 1989). This has prompted research to understand the mechanism of action of these compounds and seek new products for better management of diabetes and its complications (Ceylan-Isik *et al.*, 2008). This section summarizes the current research on various active components of herbal and traditional medicines capable of modulating DR pathogenesis (Table 1).

Traditional Chinese medicines in diabetic retinopathy

Traditional Chinese medicines (TCMs) have been used for more than 2000 years in China and other Asian countries with the fundamental aim of targeting not only the treatment of diabetes but also the prevention of its complications (Covington, 2001; Li *et al.*, 2004). The main concept on

Table 1

Modern research on natural medicines capable of modulating diabetic retinopathy-related pathogenesis

Herbal medicines	Active component	Functions	References
Goji berry (*Lycium barbarum* L.)	*Lycium barbarum* polysaccharides (LBP)	Beneficial effect for maintaining macular pigment density in age-related macular degeneration by increase fasting plasma zeaxathin levels in human clinical trial. Effective in glaucoma and modulating immune system in retinal ganglion cells in a rat hypertension model LBP antagonizes glutamate excitotoxicity in rat cortical neurons and increase Bcl-2 level in lens epithelial cells of the whole lens exposed to hydrogen peroxide	(Cheng *et al.*, 2005) (Chiu *et al.*, 2009) (Ho *et al.*, 2009) (Wang *et al.*, 2002)
Danshen dripping pills	*Salviae miltiorrhiae*	Improve visual acuity, control micro-haemorrhage Improve ischaemia of the retina and the visual field in early diabetic retinopathy; reduce the number of microaneurysms	(Qi *et al.*, 2007) (Deng *et al.*, 2005)
Ginkgo biloba	Ginkgo flavone glycosides	Beneficial outcome for the treatment of diabetic retinopathy when *Ginkgo dipyridolum* injection combined with laser photocoagulation therapy in human clinical trials Clinical improvement of diabetic dyschromatopsia in early diabetic retinopathy in a double-blind trial	(Wei *et al.*, 2005)
Ansiodus tanguticus	Anisodamine	Increase neural tissue oxygen tension in retinal hypoxia Increase blood flow and oxygen delivery to the retina-choroid and iris-ciliary body of the eye, and lipid peroxidation in the retinal cells	(Linsenmeier *et al.*, 1989; Zhang *et al.*, 1990)
Stephania tetrandra S. Moore (STMS) (Han Fang Ji)	Tetrandrine	Direct effect on retinal capillary of posterior ocular region and suppression of neovascularization of the retinal capillary in diabetic rats	(Liang *et al.*, 2002)
Radix Pureriariae	Not known	The ethanol extract of *Radix Pureriariae* inhibits glycosylation of rat lens protein	(Hirakura *et al.*, 1989)
	7-(6-O-malonyl-β-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4*H*-1benzopyran-4-one	Discovery of a new key chemical constituent proven to be useful in DR by inhibiting aldose reductase	(Duan *et al.*, 2000)
Gymnema sylvestre	A polyol, conduritol A	Beneficial effect on cataract by inhibiting lens aldose reductase	(Miyatake *et al.*, 1994)
Astragalis radix	Astragalosides	Potentially useful for the prevention of clinical diabetic complications such as diabetic retinopathy by inhibiting AGE product	(Motomura *et al.*, 2009)
Hachimi-Jio-gan (Trhmannia Eight Formula)	Not known	Controls the balance of sodium, potassium and calcium ions for maintenance of lens transparency. This finding may lead the possibility of prophylactic use in eye diseases such as diabetic cataract	(Kamei *et al.*, 1987)
Trigonella foenum graecum (Fenugreek)	Saponins, Flavanoids, 4-hydroxyisoleucine	Beneficial effect for abnormal accumulation of sorbitol and fructose in the diabetic lens Restore disintegration of the inner nuclear layer cells with reduction in rough endoplasmic reticulum and swelling of mitochondria in the diabetic retina Cataract-suppressing effect by inhibiting lens aldose reductase	(Miyatake *et al.*, 1994) (Preet *et al.*, 2006)
Vaccinium myrtillus (billbery)	Anthocyanidins	In a clinical study, 12 adult diabetic patients were treated with 600 mg of anthocyanosides daily for 2 months, followed by significant decrease in the biosynthesis of connective tissue to protect against diabetic retinopathy In 31 patients suffering from various types of retinopathy, treatment with *V. myrtillus* extract was associated with a reduced tendency towards retinal haemorrhage	(Boniface and Robert, 1996) (Perossini *et al.*, 1988)
Resveratrol (*trans*-3, 5, 4′-trihydroxystilbene)	Not known	Protects high glucose-induced ARPE-19 cells by reducing low-grade inflammation mediators, interleukin-6 and interleukin-8, COX-2, VEGF and connexion 43 down-regulations	(Losso *et al.*, 2010) (Srivastava *et al.*, 2009)
Saptamrita lauha	Flavanoid-like compounds but not specified	Control retinal haemorrhage absorption and its recurrence in retinopathic eyes	(Sharma *et al.*, 1992)

mechanisms of DR in TCMs are *yin* vacuity with dryness and heat leading to accumulation of phlegm and blood stasis, and causing not nourishing the eyes and static blood obstructing the network vessels of the eyes (Flaws *et al.*, 2002). Many clinical studies have shown the benefit of TCMs in reducing symptoms, improving visual acuity and visual field and improving the outcome under ophthalmoscopy (Ma *et al.*, 2004; Song *et al.*, 2006). Moreover, a growing body of evidence has shown the benefit of combining TCMs with Western treatment strategies (Donnelly *et al.*, 2006). Indeed, a combination of laser therapy with TCMs has been explored for DR in China (Gong, 2007). Traditionally, 'blood-vitalizing herbs' are used to treat microvascular-related DR (Han and Xu, 1988). Extracts used in TCMs provide therapeutic effects that are dependent on its related chemical compounds (Shi *et al.*, 2008). Despite the growing expenditure of TCMs for DR management, there is still no conclusive evidence to support its efficacy and issues of safety (Yeh *et al.*, 2003; Liu *et al.*, 2004; West *et al.*, 2006). Thus, the study of active compounds from the extract and its possible applicable mechanisms are required for better understanding the effect of TCMs in DR (Su *et al.*, 2007).

One human supplementation trial showed that the *Lycium (L.) barbarum* (Goji berry) intake increases the fasting plasma zeaxathin levels, beneficial for maintaining macular pigment density in age-related macular degeneration (Cheng *et al.*, 2005). *L. barbarum* polysaccharides, most abundantly present in Goji berry, induce an activation of microglia (brain macrophages) in retina (Chiu *et al.*, 2009). Indeed, Goji berry has been shown to be effective in glaucoma and in modulating immune response in retinal ganglion cells in a rat hypertension model (Chan *et al.*, 2007; Chiu *et al.*, 2009). Moreover, LPB has been shown to antagonize glutamate excitotoxicity in rat cortical neurons (Ho *et al.*, 2009). In addition, *L. barbarum* polysaccharides has been shown to increase anti-apoptotic protein Bcl-2 level in lens epithelial cells of the whole lens incubated in culture medium and exposed to hydrogen peroxide (Wang *et al.*, 2002).

Clinical study of DR treated with compound Danshen dripping pills (*Salviae miltiorrhiae*, Radix notoginseng and borneol) showed improvement in visual acuity, and control of micro-haemorrhage and microaneurysm of fundus. Moreover, the pills were effective in visual function recovery of DR (Qi *et al.*, 2007). Another study on the compound Danshen dripping pill was shown to improve ischaemia of the retina and the visual field in early DR, and to reduce the number of microaneurysms (Deng *et al.*, 2005).

Anisodamine is an alkaloid, originally isolated from *Ansiodus tanguticus* which was found to increase neural tissue oxygen tension of the retina (Linsenmeier *et al.*, 1989). Moreover, anisodamine has been shown to increase blood flow and oxygen delivery to the retina-choroid and iris-ciliary body of the eye, and to decrease lipid peroxidation in the retinal cells (Zhang *et al.*, 1990).

The ethanol extract of *Radix (R.) Pureratae* has shown to inhibit glycosylation of rat lens protein (Duan *et al.*, 2000). Moreover, a new key chemical constituent 7-(6-O-malonyl-β-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4*H*-1benzopyran-4-one was isolated from *R. Purerariae*. This new aldose reductase-inhibitory compound proved to be useful in DR (Hirakura *et al.*, 1989). The active components astragalosides from crude extract of *Astragalis (A.) Radix* has also been shown to be potentially useful for the prevention of clinical diabetic complications such as DR by inhibiting AGEs production (Motomura *et al.*, 2009).

A study of therapeutic efficacy of the root extracts of *Stephania tetrandra* S. Moore for delaying the progression of retinopathy was carried out in the streptozotocin-induced diabetic rat model. It was considered to work through the activation by its active component, tetrandrine, of suppression of neovascularization of the retinal capillary (Liang *et al.*, 2002).

Traditional Chinese formula Hachimi-Jio-gan (Trhmannia Eight Formula) controls the balance of sodium, potassium and calcium ions for maintenance of lens transparency. This finding leads to the possibility of prophylactic use of Hachimi-Jio-gan in eye diseases such as diabetic cataract (Kamei *et al.*, 1987). However, further study is warranted for human application.

Ayurvedic herbal medicines and diabetic retinopathy

Ayurveda has been widely used in India and some European countries, and recognition of its modality is increasing worldwide (Saxena and Vikram, 2004). More than 800 plants are used as traditional remedies for diabetes and its complications in the ancient Indian Ayurvedic and Unani system of medicine (Alarcon-Aguilara *et al.*, 1998; Saxena and Vikram, 2004). However, only a few medicinal herbs have been evaluated by scientific investigations (Saxena and Vikram, 2004).

A polyol, conduritol A from *Gymnema sylvestre* may be responsible for the cataract-suppressing effect by inhibiting lens aldose reductase (Miyatake *et al.*, 1994).

The seeds of *Trigonella foenum graecum*, commonly known as fenugreek, have been known for hypoglycaemic, hypocholesterolemic and hyperinsulinemic effects in diabetic patients and experimental animals (Khosla *et al.*, 1995; Puri *et al.*, 2002). It has been shown that fenugreek has a beneficial effect on abnormal accumulation of sorbitol and fructose in the diabetic lens. Moreover, disintegration of the inner nuclear layer cells with reduction in rough endoplasmic reticulum and swelling of mitochondria in the diabetic retina have been restored by fenugreek. Saponins, flavanoids and 4-hydroxyisoleucine are potential plausible effectors in reversing the histopathological and biochemical abnormalities observed in DR and warrants further investigation (Preet *et al.*, 2006). Clinical study has shown that an indigenous drug, *Saptamrita lauha* may have a role in control of retinal haemorrhage absorption and its recurrence in retinopathic eyes (Sharma *et al.*, 1992).

Western herbal medicines and diabetic retinopathy

Western herbal medicine is the most widely used form of herbal medicine although Ayurvedic and Chinese herbal medicines are becoming better known (Wohlmuth *et al.*, 2002).

The fruits of *Vaccinium (V.) myrtillus* (billbery), containing 25% anthocyanidins, have been widely used in Europe to prevent and treat DR (Murray, 1997; Camire, 2000). In a clinical study, 12 adult diabetic patients were treated with 600 mg of anthocyanosides daily for 2 months. Following

Table 2

Modern research on herbal and traditional medicines affecting PPAR-γ activation and its possible mechanisms in diabetic retinopathy

PPAR-γ activity in herbal medicine	Active component	Functions in diabetic retinopathy	References
Astragalus membranaceus and *Pueraria thomsonii*	Biochanin A	Inhibitory effect on protein glycosylation in diabetic retinopathy	(Asgary *et al.*, 2002)
Swietenia *mahagony*	Not known	Antioxidant activity of Swietenia *mahagony* seed may provide a new avenue against diabetic retinopathy	(Rodrigues *et al.*, 2010)
Korean red ginseng	Ginsenoside 20(*S*) Ginsenoside Rb2 Ginsenoside Re	Prevention of high glucose-induced apoptosis through decreased in Bcl-2 expression and increased Bax expression Protective effect against oxidative stress in the eye of diabetic rats which can be effective in the prevention of diabetic microvasculopathy	(Park, 2008) (Cho *et al.*, 2006)
Dan-shao-hua-xian formula *(Astragali Radix) (Stephania tetrandra* S. Moore)	Astragalosides Tetrandrine	Beneficial for the prevention of diabetic retinopathy by inhibiting AGEs formation Suppression of neovascularization of retinopathy in diabetes	(Wang and Cheng, 2008) (Motomura *et al.*, 2009) (Liang *et al.*, 2002)
Turmeric	Curcumin Curcuminoids	Inhibition of VEGF level in diabetes-induced retina Antioxidation property by inhibition of Ca^{2+} entry and protein kinase activity	(Zhou *et al.*, 2007) (Kowluru and Kanwar, 2007; Mrudula *et al.*, 2007) (Balasubramanyam *et al.*, 2003)

treatment, there was a significant decrease in the biosynthesis of connective tissue. The authors interpreted these results to mean that anthocyanosides have a protective property against DR (Boniface and Robert, 1996). In another study, treatment of 31 patients suffering from various types of retinopathy with *V. myrtillus* extract was associated with a reduced tendency towards retinal haemorrhage (Perossini *et al.*, 1988). Resveratrol (*trans*-3, 5, 4′-trihydroxystilbene) is a phytoalexin, particularly rich in the skin of red grapes, which has known benefit for cancer, DR, rheumatoid arthritis and cardiovascular disorders (Srivastava *et al.*, 2009; Losso *et al.*, 2010). In particular, resveratrol has been shown to protect high glucose-induced ARPE-19 cells by reducing low-grade inflammatory mediators, interleukin-6 and interleukin-8, COX-2, VEGF and connexion 43 down-regulation (Losso *et al.*, 2010).

One study has shown the beneficial outcome of the treatment of DR with laser photocoagulation therapy when combined with *Ginkgo (G.) dipyridolum* injection than the laser therapy alone in human clinical trials (Wei *et al.*, 2005). In addition, the therapeutic efficiency of the *G. biloba* extract was estimated for early DR, associated with diabetic dyschromatopsia in a double-blind trial. An improvement tendency was evidenced by *G. biloba* treatment without retinal ischemia (Lanthony and Cosson, 1988).

Herbal and traditional medicines that modulate diabetic retinopathy through PPAR-γ activation

Over the last two decades, herbal plants or their active components have been major sources of bioactive agents and continue to represent a potential 'goldmine' for novel ligands to be discovered (Egan, 2002; Shen *et al.*, 2003). However, the mechanisms of action for most of the herbal medicines associated with modulating DR have not been fully elucidated. Nevertheless, the experience obtained from their traditional use over many years should not be ignored (Elvin-Lewis, 2001). Despite numerous plant-derived PPAR-γ activators having been identified from plants in recent years (Huang *et al.*, 2009), there are no conclusive studies on DR and its mechanism of modulation through the PPAR-γ activation. The next section of this review summarizes the current studies on herbal or traditional medicine associated with PPAR-γ activation and the possible mechanisms relevant to the management of DR (Table 2).

Biochanin A is a common isoflavone from *Astragalus membranaceus* and *Pueraria thomsonii* which has been shown to induce adipocyte differentiation activation *in vitro* through or at least in part, PPAR-γ, as measured by reporter-gene activity. This finding has suggested the potential value of Biochanin A as an anti-diabetic agent (Shen *et al.*, 2006). Moreover, biochanin A has shown beneficial effect in DR by inhibition of protein glycosylation (Asgary *et al.*, 2002). *Swietenia mahagony* is native to the West Indies, and is traditionally used for the treatment of hypertension and malaria as a folk medicine in Indonesia (Nagalakshmi *et al.*, 2001). This medicinal herb has shown anti-diabetic activity with PPAR-γ transcriptional regulatory function as one of its *in vivo* mechanisms (Li *et al.*, 2005). Moreover, antioxidant activity of *Swietenia mahagony* seed may provide a new approach to diabetic-related complications (Rodrigues *et al.*, 2010).

One study has evaluated the effect of three traditional anti-diabetic herbs on the progression of diabetes. The results showed that mulberry leaf, Korean red ginseng and banaba leaf extracts significantly increased insulin sensitivity and

improved hyperglycaemia through the PPAR-γ pathway (Park *et al.*, 2005). In particular, ginsenoside 20(*S*), one of the ginsenoside metabolites, was found to increase PPAR-γ-transactivation activity and expression of glucose transporter 4 (GLUT 4) in 3T3-L1 adipocytes. Moreover, ginsenoside Rb2, an active component from Korean red ginseng, prevents high glucose-induced apoptosis through an increase in Bcl-2 expression and decrease in Bax expression in ARPE-19 cells (Park, 2008). Another active component, ginsenoside Re also has shown a protective effect against oxidative stress in the eye of diabetic rats, which is effective in the prevention of diabetic microvasculopathy (Cho *et al.*, 2006). Dan-shao-hua-xian, a TCM preparation, has been shown in a recent article to play a role in treating hepatic fibrosis by up-regulation of the gene expression and generation of PPAR-γ, and also by suppressing TNF-α production through down-regulation of the NF-κB signalling pathway (Wang and Cheng, 2008). Moreover, *Stephania tetrandra* S. Moore, one of the ingredients in Dan-shao-hua-xian, has been shown to suppress neovascularization of retinopathy in diabetes through the activation of a major chemical component, tetrandrine (Liang *et al.*, 2002). In addition, one of the other ingredient of Dan-shao-hua-xian, *A. Radix*, and its active components astragalosides, have been shown to be beneficial for the prevention of DR by inhibiting AGEs formation (Motomura *et al.*, 2009). Curcumin, the phytochemical component in turmeric has been shown to interrupt the platelet-derived growth factor and epidermal growth factor signalling pathway by stimulation of PPAR-γ gene expression in rat activated hepatic stellate cell (Zhou *et al.*, 2007). Moreover, a recent review has highlighted the importance of the anti-inflammatory property of curcumin component from turmeric by suppression of TNF-α expression and release, which is potentially mediated by the up-regulation of PPAR-γ (Jacob *et al.*, 2007). The anti-inflammatory property of curcumin has also been shown to inhibit VEGF level in streptozotocin-induced diabetic rat retina which gives a potential role in DR (Kowluru and Kanwar, 2007; Mrudula *et al.*, 2007). Curcuminoids in turmeric have shown antioxidation properties by inhibition of calcium entry and protein kinase activity, which may have therapeutic implications in DR (Balasubramanyam *et al.*, 2003).

Terpenoids are one of many bioactive phytochemicals in medicinal plants, which include carotenoids, isoprenoids and isoprenols (He *et al.*, 1997). Studies have shown that terpenoids are significant in cancer and cardiovascular diseases (Takahashi *et al.*, 2002). On the other hand, typical isoprenols from herbs and fruits, including farnesol and geranylgeraniol, activate PPAR-γ in 3T3-L1 adipocytes and HepG2 hepatocytes. In addition, these herbal derivatives up-regulate the expression of some lipid metabolic target genes of PPAR-γ, including an adipocyte-specific gene, *aP2* (He *et al.*, 1997; Takahashi *et al.*, 2002). Moreover, terpenoids such as ginkgolides from *G. biloba* improve blood flow by dilating blood vessels and reducing the stickiness of platelets for eye disorders, including DR (Braquet *et al.*, 1985; Baudouin *et al.*, 1999).

Conclusion

Diabetic retinopathy remains one of the major risk factors and a leading cause of preventable blindness worldwide. The increasing impotence of understanding the specific molecular and biochemical changes in DR leads to the requirement for development of novel therapeutic interventions. Although it is an important cause of blindness, initially DR presents few visual or ophthalmic symptoms until complete visual loss occurs (Fong *et al.*, 2004a,b). Current treatments of DR rarely improve visual function and are limited to surgical options in an advanced stage, with excessive side effects and significant financial burden. Hence, emerging treatments, possibly in combination with standard therapy, may provide superior efficacy and safety profile for the treatment or prevention of DR. Moreover, the new strategies move to a paradigm in treating the early stages of DR. The recent advancements in the knowledge of the pathogenic alterations driving ocular damage and vision loss in DR strongly focus on PPAR-γ as a valuable target to control high glucose-induced inflammation and apoptosis. PPAR-γ functions as a transcription factor and thereby controls cellular processes at the level of gene expression, through modulation by its nuclear receptor activity of selective downstream gene expression (Huang *et al.*, 2005). The complexity of PPAR-γ activation not only provides beneficial effects but also introduces risks from undesirable side effects, such as cardiovascular complications with long-term application (Roehr, 2010). PPAR-γ is an attractive and relatively unexploited target for herbal-derived medicines in DR. This review confirms that natural and traditional herbal medicines have potential as alternative or combination therapy for DR, and emphasizes their possible mechanisms through PPAR-γ activity. Despite the long history of herbal and natural traditional medicines for the management of DR, there is still no conclusive evidence on their effectiveness and safety profiles. Therefore, future studies are warranted for extensive investigation to gather proof of efficacy in various preclinical and clinical settings.

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Conflict of interest

The authors declare no conflict of interest.

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