1. Introduction

Diabetic retinopathy is a major complication of diabetes mellitus, in which the blood vessels that supply oxygen to the retina of the eye are damaged due to long-term high levels of blood sugar (hyperglycemia). It generally develops slowly over a period of years as ongoing high blood sugar levels damage the blood vessels of the retina, a light-sensitive membrane, which lies at the back of the eye and is vital to normal vision. Prolonged hyperglycemia causes irreversible pathological changes in the retina, leading to leaking or bleeding of the blood vessels or the growth of abnormal blood vessels (retinal neovascularization) and diabetic macular edema (DME) in some individuals (Mohamed et al., 2007; Cheung et al., 2010). Longer diabetes duration and poorer glycemic control are strongly associated with DR. It is characterized by abnormal retinal vascular permeability, microaneurysm formation, capillary and arteriolar closure, neovascularization and associated hemorrhage, scarring, and tractional retinal distortion and detachment. However, in early stages of diabetic retinopathy, which starts after several years of diabetes, there may be no noticeable symptoms.

It is accounted that diabetic retinopathy appears after more than 20 years of occurrence of diabetes mellitus (Frank, 2004). Diabetes mellitus can be defined as a metabolic disorder with impaired glucose utilization. It is characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin, a hormone produced by the pancreas. During eating, the pancreas automatically produces the correct amount of insulin needed for allowing glucose absorption from the blood into the cells. In individuals with diabetes, the pancreas either produces too little or no insulin or the cells do not react properly to the insulin produced. The glucose thus builds up in the blood and overflows into the urine. Therefore, the body loses its main source of fuel even though the blood contains large amounts of glucose [http://www.abatediabetes.com/diabetes.html].

The etiology of diabetes is not well defined, however, viral infection, autoimmune disease and environmental factors have been implicated to play their roles (Marjani, 2010; Kataoka et al. 1983; Paik et al. 1982; Sandler et al. 2000; Shewade et al. 2001).
While exogenous insulin and other medications can control many aspects of diabetes, numerous complications affecting the vascular system, kidney, retina, lens, peripheral nerves, and skin are common and are extremely costly in terms of longevity and quality of life. If not managed properly, diabetes can lead to both short term and long term complications. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications (Baynes et al. 1999; Baynes, 1991). Diabetes is usually accompanied by increased production of free radicals (Baynes et al. 1999; Baynes 1991; Chang et al. 1993) or impaired antioxidant defenses (Halliwell et al. 1990; Saxena et al. 1993). Mechanisms by which increased oxidative stress is involved in the diabetic macro- or micro-vascular complications are partly known.

Diabetic retinopathy (DR) is a highly specific microvascular complication of diabetes and is the commonest cause of blindness in the working population, causing an estimated 50-65 new cases of blindness per 100,000 people every year (Evans et al., 1996; Icks et al., 1997; Rhatigan et al., 1999; Cormack et al., 2001; The Royal College of Ophthalmologists, 1997). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger onset patients (Type 1 diabetes) and 1.6% of older onset patients (Type 2 diabetes) were considered blind (Fong et al., 2003). Worldwide studies have been carried out assessing the prevalence of DR. It develops in nearly all persons with type-1 diabetes and in more than 77% of those with type-2 who survive over 20 years with the disease. The number of people with DR is rapidly increasing owing to a dramatic rise in the prevalence of type 2 diabetes, reflecting the increased prevalence of obesity and metabolic syndrome observed in recent years (Cheung et al., 2010; Raman et al., 2010). At present there are approximately 93 million people suffering from diabetic retinopathy, 17 million with proliferative DR, 21 million with diabetic macular edema, and 28 million with VTDR worldwide. These data highlight the substantial worldwide public health burden of DR and invariably reveals that DR is a highly frequent complication threatening all diabetic patients (Yau, et al., 2012).
Prolonged diabetes, hyperglycemia and hypertension have been recognized as the three major risk factors associated with diabetic retinopathy which is evidenced in many epidemiological studies and clinical trials (Wang et al., 2009; Grosso et al., 2011; Robinson et al., 2012). Dyslipidemia and body mass index might also be the risk factors, but associations have not been as consistent (Lim and Wong, 2011; Benarous et al., 2011). Emerging evidence supports a genetic component for DR, but despite large studies, specific genes associated with the disease have not been clearly identified (Sobrin et al., 2011).

Diabetic retinopathy is classified into three stages viz: Background Diabetic Retinopathy (BDR), Proliferate Diabetic Retinopathy (PDR) and Severe Diabetic Retinopathy (SDR). In BDR phase, the arteries in the retina become weakened and leak, forming small, dot-like haemorrhages. These leaking vessels often lead to swelling or edema in the retina and decreased vision. In the PDR phase, circulation problems cause areas of the retina to become oxygen-deprived or ischemic. New fragile, vessels develop as the circulatory system attempts to maintain adequate oxygen levels within the retina. This phenomenon is called neovascularisation. Blood may leak into the retina and vitreous, causing spots or floaters, along with decreased vision. In the SDR phase of the disease, there is continued abnormal vessel growth and scar tissue, which may cause serious problems such as retinal detachment and glaucoma and gradual loss of vision.

The microvasculature of the retina responds to hyperglycemia through a number of biochemical changes. The pathogenesis of the development of DR is highly complex owing to the involvement of multiple interlinked mechanisms leading to cellular damage and adaptive changes in the retina (Frank, 2004). Hence, despite years of clinical and laboratory investigation, the fundamental cause(s) of DR have not been elucidated completely. Earlier, retinopathy was characterized largely by its microvascular abnormalities, including endothelial cell dysfunction, vessel leakage, and vascular occlusion and degeneration (Curtis et al., 2009). Recent evidences, however, indicate that retinal complications of diabetes are a composite of many structural and functional alterations in both the microvascular and neuroglial compartments (Antonetti et al., 2006;
Curtis et al., 2009; Villarroel et al., 2010; Barber et al., 2011). The exact mechanisms by which hyperglycemia initiates the vascular or neuronal alterations in retinopathy have not been completely defined (Curtis et al., 2009; Villarroel et al., 2010). Several mechanisms are speculated to cause the cellular damage in the retina. These include increased flux through the polyol pathway, production of advanced glycation end products (AGEs), increased oxidative stress and activation of the protein kinase C (PKC) pathway, activation of the renin-angiotensin system, but many of these hypotheses have yet to be validated in human studies or clinical trials (Frank, 2004; Cheung et al., 2010). DR also shares similarities with chronic inflammatory diseases. It is known to cause increased vascular permeability, edema, inflammatory cell infiltration, tissue destruction, neovascularization, and the expression of pro-inflammatory cytokines and chemokines in the retina. Increased expression of vasoactive factors and cytokines probably plays an important role in mediating the structural and functional changes in the retina (Wirostko et al., 2008). There is an accumulating body of evidence that inflammation and neurodegeneration also play a prominent role in the pathogenesis of experimental diabetic retinopathy (Kern, 2007; Liou, 2010; Tang and Kern, 2011), although studies in humans have not found a consistent association between systemic markers of inflammation and retinopathy (Nguyen et al., 2009). Thus, it remains uncertain whether inflammation also plays a crucial role in the development and progression of DR in humans, but it is certainly involved in development of retinopathy in animals.

Among several factors found to influence diabetic retinopathy, more important is the contribution of the biochemical changes associated with hyperglycemia. These biochemical changes include HbA1c, Protein kinase C (PKC), Vascular endothelial growth factor (VEGF), Tumor necrosis factor-alpha (TNF-α), Interleukin-1beta (IL-1β), Oxidative stress etc.

Hyperglycemia is considered as the major contributor and upstream inducer in the progression of the DR. It causes glycation of proteins as seen in hemoglobin A1C (Brownlee et al., 1984). However, several studies have reported that even intensive therapy to control blood glucose has some long-term effects on the risk of DR (Ismail-
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Beigi et al., 2010; Patel et al., 2008). It indicates that only excess plasma glucose may not account for the range of cellular and functional changes involved in DR (Warboys & Fraser, 2010). Rather, DR is the result of changes in the production pattern of a number of mediators including growth factors, cytokines/chemokines, inflammatory molecules and adhesion molecules, leading to increased blood flow, increased capillary permeability, cell apoptosis and finally angiogenesis (Ola et al., 2012). The increased retinal levels of these metabolites and factors in diabetic human and various animal models have shown to induce several biochemical pathways and molecules implicated in the progression of the disease.

Vascular endothelial growth factor (VEGF), a multi-tasking cytokine is a primary angiogenic factor which stimulates differentiation, survival, migration, proliferation, tubulogenesis and vascular permeability in endothelial cells and mediates retinal neovascularization (Casper and Coen, 2005). Thus, it bears an important role in pathogenesis of DR. VEGF levels are elevated in the vitreous fluid of DR patients (Watanabe et al., 2005).

Di-Acyl Glycerol (DAG), one of the major pathways of diabetes greatly enhances Protein Kinase-C (PKC), which is linked to vascular dysfunctions and pathogenesis of DR (Geraldes & King, 2010). In several cellular and structural abnormalities that occur in DR, increased PKC activation has been implicated (Curtis & Scholfield, 2004; Das Evcimen & King, 2007), which results in increase in blood flow, basement membrane thickening, extracellular matrix expansion, vascular permeability, apoptosis, angiogenesis, leukocyte adhesion and cytokine activation (Alghadyan, 2011; Aiello et al., 2006).

PKC and other diabetes-induced metabolic factors including AGEs, polyols and oxidative stress activate proinflammatory mediators, thereby releasing proinflammatory cytokines, such as interleukin-1β (IL-1β) and TNF-α. These cytokines were found to be elevated in vitreous of diabetic patients, and their role in retinal pathogenesis leading to PDR has been characterized (Adamiec et al., 2010; Huang et al., 2011; Noma, et al., 2009). The increased levels of IL-1β and TNF-α in diabetic retina is related to blood retinal barrier
(BRB) breakdown, retinal leukostasis and apoptosis associated with DR (Adamis & Berman, 2008; Bertoni et al., 2010).

Persistent hyperglycemia causes increased production of free radicals especially reactive oxygen species (ROS), for all tissues from glucose auto-oxidation and protein glycosylation (Bonnefont et al., 2000). ROS play an important role in the causation and complications of diabetes mellitus (Mohamed et al., 1999) and oxidative stress is suggested as a mechanism underlying DR (Kowluru & Chan, 2007).

Because of a steep rise in the incidence and prevalence of diabetic retinopathy in the last decade, it has become a matter of big concern. Hence, prevention and treatment of this disease needs to be focused. Presently, laser therapy is the only leading treatment option in DR and that too just limits the damage but does not prevent it. No satisfactory pharmacologic therapy for the treatment of DR is available. There is, thus, a great need to develop new therapeutic approaches to reduce the burden of diabetic retinopathy. The World Health Organization has recommended the evaluation of the effectiveness of medicinal plants in condition where we lack the conventional allopathic treatment of diabetes (WHO, 1980; Upathaya et al., 1984). This prompted us to find the drugs which may be able to inhibit the progression of DM to the DR.

In the indigenous Indian system of medicine (Ayurveda), many herbal medicines have been experimentally evaluated for the treatment of diabetes. Based upon the hypoglycemic, anti-angiogenic, antioxidant and anti-inflammatory activities, we selected few herbal drugs for this study with an objective to explore their potential in prevention and management of diabetic retinopathy.