INTRODUCTION

Diabetes, a chronic metabolic disorder, has assumed pandemic proportions all over the globe. The latest WHO estimate shows at least 180 million people worldwide have diabetes and this is likely to increase to at least 366 million by 2030 (Biton, 2008; CDC, 2008; King, 2008; Veves et al., 2008; Danaei et al., 2009). The top ten countries in number of sufferers are India, China, USA, Indonesia, Japan, Pakistan, Russia, Brazil, Italy and Bangladesh. According to Indian Council of Medical Research, there are more than 35 million diabetics in India and this figure will rise to 80 million by 2030. The developing countries will show more of this increase due to population growth, ageing and unhealthy diets. Another worrisome aspect is the growing incidence of Type II diabetes at a younger age. The mean age of diabetes in developing countries is between 35 and 64 years implying that the most productive years of patient’s life are going to be affected. Diabetes has become one of the major causes of premature illness and death, mainly through increased risk of cardiovascular disease. The number of deaths attributed annually to diabetes is around 3.2 million (CDC, 2005, 2006, 2008, Biton, 2008; King, 2008).

The increasing prevalence of diabetes represents a significant burden to human health because of its long-term and often serious complications. These include nephropathy, retinopathy, neuropathy, cardiovascular disease and cognitive decline (Biessels et al., 2007; Veves et al., 2009; Paul et al., 2009; Rosengard-Barlund et al., 2009; Sima et al., 2009; Alvarez et al., 2009). These disease-specific complications lead to increased morbidity and reduced life-expectancy. Diabetes also has an economic cost, with total direct and indirect medical costs >$132 billion in the United States alone (King, 2008; O’Connor, 2009).

Diabetic neuropathy is the most common complication of diabetes. While estimates vary, depending on the methods used to diagnose diabetic neuropathy, it is generally held that at least 50% of all diabetic patients will develop neuropathy in their lifetime (Boulton et al., 2005; Feldman et al.,
Diabetic neuropathy manifests itself in ~30% of the hospital-based population and ~25% of community-based samples of diabetic patients (Figueroa-Romero et al., 2008; Ziegler, 2008). This high prevalence of neuropathy is likely an underestimate as several recent studies report that patients with impaired fasting glucose and/or impaired glucose tolerance also exhibit neuropathy at the time of diagnosis. Diabetic neuropathy is the most common cause of foot ulcers and nontraumatic amputations in the Western world. Patients with diabetic neuropathy report a poor quality of life secondary to pain, disability and recurrent hospitalizations. It is estimated that in the United States, the annual cost of diabetic neuropathy is nearly $11 billion dollars and increasing annually in parallel with the alarming increase in the incidence and prevalence of diabetes (www.diabetes.org). Although there are many approaches to the treatment of painful diabetic neuropathy, achieving more than 50% relief is rare and side effects limit the dose titration (Ziegler, 2006, 2008; Tesfaye, 2009).

The evidence of the impact of diabetes on central nervous system considerably grew up in the last decade. In humans, diabetes mellitus is associated with moderate impairments in cognitive function and patients present a high risk of affective disorders, dementia and Alzheimer disease (Biessels et al., 1994; Sima et al., 2004; Northam et al., 2006; Selvarajah and Tesfaye, 2006; Brismar et al., 2007; Alvarez et al., 2009). The hippocampus, a major limbic structure of the brain, is known to be very sensitive to stress and is strongly affected by diabetes (Cameron and Gould, 1994; De Kloet et al., 1998; Eichenbaum, 2000; Lupien and Lepage, 2001). In streptozotocin-induced model, hippocampal astrogliosis, low proliferation rate in dentate gyrus, poor neurogenesis and reduced number of hilar neurons is described (Saravia et al., 2002, 2004; Beauquis et al., 2006, 2008; Revin et al., 2005). Cognitive decline in diabetes is characterized by lowered performance on several cognitive domains, most notably slowing of mental speed and diminished flexibility (Brands et al., 2004; Sima et al., 2009). The reported prevalence is about 40% in long-standing or poorly controlled diabetes.
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(Dejgaard et al., 1991). To facilitate research into this area and to increase recognition of the disorder, Mijnhout et al. (2006) proposed a new term - 'diabetes-associated cognitive decline'. This term is not suggestive of a particular pathogenesis, but merely describes a state of mild to moderate cognitive impairment, in particular, psychomotor slowing and reduced mental flexibility, not attributable to other causes.

Extensive research has implicated four major pathways of glucose metabolism in the development of microvascular complications. These include: 1) increased polyol pathway activity leading to sorbitol and fructose accumulation, NAD(P)H-redox imbalances, and change in signal transduction; 2) nonenzymatic glycation of proteins and yielding advanced glycation end products (AGEs); 3) activation of protein kinase C (PKC) thereby initiating a cascade of stress response including oxidative stress, and 4) increase in hexosamine pathway flux (Brownlee, 1992; Windebank and Feldman, 2001; Stevens et al., 2002; Edwards et al., 2008). Only recently the link has been established between all four pathways that provide a unified mechanism of tissue damage and that link is hyperglycemia mediated superoxide overproduction by the mitochondrial electron transport chain. In the diabetic state, unchecked superoxide accumulation and resultant increase in polyol pathway activity, AGE accumulation, PKC activity, and hexosamine flux trigger a feed-forward system of progressive cellular dysfunction (Mastrocola et al., 2005; Maiese et al., 2007). Thus, striving for superior antioxidant therapy becomes an essential endeavor for the prevention of these devastating complications. Recent studies also reveal that a variety of growth factors and cytokines are induced through complex signal transduction pathway involving protein kinase C, mitogen-activated protein kinases, and the transcription factor NFκB in diabetic complications. High glucose, AGEs and ROS act in concert to induce growth factors and cytokines (King, 2008).

At present, apart from improving glycaemic control, there is no licensed treatment for diabetic neuropathy and associated cognitive decline (Boulton et al., 2005; Feldman et al., 2005; Little et al., 2007; King, 2008, Biton, 2008). However, even the strict hyperglycemia control could not
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prevent incidence of these complications. Thus, early diagnosis and improvement in understanding of the pathogenesis of the pain in diabetic neuropathy and associated cognitive decline may lead to more targeted treatments, with hopefully greater efficacy and lesser side effects. Drug selection should consider medical and psychiatric co-morbidities, potential adverse effects and drug interactions in an individual patient (Backonja et al., 2006).

Moreover, there is growing evidence that unless there is an immediate intensive treatment of hyperglycemia at the onset of diabetes, the hyperglycemia-induced metabolic stress leaves permanent vascular abnormalities in the target organs regardless of tight glycemic control in the later stage. This particularly negative phenomenon has been defined as "metabolic memory" (Brownlee, 2001; Drzewoski et al., 2009). This phenomenon was first observed in preclinical studies and was later confirmed in large clinical trials. The mechanisms of metabolic memory have not been fully clarified as yet. However, it has been well documented that poor metabolic control at the onset of diabetes leads to excessive generation of oxygen free radicals in mitochondria and overproduction of AGEs. These changes activate a number of cellular pathways which in turn cause micro- and macroangiopathic complications (Ceriello et al., 2009).

Thus the present research work is an attempt towards exploring various pathophysiological pathways especially the role of oxidative-nitrosative stress and secondary mediators such as transforming growth factor-beta (TGF-β), cytokines such as TNF-α, IL-1β, nuclear factor such as NFκB and caspase-3, an apoptotic marker, in diabetic neuropathic pain and associated cognitive decline. Moreover, the possible beneficial effect of insulin and three interventions with established antioxidant activity i.e. tocotrienol, lycopene and sesamol were evaluated in preventing these complications in diabetic rats.