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Review

Experimental evidence for curcumin and its analogs for management of diabetes mellitus and its associated complications

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ABSTRACT

Diabetes mellitus is a serious world health problem and one of the most studied diseases; a major concern about its treatment is that β-cell mass and functionality is hard to restore. In addition, it is frequently associated with severe complications, such as diabetic nephropathy and cardiomyopathy. The anti-inflammatory, anti-oxidative and anti-apoptotic properties of curcumin have made it a promising molecule for the treatment of this pathology; however, its solubility and bioavailability problems are still the subject of multiple studies. To cope with those difficulties, several approaches have been evaluated, such as the development of pharmaceutical formulations and curcumin analogs. This review discusses some of the studied therapeutic targets for curcumin in diabetes as well as the structural characteristics and targets of its analogs. The shortening of the central seven-carbon chain of curcumin has given rise to compounds without glucose-lowering effects but potentially useful for the treatment of diabetes complications; whereas preserving this chain retains the glucose-lowering properties. Most of the analogs discussed here have been recently synthesized and tested in animal models of type 1 diabetes; more studies in models of type 2 diabetes are needed.

Contents

1. Introduction

Diabetes mellitus can be defined as a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin activity or both (Berná et al., 2014). It is estimated that 382 million people in the world have diabetes and, by 2035, this number will increase to 592 million (International Diabetes Federation, 2013). Many therapeutic strategies have been

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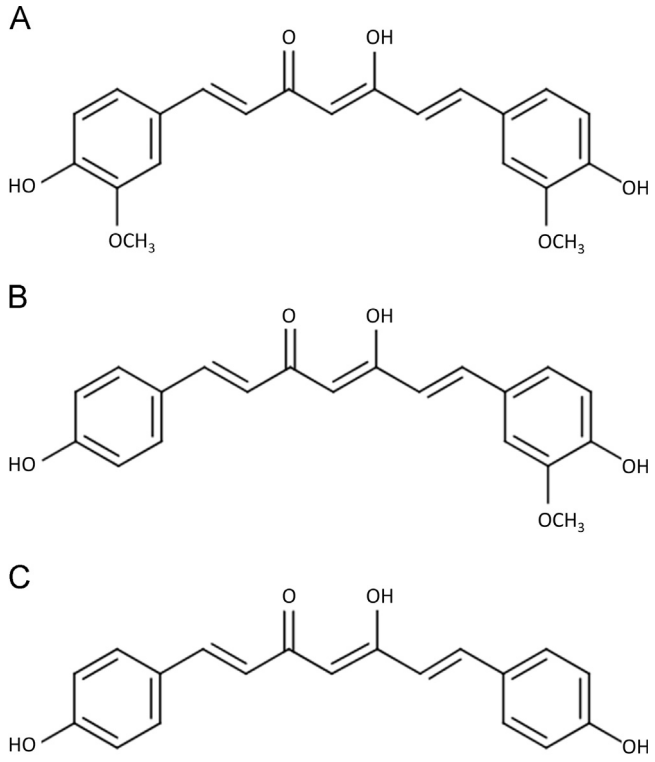

Fig. 1. Chemical structures of curcuimoids. Curcumin (A), demethoxycurcumin (B) and bisdemethoxycurcumin (C).

tested to treat or ameliorate diabetes and its complications: islet transplantation, gene therapy, stem cell therapy, as well as immunosuppressive, anti-inflammatory and anti-hyperglycemic drugs (Aathira and Jain, 2014; Agrawal and Kant, 2014; Liu and Wu, 2014). Natural products, including lignanes, flavonoids, polyphenols and terpenoids and their derivatives are emerging as a prospective alternative to treat diabetes (Hung et al., 2012).

Curcumin is a natural product from the rhizome of *Curcuma longa*, containing mainly three compounds: curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%) (Aggarwal et al., 2003) (Fig. 1). The broad variety of curcumin targets such as transcription factors, kinases, enzymes, adhesion molecules, proteases, cell surface receptors, transporters, and apoptotic factors (Beevers and Huang, 2011) makes this natural product potentially suitable for the treatment of diverse conditions: bacterial and viral diseases, inflammation, cancer, neurodegenerative diseases, and diabetes, among others (Beevers and Huang, 2011). In spite of all these features, the poor bioavailability of curcumin, because of its extensive metabolism, is still a concern (Anand et al., 2007; Beevers and Huang, 2011). Several strategies to improve the pharmacokinetic properties of curcumin have been tested; for instance, the synthesis of derivatives or analogs and the development of pharmaceutical formulations. Although glucose-lowering effects of curcumin are well known (Seo et al., 2008; Shao et al., 2012), experimental evidence about the use of its analogs to treat diabetes and its complications in animal models is quite recent. In this paper, we review those curcumin analogs that have shown promising results for the treatment of diabetes and its complications, focusing first on those with anti-hyperglycemic properties and then discussing those compounds that ameliorate diabetes complications without any glucose-lowering effect.

The vast majority of the evidence discussed here comes from studies performed in experimental animals; therefore, it is important to consider that not all the information obtained from animals can predict the effects that will be observed if a certain substance is tested in humans, and solid evidence is needed before moving from preclinical studies to clinical trials (Ioannidis, 2012).

2. Diabetes and associated complications

Type 1 diabetes mellitus results from the interplay among β cells, the immune system, as well as environmental and genetic factors, resulting in the cellular-mediated autoimmune destruction of pancreatic β cells and causing patients to require exogenous insulin (Dib and Gomes, 2009). Type 1 diabetes mellitus frequently develops in children and young adults. On the other hand, type 2 diabetes mellitus appears more frequently in older adults and it is associated with obesity and insulin resistance, together with defects in β cell function (Guilherme et al., 2008). In early stages of the disease, normal or excessive basal insulin levels can be observed, as a compensatory mechanism for insulin resistance (Skovsø, 2014; Weyer et al., 1999). Transition from prediabetes to established type 2 diabetes involves the loss of a significant portion of the functional β cell mass (Butler et al., 2003). Additionally, diabetes results in damage to multiple organs such as liver, heart, and kidney (Berná et al., 2014; Chiang et al., 2011; Navarro-González et al., 2011).

Pancreatic β cell death is a cause of deficient insulin production in types 1 and 2 diabetes mellitus (Cnop et al., 2005). It is considered that oxidative stress and inflammation play a central role in the pathogenesis of diabetes (Donath and Shoelson, 2011; Oberley, 1988). Reactive oxygen species activate the C-Jun NH2-terminal kinase (JNK) pathway, leading to the translocation of pancreatic and duodenal homeobox 1 (PDX-1) and, consequently, to β cell dysfunction (Kawamori et al., 2003); as discussed below (Sections 4.1 and 4.2), JNK pathway is emerging as a relevant target for curcumin analogs. Endothelial dysfunction is a common phenomenon in diabetes and it is the result of the hyperglycemia-induced apoptosis, due to reactive oxygen species and superoxide anion production, and the decrease in antioxidant enzymes activity (Du et al., 1999; Kesavulu et al., 2000). Hyperglycemia is also closely related to inflammation and diabetes-associated complications; for instance, cardiomyopathy and nephropathy (Pan et al., 2012). In fact, diabetic nephropathy is the main cause of morbidity and mortality among diabetic patients (Pan et al., 2014a).

Diabetic nephropathy is a major cause of end-stage kidney disease (Alsaad and Herzenberg, 2007), caused by long-standing diabetes mellitus (Lv et al., in press); it is characterized by progressively increasing proteinuria and blood pressure, along with impairment of glomerular filtration (Alsaad and Herzenberg, 2007). Alterations in lipid and glucose metabolism, excessive reactive oxygen species production, inflammation, fibrosis, and hemodynamic factors are possible causes of this complication (Lv et al., in press).

Similarly, diabetes mellitus is a risk factor for cardiovascular disease (Saisho, 2014), the leading cause of death in the world (Gersh et al., 2010). Coronary artery diseases, atherosclerosis, and peripheral vascular diseases are some of the vascular complications associated with diabetes mellitus (Liu et al., 2014). Diabetic cardiomyopathy is associated with both types 1 and 2 diabetes and it is characterized by increased extracellular matrix production and left ventricular hypertrophy without hypertension or other heart diseases (Fang et al., 2004).

It has been suggested that oxidative stress, inflammation, and endoplasmic reticulum stress could interact and amplify each other during diabetes (Son et al., 2013); for that reason, many current therapeutic strategies are addressed to counteract these mechanisms of damage.