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Curcumin Derivatives in Experimental Diabetes

Rezq AM*

Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Egypt

Abstract

Curcumin, from the rhizomes of Curcuma longa, is characterized by its anti-diabetic properties, among other healing properties primarily because it is a relatively safe and inexpensive. The application of curcum derivatives for the treatment of experimental diabetes and its complications has paced long ways. Curcumin and its derivatives affect most of aspects of diabetes; including plasma insulin levels, hyperglycemia, hyperlipidemia, and pancreatic islet regeneration with enhanced insulin synthesis and secretion. Such derivatives were developed to overcome the poor bioavailability of natural curcumin. Promising derivatives with conserved natural functional groups of curcumin and some suitable carrier systems need to be extended to clinical trials.

Background

The last decade has witnessed a strong wave of scientific investigations to several aspects of traditional medicine. One striking example is the use of curcumin from turmeric (*Curcuma longa*), for the treatment of several variable conditions, including diabetes-the worldwide epidemic level syndrome [1]. In 1972, the first report to show the blood glucose lowering effect of curcumin was published [2]. Because of the poor solubility/systemic bioavailability of natural curcumin, several of its derivatives we developed. The present review is focusing on recent developments in the field of curcumin derivatives reported to possess superior activity in the treatment of experimental diabetes, with emphases on the author's own experience.

Curcumin Derivatives

Countless numbers of its chemical derivatives, analogs, and drug vehicle systems were developed, [3]. Such compounds were extensively studied in treatment of diabetes in experimental animal models and a few clinical trials of type-2 diabetes. Derivatization of curcumin, [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] usually run through the phenolic hydroxy groups, the methoxy groups, the reactive methylene group of the linker or the keto groups. However, the antioxidant and antidiabetic activities seem to require one or more oxysubstituents on aryl rings, preferably in an ortho orientation [4]. In 2004, it was demonstrated that phenol and methoxy groups were essential to promote mitochondrial permeability transition pore opening [5].

In an integrated successful step a carboxylated radical was introduced besides the phenolic hydroxyl group, to conserve intact all the natural functional groups retaining the essential potencies of natural curcumin. The derivative was further covalently linked to each of bovine serum albumin, casein and gelatin [6-8]. The bioavailability monitoring issue was also taken care of in terms of dose dependent bioavailability indicators of curcumin actions [9].

Curcumin Treatment of Experimental Diabetes

In most of the studies, the experimental laboratory diabetic rat model used was the streptozotocin (STZ) induced diabetes [10] with daily oral administration of curcumin in a dose of 80 mg/kg BW, (or the molar equivalent dose of its derivatives) until the treatment significantly decreased blood glucose [11]. In addition, besides the effect of curcumin and its derivatives on the glycemic state in diabetic rat models it also elevated plasma insulin levels with involvement in activation of liver enzymes that are associated with glycolysis, gluconeogenesis, and lipid metabolism [12].

To prove superiority over natural curcumin, several studies were conducted for the treatment of different conditions known to respond to natural curcumin. Concerning diabetes, in a study that applied the gelatin carried curcumin derivative Ref…, (containing only 3.0% by weight) the treatment significantly lowered the plasma glucose, increased plasma insulin, decreased total cholesterol, triglycerides, LDL cholesterol and increased HDL cholesterol levels. Also, it decreased lipid peroxides (malondialdehyde) in the pancreas, aorta and liver attenuating mitochondria dysfunction in STZ-diabetic rat model. It was postulated that heme-oxygenase induction seems to play an important role in the anti-diabetic effects [13].

Another long term study on pancreatic islet regeneration in STZ-diabetic rat model using the carboxylated curcumin derivative without a carrier protein for 40 days showed that the plasma glucose to decrease to its starting pre-experimental level in about 6 months, while insulin and C-peptide almost returned to its starting pre-experimental levels after 10 months. Histopathological examination of treated diabetic rats after 6 months the appearance of primitive cell collections, large insulin positive cells and CD105 positive cells in the adipose tissue infiltrating the pancreatic tissues. This was followed by the gradual appearance of insulin positive cells in the islets while, CD 105 positive cells remained in the adipose tissue. The novel curcumin derivative possesses antidiabetic actions and enhances pancreatic islets regeneration [14]. It also improves insulin synthesis and secretion in vitro in isolated STZ-treated pancreatic islets through inhibition of the JNK pathway, up-regulation of the gene expressions of HO-1, TCF7L2, and GLP-1 and enhances the levels of calcium and zinc [15].

On the other hand, as concerns the diabetic complications, the signaling mechanisms of curcumin derivative in experimental type-1 diabetes with cardiomyopathy was examined, it was found that it decreased plasma glucose, glycated (GHb) and increased insulin levels significantly in STZ-diabetic rats. Heme-oxygenase-1 (HO-1) expression and HO activity were significantly increased in the heart and pancreas. The curcumin derivative prevented diabetes-induced upregulation of ANP, MEF2A, MEF2C and p300 and improved left ventricular function [16].

***Corresponding author:** Rezq AM, Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Egypt, Tel: 00201001400357; E-mail: ameenrezq@yahoo.com

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The gelatin covalently linked curcumin derivative enhanced erectile function in diabetes induced erectile dysfunction by increasing intra-cavernosal pressure (ICP), cGMP levels, HO-1, eNOS, neuronal NOS (nNOS), and Nrf2 with significant reductions in NF-KB, p38, and iNOS [17]. Further, curcumin ameliorated STZ-induced testicular damage and apoptotic germ cell death by decreasing oxidative stress [18].

Other diabetic complications as neuropathy retinopathy and nephropathy are also ameliorated by curcumin treatment. An excellent more detailed review article on the present subject appeared on 2013 [19].

Conclusion

The strong wave of ongoing research on the use of curcumin and its derivatives for the treatment diabetes and its associated disorders has confirmed the scientific basis for their role in this aspect. Curcumin and its derivatives affect most of aspects of diabetes, including plasma insulin levels, hyperglycemia, hyperlipidemia, and pancreatic islet regeneration. The novel curcumin derivatives enhances improves insulin synthesis and secretion *in vitro* in isolated STZ-treated pancreatic islets and enhances the levels of calcium and zinc. Clinical trials of curcumin or its derivatives to extend their value in the treatment of diabetes and other associated disorders are very limited so far. Promising derivatives with conserved natural functional groups of curcumin and some suitable carrier systems seems a reasonable approach in view of the recent experimental data that needs to be extended to clinical trials.

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