

Review Article

CURCUMIN AND ITS NANOFORMULATIONS: A COMPREHENSIVE OVERVIEW FOR THE MANAGEMENT OF DIABETES COMPLICATIONS

JUNMONI NATH*, BHUPEN KALITA, GOURANGA DAS

Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Sciences, Azara, Guwahati 781017
Email: junmoninath2014@gmail.com

Received: 14 Apr 2019, Revised and Accepted: 13 Jun 2019

ABSTRACT

Diabetes is a chronic metabolic disorder that has reached pandemic proportions, and which is a major cause of morbidity and mortality worldwide. Type 1 diabetes is an autoimmune disorder resulting in almost complete destruction (98%) of insulin secreting beta cells in the pancreas, while type 2 diabetes is considered to be a disease of protein misfolding where, in addition to the average 65% loss of beta cell mass, insulin resistance occurs in target organs. Diabetic complications, such as retinopathy, nephropathy, neuropathy and cardiovascular disease, are common and majorly impact a patient's quality of life. Curcumin is the yellowish polyphenolic component of the dietary spice turmeric, which is the rhizomes of *Curcuma longa*, a herb in the ginger family (Zingiberaceae). Curcumin effectively reduces glycemia and hyperlipidemia but also has beneficial effects on diabetic complications due to its anti-inflammatory and antioxidant properties, in a relatively inexpensive and safe manner. New improved methods of delivering curcumin are being developed including nanoparticles and lipid/liposome formulations that increases its absorption and bioavailability as curcumin is poorly absorbed by the digestive system and undergoes glucuronidation and excretion rather than being released into the serum and systemically distributed. Development and refinement of these technologies will enable cell-directed targeting of curcumin and improved therapeutic outcome. The current review focuses on the antidiabetic efficacy of curcumin and nano-drug delivery approaches in attenuating diabetes and its complications.

Keywords: Curcumin, Diabetes, Nanoparticle, Liposomes

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DOI: <http://dx.doi.org/10.22159/ijcpr.2019v11i4.34932>

INTRODUCTION

Diabetes, a metabolic disorder, has been categorized as Type 1 and Type 2. Type 1 diabetes is an autoimmune disorder resulting in almost complete destruction (98%) of insulin secreting beta cells in the pancreas, while type 2 diabetes is considered to be a disease of protein misfolding where, in addition to the average 65% loss of beta cell mass, insulin resistance occurs in target organs [1].

Inflammatory cytokines, transcription factors and enzymes, oxidative stress, intracellular sorbitol and tissue advanced glycation end products (AGEs) accumulation, activation of protein kinase-c (PKC) polyol pathway and mitochondrial superoxide production all play a role in the development of diabetic complications [2]. Curcumin, the yellowish polyphenolic component of the dietary spice turmeric, which is the rhizomes of *Curcuma longa*, a herb in the ginger family, effectively reduces glycemia and hyperlipidemia but also has beneficial effects on diabetic complications due to its anti-inflammatory and antioxidant properties, in a relatively inexpensive and safe manner [3, 4]. Several studies have designated that curcumin has pleiotropic effects and a wide spectrum of molecular targets that regulate several pathways, intracellular elements, and key enzymes [5, 6]. However, the natural curcumin is linked with some major drawbacks such as poor absorption, low bioavailability, high metabolic rates and rapid excretion from the body. Notwithstanding a century of continuous research inventions and efforts have aimed to overcome the obstacles of native curcumin, the invasion of nanoparticle formulations assimilated a definitive change for treating a wide range of diseases utilizing nano-curcumin through efficient drug distribution process. The several studies report the development and *in vitro* evaluation of nano-curcumin that is proposed for site-specific delivery of curcumin with high permeability, lengthier circulation and improved biodistribution which brings major efficacious responses [7]. Thus, to enhance the same, various nanoparticle-based tactics have also been sought, such as encapsulation in liposomes, chitosan and solid-lipid microparticles based technique utilizing bovine serum albumin to allocate the various impairments such as poor absorption rate, low bio-availability, and distribution, targeted delivery to the

affected tissue of interest which limits its appropriate therapeutic effects [8-10]. This review seeks to briefly abridge the sufficient scientific literatures regarding curcumin as a potential treatment for diabetes and its associated complications.

Methodology

To formulate this review, all the available literature regarding to this topic was collected through electronic databases including Pubmed, Web of Science, Medline, Embase, Scencedirect, Scopus, Cochrane Library, and Google Scholar.

Curcumin and glycemia

The effect of curcumin on glycemia has been studied by using several experimental models of diabetes. Oral administration of curcumin in several dosages [11-14] stopped weight loss, reduced glucose and glycated hemoglobin A1c (HbA1c) levels and enhanced insulin sensitivity, and hypoinsulinemia [15] in alloxan-induced diabetic rats, streptozotocin (STZ-) induced rats, and STZ-nicotinamide-induced rat models, all of which resemble Type 1 DM. Similarly, oral administration of curcumin enhanced glucose homeostasis and insulin resistance in rats with high-fat diet-induced Type 2 DM [16].

Curcumin reduces circulating free fatty acids (FFAs). FFA-induced lipotoxicity is an significant contributor of insulin resistance. This mechanism has been proposed to deteriorate pancreatic β -cell function [17] and impair the insulin signaling pathway through activation of NF- κ B. Downstream products of the NF- κ B pathway, such as IL-6, interfere with the transcription of insulin receptors (such as insulin receptor substrate-1) and transporters (such as GLUT-4), thus impairing insulin sensitivity [18]. Finally, curcumin has been reported to induce peroxisome proliferator-activated receptor gamma activation [19].

Curcumin and diabetic retinopathy

Diabetic retinopathy (DR) is one of the most severe ocular sequelae due to chronic hyperglycemia. DR is the major cause of vision loss, affects the photoreceptors and blood vessels of the retina and is considered as one

of the most devastating complications of diabetes. The factors that are thought to play a role in the development of DR are disturbances in retinal metabolism, elevated nonenzymatic glycation, oxidative stress, and Protein Kinase c (PKC) function [20, 21].

It has been reported that a novel curcumin-lecithin delivery form (2 tablets per day containing 100 mg curcumin for 4 w), improved retinal flow, DME and visual acuity in diabetic patients [22]. It has been found that through positive modulation of the antioxidant redox system in the diabetic rats curcumin exhibits significant hypoglycemic effects., Retinal GSH levels and activity of antioxidant enzyme, superoxide dismutase(SOD) were attenuated after supplementation [23]. It also has been reported that the retinal antioxidant capacity can be restored by curcumin treatment, and also eradicates expression in the retina of proinflammatory cytokines, tumor necrosis factor (TNF- α), vascular epithelial growth factor (VEGF) and Intercellular Adhesion Molecule-1(ICAM-1) in diabetic rats [23-27]. PKC β II translocation can be inhibited by curcumin, which is induced through VEGF in human RECs [28]. Furthermost evidence supports the beneficial effect of curcumin treatment for DNA damage reduction through suppression of NF- κ B activation, and repositioning of oxidatively modified DNA and nitrotyrosine in the diabetic rat retina [29].

Curcumin has been reported to show shows antiapoptotic effect in the diabetic retina through high-expression of Bcl-2, down regulation of Bax and glutamine synthetase, mitigation of cell death in Müller cells, and a decrease in glial fibrillary acidic protein (GFAP) levels. Thus these findings suggests that curcumin could delay the beginning of apoptosis, a predictor of the DR formation, in retinal cells [30].

The formation of Cataract in STZ or the selenite rat model of diabetes can also be prevented by curcumin. Especially, curcumin down-regulates the main proteins (Heat Shock Protein 70, α A-crystalline, and α B-crystallin) involved in the protection of eye lens transparency and are overexpressed in cataracts [31-33]. Curcumin when delivered in the form of nanomicelle through nasal route was found to exert a beneficial effect on diabetic keratopathy and resulted in the promotion of corneal epithelial or nerve wound healing in STZ-induced diabetic mouse [34].

Curcumin is also helpful in early retinal vascular leakage, by suppression of Calcium/calmodulin-dependent protein kinase II (CaMKII)/NF- κ B signaling in diabetic rat retina [35-37]. Diabetic patients are likely to develop corneal disorders, such as degeneration of nerve fibers, corneal neovascularization (CNV), corneal epithelial damage, corneal ulcers, reduced corneal sensitivity, reduced tear secretion and tear film [38, 39]. The most common cause of vision loss worldwide is CNV. Curcumin has been found to ameliorates CNV formation through suppression of low density lipoprotein receptor-related protein 6 (LRP6) phosphorylation and β -catenin nuclear localization, two markers of the activated Wnt/ β -catenin pathway [40].

Curcumin and diabetic neuropathy

Diabetic neuropathy develops as a result of hyperglycemia-induced peripheral nerve damage [41]. The NF- κ B transcription factor in peripheral neurons is activated due to Hyperglycemia induced oxidative stress. The NF- κ B-mediated proinflammatory cytokines such as IL-6, TNF- α , cyclooxygenase-2, and inducible nitric oxide synthase (iNOS) generation drives the neuroinflammatory-mediated nerve damage in peripheral neuropathy [42]. Depletion of endogenous antioxidants occurs due to the generation of High reactive nitrogen species/ROS. It has been found that tetrahydrocurcumin, a major metabolite of curcumin, by induction of antioxidant defenses, is able to inhibit the development of STZ-induced diabetic nephropathy and neuropathy [43].

Curcumin is also reported to exhibit an anti-TNF- α activity and nicotinamide adenine dinucleotide phosphate oxidase inhibitory effect through which it ameliorates the sensorimotor disturbances associated with diabetic neuropathy [44]. Again, a grouping of glioclazide plus curcumin and insulin and curcumin, and have proved the high efficacy of combination treatments in preventing the STZ-

induced alterations in sensory and motor functions compared with insulin or glioclazide monotherapy in diabetic rat models [45].

Curcumin supplement (60 mg/kg; p. o.) has been shown to significantly reduce cognitive impairment, dysfunctional cholinergic activity diabetic encephalopathy, neurodegeneration and neuroinflammation in diabetic rats [46]. Also it has been reported that curcumin supplement ameliorated the slowing nerve conduction and CNS dysfunction in diabetic rats [47-49].

Curcumin and diabetic nephropathy

Diabetic nephropathy (DN) is the most common cause of end stage renal failure [50, 51]. Various mechanisms such as oxidative stress, renal hemodynamic changes, increased non-enzymatic glycosylation of proteins, lipid disorders, and the activation of the polyol and mitogen-activated protein kinase signaling pathways has been suggested to play a role in the development of diabetic nephropathy. Pathophysiological characteristics in the early stage of DN such as mesangial cell expansion, the accumulation of extracellular collagen, fibronectin, and laminin, glomerular and tubular membrane thickening, tubulointerstitial fibrosis, glomerulosclerosis, and finally renal endothelial dysfunction occurs in diabetic kidney disease [52].

Also, oral turmeric supplementation showed beneficial effects on glomerular function and inflammation in a clinical study performed on patients with overt Type 2 DM associated nephropathy. Moreover, curcumin (100 mg/kg/day, p. o. 8 w) treatment down-regulates the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits, NOX4 and p67phox, which are an underlying mechanism for boosting ROS production [53, 54]. Curcumin was found to mitigate nephropathy through the induction of antioxidant defenses and reduction of ROS mediated oxidative stress and the inflammatory cascade in kidneys regardless of the signaling pathway through which it acts. It was also reported to increase the function of kidney and integrity by reducing proteinuria and inhibiting leaching of renal enzymes and acid phosphatases [55].

Nanoformulations of curcumin

The major rate-limiting factor in allowing curcumin to exert its therapeutic effect is its poor oral bioavailability. Thus, various formulation strategies such as micronization, nanonization, amorphous solid dispersion, combination with piperine, complexation with hydroxypropyl- β cyclodextrin complex, and spraydried curcumin-milk composite have been tried to increase the oral bioavailability of curcumin [56]. Of the many approaches, nanoparticle-based delivery systems will probably be suitable for highly hydrophobic agents like curcumin circumventing the pitfalls of poor aqueous solubility, however further investigations are needed to understand the ability of nanoparticles in delivering very high dose compounds such as curcumin. Use of polymeric nanoparticles has been actively explored as oral delivery vehicles for pharmaceutically challenging compounds [57, 58]. The self-nanoemulsifying drug delivery system formulation of curcumin had higher physiological concentrations of curcumin and more improvement in sensorimotor nerve disturbances associated with diabetic neuropathy than naïve curcumin. It also reduced neuroinflammation associated with neuropathy by reducing the expression of proinflammatory mediators such as IL-6, TNF- α , and iNOS through inhibition of NF- κ B [48].

Also it has been reported that nanocurcumin (curcumin encapsulated PLGA nanoparticles) demonstrated a better performance in comparison with curcumin, as far as delay of cataract development is concerned, in four different ways: 1) by preventing protein carbonyl levels to rise 2) by normalizing AR activity (an enzyme playing a critical role in the polyol pathway) and subsequently reducing sorbitol levels 3) by reducing AGE formation in soluble protein fraction and 4) by improving the total and soluble protein levels, as protein in-solubilization is the final step to lens opacification and cataract [59].

CONCLUSION

Recent research has provided the scientific basis for "traditional" curcumin and confirmed the important role of curcumin in the

prevention and treatment of diabetes and its associated disorders. Curcumin could favorably affect most of the leading aspects of diabetes, including insulin resistance, hyperglycemia, hyperlipidemia, and islet apoptosis and necrosis. In addition, curcumin could prevent the deleterious complications of diabetes. Despite the potential tremendous benefits of this multifaceted nature product, results from clinical trials of curcumin are only available in using curcumin to treat diabetic nephropathy, microangiopathy and retinopathy so far. Studies are badly needed to be done in humans to confirm the potential of curcumin in limitation of diabetes and other associated disorders. Further, multiple approaches are also needed to overcome limited solubility and poor bioavailability of curcumin. These include synthesis of curcuminoids and development of novel formulations of curcumin, such as nanoparticles, liposomal encapsulation, emulsions, and sustained released tablets. Enhanced bioavailability and convinced clinical trial results of curcumin are likely to bring this promising natural product to the forefront of therapeutic agents for diabetes by generating a "super curcumin" in the near future.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declare none

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