Antioxidant and Antiinflammatory Activities of Curcumin on Diabetes Mellitus and its Complications

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Abstract: Diabetes mellitus (DM) has reached pandemic status and shows no signs of abatement. It can severely impair people’s quality of life and affects patients all over the world. Since it is a serious, chronic metabolic disease, it can bring about many kinds of complications, which can in turn increase mortality. In recent decades, more and more studies have shown that oxidative stress and inflammatory reactions play critical roles in the pathogenesis of DM. There is an increasing demand for natural anti-diabetic medicines that do not have the same side effects as modern drugs. Curcumin, a phytochemical found in the spice turmeric, has been used in India for centuries, and it has no known side effects. It has been shown to have some beneficial effects against various chronic illnesses. Many of these therapeutic actions can be attributed to its potent anti-oxidant and anti-inflammatory activities. In view of the oxidative stress and inflammatory mechanisms of DM, curcumin can be considered suitable for the prevention and amelioration of diabetes. In this review, we summarize the nosogenesis of DM, giving primary focus to oxidative stress and inflammation. We discuss the anti-oxidant and anti-inflammatory activities of curcumin in DM and its ability to mitigate the effects on DM and its associated complications in detail.

Keywords: Diabetes mellitus, curcumin, oxidative stress, inflammatory cytokines.

1. INTRODUCTION

The International Diabetes Federation (IDF) claims that DM, a non-communicable disease, is becoming a global problem with serious consequences to human life and health. A multi-country joint research project showed the age-standardized prevalence of adult diabetes to be 9.8% in men and 9.2% in women in 2008, from 8.3% and 7.5% in 1980. The number of DM patients increased from 153 million in 1980 to 347 million in 2008 [1]. The data from this investigation were obtained from adults aged 25 years and older in 199 countries and territories (370 country-years and 2.7 million participants). According to another study, the estimated worldwide prevalence of DM among adults was 285 million in 2010, and this value is predicted to rise to around 439 million by 2030 [2]. An effective plan for the global management of DM is yet to be established. Various kinds of antidiabetic drugs have been developed, but most of them have side effects. It has been claimed that curcumin, the primary active component of turmeric, is an efficient antioxidant and anti-inflammatory agent. As shown in its long history as a dietary spice, it can regulate numerous disorders without side effects. In this article, we retrieve and analyze the research findings of the past ten years, showing the latest developments of the treatment of DM with curcumin.

2. OXIDATIVE STRESS AND INFLAMMATORY REACTIONS IN THE PATHOGENESIS OF DM

DM is a serious chronic metabolic disease, predisposing patients to ill health even multiple-organ dysfunction [3]. Type 2 diabetes mellitus (T2DM) is the predominant form of the disease, accounting for at least 90% of all cases of DM [4]. DM is characterized by hyperglycemia, insulin resistance, and decreased insulin secretion. Among these, insulin resistance is a classic feature of T2DM [5]. There are convincing data indicating that insulin resistance has a genetic component [6]. DM is also associated with acquired factors such as lifestyle, obesity, and hormone levels. However, the underlying details of the way these determinants cause DM are still uncertain. For decades, many studies have demonstrated that oxidative stress and inflammatory reactions play critical roles in the pathogenesis of DM, especially T2DM [7–10]. Now, we will give a brief summary of the biochemistry and molecular cell biology of these two mechanisms.

2.1. Oxidative Stress

Hyperglycemia can lead to oxidative stress, mainly through the increased production of mitochondrial free radicals, typically reactive oxygen species (ROS) [11,12]. In mitochondria, endogenous antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and glutathione peroxidase (GPx)) can protect the body from free radicals. These enzymes typically include glutathione (GSH), vitamin C, and vitamin E [13]. During hyperglycemia, elevated generation of free radicals depletes the antioxidant defense system, which leads to the activation of oxidative stress-activated signaling pathways and increased production of glucose-derived advanced glycosylation end products (AGEs), which leads to oxidative damage to membranes, disruption of cellular functions, and aggravation of lipid peroxidation (LPO) [14,15]. Hyperlipemia can aggravate oxidative stress by increasing mitochondrial uncoupling and β-oxidation [16]. All of these events ultimately contribute to β-cell dysfunction and insufficient production of insulin, which in turn worsens hyperglycemia promotion in the development of DM.

Evans et al. described the signaling proteins involved in oxidative stress pathways [7]. These include nuclear factor-kB (NF-kB), p38 MAPK, NH2-terminal Jun kinase/stress-activated protein kinase (JNK/SAPK), and protein kinase C (PKC). NF-kB, a transcription factor, is a target of activation by oxidative stress and inflammatory cytokines. It serves as a hub in the pathway [17].

2.2. Inflammatory Reaction and Inflammatory Cytokines

Immune and metabolic pathways are closely linked and interdependent. The normal inflammatory reaction favors a catabolic state, but it suppresses anabolic pathways such as the highly conserved insulin anabolic pathway. DM fosters inflammation and dysregulation of insulin. Hyperlipemia, like hyperglycemia, is a cardinal symptom of diabetic patients. It can also give rise to the production of ROS, increasing levels of LPO and the activation of
the inflammatory process. It has been reported that ROS can alter nuclear histone acetylation and deacytination, leading to activation of NF-κB [18]. Another study found that inflammatory stimulation could activate several serine/threonine kinases (such as JNK, PKC-0, and inhibitor of NF-κB kinase (IKK)) contributing to the inhibition of insulin signaling pathways [19]. Some other signaling proteins, such as those of the suppressor of cytokine signaling (SOCS) family, were also found to contribute to inflammation-induced insulin resistance [20]. Although the details of the mechanisms have not been yet fully resolved, some studies have shown that nuclear chromatin remodeling events and specific transcription mechanisms occur in the nucleolus and that these events are mediated via NF-κB and cause the expression of various inflammatory factors [21, 22].

Kathryn et al. published a summary of the cytokines involved in obesity [9]. They include TNF-α, IL-6, leptin, adiponectin, visfatin, resistin, IL-1, IL-1Ra, IL-8, IL-10, MCP-1, MIF, MCP-1, TGF-β, soluble TNFR, C-reactive protein, and haptoglobin. The study also demonstrated that obesity could overload the functional capacity of the endoplasmic reticulum (ER) leading to ER stress, which could in turn lead to the activation of inflammatory signaling pathways and a rise in mitochondrial production of ROS, worsening oxidative stress [23–25]. The close ties between obesity and T2DM, raise the question of whether these inflammatory cytokines also mediate insulin resistance.

All this evidence shows that oxidative stress and inflammatory reactions are closely interrelated and mutually reinforcing (Fig. 1). It also shows that the treatment of diabetes mellitus with antioxidant and antiinflammatory agents would be a good choice. Identification of the molecular basis of the protection afforded by these kinds of agents can give rise to novel therapies ameliorating DM and its complications.

3. CURCUMIN AND ITS THERAPEUTIC EFFECTS

Modern drugs, such as insulin and other oral hypoglycemic agents, have therapeutic effects when properly administered. However, these treatments can be painful and tedious and may involve several side effects [26]. Side-effect-free management of DM is still a challenge to the modern medical system. There is an increasing recognition of the potential therapeutic benefits of alternative treatments that have anti-diabetic activity but no side effects. This has fostered a growing interest within the research community to evaluate as many dietary sources and medicinal herbs as possible for any ability to control DM and its complications. In view of the recent scientific view that multitargeted therapy is better than monotargeted therapy for most diseases, dietary sources and medicinal herbs would be considered ideal antidiabetic agents.

Turmeric derived from the rhizome of the plant Curcuma longa has been used in India for centuries both as a spice and in the treatment of disease. It has no known side effects. Turmeric contains many phytochemicals. Of these, curcumin, demethoxycurcumin, and bisdemethoxycurcumin have been isolated. An estimated 2–5% of turmeric is made up of curcumin. It was first isolated from turmeric in 1815, and its structure was delineated in 1910 as diferuloylmethane [27]. Many therapeutic activities have been assigned to turmeric for various diseases. A majority of these activities are mainly due to curcumin, but bisdemethoxycurcumin was also found to exhibit higher activity than curcumin in some systems [28,29].

The edible history of curcumin demonstrates it without any toxicity. Recently, a phase-one clinic trial with 25 subjects using up to 8000 mg/d of curcumin for 3 months found no toxic reaction [30]. Chainani-Wu et al. investigated curcumin’s safety through 6 clinic trials (including the one discussed above) and 5 animal experiments [31]. Their results showed it to have anti-toxicity except some gastric irritation symptoms in human beings, but high doses of orally administered curcumin have been found to cause hepatotoxicity in some rats. Although curcumin is very safe, it exhibits poor bioavailability. This may be due to its poor absorption, rapid metabolism, and rapid systemic elimination [32]. Curcumin’s poor bioavailability after oral administration limits its ability to reach beneficial concentrations. However, it has nonetheless been shown to reach such efficacious levels in the gastrointestinal tracts of humans and other animals [33]. There are certain strategies now being explored that may improve the bioavailability of curcumin, including modulation of route and medium of curcumin administration, blockage of metabolic pathways by concomitant administration with other agents, and structural modifications [32].

So far, many studies have focused considerable interest on curcumin due to its potential to treat many different disorders. These studies have shown curcumin to act against various illnesses by modulating targets such as transcription factors, cytokines, enzymes, and genes (Fig. 2) [34–40]. Most of these activities can be attributed to its potent antioxidant capacity [33]. Curcumin has also been found to be at least 10 times more active as an antioxidant than Vitamin E [41]. The antioxidant activity of curcumin can be mediated through free radical scavenging capability and up-regulation of antioxidant enzymes in most conditions. Studies have also shown that the phenolic hydrogens play a major role in the anti-oxidant activity [42, 43]. The inhibitive action of curcumin on
## Disease Targets

<table>
<thead>
<tr>
<th>(1) Chronic disease</th>
<th>Molecular Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>(1) Enzymes</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>COX-2, CTGF, CyclinD1, Gsp70, iAP, iNOS, LDL-R, LOX, MDR-1, MMP, NAT-1, TIMP-3</td>
</tr>
<tr>
<td>Cancer</td>
<td>(2) Growth factors</td>
</tr>
<tr>
<td>Cataract</td>
<td>EGF, EGF-RK, FGFR, HGF, NGF, PDGF, TGF-β, VEGF</td>
</tr>
<tr>
<td>Liver/Lung/Renal diseases</td>
<td>(3) Genes expression</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>COX-1, COX-2, CTGF, CyclinD1, Gld, Gsp70, iAP, iNOS, LDL-R, LOX, MDR-1, MMP, NAT-1, TF, TIMP-3</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>(4) Inflammatory cytokines</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>IL-1, IL-12, IL-18, IL-2, IL-5, IL-6, IL-8, MCP-1, MIF, TNF</td>
</tr>
</tbody>
</table>

## (2) Inflammatory diseases

| Arthritis                   | (5) Protein Kinases                |
| Allergy                     | AKT, cAK, CDPK, cPK, EGFR, ERK, FAK, HER2, IKK, JAK, JNK, p53, Phk, PKA, PKB, PKC, Src, TK, TYK2 |
| Fever                       | (6) Receptors                      |

## (3) Autoimmune diseases

| Multiple sclerosis          | (7) Transcriptional factors        |
| Myocarditis                 | AP-1, CBP, Egr-1, EpRE, HIF-1, Keap1, NF-κ B, Nrf-2, PPAR, STAT1, STAT3, STAT4, STAT5, β-catenin |
| Rheumatoid arthritis        | (8) Others                         |
| Systemic lupus erythematosis| Bel-2, Bel-xL, CYP, DFF40, ELAM-1, E-selectin, HSP, ICAM-1, Notch-1, p53, SHP-2, sPA, VCAM-1, WT1 |

Type 2 diabetes mellitus

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LPO has also been studied in different models. Due to LPO’s central role in inflammation, the suppression of LPO could lead to suppression of DM [35,36]. Previous studies have identified many kinds of molecules and proteins involved in inflammation, and most of them can be inhibited by curcumin, as shown in Fig. 2. As part of the exploration of the molecular mechanisms of curcumin, many structural analogs of curcumin were synthesized. Among these, tetrahydrocurcumin (THC) is the one most frequently studied in DM, and it has been reported to be more active than native curcumin [44]. In the following article, we discuss the antioxidant activity of curcumin as studied in several experiments performed on diabetic models, the manner of administration of curcumin, the dose, and interactions with other molecules and proteins.

Balasubramanyam et al. collected fresh blood from diabetic and healthy adult volunteers [50]. The blood was treated and cell suspensions were incubated for 10 min with curcumin (1 μM to 100 μM). Results demonstrated that curcumin abolished both phorbol-12 myristate-13 acetate (PMA) and thapsigargin-induced ROS generation in cells from both control and diabetic subjects in a dose-dependent manner. They also found that curcumin could interfere with PKC and calcium regulation. Cytosolic calcium can regulate many physiological processes and enzymes, and it is tightly controlled. The sarco/endoplasmic reticulum Ca2+ ATPase (SERCA) is one of the major mechanisms through which low levels of cytosolic calcium are maintained. It has been reported that curcumin can inhibit all subtypes of SERCA [51]. PKC can combine simultaneously with oxidants and antioxidants. It is inclined to combine with oxidants under pathologic conditions resulting in increasing the production of ROS. In this study, curcumin could inhibit its activity and so mitigate oxidative stress.

Curcumin’s ability to scavenge free radicals may be due to the presence of the 2-p-hydroxy group mentioned above. When curcumin is irradiated, stable photoproducts, such as vanillin and ferulic acid are produced without altering this group [52]. Mahesh and colleagues studied the antioxidant properties of photo-irradiated curcumin in diabetic rats [53,54]. Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 40 mg/kg) and photo-irradiated curcumin (10 mg/kg) was administrated using an intragastric tube for 45 days. The results showed that photo-irradiated curcumin could nearly normalize the activities of SOD and CAT, and the levels of LPO markers (TBARS and hydroperoxides). The underlying mechanism discussed by the authors was that photo-irradiated curcumin prevented auto-poly-ADP-riboseylation of PARP (poly (ADP-ribose) synthetase/polymerase) and stabilized antioxidant activity of curcumin as studied in several experiments performed on diabetic models, the manner of administration of curcumin, the dose, and interactions with other molecules and proteins.
the Reg gene transcriptional complex, promoting the regeneration of β cells.

In 2007, Meghana et al. incubated isolated islets from C57/BL6j mice with curcumin and then investigated the effects of exposing β cells to different concentrations of curcumin (10, 20, 40, and 80 μM) for different lengths of time (24, 42, and 72 h) [55]. The hypothesis of this study was similar to that of Mahesh et al. Specifically, it was that most β cell damage could be attributed to the extensive oxidative stress caused by streptozotocin-induced collapse of free radical scavenging potential and overactivation of poly ADP-ribose polymerase-I [56]. The data demonstrated that curcumin neither prevented poly ADP-ribose polymerase-I activation nor led to overexpression of Cu/Zn superoxide dismutase, which had not been studied by Mahesh et al. However, curcumin was found to prevent streptozotocin-induced islet β cell death by scavenging free radicals, as evidenced by the significantly lower levels of ROS, peroxynitrite, and nitric oxide observed. This experiment also demonstrated that prophylactic use of curcumin could repair damaged islets without affecting the normal function of the cellular structures.

That same year, Suryanarayana et al. also investigated the antioxidant activity of curcumin in diabetic rats [57]. Three-month-old Wistar-NIN rats were rendered diabetic by intraperitoneal injection of STZ (35 mg/kg). They were fed the AIN-93 diet containing 0.002% or 0.01% curcumin for a period of eight weeks. They found that dietary curcumin could effectively control oxidative stress by inhibiting increases in the concentrations of TBARS and protein carbonyls. However, all the three studies found that curcumin’s antidiabetic properties involved enhancing the activities of four antioxidant enzymes.

Bone marrow transplantation may have significant value in the treatment of diabetes. However, the oxidative stress generated by hyperglycemia can hamper the recruitment of newly introduced BM-cells to pancreatic islets [58]. Mona et al. investigated the therapeutic potential of curcumin (10 mM; 100 μl/mice, i.p., for 28 days) combined with bone marrow transplantation in mice rendered diabetic by a single injection of STZ (40 mg/kg) [59]. Results showed that curcumin, either alone or combined with bone marrow transplantation, up-regulated activities of antioxidant enzymes, blunted LPO, and suppressed serum levels of TNF-α and IL-1β, boosting islet regeneration.

Although the experimental subjects, the induced dose of STZ, the manner of administration, and the dose varied across these three experiments, curcumin was still found to alleviate the symptoms of diabetes and slow down its development. The underlying antioxidant mechanisms of curcumin were discussed, including its ability to prevent auto-poly-ADP-ribosylation of PARP, interfere with PKC and calcium regulation, and inhibit the increase of TBARS and protein carbonyls. However, all the three studies found that curcumin’s antidiabetic properties involved enhancing the activities of antioxidant enzymes, scavenging free radicals, and reducing levels of LPO.

4.1.2. Tetrahydrocurcumin (THC)

Tetrahydrocurcumin (THC) is one of the major metabolites of curcumin. It has been reported that THC exhibits the same physiological and pharmacological properties as curcumin [60]. Both THC and curcumin have identical β-diketone structures and phenolic groups, but THC lacks the double bonds. It has also been reported that THC has the strongest antioxidant activity of all the curcuminoids and more potent antioxidant activity than curcumin [44, 61]. In recent years, Murugan P and Pari L studied the effects of THC and curcumin on diabetic rats. They claim that THC is superior to curcumin in many ways. Briefly, T2DM rats were induced by a single injection of nicotinamide (110 mg/kg) followed by intraperitoneal injection of STZ (45 mg/kg or 65 mg/kg) 15 min later. THC (80 mg/kg) and curcumin were administered in aqueous suspension daily for 45 days using an intragastric tube. Their findings are summarized below.

One hypothesis regarding the mechanism of DM is that because of the depletion of antioxidant defense system in DM, the increase of ROS generation causes aggravated oxidative stress and a cascade of effects, ultimately resulting in functional and structural integrity of cell and organelle membranes [62]. On the basis of this hypothesis, Murugan and Pari found THC to significantly increase the activities of antioxidant enzymes (SOD, CAT, GSH, GPx), reduce levels of glutathione, vitamin C, and vitamin E, and decrease levels of TBARS and hydroperoxides in the liver and kidneys [63]. It was found to play the same role in plasma [64]. This suggested that its action in protection against LPO-induced membrane damage. THC could also decrease the levels of blood glucose and plasma glycopolymers (tissue hexose, hexosamine, and fucose) indicating that it exerted a significant beneficial effect against glycopolymor moiety [65]. Reduction in ATPase activity can affect intracellular ions (such as Na+ , K+, and Ca2+) and alter the signal transduction pathway leading to cellular dysfunction. In a later study, they found that THC could not only regulate the levels of plasma insulin, hemoglobin, and erythrocyte antioxidants, but also recover the activities of membrane-bound total ATPase, Na+ /K+-ATPase, Ca2+-ATPase, and Mg2+-ATPase [66]. The latest report from this laboratory showed that THC could inhibit oxidative stress and cell damage in liver and kidneys by removing electrons, chelate metals, and free radicals out of the cells, enhancing antioxidant enzyme activities, and eventually contributing to the improvement of tissue dysfunction, as shown in T2DM rats [67].

Bisdemethoxycurcumin (BDMC), another phytochemical from turmeric, is reported to exert stronger antioxidant activity at lower concentrations than the other two [68, 69]. This may be due to its chemical construction, which involves a hydroxyl group at the ortho position [70]. There was also an experiment showing that BDMC could protect β cells against ROS-mediated damage by enhancing the activities of antioxidants and reducing hyperglycemia, as shown in diabetic rats [71].

4.2. Anti-inflammatory Activity and Anti-inflammatory Cyto- kines

As shown in (Fig. 2), curcumin’s molecular targets are extensive and diverse. In DM, it plays the role of an antioxidant. In this capacity, it can also regulate the secretion of various inflammatory cytokines through signaling proteins and enzymes, contributing to its antidiabetic properties. Here, we give a brief review of curcumin’s anti-inflammatory activity, especially its ability to inhibit inflammatory cytokines.

Obesity is a major risk factor for the development of T2DM. The pathophysiology of obesity involves significant inflammatory components. First, we discuss the anti-inflammatory action of curcumin in obesity models. Woo HM et al. isolated mesenteric adipose tissue from obese mice and used it to make an adipose tissue-conditioned medium [72]. RAW 264.7 macrophages were treated with this medium combined with spice-derived components. The results showed that three of these components, including curcumin, significantly inhibited cellular production of proinflammatory mediators, such as TNF-α, nitric oxide, and MCP-1. The following year, Weisberg et al. found that curcumin could decrease the expression of hepatic TNF-α, hepatic MCP-1, suppressor of cytokine signaling-3 (SOCS-3), and chemokin (C-C motif) ligand-2 (CCL2) in ob/ob mice [73]. Curcumin was found to decrease the activity of NF-κB p65 and trigger the release of adipoctin in the livers of both DIO (diet-induced obesity) and ob/ob mice. The experiment also investigated the expression of SOCS-1 and IL-1β, but curcumin did not show any discernible effect on either.

Due to the oxidative stress status of DM, the increased ROS can alter nuclear histone acetylation and deacetylation leading to the activation of NF-κB. This causes the release of various inflamma-
curcumin could modulate NF-κB signaling pathway by reducing HAT activity and by reducing the levels of p300 and acetylated CBP/p300 gene expression [75]. This was found to contribute to decreases in the release of inflammatory cytokines (IL-6, TNF-α, and MCP-1). Several subsequent experiments also demonstrated that curcumin could play an anti-inflammatory role in DM through inhibition of the release of TNF-α and IL-1β [59, 76]. Another hypothesis states that cytokines could in turn give rise to free radicals and stimulate increased expression of inducible nitric oxide synthase (iNOS) [77]. This could promote the generation of nitric oxide and translocation of NF-κB, eventually leading to islet cell death [22, 78]. Kanitkar et al. investigated the effects of curcumin pretreatment in vitro and in vivo [79]. They found that curcumin normalized NF-κB translocation by inhibiting phosphorylation of inhibitor of kappa B alpha (IkBα), leading to a decrease in cytokine concentrations (TNF-α, IL-1β, and IFNγ) in vitro. In vivo, curcumin was also found to decrease levels of TNF-α and IL-1β, sustain euglycemia, and maintain pancreatic GLUT2 levels in mice with MLD-STZ-induced (multiple low doses of streptozotocin) diabetes. Kanitkar et al. have also shown the antioxidant activity of curcumin in DM in the early time, which has been mentioned above [55]. In a similar manner, Jain et al. also investigated the effects of curcumin on the risk of vascular inflammation in DM, in both in vitro and in vivo [80]. The experiment showed that curcumin supplementation reduced TNF-α, IL-6, IL-8, and MCP-1 secretion in cultured monocytes treated with high levels of glucose in vitro and decreased blood levels of TNF-α, IL-6, and MCP-1 in STZ-induced diabetic rats in vivo. They also used an erythrocyte cell model to show that curcumin could prevent protein glycosylation, ROS production, and increased levels of LPO attributable to high levels of glucose [81].

In short, curcumin can inhibit the release of various inflammatory cytokines in both blood and tissue through the regulation of some other molecules and proteins, substantially ameliorating DM (Table 1).

Table 1. Effects of Curcumin on Inflammatory Cytokines, other Molecules, and other Proteins in DM and in Obesity

<table>
<thead>
<tr>
<th>Refs.</th>
<th>Diabetic model</th>
<th>Method of administration</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>[72]</td>
<td>Raw 264.7 macrophages treated with adipose-tissue-conditioned medium (tissue from obese mice).</td>
<td>Active spice-derived components, including Cur, mixed into the medium.</td>
<td>↓: TNF-α, MCP-1, NO</td>
</tr>
<tr>
<td>[73]</td>
<td>(1). DIO mice: wild-type C57BL/6J mice received high-fat diet containing 35% fat by weight.</td>
<td>Predesignated diet containing a 3% by weight admixture of Cur: (1). DIO mice, for 4-8 weeks. (2). ob/ob mice, for 16-18 weeks.</td>
<td>↓: NF-κB ↑: Adiponectin</td>
</tr>
<tr>
<td>[79]</td>
<td>(1). Live islets that were isolated from normal mice and exposed to a combination of cytokines. (2). MLD-STZ-induced diabetic mice</td>
<td>(1). Pretreated with Cur, 10 μM, for 24 hours. (2). Pretreated with Cur, 7.5 mg/kg/d, p.o. for 5 days.</td>
<td>↓: TNF-α, IL-1β, IFNγ ↓: TNF-α and IL-1β</td>
</tr>
<tr>
<td>[80]</td>
<td>(1). Human pro-monocytic cell line treated with HG (35 mM). (2). STZ-induced diabetic rats (65 mg/kg).</td>
<td>(1). Cur cell-culture, 0-10 μM, for 24 hours. (2). Cur, 100 mg/kg/day, p.o. for 7 weeks.</td>
<td>↓: TNF-α, IL-6, IL-8, and MCP-1 ↓: TNF-α, IL-6, MCP-1</td>
</tr>
<tr>
<td>[75]</td>
<td>THP-1 cells cultured in RPMI medium with HG (25 mM).</td>
<td>Cur in RPMI medium, 1.5-12 μM, for 72 hours.</td>
<td>↓: TNF-α, IL-6, MCP-1</td>
</tr>
<tr>
<td>[59]</td>
<td>MLD-STZ-induced diabetic mice.</td>
<td>Cur dissolved in DMSO, further diluted in PBS (10 mM), 100 μl/mouse, i.p. for 28 days.</td>
<td>↓: TNF-α and IL-1β</td>
</tr>
<tr>
<td>[76]</td>
<td>T2DM rats induced by HFD.</td>
<td>(1). Protection regimen: HFD + Cur, 80 mg/kg/d., p.o. for 60 days. (2). Treatment regimen: HFD then Cur, 80 mg/kg/d, p.o. for 15 days.</td>
<td>↓: TNF-α</td>
</tr>
</tbody>
</table>

Cur, curcumin; THP-1 cells, human monocyctic cells; HG, hyperglycemic; HFD, high-fat diet.
5. EFFECTS OF CURCUMIN ON DM

5.1. Protection of Islets

A reduction of β-cell mass in the pancreas is a primary pathological characteristic of both T1DM and T2DM. The regeneration state of pancreatic islets is one of the therapeutic goals of DM and its complications [82]. Pancreatic islet cell death is an orchestrated cellular event that occurs after oxidative stress or inflammatory reaction [83]. Curcumin can ameliorate DM through its anti-oxidative and anti-inflammatory activities. Some studies have shown that curcumin can modulate the regeneration of β cells and the secretion of insulin [53, 54, 56]. Meghana et al. found that prophylactic use of curcumin could increase insulin secretion through the scavenging of free radicals and effectively rescue islets from damage without affecting the normal function of cellular structures [55]. Kanitkar et al. found that curcumin eventually prevents cytokine-induced islet death and the loss of pancreatic β-cell mass in MLD-STZ-induced diabetic mice [79]. Pathological sectioning of the pancreas showed markedly reduced necrotic pancreatic sections, especially when curcumin was administered before MLD-STZ. Islets have been found to regenerate from duct epithelial cells [84]. Chanpoo et al. confirmed this pathophysiological phenomenon in diabetic mice [85]. Experimental results also showed that curcumin could promote the regeneration of islets after 12 weeks of treatment. Micrographs of stained pancreas showed that neogenesis among the islets of Langerhans was characterized by increases in the number of small islets near the ducts and by the absence of islets.

Murugan and Pari found that THC could significantly improve specific insulin binding to the relevant receptors and increase the number of total cellular insulin binding sites, finally resulting in a significant increase in plasma insulin [65]. In their other studies of THC in DM, nearly all experiments demonstrated that THC could markedly increase plasma insulin levels and that it did so mainly through its potent anti-oxidant activity [63–66, 86, 87].

5.2. Improvement of Metabolism

DM’s typical symptoms involve disturbances in the glucose and lipid metabolism. Changes in the levels of these two indicators can be used to assess the condition of DM. In most studies of DM, both of these two indicators (especially blood glucose levels) are assessed. In view of the pathogenesis of DM, inflammatory cytokines/signaling proteins and hyperglycemia/hyperlipemia can interact with each other leading up to a vicious circle. In most of the studies discussed above, curcumin and curcuminoids were found to regulate glucose and lipid metabolism in DM. Here, we summarize the anti-hyperglycemia and anti-hyperlipemia effects of curcumin (covering some of the studies mentioned above) and discuss other mechanisms by which curcumin might regulate metabolism.

5.2.1. Improvement of Glucose Metabolism

Hyperglycemia is a central risk factor of DM. It can mediate the production of extracellular matrix proteins and vasoactive factors, and contributes to the initiation of several of the complications of chronic diabetes [88]. Numerous clinical trials and animal experiments have proved curcumin to be an effective anti-hyperglycemia agent, even though the underlying mechanisms are not clear.

The hypoglycemic effects of curcumin are distinct from its anti-oxidant and anti-inflammatory activities. Arun et al. found that administration of curcumin could reduce the blood sugar, Hb and glycosylated hemoglobin (HbA1c) levels in diabetic rats, while decreasing influx of glucose into the polyol pathway and it was found to lead to an increased NADPH/NADP ratio and elevated GPx activity [89]. Some of these studies also demonstrated that curcumin and curcuminoids can significantly improve glycemic status while increasing the activity levels of antioxidative enzymes and scavenging free radicals [53,54,712,90]. Studies on the anti-inflammatory effects of curcumin have shown that it can visibly reduce BG (blood glucose) and HbA1c levels and inhibit the activity of inflammatory cytokines [73, 76, 79, 80]. BG was also modulated by curcumin in its anti-oxidant and anti-inflammatory capacities [121,122]. Most studies on the matter have shown that curcumin can decrease BG levels in DM. Exceptions have been few (Table 2).

Glucose metabolism and lipid metabolism interact with each other via metabolic pathways. Adipocytes play a crucial role in the regulation of homeostasis. Adipocyte differentiation is a tightly controlled process regulated by peroxisome proliferator-activated receptor-γ (PPAR-γ) and CCAAT/enhancer binding protein-R [91]. Curcumin and other turmeric phytochemicals have been found to suppress the increase of BG levels in diabetic KK-Ay mice. This might be due to the contribution of PPAR-γ activation to the stimulation of adipocyte differentiation [92, 93]. PPAR-γ is the predominant molecular target of insulin-sensitizing thiazolidinedione drugs such as pioglitazone, troglitazone, and rosiglitazone, which have been used in diabetic patients for many years [94]. Curcumin may exert a therapeutic action similar to that of insulin-sensitizing thiazolidinedione drugs.

Insulin can directly control the activities of certain metabolic enzymes via phosphorylation and dephosphorylation mechanisms and so regulates glucose metabolism. In DM, the hyposecretion of insulin can cause the activity levels of these metabolic enzymes to vary to a certain extent. In diabetic db/db mice, curcumin was found to significantly lower BG and HbA1c levels through increasing hepatic glucokinase activity and inhibiting glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity [95]. In diabetic rats, the activity of SDH (sorbitol dehydrogenase), which can catalyze the conversion of sorbitol to fructose, was also significantly decreased after treatment with curcumin [89]. THC was also found to decrease HbA1C, hemoglobin, and glycogen levels in STZ-NA-induced diabetic rats by reversing the altered activities of gluconeogenic enzymes such as glucose-6-phosphatase, fructose-1,6-bisphosphatase, and glycolytic enzymes such as glucokinase and hexokinase [96].

However, some studies reported that curcumin could not reduce the high levels of BG in diabetic rats or mice. Some researchers found that oral administration of curcumin had no detectable influence glucose metabolism in iron-induced hepatotoxic and STZ-induced rats [97, 98]. More recently, several studies have reported that curcumin had no effect on hyperglycemia in diabetic rats, though it did reduce oxidative stress and increase insulin secretion ameliorating diabetes [49, 57, 85, 99, 100]. One possible cause of this might be that curcumin administration may improve the neogenesis of proliferating β cells. However, the cells recruited were so immature that they could not function normally or were poorly functional [85].

5.2.2. Improvement of Lipid Metabolism

Obesity is a typical physical sign in most of T2DM patients, whose blood lipid levels are ordinarily higher than those of healthy individuals. From the above discussion, it is clear that curcumin can in most cases inhibit the release of inflammatory cytokines and accommodate glucose metabolism. Considering the close connection between glucose and lipid metabolism and considering inflammation and obesity, it is reasonable to conclude that curcumin can regulate lipid metabolism as well. We discuss here the hypolipemic property of curcumin in DM, from the aspects of metabolic enzymes, gene expression, and inflammation.

The earlier studies have demonstrated that dietary curcumin has distinct tendency to reduce cholesterol (TC), triglyceride (TG), and phospholipid (PLS) levels in liver and plasma of STZ-HFD-induced rats while increasing the activity of cholesterol-7a-hydroxylase and HMG CoA reductase [98, 101]. In recent years, some studies have also found that curcumin can decrease blood lipid levels by regulating the activity levels of these two enzymes [90, 102, 103]. In db/db
The close relationship between lipid metabolism and inflammation, leaves no doubt that curcumin can modulate blood and tissue lipids levels and perform an anti-inflammatory role at the same time. It has been reported that curcumin can significantly reduce macrophage infiltration into white adipose tissue and increase production of adiponectin by adipose tissue [73]. Some researchers have concluded that the anti-diabetic properties of curcumin might be attributable at least in part to its anti-inflammatory activities, as suggested by attenuating TNF-α levels and by its anti-lipolytic effect, which is shown in the attenuation of plasma FFA [76]. Curcumin was also found to regulate blood levels of a variety of lipids and lipoproteins (TC, LDL, HDLC, and TG) through its antioxidant activity [90].

5.3. Amelioration of Diabetic Complications

DM involves many complications, including nephropathy, retinopathy, neuropathy, and vascular damage, all of which can increase mortality. As it has been reported in 2000, the overall global mortality attributable to diabetes was 2.9 million deaths, most of which involved T2DM [108]. Another investigation claimed that heart disease was the immediate cause of 68% of diabetes-related deaths in the U.S., whereas renal failure was the most common immediate cause of diabetes-related deaths in Asia [109]. A large number of experiments have covered the preventive and ameliorative effect of curcumin on various types of diabetic complications, including heart disease and renal failure. There is some question regarding whether microangiopathy is the initial pathological change behind renal failure. We discuss the curative effects of curcumin with respect to these two types of diabetic complications.

5.3.1. Vasculopathy

Diabetic vasculopathy can be divided into macroangiopathy and microangiopathy [110]. Endothelial dysfunction and microangiopathy

### Table 2. Effects of Curcumin on BG levels in DM

<table>
<thead>
<tr>
<th>Refs.</th>
<th>Diabetic models</th>
<th>Curcumin administration*</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>[98][101]</td>
<td>STZ-induced rats (60 mg/kg)</td>
<td>Cur, 0.5% Diet, for 8 weeks.</td>
<td>(−)</td>
</tr>
<tr>
<td>[49]</td>
<td>STZ-induced rats (40 mg/kg)</td>
<td>Cur, 200 mg/kg/d, for 14 days.</td>
<td>(−)</td>
</tr>
<tr>
<td>[89]</td>
<td>AM-induced rats (150 mg/kg)</td>
<td>Tur/Cur, 100/80 mg/kg/d, for 21 days.</td>
<td>(+)</td>
</tr>
<tr>
<td>[90]</td>
<td>STZ-induced rats (60 mg/kg)</td>
<td>Tur, 300 mg/kg/d, for 8 weeks.</td>
<td>(+)</td>
</tr>
<tr>
<td>[71]</td>
<td>STZ-induced rats (40 mg/kg)</td>
<td>BDMCA, 15 mg/kg/d, for 45 days.</td>
<td>(+)</td>
</tr>
<tr>
<td>[53][54]</td>
<td>STZ-induced rats (40 mg/kg)</td>
<td>Pi-Cur, 10/30 mg/kg/d, for 45 days.</td>
<td>(+)</td>
</tr>
<tr>
<td>[100]</td>
<td>STZ-induced rats (55 mg/kg)</td>
<td>Cur, 200 mg/kg/d, for 24 weeks.</td>
<td>(+)</td>
</tr>
<tr>
<td>[57][99]</td>
<td>STZ-induced rats (35 mg/kg)</td>
<td>Cur, 0.01% AIN-93 diet, for 8 weeks.</td>
<td>(−)</td>
</tr>
<tr>
<td>[95]</td>
<td>db/db mice</td>
<td>Cur, 200 mg/kg/d, for 6 weeks.</td>
<td>(+)</td>
</tr>
<tr>
<td>[73]</td>
<td>(1). DIO mice (2). ob/ob mice</td>
<td>Cur, 3% Diet: (1). for 4-8 weeks. (2). for 16-18 weeks.</td>
<td>(+)</td>
</tr>
<tr>
<td>[79]</td>
<td>MLD-STZ induced mice</td>
<td>Pr-Cur, 7.5 mg/kg/d, for 5 days.</td>
<td>(+)</td>
</tr>
<tr>
<td>[80]</td>
<td>STZ-induced rats (65 mg/kg)</td>
<td>Cur, 100 mg/kg/d, for 7 weeks.</td>
<td>(+)</td>
</tr>
<tr>
<td>[85]</td>
<td>STZ-induced mice (60 mg/kg)</td>
<td>Cur, 200 mg/kg/d, for 12 weeks.</td>
<td>(−)</td>
</tr>
<tr>
<td>[76]</td>
<td>HFD-induced rats</td>
<td>See Table 1.</td>
<td>(+)</td>
</tr>
</tbody>
</table>

*All curcumin and curcuminoids were administered orally.

Tur, turmeric; Cur, curcumin; Pi-Cur, photo-irradiated curcumin; Pr-Cur, pretreated with curcumin; BDMCA, bis-ohydroxycinnamoyl methane; AM, alloxan monohydrate.

(+) Curcumin could significantly decrease BG levels of DM.

(−) Curcumin had no significant effect no BG levels.

mice (which have a mutation in the leptin receptor gene), Seo KI et al. found that curcumin significantly lowered the hepatic activities of fatty acid synthase, b-oxidation, 3-hydroxy-3-methylglutaryl coenzyme reductase, and acyl-CoA: cholesterol acyltransferase (LCAT), while increasing the levels of hepatic glycogen and skeletal muscle lipoprotein lipase contributing to lowering plasma free fatty acid (FFA), TC, and TG concentrations [95]. THC was also found to reduce LCAT activity while lowering lipid levels in plasma and tissue (liver and kidney) [104]. In another experiment, curcumin not only reduced the activity levels of these enzymes in HFD hamsters (the rodent species most closely related to humans with respect to lipid metabolism), but also elevated the levels of high-density lipoprotein cholesterol, apolipoprotein (apo) A-I, and paraoxonase activity in plasma, finally reducing TC and TG levels [105]. Curcumin also increased the level of phosphorylation of 5’AMP-activated protein kinase, reduced glyceral-3-phosphate acyl transferase-1 activity, and increased carnitine palmitoyltransferase-1 expression, which decreased the rate of fatty acid esterification in mice [106].

Adipocyte differentiation is regulated by peroxisome PPAR-γ and CCAAT/enhancer binding protein-R. It has been shown that curcumin could suppress 3T3-L1 adipocyte differentiation and decrease serum cholesterol while inhibiting the expression of PPAR-γ and CCAAT/enhancer binding protein-R [106]. Curcumin was also found to interrupt Wnt signaling and suppress gene expression of lectin-like oxidized LDL receptor-1 (LOX-1) contributing to blockage of the transport of extracellular ox-LDL into cells and to lower levels of low-density lipoprotein (LDL) in the plasma [107]. Minji Kim et al. found curcumin to have an appreciable impact on lipid levels in serum, tissue and feces, and up-regulated hepatic CYP7A1 mRNA level by 2.16-fold [102]. They considered the increases in CYP7A1 gene expression to account for the hypolipemic effect of curcumin.
thy become detectable long before clinical manifestations of diabetic vascular complications (including nephropathy and retinopathy) appear [111]. Oxidative stress is one of the important mechanisms involved in diabetic vasculopathy, and it always involves an increase in the levels of inflammatory cytokines [112]. Curcumin should be highly effective against this pathological change, and its clinical products have been used when available. One clinical trial showed that NCB-02 (standardized preparation of curcuminoids) can significantly reduce levels of malondialdehyde, ET-1, IL-6, and TNF-α in T2DM patients [113]. NCB-02 was found to have a more favorable effect on endothelial dysfunction than atorvastatin. Another clinical trial showed that Meriva, a lecithinized formulation of curcumin) could relieve high-perfusion microangiopathy (HPM), favoring effect on endothelial dysfunction than atorvastatin. An-

improved the mesenteric arteriolar response to acetylcholine.

120. The mechanism underlying this action might involve positive

thickness that occur in the retina during diabetic retinopathy [119, 

degeneration and the increase in capillary basement membrane

matrix, promotes endothelial cell proliferation and differentiation,

and mediates endothelial-dependent vasodilatation [116]. Many

studies have indicated that curcumin can efficiently regulate this

type of vasodilation in diabetic microangiopathy. One study of diabetic nephropathy showed curcumin to significantly inhibit the expression of VEGF in podocytes and renal tubules [117]. DM can lead to eye disorders, of which diabetic retinopathy is one of the most devastating. It can accompany type 1 or type 2 diabetes and it is a leading cause of blindness among middle aged and older people [118]. It has been reported that curcumin can prevent the structural degeneration and the increase in capillary basement membrane thickness that occur in the retina during diabetic retinopathy [119, 120]. The mechanism underlying this action might involve positive modulation of the antioxidant system and prevention of VEGF expression [120]. Curcumin has also been found to prevent endothelial dysfunction in the iris tissue in diabetic rats [121]. Curcumin has been found to suppress leukocyte adhesion and protected the function of the endothelial cells of iris through its anti-oxidant, hypoglycemic, and hypolipidemic roles. Diabetic cataracts are another serious eye disease. They have a severe impact on elderly patients. Studies have shown that curcumin can prevent alterations in hydrophobicity and structural changes by countering the hyper-glycemia-induced oxidative stress and by increasing α-crystallin

chaperone activity. This ultimately leads to delays in the progresson and maturation of diabetic cataracts [99, 122].

5.3.2. Nephropathy

Nephropathy is one of the most common life-threatening complications of diabetes mellitus. It affects about 15–25% T1DM patients and 30–40% T2DM patients [123]. It is usually attributed to metabolic consequences of glucose regulation, and hemodynamic changes in the kidney tissue. It has a direct correlation with microangiopathy [124]. The pathogenesis of progressive nephropathy may be associated with lipid abnormalities. The degree of lipid and lipoprotein abnormality shows a direct correlation with the severity of proteinuria, which roughly parallels the rate of dete-
roration of renal function [125]. Earlier studies have shown that dietary curcumin can significantly reduce lipid levels in the liver tissue and plasma [98, 101]. The same laboratory later found that curcumin could reverse the abnormal state of enzymuria and albuminuria by regulating enzyme activity and reducing lipid levels, eventually bringing about significant beneficial modulation of the progression of renal lesions in diabetes [126].

ROS plays a key intermediate role in the pathophysiology of diabetic nephropathy [127]. In recent years, most studies on diabetic nephropathy have demonstrated that the anti-nephropathy effect of curcumin is mainly due to its anti-oxidant activity [128–131]. Later studies have focused on the molecules and proteins related to oxidative stress and renal function. Chiu 3 et al. found that curcumin treatment could prevent the upregulation of vasoactive factors (endothelial nitric oxide synthase, eNOS, and endothelin-1), transforming growth factor-β1 (TGF-β1), and extracellular matrix (ECM) proteins in the kidneys [131,132]. Curcumin was also found to significantly diminish the activity of high-glucose-induced PKC-α, PKC-β1, and phosphorylated ERK1/2 to attenuate the expression of connective growth factor (CTGF), osteopontin, p300, and ECM proteins (such as fibronectin and type IV collagen), and to ameliorate the expression of VEGF and VEGF receptor II (FLK-1) [133]. These effects of curcumin, especially its anti-fibrotic ef-

fect, are mainly attributable to its strong anti-oxidant properties. Other studies have reported that curcumin can decrease expression of HSP-27 and p38-MAPK and enhance the phosphorylation of both p38-MAPK and downstream HSP-25. It has also been shown to regulate the dephosphorylation and acetylation of histone H3 and dramatically inhibit the activation of COX-2 and caspase-3 [133, 134]. However, one of these studies showed that dietar curcumin failed to attenuate albuminuria. This might be due to a decrease in renal HSP-25 or stimulation of the 12/15 lipoxygenase pathway [133].

5.3.3. Wound Healing

In 1999, Sidhu et al. had found that wounds of diabetic mice treated with curcumin showed earlier re-epithelialization, improved neovascularization, increased migration of various cells into the wound bed, and a higher collagen content, as well as an increase of TGF-β1 [135]. In wound healing, orally administered curcumin was not found to exert a strong therapeutic effect. The development of suitable carrier vehicles capable of delivering the curcumin mole-
cule in a sustained manner at therapeutic levels is of clinical signifi-
cance. One study has demonstrated the feasibility of a curcumin-
loaded poly(epsilon-caprolactone) nanofibers in diabetic wound healing [136]. This study reported that curcumin-loaded PCL nanofibers maintained the viability of human foreskin fibroblast cells (HFF-1) under oxidative stress conditions in vitro. This was attributed to curcumin’s anti-oxidant activity, as demonstrated by ORAC assay, and its anti-inflammatory activity, as demonstrated by low levels of IL-6. In vivo, it was found to increase the rate of wound closure in diabetic mice.

5.3.4. Diabetic Neuropathic Pain

Diabetic neuropathic pain (DNP) is generally considered one of the most common complications of DM affecting both types of
diabetes equally. DNP is also one of the most difficult types of pain to treat. In recent decades, many studies have demonstrated that curcumin can attenuate various kinds of neuropathic and inflammatory pains. Sharma et al. studied the anti-nephrotic effect of curcumin and found it to significantly attenuate thermal hyperalgesia and hot-plate latencies in diabetic mice through its inhibitory action on NO and TNF-α release [128, 137]. In a later study, they found that insulin combined with antioxidant (resveratrol and curcumin) therapy could cause improvement in neuropathic conditions in diabetes and inhibit NO and TNF-α levels [138]. TNF-α is implicated in the initiation of neuropathic pain signaling pathway. It is therefore reasonable to conclude that curcumin can further activate the proteins p38-MAPK, JNK, and ERK in the downstream signaling pathway of neuropathic pain.

5.3.5. Diabetic Encephalopathy

A great deal of evidence has shown that diabetes may also have negative impacts on the central nervous system, here called diabetic encephalopathy (DE) [139]. Many studies have described a series of neurobehavioral and neuropsychological changes in patients with type 1 and type 2 diabetes, suggesting that DE should be recognized as a complication of DM [140]. It has also been reported that oxidative stress plays a crucial role in the development of diabetes-associated neuronal disorders [141]. Both clinical and animal studies have shown that oxidative stress can damage various parts of the brain, causing morphological abnormalities and memory impairment [142, 143]. Curcumin, a potent antioxidant, can probably mitigate DE.

Diabetic rodent brains show a marked increase in lipid peroxidation and a simultaneous decrease in endogenous antioxidant enzymes [144, 145]. Studies have found that curcumin and curcuminoids can significantly attenuate cognitive deficits, cholinergic dysfunction, oxidative stress, and inflammation in diabetic rats and regulate serum TNF-α and TBARS levels and antioxidant enzymes activity levels in both the cerebral cortex and the hippocampus. Murugan and Pari also found that THC can cause significant increases in the levels of antioxidant enzyme activity in the brains of diabetic rats [146]. Curcumin was also found to attenuate the upregulated expression of AdipoR1, p-AMPK α1, Tak1, GLUT4, NADPH oxidase subunits, caspase-12, and 3-NT in the cerebella of diabetic rats, which indicated that curcumin could ameliorate DE through the down-regulation of the AMPK-mediated gluconeogenesis associated with its antioxidant property [147]. SOD has been implicated as a major source of end-organ damage in diabetes. It acts by altering mitochondrial respiratory chain complexes, damaging mechanisms of energy conservation, which eventually contributes to neuronal cell death [148]. It has been reported that curcuminoid administration causes elevated neuromic mitochondrial complex I and IV activity and ATP levels in diabetic brains and that it does so by reducing nitrite levels and exerting antioxidant activity [145].

Studies have also found that curcumin can directly affect the functional proteins associated with cognizance. Peeyush et al. claimed that curcumin plays a vital role in regulating altered expression of genes encoding acetylcholine esterase, muscarinic M1, M3, α7 nicotinic acetylcholine, and insulin receptors in the cerebella and cerebral cortices of diabetic rats [149,150]. Another study reported that curcumin could potentially regulate diabetic-induced malfunctions of dopaminergic signaling (dopamine D1/D2 receptors), transcription factor CREB, and phospholipase C expression in the cerebral cortex and cerebellum, reversing the abnormal emotional and cognitive functions of diabetic rats [151].

6. CONCLUSION

Many different methods of assessing the pathogenesis of DM have been hypothesized. Oxidative stress and inflammatory reactions have been found to play a crucial role in the occurrence and development of DM. Curcumin, a potent antioxidant, not only scavenges free radicals and enhances the activities of antioxidant enzymes but also inhibits inflammatory responses. Its multitargeted effects in diabetes involve many kinds of signaling proteins (e.g. NF-κB, PKC, ERK1/2, p38-MAPK, PARP, SERCA, and CCR-2) and a variety of inflammatory cytokines (e.g. NF-α, IL-1β, IL-6, IL-8, MCP-1, and IFN-γ). In this way, curcumin can ameliorate the signs and symptoms of DM. These include fostering islet regeneration, increasing insulin secretion, and reducing the levels of glucose, HbA1c, and certain kinds of lipids and lipoproteins in plasma and tissue. These effects can also be caused by curcumin’s direct regulation of multiple metabolic enzymes (e.g. glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, cholesterol-7a-hydroxylase, and sorbitol dehydrogenase) and other indirect effects. Many published studies have also indicated that curcumin can attenuate several of the complications of diabetes, including DE, and that it does so mainly through its anti-oxidant and anti-inflammatory activities. Although nearly all of these studies are animal experiments and a few of them found curcumin to be ineffective, the majority of available experimental evidence suggests that curcumin is suitable for widespread clinical use in the prevention and amelioration of DM.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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