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Curcumin: A Natural Product for Diabetes and its Complications

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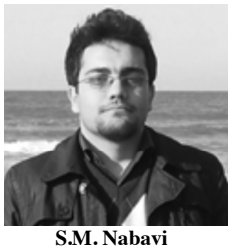

S.M. Nabavi

Abstract: Curcumin is the yellow-colored bioactive constituent of the perennial plant, Curcuma longa L., which possesses a wide range of physiological and pharmacological properties such as antioxidant, anti-inflammatory, anticancer, neuroprotective and anti-diabetic activities. Anti-diabetic activity of curcumin may be due to its potent ability to suppress oxidative stress and inflammation. Moreover, it shows a beneficial role on the diabetes-induced endothelial dysfunction and induces a down-regulation of nuclear factor-kappa B. Curcumin possesses a protective role against advanced glycation as well as collagen crosslinking and through this way, mitigates advanced glycation end products-induced complications of diabetes. Curcumin also reduces blood glucose, and the levels of glycosylated hemoglobin in diabetic rat through the regulation of polyol pathway. It also suppresses increased bone resorption through he inhibition of osteoclastogenesis and expression of the AP-1 transcription factors, c-fos and c-jun, in diabetic animals. Overall, scientific literature shows that curcumin possesses anti-diabetic effects and mitigates diabetes complications. Here we report a systematical discussion on the beneficial role of curcumin on diabetes and its complications with emphasis on its molecular mechanisms of actions.

Keywords: Curcuma longa L., curcumin, diabetes, inflammation, oxidative stress.

1. INTRODUCTION

The term diabetes refers to a class of metabolic diseases which are characterized by high blood glucose levels which are caused by abnormalities in insulin secretion, insulin function, and/or both of them [1]. It has been reported that diabetic chronic long-term hyperglycemia induces different organ damages and dysfunctions such as diabetic retinopathy, neuropathy, cardiomyopathy, nephropathy, angiopathy, and diabetic foot [2-9].

Diabetes is commonly classified into 4 major groups including type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and other specific types, such as congenital diabetes, which is due to genetic insulin secretion defects, cystic fibrosis-related diabetes, and steroid diabetes. The latter are caused by genetic defects in the β-cell function, insulin function, exocrine pancreas diseases, endocrinopathies, drugs- or chemicals-induced diabetes, and infections-induced diabetes [10].

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Type 1 diabetes is caused by autoimmune β-cell destruction in the pancreas and leads to absolute insulin deficiency [11]. Type 2 diabetes is a metabolic disorder with variable phenotypic expression, including β-cell insufficiency and insulin resistance [12]. Gestational diabetes mellitus is diagnosed in 7% of all pregnancies which is known as glucose intolerance with onset recognition during pregnancy [13].

Diabetic may be associates with short-term and/or long-term complications including diabetic retinopathy, nephropathy, peripheral neuropathy, cardiomyopathy, angiopathy, diabetic foot (which often leads to amputations), and neuropathic arthropathy, also known as Charcot joints [14-19]. Long term autonomic neuropathy is reported to induce gastrointestinal, cardiovascular injuries, genitourinary and sexual dysfunctions [20]. There is a close correlation between diabetes and risk of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular diseases in diabetic patients [21-23]. Moreover, diabetic patients show more risk of hypertension and abnormalities in lipoprotein metabolism, in comparison with healthy people [24, 25]. A growing body of evidence shows that oxidative stress and inflammation cytokines and chemokines play an important role in the initiation and progression of diabetes [26-28].

In view of their debilitating role in pathogenesis of different diseases, a revolution has occurred during the last dec-

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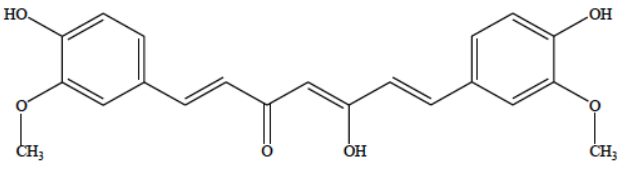
ades aimed at development of effective therapeutic strategies that address these pathological aspects [29-32]. Due to the fact that most of diabetic complications are hard to heal or even irreversible, preventive strategies has superiority over other therapeutic protocol and stated goal of American Diabetes Association [33]. Extensive reports show that several bioactive dietary compounds (known as nutraceuticals), such as polyphenols, are able to control the underlying cellular mechanisms which often lead to oxidative stress and inflammation [34-39] which is involved in diabetes pathogenesis [40, 41].

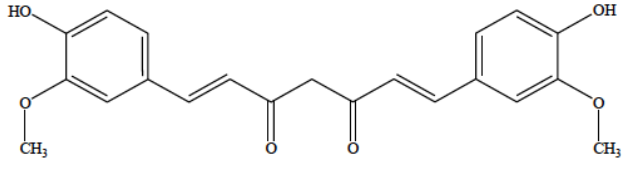
Plants are rich sources of polyphenolic compounds [42-46] which have been used traditionally as antidiabetic agents [47-49]. Among them, much attention has been paid to some edible species due to their negligible adverse effects [50]. Curcumin is a "famous" polyphenolic compounds with a plethora of therapeutical effects such as antioxidant, antiviral, anticancer, anti-inflammatory, etc. [51-56]. Considering its wide uses in the traditional and modern medicine, as well as culinary uses, curcumin can be considered safe [57]. Extensive evidence has demonstrated the promising role of curcumin on diabetes and its complications via modulating several cellular mechanisms [58-62]. In this paper we aim to review the literature data on the therapeutic effects of curcumin in diabetes.

2. CHEMISTRY OF CURCUMIN

As shown in Fig. (**1**), chemical skeleton of curcumin (1, 7-bis [4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) contains different functional moieties which are bonded to two phenol rings [51]. These two phenol rings are linked by two sets of α- and β-unsaturated carbonyl moieties (Fig. **1**) [63, 64]. These unsaturated moieties can significantly react with some biological nucleophiles such as glutathione, etc. [65, 66] by Michael addition and afford interesting C-C adducts. There are two methoxy aryl moieties at the ortho position as well as a hydroxyl substituent and conjugated β-diketone moieties in its chemical structure (Fig. **1**) [67]. Curcumin can be found in different tautomeric forms such as 1,3-diketo and two different equivalent enol forms [68, 69].



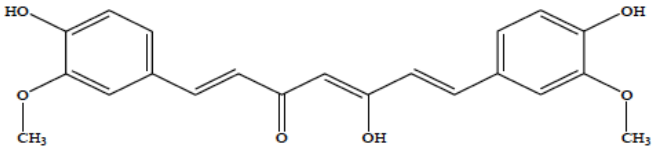
Enol form



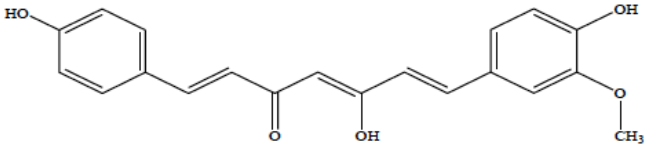
Keto form

Fig. (1). Chemical structure of tautomeric forms (enol and keto forms) of curcumin.

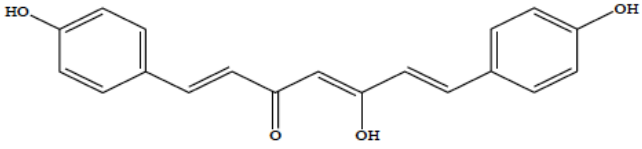
It has been reported that there are differences in the methoxy substituents among the chemical structures of diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin (Fig. **2**), which have a crucial role in the biological and pharmacological actions of these compounds [51]. Moreover, α- and β-unsaturated diketone moiety in the chemical framework of curcumin has a crucial role in the inhibition of nuclear factor-kB (NF-kB) and reactive oxygen species (ROS)-production [70-73].



Diferuloylmethane



Demethoxycurcumin



Bisdemethoxycurcumin

Fig. (2). Chemical structure of diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin.

Some examples of curcumin derivative synthesis have been developed with the aim to develop medical applications against serious chronic diseases such as cancer, by using metal/organic framework nanoparticles. Active natural and non-toxic molecules are incorporated in these novel systems using curcumin, giving new curcumin analogues more complex with low cytotoxicity. Thus, an example of these systems is curcumin interaction with Ag+ to produce silver nanoparticles (Fig. **3**) [74].

This novel method used to treat a bacterial strain can be the starting point of new applications by using low concentrations of curcumin or its derivatives without side-effects. In this sense, another innovative system consists in the loading of curcumin onto starch maleate (SM) under mild conditions by mixing dissolved curcumin. Later curcumin-loaded starch-maleate (CurSM) nanoparticles were subsequently precipitated from a homogeneous mixture of these solutions in ethanol based on the solvent exchange method. This method allows to reach a curcumin loading capacity of 15 mg/g within 12 h. Thus, CurSM nanoparticles exhibited substantially higher water solubility of 6.0 × 10-2 mg/mL, which is about 300 times higher than that of pure curcumin [75]. The bioaccessibility of curcumin due to this synthesis can improve its pharmacological action on the living organism.

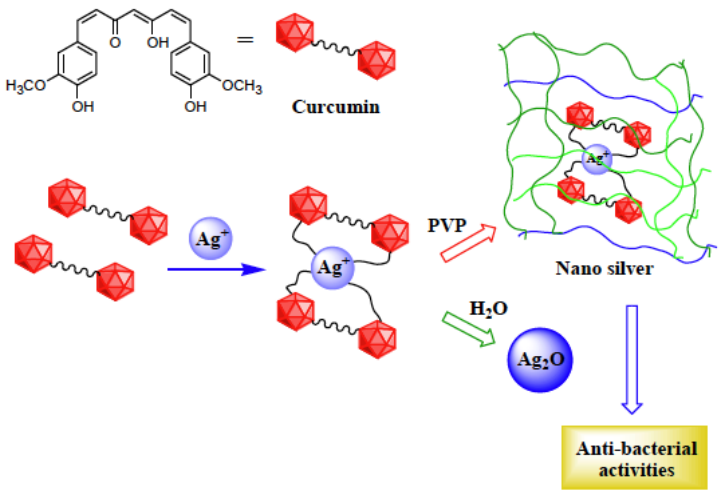


Fig. (3). Nanosilver synthesis from Ag^+ using curcumin. Polyvinylpyrolidone (PVP), Silver oxide (Ag_2O), Silver ion (Ag^+).

Plants are a rich source of molecules which can lead to the development of new drugs with unsuspected pharmacological properties. The natural curcuminoids have gained considerable attention in recent years for their multiple beneficial therapeutic activities. Hence, the synthesis of curcumin-β-di-glucoside was carried out in good yield and in a biphasic reaction medium using a phase transfer catalyst under simple and eco-friendly conditions (Fig. **4**). This novel glucosyl curcumin had been synthesized as anticancer drug, whereas its "hydrogenated" derivative (α,β-unsaturated double bond) has been proposed as ingredient in achromatic food and in cosmetic applications [76].

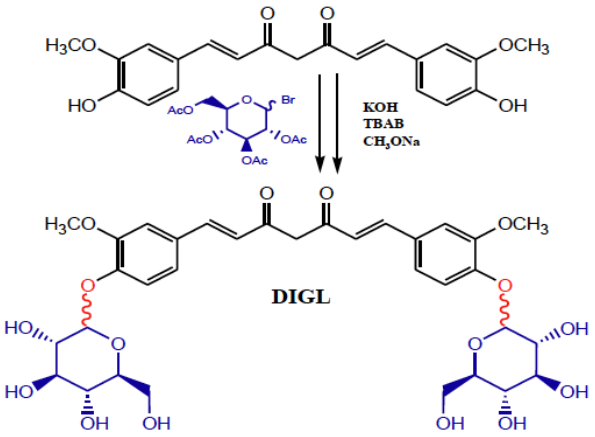


Fig. (4). Synthesis of curcumin-4,4-β-di-glucoside (DIGL).

Another synthetic route to afford new curcumin derivatives called 3,4-dihydropyrimidin-2(1H)-one/thione were synthesized in good yield by a one-pot multicomponent cyclocondensation using curcumin, substituted aromatic aldehydes, and urea/thiourea in ethanol and concentrated sulfuric acid. These analogues were studied for their anticancer evaluation on leukemia, melanoma, lung, colon, central nervous system, renal, prostate, and breast cancers cell lines [77].Finally, an interesting curcumin derivative is obtained using an innovative approach toward multiple carbon-carbon bond-formations that relies on the multifaceted catalytic properties of titanocene complexes. Thus, C1-C7 analogs of curcumin, e.g., I (R = H, COMe, $SiMe_2CMe_3$) are synthesized for evaluation as brain and peripheral nervous system anti-cancer agents (Fig. **5**).

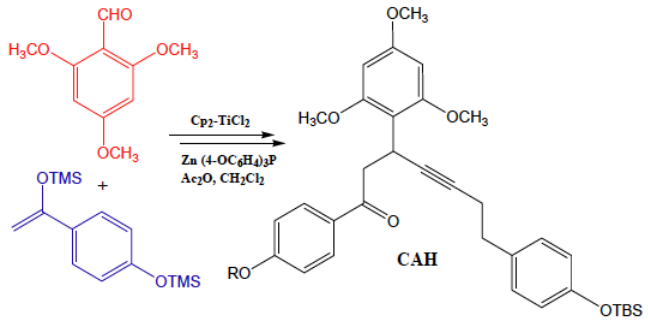


Fig. (5). Synthesis of curcumin-derived arylheptanoids (CAH).

C2-Arylated analogs proved efficacious against neuroblastoma (SK-N-SH & SK-N-FI) and glioblastoma multiforme (U87MG) cell lines. Therefore, these curcumin analogues are potential chemotherapeutic agents that can be use deficiently against cancer cell lines with medium selectivity across *in vitro* assays [78].

3. PHYSICO-CHEMICAL PROPERTIES

Spectrophotometric examination showed that the maximum absorption of curcumin occurs at the wavelength of 425 nm [79]. Its chemical structure, which was identified in 1913, is characterized by two-feruloyl chromophores bound through a methylene moiety [80]. At alkaline pH, curcumin is unstable and degrades within 30 min to the compounds trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexanal, ferulic acid, vanillin and feruloylmethane [81]. The two aryl rings are symmetrically connected via ortho-methoxy phenol groups in conjugation via a β-diketone moiety, which confers different properties at solid state and in solutions [67]. The functionality of the β-diketone moiety plays an important role in the intramolecular transfer of the hydrogen atom which leads to form keto-enoltautomeric and different conformations [82]. Nuclear magnetic resonance (NMR) spectroscopic studies of curcumin in deuterated chloroform

($CDCl_3$) [83] have shown that curcumin was identified as enol form in non-polar and aprotic solvents, due to the intramolecular transfer of hydrogens. Curcumin is found as stable form at low pH in different aqueous solutions. However, as reported above, curcumin can be hydrolyzed and degraded at alkaline pH [84, 85]. It has also been reported that in aqueous solutions, curcumin has been exposed to hydrolytic degradation. Therefore, it can be concluded that pH should be up to 7 for its preparations. Curcumin is also subject to photo-degradation, and therefore, exposure of curcumin to sunlight in solutions and in solid state induce the formation of various degradation products, such as benzaldehyde, cinnamaldehyde, benzocalcone and flavanone [86].

Curcumin has three ionizable protons, two hydroxyl phenol as well as a third as enol form. Hence, three ionization constants were evaluated for both experimental and theoretical examinations.

4. SOURCES AND EXTRACTION OF CURCUMIN

Curcumin is the main bioactive constituent of Curcuma Longa (Zingiberaceae), from which curcumin is extracted and concentrated [79]. Demethoxycurcumin and bismethoxy derivatives are also found in different proportions [87]. A yellow-orange powder, obtained from the root and the rhizome of Curcuma longa, is used throughout the world and is considered the main ingredient of curry containing about 2% of curcumin [88].

Nowadays, much attention has been paid to ascertain the best extraction method for natural products [89, 90]. Acetone, methanol, ethanol, and isopropanol are indicated by the Food and Agriculture Organization of the Unites Nations (FAO) and the World Health Organization (WHO) as suitable solvents for extraction of curcumin from its natural sources [91, 92]. The Commission Directive 95/45/EC also indicated that hexane, ethyl acetate, dichloromethane, carbon dioxide and n-butanol can be used for extraction of curcumin [93]. This compound with very poor solubility is traditionally extracted with common techniques, such as Soxhlet extraction, sonication and other methods that use organic solvents [94]. It is well known that traditional extraction of curcumin is associated with different drawbacks including time consuming, laborious, low selectivity and low extraction yields [88, 95, 96]. In addition to these drowbacks, traditional extraction is based on the application of high amount of toxic solvents [88, 95, 96]. Nowadays, extraction techniques have successfully controlled the above-mentioned problems. The most effective and suitable new extraction techniques for curcumin extraction include supercritical fluid extraction (SFE) and subcritical water extraction (SWE) [92, 97]. SFE and SWE have more selectivity, need shorter extraction times, and usually do not need toxic solvents [92, 97]. Pressurized hot water extraction (PHWE) is known as green and environmentally friendly technique which can be used for curcumin extraction. Temperature, pH, and buffer concentration have important role in the extraction yield of curcumin. Several authors have obtained comparable yields with these solvent extraction methods and these results could mark a radical change in extraction methods, resulting in less environmental pollution [92, 92].

5. BIOAVAILABILITY OF CURCUMIN

Curcumin poor bioavailability reduces its clinical use [98, 99]. The low bioavailability of curcumin is mainly due to its low absorption, rapid metabolism, and quick elimination [99]. Therefore, much attention has been paid to the discovery of novel delivery systems for increasing the bioavailability of curcumin [98, 99] and at the investigation of the bio-functional and therapeutic role of curcumin in clinical trials. Curcumin has hydrophobic characteristics and is poorly dissolved in aqueous solution [100]. In addition, curcumin and its solutions can be easily degraded by UV light which is known as another major limitation of curcumin uses [85, 101, 102]. Until now, the use of different delivery systems such as piperine, liposomal curcumin, nanoparticles and complexion with phospholipids are reported for increasing the bioavailability of curcumin [103-105]. Furthermore, the synthesis of structural analogs of curcumin may increase its bioavailability and pharmacological properties [98, 106].

6. TOXICITY OF CURCUMIN

There are negligible scientific reports about the toxicity of curcumin in animals and humans even at chronic high concentrations [88, 107-109]. In fact, curcumin has been used in both traditional medicine and human diets from ancient times [88, 107-109]. In 1996, FAO and WHO Expert Committee on Food Additives concluded that curcumin acceptable daily intake (ADI) is about 3 mg/kg bw/day [110-112]. The European Food Safety Authority (EFSA) established the same ADI value [117, 118]. However, curcumin consumption at high doses may be associated with teratogenic effect, embryo-toxicity and also reproductive toxicity [113]. Moreover, at high doses curcumin induces chromosome aberrations and astrocyte cell death [114, 115]. In addition, curcumin induces human gallbladder contraction and therefore it is not recommended for gallstones patients [116]. Despite to this, there is a lack of scientific information about systematic toxicity of curcumin and, therefore, it can be suggested that future studies should be performed to fully address the toxicity of curcumin. Respect to the few reports about toxicity of curcumin, it will be difficult to make a clear decision about its recommended effective and safe doses.

7. CLINICAL IMPACTS

A search was made in the http://clinicaltrial.gov/ and http://www.ncbi.nlm.nih.gov/pubmed/ with keyword "Curcumin and diabetes" and "Curcuminoids and diabetes" at July 28, 2014. The search in http://clinicaltrial.gov/ showed that there is one completed study and three clinical trials with unknown status till July 28, 2014. The results are summarized in Table **1**. In addition, the search in http://www.ncbi.nlm.nih.gov/pubmed/ showed that there are 6 published clinical trials regarding the beneficial effects of Curcumin on diabetes and its complications (Table **2**). However, curcumin is the main constituent of Curcuma longa L., which is known as one of the most common food additive all over the world. Compared to different adverse effects of synthetic anti-diabetic drugs, curcumin can be recommended for future clinical trials on diabetes and its complications.

Table 1. Completed clinical trials on the effects of curcumin on diabetes and its complications according to http://clinicaltrial.gov/.

Identifier	Study Type	Status	Title of Study
NCT01052025	Interventional	Unknown	Curcumin therapy in patients with impaired glucose tolerance and insulin resistance
NCT01052597	Interventional	Unknown	Curcumin for type 2 diabetic patients
NCT01029327	Observational	Completed	Effects of curcumin on postprandial blood glucose, and insulin in healthy subjects
NCT01646047	Interventional	Unknown	Diabetes visual function supplement study

Table 2. Search results on the effects of curcumin on diabetes and its complications according to http://www.ncbi.nlm.nih.gov/pubmed/.

PMID	Author	Year	Title of study
23241930	Steigerwalt *et al.* [165]	2012	Meriva®, a lecithinizedcurcumin delivery system, in diabetic microangiopathy and retinopathy.
22930403	Na *et al.* [165]	2013	Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial.
22773702	Chuengsamarn *et al.* [62]	2012	Curcumin extract for prevention of type 2 diabetes.
22108476	Appendino *et al.* [167]	2011	Potential role of curcuminphytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study.
21627399	Khajehdehi *et al.* [168]	2011	Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study.
18588355	Usharani *et al.* [169]	2008	Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study.

8. CURCUMIN AND DIABETES

Curcumin has been shown to possess potent glucose-lowering effect [119, 120] and this is thought to be due to the antioxidant and anti-inflammatory activities of curcumin [120]. Nevertheless, it is important to recognize the fact that over the years curcumin has been found to possess a variety of pharmacological properties, which make this a golden spice.

A search of the NCBI database using the terms 'curcumin and diabetes' retrieved about 305 research articles over the last 15 years. In these investigations a variety of pharmacological properties of curcumin against diabetes have investigated. This has led to the use of curcumin not only against diabetes but also against diabetic complications.

Advanced glycation end products (AGEs) accumulation is a common pathology associated with hyperglycemia. It is well recognized that both hyperglycemia and AGEs can contribute to tissue oxidative stress leading to loss of homeostasis. One of the earlier reports on the protective effect of curcumin on AGE formation and accumulation due to diabetes was demonstrated by Sajithlal *et al.* [121] and interestingly the authors also emphasized the importance of their findings in terms of collagen-cross linking and browning. A similar finding on the beneficial effect of curcumin in preventing AGE formation in islets and thus increasing islet viability was subsequently demonstrated [122]. The mechanism through which curcumin suppresses AGE formation is suggested to involve the suppression of AGE receptor (RAGE) expression through the activation of peroxisome proliferator-activated receptor gamma (PPARγ) activity and increase in glutathione synthesis [123]. Thus, inhibition of hyperglycemia-induced AGE formation appears to be one of the important mechanisms of the anti-diabetic action of curcumin [123, 124-126]. PPARγ is a type II nuclear receptor. It is mainly found in adipose tissue, colon and macrophages. PPARγ primarily regulates fatty acid storage and metabolism of glucose [123]. Thus, PPARγ has important consequences under diabetic conditions. Several studies have shown the importance of curcumin in enhancing PPARγ activity [127-129], wherein ethanolic extracts of turmeric have been found to possess PPARγ-ligand binding activity [127]. Under diabetic conditions, the curcumin-induced PPARγ activation could have important consequences in terms of inhibition of

hyperglycemia-induced hepatic stellate cell activation by reducing surface expression of glucose transporter 2 (GLUT2) [130, 131]. Hence, curcumin induced PPARγ protects against abnormal cellular accumulation of glucose and AGE, which are two important consequences of diabetes.

Polyol pathway is a salvage pathway induced in cells due to hyperglycemia. Aldose reductase (ALR) is the rate-limiting enzyme whose activation is considered to be one of the major contributors to diabetic complications [132]. The next enzyme in the pathway, sorbitol dehydrogenase, is responsible for the conversion of sorbitol, obtained from the first reaction with aldose reductase, to fructose. Both sorbitol and fructose are deleterious to cells, since sorbitol can accumulate inside cells resulting in osmotic imbalance, and fructose is a known free radical generator. Thus, inhibition of aldose reductase or sorbitol dehydrogenase could result in alleviation of complications associated with diabetes. Curcumin, was shown to be a good inhibitor of sorbitol dehydrogenase [133] than turmeric and this could be attributed to the hypoglycemic effect of curcumin [133], resulting in lower polyol pathway activation. Aldose reductase, the primary enzyme in the polyol pathway was subsequently shown to be inhibited by curcumin [134]. More specifically, ALR2 was demonstrated to be inhibited by curcumin with an IC_{50} value of 10 μM in a non-competitive manner but not ALR1 or other related members [134]. However, an earlier study by Kang *et al.* [135], using non-diabetic vascular tissue has demonstrated that up regulation of ALR activity might actually be beneficial. The authors show that curcumin was able to increase ALR activity by increasing the nuclear translocation of nuclear factor erythroid 2–related factor 2 (Nrf2) through the activation of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and p38 mitogen-activated protein kinases (p38 MAPK) pathway. This enhancement in ALR was suggested to confer protection against cellular oxidative stress [135]. This is interesting, since the pharmacological activity of curcumin on ALR appears to be context drive; always offering beneficial effects.

Oxidative stress is a known mediator in the pathogenesis of diabetes, resulting in islet destruction and hyperglycemia [132]. Onset of diabetes is associated with enhanced free radical generation and loss of endogenous antioxidants in pancreas [132]. Thus, supplementation with curcumin, a potent and well recognized antioxidant, could confer protection against pancreatic oxidative stress and injury. Several studies have indeed shown the importance of curcumin supplementation during diabetes in rescuing endogenous antioxidants such as vitamin C, E, superoxide dismutase and catalase [122, 136, 137] and inhibiting lipid peroxidation in pancreas due to oxidative stress [136-139]. Similarly, Soto-Urquieta *et al.* [140] reported that curcumin administration mitigate hyperglycemia-induced liver and kidney damage in db/db mice through normalization of mitochondrial function and suppression of nitric oxide synthesis and lipid peroxidation. Curcumin and its analogs also can inhibit from β cell dysfunction through inhibition of C-Jun NH2-terminal kinase (JNK) pathways via suppression of oxidative stress and consequently leading to inhibition of pancreatic and duodenal homeobox 1 (PDX-1) translocations [141].

Recent study performed by Tsuda [142] showed that curcumin administration increases the secretion of Glucagon-like peptide-1. This activity is essential for the promising effect of curcumin on prevention and treatment of diabetes. One interesting study by Best *et al.* [143] has implicated the ability of curcumin in stimulating beta-islets, which leads to insulin secretion. This study necessarily suggests that curcumin, apart from its antioxidant and anti-inflammatory action, could also stimulate residual and/or weakened beta cells to secrete insulin. This action of curcumin has effect on membrane channels resulting in enhanced insulin secretion. Similarly, curcumin was suggested to stimulate hemeoxygenase-1 system in beta cells *in vitro*, through Nrf2 nuclear translocation [144].

Another study has shown the relevance of curcumin-induced expression of antioxidants like hemeoxygenase-1 in isolated human islets [145], which could have importance for islet transplantation. A very recent study has indeed shown hemeoxygenase-1 and Nrf2 activation under *in vivo* conditions [131], substantiating the huge importance of this protective axis in countering hyperglycemia-induced effects.

Hyperlipidemia is one of the diabetic complications resulting in abnormal lipid metabolism. Curcumin was shown to possess antihyperlipidemic activity by increasing high-density lipoprotein (HDL) in serum of diabetic rats [126], suggesting the beneficial effects of curcumin on general metabolic changes associated with diabetes. On similar lines, curcumin had an inhibitory effect on hepatic gluconeogenesis through activation of adenosine monophosphate (AMP) kinase and inhibition of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities [146-148]. In this sense, it is clear that curcumin not only causes hypoglycemia by rescuing beta cells, it also inhibits hepatic gluconeogenesis, thus regulating whole-body glucose metabolism. Curcumin and it analogs have also been reported to improve carbohydrate metabolism through inducing of protein kinase B (PKB) and glycogen synthase kinase3 beta(GSK-3β) [141]. In addition, Cheng *et al.* [149] have also shown that curcumin enhances glucose uptake by skeletal muscles by activating muscarinin M-1 cholinoceptors and also by improving insulin resistance [150]. On the other hand, curcumin was shown to inhibit hepatic stellate cell activation by its inhibitory effect on insulin signaling [151] and GLUT2 membrane translocation [130]. Curcumin has also been shown to be important for inhibiting not only liver but also pancreatic α-amylase [152] that could result in better control of post-prandial hyperglycemia.

Diabetes is characterized by high levels of inflammation in pancreas involving a variety of cytokines that could result in beta islet destruction. This induces recruitment of immune cells to the pancreas and islet destruction that is characteristic of autoimmune diabetes. Moreover, high glucose levels are known to induce vascular inflammation too, via glucose induced epigenetic changes [153]. Curcumin has been shown to regulate histone deacetylases (HDACs), histone acetyltransferases (HATs) and NF-kB activation, which could result in the decrease of hyperglycemia-induced inflammation [139,153, 154]. A previous study employing rodent model of autoimmune diabetes has shown that curcumin is responsible for modulating T cell responses leading to the inhibition of

proliferation and interferon γ (IFNγ) production [155]. In addition, the same study also showed the ability of curcumin to inhibit dendritic cell activation of T cells. These results suggest that curcumin could prevent pancreatic infiltration by leucocytes, thus reducing severity of autoimmune diabetes. Such an effect on immune response could also prove the beneficial effects in terms of islet transplantation. Indeed, islet transplantation is gaining prominence for the treatment of diabetes and few studies have shown the importance of curcumin not only in preserving islet transplants [139, 154] but also regeneration of islets in the recipient [139, 156]. Some of the mechanism of action of curcumin in such transplants could involve enhanced vascular endothelial growth factor (VEGF) and platelet endothelial cell adhesion molecule (PECAM) expression and decreased caspase activity [157], together with immune modulating ability of curcumin. Potentially, curcumin could also be helpful in preventing misfolding and accumulation of islet amyloid polypeptide in pancreas [158] and this is achieved by the ability of curcumin disassembling α-helix in maturing assemblies of islet amyloid polypeptides [159]. In particular, curcumin clearly facilitates anti-inflammatory reaction during islet transplantation and also prevents misfolded protein response in islet cells, which otherwise could end up generating new and autoimmune antigenic determinants.

Apart from this, one of the major functions of curcumin is the enhancement of the specificity of insulin-binding to insulin receptor, which might prove critical in the overall glucose metabolism during both type 1 and type 2 diabetes. Using erythrocytes from diabetic rats, Murugan *et al.* [160] have clearly shown that curcumin not only enhances insulin receptor on erythrocyte membrane but also improves affinity binding of insulin. This could result in elevated plasma insulin levels [161] and lower blood glucose. A recent study [162] has provided convincing evidence that curcumin also inhibits pancreatic phosphodiesterases. Phosphodiesterases are negative regulators of insulin secretion by its ability to degrade cyclic adenosine monophosphate (cAMP), which is essential for insulin secretion in beta cells. Thus, dose-dependent inhibition of islet phosphodiesterases by curcumin [162] offers new insights into its anti-diabetic action. In fact, a double-blind, placebo-controlled trial involving overweight/obese type 2 diabetic patients showed reduced insulin resistance when the patients were supplemented with curcuminoids [150].

CONCLUSION

Even though curcumin has huge potential as an effective anti-diabetic drug, one major problem associated with curcumin is its bioavailability. Poor absorption, rapid metabolism and rapid systemic elimination are considered to be the major reasons for its low bioavailability [98]. Under these circumstances nanotechnology-based approaches have become very important in increasing the bioavailability and efficiency of curcumin. In the case of diabetes, such strategies include bis[curcumino]oxovanadium complex [163], dual function vanadyl, gallium and indium curcumin complexes [164], curcumin microcapsules [154] etc. These approaches have shown elevated efficacy and bioavailability of curcumin and reduced clearance. It remains to be defined whether such strategies can successfully propel curcumin to the forefront of anti-diabetic therapeutics.

CONFLICT OF INTEREST

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

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