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Utility of curcumin for the treatment of diabetes mellitus: Evidence from preclinical and clinical studies

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ABSTRACT

Turmeric or *Curcuma longa* is a natural product, whose medicinal properties have been extensively studied and a wide variety of therapeutic effects on several diseases such as neurodegenerative, hepatic and renal damage, cancer, and diabetes have been mainly attributed to its curcuminoid content. In the last decades, diabetes mellitus has become an alarming worldwide health issue, because of the increasing number of people suffering from the disease, as well as the devastating consequences for them. In this paper, we review the current basic and clinical evidence about the potential of curcumin/curcuminoids for the treatment of diabetes mellitus, mainly by its hypoglycemic, antioxidant, and anti-inflammatory properties. The activity of curcumin (or curcuminoids) as a hypoglycemic agent or just as an adjuvant to improve the metabolic profile and to ameliorate the associated complications of diabetes mellitus, such as diabetic nephropathy and cardiopathy is discussed. The interactions between curcumin and conventional antidiabetic drugs might be explored for the therapeutic management of diabetes mellitus.

Contents

1. Introduction

Diabetes mellitus is a multifactorial chronic metabolic disorder that involves the inability to produce insulin or to use it properly,

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resulting in altered metabolism of carbohydrates, fats, and proteins, and long-lasting hyperglycemia [1,2]. The World Health Organization (WHO) has estimated that 439 million people will be diabetic in 2030 [3]. Additionally, in 2012, the cost of treating diabetes mellitus was $245 billion dollars in the USA [4]. In Mexico, the national survey of health and nutrition (ENSANUT) reported that, at the time of the survey, 9.4% of people over 20 years old have been diagnosed with diabetes mellitus [5].

In 2017, the American Diabetes Association classified diabetes mellitus as follows: 1) type 1 diabetes, that is characterized by autoimmune β-cell destruction and absolute insulin deficiency; 2) type 2 diabetes (90–95% of all diabetes cases), which is distinguished by a progressive loss of β-cell insulin secretion and insulin resistance, hence the body cannot properly use the insulin it produces; 3) gestational diabetes mellitus, a disorder that is diagnosed in the second or third trimester of approximately 7% of all pregnancies; and 4) specific types of diabetes from other causes, such as monogenic diabetes syndromes, diseases of the exocrine pancreas (e.g. cystic fibrosis–related diabetes), and drug- or chemical-induced diabetes (e.g. nicotinic acid and glucocorticoid use), which represent <5% of patients with diabetes [2,6].

All types of diabetes mellitus produce serious acute and chronic complications that can increase the overall risk of premature death. Acute complications include hypoglycemia, ketoacidosis or non-ketotic hyperosmolar coma; while chronic complications include cardiovascular diseases, chronic renal failure, as well as damage to retinal, nervous, and vascular tissues [7]. During pregnancy, it can cause fetal death, preeclampsia, and eclampsia, among other complications [2,8].

Although numerous studies have shed light on the multifactorial nature of diabetes mellitus, insulin resistance and pancreatic β-cell dysfunction are the hallmarks of this disease [9]. Insulin resistance is the consequence of an impairment of the signaling cascade that is normally activated by insulin binding to its receptor, resulting in inadequate glucose and lipid metabolism [10]; as a compensatory mechanism, it is possible that pancreatic β-cells have to work exhaustively, triggering changes in the activity of its regulatory elements and gene expression pattern [11]. At the molecular level, several molecules and signaling pathways are altered, some of them involved in metabolic processes and other ones in (anti) inflammatory and (anti) oxidative activity; for instance, mitogen-activated protein kinases (MAPK)/c-Jun N-terminal kinase (JNK) pathway, whose activation is intimately linked to oxidative stress and that inhibits insulin signaling [12]; AMP-activated protein kinase (AMPK) that activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, an important mechanism for cell survival, apoptosis regulation, modulation of antioxidant enzymes concentration [13], and that is also crucial for the adequate glucose transport in muscle cells, adipocytes and hepatocytes [14]; nuclear factor-κB (NF-κβ) intracellular pathway, that regulates the transcription of pro-inflammatory cytokines and that is activated by the IκB kinase (IKK) [15]; protein kinase C (PKC), which is activated by oxidative stress and leads to the activation of pro-inflammatory pathways [16]; Ras homolog gene family member A (RhoA)/Rho kinase pathway, whose activation leads to kidney [17] and heart [18] complications, mainly by favoring the accumulation of matrix proteins; insulin receptor substrates 1 and 2 (IRS-1/2) that are necessary for insulin effects and negatively affected by inflammatory cytokines [19]; glycogen synthase kinase-3β (GSK-3β), that not only regulates glycogen synthase but also cell survival and death [20]; forkhead box protein O 1 (FoxO1), which regulates multiple functions such as glucose and lipid metabolism, redox homeostasis, cell cycle progression, and apoptosis [21]; and glucagon-like peptide 1 (GLP-1) that stimulates insulin production and inhibits the secretion of pro-inflammatory cytokines [22] (Fig. 1).

At the cellular level, β-cell dysfunction is manifested by progressive β-cell failure and structural changes, with combined loss of β-cell number and insulin-secretory capability [23], leading to β-cell dedifferentiation [24–26], a phenomenon that is importantly given by apoptosis [27] through various mechanisms, such as oxidative stress [28,29], endoplasmic reticulum stress (ERS) [30,31], mitochondrial dysfunction [32,33], autophagy deficiency [34,35] and inflammation [36–39] (Fig. 1).

During the last decades, research has aimed to develop effective therapeutic strategies against diabetes mellitus, insulin resistance, and pancreatic β-cell dysfunction by implementing lifestyle changes, the use of therapeutic agents, as well as pharmacological and surgical interventions [40–43]. Current drugs produce a range of adverse effects, such as weight gain, cardiovascular disease, hypoglycemia, and gastrointestinal alterations [44], besides the economic burden they represent. As an attempt to reduce these side effects and, at the same time, to take advantage of nutritional and medicinal properties of some plants and their isolated compounds, natural products have gained considerable attention worldwide [45–49]. Several of these compounds have been obtained from microbes or from plants, such as: metabolites of *Lactobacillus* [50], *Streptomyces* [51], *Camellia sinensis* [52], *Pinus pinaster* [53], *Sophora tonkinensis* [54], *Ipomoea batatas* [55,56], and *Curcuma longa* [57–61].

Turmeric or *Curcuma longa* is an herbaceous plant of the family *Zingiberaceae* that has been considered an important therapeutic agent in Indian and Chinese traditional medicine; it is mainly cultivated in tropical and subtropical regions [62]. Turmeric contains 69.4% carbohydrates, 6.3% protein, 5.1% fat, 5.8% essential oils, and 3–6% of curcuminoids [63]; the main curcuminoids in commercial curcumin are ≈ 77% curcumin (curcumin I), ≈17% demethoxycurcumin (curcumin II), ≈3% bis-demethoxycurcumin (curcumin III), and cyclocurcumin (curcumin IV) [64].

Curcumin has multiple biological and pleiotropic activities as an antioxidant [65–68], antibacterial [69,70], antineoplastic [71,72], antiproliferative [73], and anti-inflammatory agent [74–77]. Furthermore, curcumin has therapeutic potential against neurodegenerative disorders [78,79], cardiovascular diseases [76,80], hepatic damage [81,82], renal diseases [67,83–85] and diabetes mellitus [61,86,87]. This review is focused on the most recent basic and clinical research regarding the antidiabetic properties of curcumin.

2. Curcumin as an antihyperglycemic agent: evidence from basic research

2.1. Effects of curcumin on glucose and lipid metabolism

In the search for alternatives to current medication for diabetes mellitus, curcumin has gained attention in the last decade for its antidiabetic properties [47], giving rise to numerous studies, mainly in *in vitro* and in animal models. The range of beneficial effects of curcumin in diabetes mellitus and its complications has been attributed to its ability to interact with many key molecules and pathways involved in the pathophysiology of this disease [88–90].

Recently, Kato et al. [89] reported a reduction in glucose intolerance after administering theracurmin (a formulation that makes curcumin more bioavailable when it is orally administered to rats [91]); such effect was accompanied by increased levels of plasma GLP-1 [89] and it was prevented by the G protein-coupled receptor (GPR) 40/120 antagonist, GW1000, and by the phospholipase C inhibitor, neomycin, suggesting that the increased secretion of GLP-1 is likely to be mediated by a cAMP-independent GPR40/120

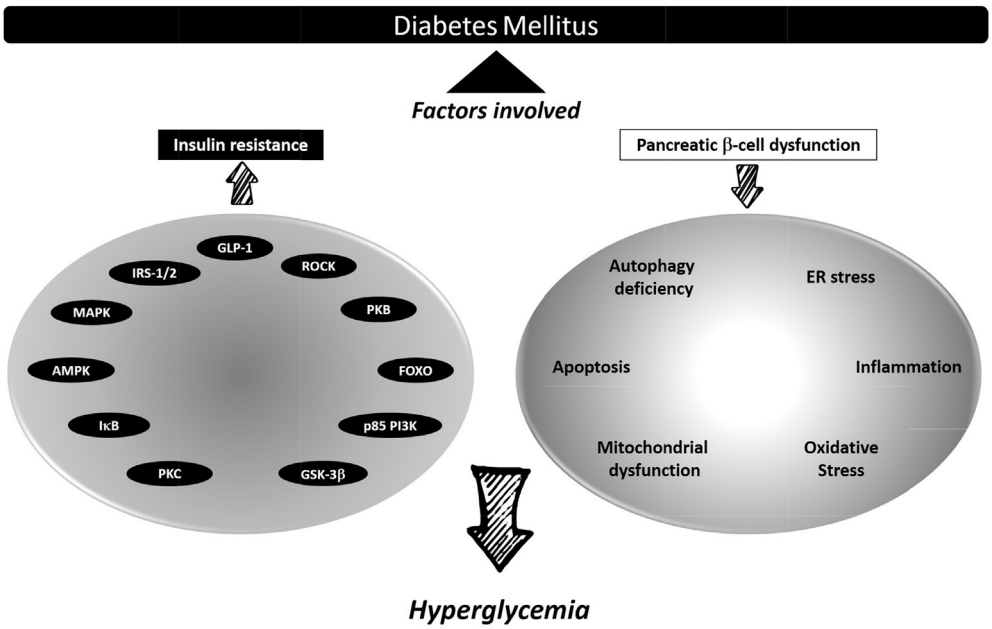

Fig. 1. Representative scheme of mechanisms involved in the development of diabetes mellitus. Hyperglycemia is associated with alterations at both the molecular and cellular levels, which contribute to the mechanisms leading to insulin resistance and β-cell dysfunction. Glucagon-like peptide 1 (GLP-1); insulin receptor substrate 1 and 2 (IRS-1/2); mitogen-activated protein kinases (MAPK); AMP-activated protein kinase (AMPK); IκB kinase (IκB); protein kinase C (PKC); Rho-associated coiled-coil containing protein kinase (ROCK); protein kinase B (PKB); forkhead box protein O (Foxo); PI3K subunit (p85); phosphatidylinositol 3-kinase (PI3K); Glycogen synthase kinase-3β (GSK-3β).

pathway. The secretion of GLP-1 would lead to insulin release, with the consequent lowering-glucose effect [89].

The utility of curcumin has been tested in several *in vivo* and *in vitro* models implying insulin resistance; for instance, curcumin reduced insulin resistance in rats with metabolic syndrome [92] or with polycystic ovarian syndrome, and in cultured human liver HepG2 cells [93]. It has been suggested that the JNK/IRS pathway could be a curcumin target to deal with insulin resistance [90]; interestingly, as insulin resistance is considered as a component of Alzheimer disease [94], curcumin has also been tested in animal models of the disease, being able to decrease insulin resistance by activating the IRS/PI3K/Akt pathway and increasing the expression of glucose transporters (GLUT) 1 and 3 [95,96]. Such mechanism is normally activated by the action of insulin on its receptor and it plays a pivotal role in glucose metabolism and transport [96].

An interesting pathway involved in glucose metabolism is the PI3K/Akt/GSK-3β pathway, whose malfunctioning is associated with the development of metabolic disorders [97]; particularly, GSK-3β is an enzyme that inhibits glycogen synthase by phosphorylation, and it is considered as another relevant curcumin target because, according to simulated docking experiments, curcumin fits within the binding pocket of the enzyme [88]. This binding results in the inhibition of GSK-3β and thus, in increased glycogen synthesis in the liver of fasting mice in a dose-dependent manner [88]. Curcumin has also demonstrated to protect cultured neonatal rat cardiomyocytes against high glucose-induced apoptosis by increasing Akt and GSK-3β phosphorylation [97]. A similar effect was also observed *in vivo*, in a rodent model of type 2 diabetes; curcumin reduced glucose blood levels and myocardial dysfunction, and other parameters in the heart of the animals, such as fibrosis, oxidative stress, inflammation, and apoptosis; all these findings were attributed to the curcumin-induced stimulation of Akt and GSK-3β [98].

It is well known that obesity is intimately linked to diabetes mellitus [99] and that the adipokines secreted by adipose tissue are associated with insulin resistance and glucose homeostasis/dyshomeostasis [100]. To this respect, leptin is a hormone that normally inhibits the appetite, by its actions on the brain, and contributes to insulin sensitivity, among other functions [101]; however, in the context of coexistent obesity/hyperleptinemia/diabetes mellitus, a condition called leptin resistance can be present, leading to overfeeding, fat accumulation, and a series of alterations in lipid and glucose metabolism [101]. Curcumin has shown an inhibitory effect on leptin actions and a decrease in its concentration in several *in vitro* and animal models [102–106]. In the *in vitro* experiments by Song et al. [104], they observed a decrease in fat accumulation and leptin concentration, accompanied by increased lipolysis and expression of adipose triglyceride lipase, and hormone-sensitive lipase, in adipocytes exposed to an ethanolic turmeric extract. They also found that rats fed a high fat-high cholesterol diet increased their leptin plasma concentration and body weight compared with controls, and that the turmeric extract counteracted such effects [104]. Furthermore, it is believed that the anti-adipogenic effects of curcumin could be mediated by the inhibition of the phosphorylation of extracellular signal–regulated kinases (ERK), JNK, and p38, and the suppression of the transcription factors CCAAT-enhancer-binding protein α (C/EBP α) and peroxisome proliferator-activated receptor γ (PPARγ), at the same time that curcumin activates the Wnt/β-catenin signaling pathway [107].

As curcumin decreased the activity of fatty acid synthase and increased hepatic fatty acid β-oxidation in high-fat–fed hamsters, Jang et al. [102] proposed that these mechanisms could be responsible for preventing hyperlipidemia. Curcumin could also exert an inhibitory effect on the expression of the transcription factors sterol regulatory element-binding proteins (SREBPs) in liver and adipose tissue, as shown by Ding et al. [57] *in vivo* and *in vitro*; because SREBPs regulate genes related to lipid biosynthesis and clearance [108], treatment with curcumin lead to an improvement of lipid profile and a reduction in body weight gain in mice fed with a high-fat diet [57]. The same study reported a recovery of insulin resistance by phosphorylation of IRS and Akt [57].

Curcumin improved the lipid profile in animals with hyperlipidemia [102], metabolic syndrome [92], and diabetes [109], decreasing plasma triglycerides and non-high-density lipoprotein (HDL)-cholesterol, and increasing HDL-cholesterol.

Given this information, curcumin has been seen as a molecule with a very high potential for diabetes mellitus treatment, especially for type 2 diabetes; however, the main challenges to make curcumin more available have been its poor oral absorption and low solubility [110]. Some strategies have been tested to face these issues; when a curcumin extract (100 mg/kg/day for 4 weeks) was administered in combination with quercetin and piperine to rats with streptozotocin and nicotinamide-induced diabetes [60], it displayed hypoglycemic effects and improved the lipid profile to the same extent as glibenclamide (10 mg/kg/day) and it was superior to the curcumin extract alone. The authors attributed the observed effects to an increased bioavailability of curcumin, instead of a pharmacological effect of the coadjutants, as they were used at sub-optimal doses [60]. Another strategy has been the complexation of curcumin (150 mg/kg for 45 days) with zinc, resulting in better antidiabetic properties of the complex compared with curcumin or zinc alone, when administered to diabetic rats [111].

Recently, a more complete characterization of a nanoformulation, made of CUR-loaded pluronic nanomicelles (CURnp), was made [112]. This formulation was tested and compared against "native curcumin", in a model of streptozotocin-induced diabetes in rats; it resulted to be more resistant to degradation and to deliver a higher quantity of curcumin in *in vitro* experiments, it was more effective in reducing fasting glucose levels in rats compared with "native curcumin" and it was also superior in the oral glucose tolerance test [112]. Both tested formulations reduced in a similar degree the concentration of triglycerides and cholesterol and did not have any significant impact on insulin concentration in pancreatic tissue [112]. Interestingly, the curcumin nanoformulation restored and increased the gene expression of pancreatic duodenal homeobox-1 (Pdx-1) and NK6 homeobox-1 (Nkx6.1) beyond the values of controls [112]; both of these transcription factors are needed for survival, proliferation, and functioning of β-pancreatic cells [113,114].

In all the cases commented above a complete reversal of the diabetic condition was not achieved; probably, a longer time of treatment is needed, or the observed changes correspond to the maximum possible effect. Interestingly, the picture is different when the lipid profile has been analyzed, highlighting the potential of curcumin as a hypolipidemic agent, regardless of the type of formulation tested. This possibility has also been just emphasized by Panahi et al. [115]: as curcumin has a lowering effect on triglycerides and statins on cholesterol, both of them could be used together as an integral therapy for those disorders that are accompanied by hyperlipidemia.

2.2. Effects of curcumin on inflammation and oxidative stress

Oxidative stress and inflammation are important contributors to the pathophysiology of diabetes mellitus and its complications [116,117]; several natural products, their extracts, or isolated compounds have been tested to deal with these issues; for instance, catechin [118], epigallocatechin-3-gallate [119], *Embelia ribes* [120], *Hunteria umbellata* [121], and also curcuminoids [87,122], just to name a few.

Curcumin has been observed to deal with oxidative stress in models of diabetes mellitus by increasing the activity of antioxidant enzymes such as paraoxonase-1 [102,123], superoxide dismutase 1 (SOD1), catalase [124], and glutathione peroxidase [122,124], which are key enzymes for the antioxidant defense. The relative biological activity of each curcuminoid in *Curcuma longa* has been a subject of debate; hence, some studies have been made to this respect: of the three main curcuminoids, curcumin displayed the highest antioxidant power, followed by demethoxycurcumin and bisdemethoxycurcumin, when tested in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and the ferric reducing ability of plasma (FRAP) assays [59]; while bisdemethoxycurcumin was the one with the highest anti-inflammatory activity [125].

Inflammation and oxidative stress are closely related to each other in diabetes, and curcumin has shown the potential to fight against them, as observed by Maithilikarpagaselvi et al. [122]. Curcumin was able to deal with inflammation and oxidative stress in the muscle of fructose-fed rats by avoiding the degradation of the inhibitor of kappa β (IκBα) and decreasing the oxidative stress-sensitive kinases (ERK 1/2 and p38); consequently, it prevented the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) pathway and the subsequent production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and C-reactive protein [122].

The inhibition of the NF-κβ signaling pathway by curcumin during diabetes brings benefits not only for pancreatic tissue but also for several organs; for instance, spleen [87], kidney [126], liver, and adipose tissue [127], contributing to ameliorate the complications that usually accompany diabetes mellitus. Interestingly, the activity of NF-κβ is also regulated by GSK-3β, which, as discussed in section 2.1, is intimately linked to the pathophysiology of diabetes mellitus [128].

Another relevant pathway for curcumin in diabetes is the nuclear factor E2-related factor 2 (Nrf2)/Keap1/ARE pathway, which regulates the transcription of over 100 genes related to oxidative stress, cell survival, and inflammation [116,129]. Curcumin reversed the detrimental effects on Nrf2 signaling in some *in vivo* and *in vitro* experiments [130–133] and these benefits are more apparent in the kidney (see section 2.4).

Oxidative stress and inflammation, as implicit pathophysiological processes of diabetes, frequently overshadow the benefits that some alternatives for the treatment of the disease can provide; for instance, bone marrow transplantation. The concomitant administration of curcumin to diabetic mice that were transplanted with bone marrow cells, reopened this option due to, when curcumin was administered to diabetic mice that underwent bone marrow transplantation, the regeneration of pancreatic islets was more evident compared with the transplant alone [124]. Also, curcumin, by itself or in combination with bone marrow transplantation, improved the antioxidant enzyme profile and decreased the expression of TNF-α and interleukin-1beta (IL-1β) [124]; this improvement on inflammatory and antioxidant profile was also reported by Kelany et al. [92] in fructose-fed rats.

2.3. Effects of curcumin on endoplasmic reticulum stress in diabetes

Endoplasmic reticulum (ER) plays a central role in the metabolism of carbohydrates, lipids and proteins [134]. When its functioning is disturbed, a process named ERS begins, potentially leading to cell death [135]; this process involves the disruption of protein folding (unfolded protein response) and the accumulation of protein aggregates [134]. Glucose dyshomeostasis and redox imbalance are among the diabetes-related conditions that can trigger ERS [134].

In these situations, ER response is mediated by sensors located on membrane surface, such as serine/threonine-protein kinase/endoribonuclease 1α, activating transcription factor 6 and protein kinase R-like endoplasmic reticulum kinase, which in turn trigger signaling pathways related to cell death (NF-κβ, JNK, p38, and caspases) [87]. Under conditions of oxidative stress, cells might commit themselves to apoptotic death via ER-dependent apoptotic

pathways [87]. It is known that ERS is an important component of insulin resistance and type 2 diabetes, contributing to altered insulin receptor signaling, mainly by over-activation of JNK [136].

Natural products such as moutan cortex [137], *Abelmoschus manihot* [138], and curcumin [87] have resulted effective in dealing with ERS in animal models of diabetes. The administration of curcumin to STZ-induced diabetic rats inhibited ERS, and the consequent apoptosis and inflammation in the liver [139]; the authors of this study suggested that the beneficial effect of curcumin could be, at least in part, due to modulation of the unfolded protein response signaling pathway [139] Similar results were observed when curcumin was tested against testicular damage in diabetic rats; curcumin protects testes from oxidative and ER stress by ameliorating hyperglycemia and testicular damage markers, it regulated intracellular redox balance, it attenuated NF-κβ-mediated inflammation, and it activated PI3K/Akt-dependent signaling mechanisms [140]. In addition, curcumin activated the protective Nrf-2 pathway and inhibited the stress-induced proteins (JNK and p38) [140].

2.4. Effects of curcumin on diabetic nephropathy

Diabetes mellitus is a major cause of morbidity and mortality in the United States and Europe [141] and has become the most common single cause of chronic kidney disease in the world [142]. About 40% of diabetic patients develop diabetic nephropathy, which is a microvascular complication [143,144] characterized by renal hemodynamic alterations and structural injury, in association with glomerular hyperfiltration; the latter is mainly caused by an increase of both renal plasma flow and glomerular capillary hydrostatic pressure [145,146]. The major histological changes in diabetic nephropathy occur in the glomeruli and tubules, where hypertrophy, thickening of basement membrane, and expansion of the mesangium take place, also accompanied by cell proliferation and accumulation of extracellular matrix components, that result in glomerulosclerosis, progressive nephron lost, and tubular injury [145,147]. The exact mechanisms that trigger the development of diabetic nephropathy are unknown, but various factors related to hyperglycemia have been postulated: advanced glycosylation of proteins, increased aldose reductase activity, activation of cytokines and growth factors, induction of oxidative stress, activation of protein kinase C and hexosamine pathway activation [7].

The development of effective strategies using therapeutic agents with nutraceutical and medicinal value have been of great relevance for the treatment of diabetic nephropathy. In a previous review [68], we discussed the protective curcumin role in diabetic nephropathy, due to a reduction of the inflammatory response and the prevention of oxidative stress, by preserving antioxidant enzymes and inducing the master regulator of antioxidant response, Nrf2. Sun et al. [148] evaluated the effect of curcumin administration (100 mg/kg/12 weeks) on diabetic nephropathy in a model of streptozotocin-induced diabetes, showing that curcumin ameliorates the progression of renal disease. Diabetic animals receiving curcumin showed lower 24-hour urine protein values, decreased structural changes in kidney, and increased creatinine clearance. In addition, the inflammatory response in the curcumin-treated animals was attenuated, by reducing renal macrophages infiltration and the expression of monocyte chemoattractant protein-1, IL-1β, IL-6, and TNF-α [148]. The nephroprotective effect during curcumin treatment was attributed to an anti-inflammatory mechanism through the decrease in caveolin-1 phosphorylation at Tyr^{14}, suppressing the activation of toll-like receptor 4 [148]. In another study, this group reported that functional connections between caveolin-1 phosphorylation and reactive oxygen species (ROS) can be regulated by curcumin; therefore, high glucose-induced podocyte apoptosis was mitigated *in vitro* and in rats with diabetic nephropathy [149].

Curcumin prevented a series of events associated with epithelial-mesenchymal transition in the NRK-52E normal rat kidney tubular epithelial cell line, including the downregulation of E-cadherin and the increased expression of α-smooth muscle actin, associated with the Nrf2-activation and subsequent heme oxygenase-1 induction [133]. Additionally, the inhibition of transforming growth factor beta 1 (TGF-β1), fibronectin [150], and collagen IV [151] were also involved in the mechanism by which curcumin protects against diabetic nephropathy.

Recently, Lu et al. [151] showed that curcumin possesses potent antifibrotic effects, by inhibiting inflammasome activity. The inflammasome is composed of the NOD-like receptor 3 protein, caspase-1, and the adaptor protein apoptosis-associated speck-like protein containing a caspase-activating recruitment domain [151].

Some curcumin derivatives have also been effective for ameliorating diabetic nephropathy. Wang et al. [152] administered the curcumin analogue C66 to diabetic mice for six months, reducing glomerulosclerosis and tubulointerstitial fibrosis. These effects might be in part mediated by inhibition of the JNK pathway; JNK is responsible for the phosphorylation of a wide diversity of proteins, with the involvement of p300/CBP-mediated histone acetylation [152] or by upregulating Nrf2 function [153]. Furthermore, the effect of J17 has also been studied, since it is a molecule with structural similarities to curcumin that, exhibited good anti-inflammatory activities and anti-fibrosis activity via suppression of p38 and Akt signaling pathway activation [154].

2.5. Effects of curcumin on diabetic cardiomyopathy

Diabetic cardiomyopathy refers to systolic or diastolic left ventricular dysfunction and is a frequent complication of diabetes mellitus [155]. Curcumin has shown to reduce several of the detrimental effects of diabetes on the heart of rats; for instance, apoptosis, fibrosis, hypertrophy, and oxidative stress [80,97,156].

The administration of 300 mg/kg/day of curcumin for 16 weeks, to rats treated with a low dose of streptozotocin, reduced fibrosis in the cardiac tissue; specifically, the deposition of type I and type III collagen [80]. The results of this experiment together with the evidence from the exposure to human cardiac fibroblasts to 30 glucose mmol/l, and subsequently exposed to curcumin, yielded information of the possible mechanism of action: curcumin was able to inhibit TGF-β1 and then its downstream Smad-dependent and independent pathways, which activate myofibroblasts, increase the production of extracellular matrix and decreases its degradation [157].

In the study of Yu et al. [97] primary cultures of neonatal cardiomyocytes were exposed to the same glucose concentration (30 mmol/l), producing ROS and apoptosis that were prevented by curcumin. Because NADPH oxidase is directly involved in cardiomyocyte remodeling [158], they studied two molecules that are known to regulate it and whose phosphorylation was induced by curcumin, Akt and GSK-3β From this work, the authors proposed another mechanism for the cardioprotective effect of curcumin: the inhibition of the NADPH-induced oxidative stress would be mediated by a PI3K/Akt/GSK-3β signaling pathway [97]. A similar conclusion had been reached from a previous study *in vivo* [98].

Under hyperglycemic conditions, myocyte hypertrophy is also observed [159]; curcumin seems to counteract this feature *in vitro* by reverting the reduced expression of PPARγ, Akt, and endothelial nitric oxide synthase (eNOS), therefore restoring nitric oxide concentration and protecting the cells from morphological and functional changes produced by a high glucose concentration [156].

Streptozotocin also produces increased weight and oxidative stress in the heart of rats; this damage was reverted by the

administration of 200 mg/kg/day during six weeks [160]. Curcumin restored the activity of some antioxidant enzymes, such as catalase, SOD1, and glutathione-S-transferase, as well as glutathione levels. In addition, the streptozotocin-induced increase of lactate dehydrogenase activity, a marker of heart damage, was ameliorated by curcumin [160].

3. Curcumin as an antihyperglycemic agent: evidence from clinical studies

As described before, the use of curcumin in *in vitro* and in animal models of diabetes seems to have revealed an amazing variety of potential mechanisms of action to treat diabetes mellitus, which in recent years has led to several attempts to reach the same results in humans; however, as discussed below, the results in clinical trials have been inconsistent to a certain degree.

Na et al. [161] administered curcumin at a dose of 300 mg/day to overweight/obese type 2 diabetic patients, and they found that the treatment reduced body mass index (BMI), fasting blood glucose, glycosylated hemoglobin, insulin resistance index (HOMA-IR), and free fatty acids. It is worth mentioning that the decrease in glucose was only 18% and that of glycosylated hemoglobin was 11% compared to baseline within the group. The same group later found that the reduction in free fatty acid levels could be due to curcumin diminishes adipocyte-fatty acid binding protein (A-FABP) [162], an adipokine secreted from adipocytes [163] and other tissues that coordinate lipid-mediated processes [164].

A randomized double-blind placebo-control add-on clinical trial by Rahimi et al. [165] also showed that curcumin, administered orally (in nanomicelles) for three months, improved the lipid profile and decreased fasting blood glucose, glycosylated hemoglobin, and BMI. The authors of this study pointed out that "all other necessary medications were given to subjects" (add-on therapy), without specifying the kind of drug they used; therefore, it is not possible to know the influence of that medication on curcumin pharmacokinetics or on the observed effects. Oppositely, at a dose of 500 mg/day for 15 or 30 days, curcumin did not produce glucose-lowering effects neither changes in lipid profile in patients that were also under treatment with one or more of the following drugs: insulin, metformin, rosiglitazone, glibenclamide, gliclazide, acarbose or aspirin; except for the diminished concentration of LDL-cholesterol [166]. The possibilities in this last case could be: a) effects on lipid profile were not so evident because the dose in this study was smaller than that used in other studies where improvement of lipid profile was observed; for instance, the one by Panahi et al. [86], b) curcumin was not protected against degradation as in the study by Rahimi [165] or c) curcumin effects are negligible compared with the antidiabetic drugs that patients were taking.

As mentioned in section 2.3, diabetic nephropathy represents one of the most severe complications of diabetes mellitus. The nephroprotective effect of curcumin has also been tested in humans. Yang et al. [166] found that curcumin improved renal function as showed by the reduction of BUN (blood ureic nitrogen) and urinary microalbumin. The nephroprotective effect of curcumin was attributed to the activation of the Nrf2 anti-oxidative system, which was observed in lymphocytes of the curcumin-treated patients with type 2 diabetes mellitus; this mechanism had also been observed in animal models of diabetes [132]. Results regarding this nephroprotective effect are equally contradictory, as in another randomized double-blind placebo-controlled clinical trial in patients with diabetic or nondiabetic proteinuric chronic kidney disease, curcumin (320 mg/day for eight weeks) did not improve proteinuria, estimated glomerular filtration rate, nor Nrf2 activation [167]. In other study, patients received a dose equivalent to 66.3 mg of curcumin/day (administered in capsules containing 500 mg of turmeric) for two months, without any change in their medication [168]. Although glucose and lipid profile did not change significantly, serum TGF-β and urinary IL-8 decreased; both TGF-β and IL-8 are associated with the pathophysiological mechanisms leading to diabetic kidney disease [168]. The fact that a low content of curcuminoids was present in the administered capsules and a pharmacological effect was observed, may be a sign of certain relevance of the other compounds in turmeric, as pointed out by several authors [169–171].

In another randomized double-blind placebo-controlled study, curcuminoids (1000 mg/day) mixed with piperine were administered to type 2 diabetes mellitus patients, but no influence on glucose and glycosylated hemoglobin levels were found after twelve weeks of treatment [61]; they observed that curcumin administration reduced malondialdehyde levels and increased total antioxidant capacity and SOD1 activity [61]. In another paper, the same research group [86] reported that curcumin treatment improved the lipid profile of patients, displaying increased levels of HDL-cholesterol and reduced levels of Lp (a). Importantly, Lp (a) is a plasma lipoprotein consisting of apolipoprotein(a) covalently bound to apolipoprotein B-100, which has been associated with increased cardiovascular risk and, given the scarcity of pharmacological alternatives to reduce its levels [86,172], curcuminoids could represent a plausible option to ameliorate the complications associated with increased levels of Lp (a) in diabetes mellitus.

One of the largest randomized, double-blinded, placebo-controlled trials with curcumin, in terms of duration (9 months of treatment) and sample size (n = 240) was that of Chuengsamarn et al. [173]; although in this case, curcumin was used with preventive purposes in a pre-diabetic population. Unlike other studies, the interference of other medications frequently prescribed for diabetes mellitus was avoided. Interestingly, none of the participants in the curcumin-treated group (1500 mg of curcuminoids per day) developed diabetes mellitus after being treated for 9 months, while 16.4% of the people in the placebo group did [173]. Beneficial effects were observed in several parameters such as weight and waist circumference; also reduced glucose, insulin, and C-peptide concentrations; increased adiponectin levels; and lowered insulin resistance [173]. Later, this group of researchers performed another double-blinded placebo-controlled study with an ethanolic extract of curcumin, at the same previous dose, in type-2 diabetes mellitus patients [174]; the main finding of this study was a reduction in the atherogenic risk, as shown by a decreased pulse wave velocity (a surrogate marker of atherosclerosis), which was also accompanied by a series of changes in metabolic parameters, such as decreased leptin, triglyceride, uric acid concentrations, HOMA-IR, as well as lower values of visceral and total body fat [174].

Spranger et al. [175] identified increased levels of the inflammatory cytokine IL-6 as an independent predictor of incident type 2 diabetes in a European population. In this regard, a recent meta-analysis concluded that curcumin supplementation could be useful to lower circulating IL-6 levels; in the specific case of diabetes, two randomized, placebo-controlled studies in individuals with type 2 diabetes, found that curcumin lowers circulating IL-6 and TNF-α [162,176].

One of the main concerns regarding the potential of curcumin/curcuminoids as therapeutic agents has been the likelihood of reaching its target. In a recent paper, the medicinal properties of curcuminoids have been questioned, mainly because of its poor stability and pharmacokinetic properties [177]. Indeed, curcumin is poorly absorbed and easily degraded; thus, it has low bioavailability [86,178]. That is the reason why different approaches have been tried to increase curcumin bioavailability; for instance, co-administration with piperine [61,86], nanomicelles containing

curcumin [165], and phytosomes (a lecithin formulation) [179]. This lecithinized curcumin delivery system was tested in patients with diabetes mellitus suffering from microangiopathy and retinopathy at a dose equivalent to 200 mg/day and preserving the original medication; the authors found positive microcirculatory effects [180].

Another concern is the efficacy of curcumin because the inconsistency of its glucose-lowering effects when tested in double-blind placebo-controlled trials, and the number of publications suggesting that curcumin can exert a beneficial effect in a wide variety of diseases [177]. The possibility that curcumin has a lot of therapeutic effects has been attributed to its inhibitory effect on GSK-3β, which regulates the activity of many factors upstream and downstream and is involved in the pathophysiology of many diseases, such as diabetes mellitus, cancer, malaria and Alzheimer disease [20,88] but, according to Nelson et al. [177], the stability of curcumin should be carefully revised before considering the GSK-3β activity assays (and other assays too) as a solid evidence of the therapeutic effects of curcumin.

Once again, although the hypoglycemic properties of curcumin are not a constant along all the studies, the hypolipidemic effects seem to be more consistent, except when very low doses were used. In addition to the fact that a dose of curcumin has not been established, different formulations have been used in the existing studies, probably affecting the observed outcomes. A summary of the clinical studies of curcumin in diabetes is given in Table 1.

4. Interactions between curcumin and antidiabetic drugs

The increased use of combined natural products and conventional drug rises the need of knowing their possible pharmacological interactions. This field has been little explored for curcumin and the few existing studies about its pharmacological interactions with conventional antidiabetic drugs are mainly with sulfonylureas [181,182]. Experiments *in vitro* show that curcuminoids are able to inhibit the activity of a variety of cytochromes such as CYP1A2, CYP1B1, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP2E1, and CYP3A4; it also increased the activity or CYP1A1 (see Ref. [183] for a detailed review on this topic). In addition, clinical studies have shown that curcumin inhibits CYP1A2 and induces CYP2A6 [183]. These actions on cytochromes highlight the potential of pharmacological interactions between curcuminoids and conventional drugs that are metabolized by them; for instance, tolbutamide, glibenclamide, glimepiride, gliclazide, glipizide, and gliquidone are antidiabetic drugs that are metabolized by CYP2C9; glibenclamide is also metabolized by CYP3A4 [44].

Table 1
Summary of clinical trials of curcumin in diabetes mellitus.

Type of study	Characteristics of patients (n)	Curcumin or curcuminoids/dose/time of treatment	Hypoglycemic effect (% of decrease in fasting blood glucose)	Main findings	Reference
Randomized, double-blinded, and placebo-controlled clinical trial	Type 2-diabetes (n = 106 placebo group, n = 107 curcuminoid group)	Ethanolic curcuminoid extract/1500 mg of curcuminoids/day/6 months	Significant (we did not access the supplementary material)	Improvement of related atherogenic risk parameters (e.g. pulse wave velocity), ↑ serum adiponectin, ↓ leptin, ↓ HOMA index, improved lipid profile, ↓ visceral and total fat.	[174]
Randomized, double-blinded, and placebo-controlled trial	Type 2-diabetes, 18–65 years old (n = 118)	Capsule containing 5 mg of piperine + 500 mg of curcuminoid powder/12 weeks	No significant difference	Improvement of all the components of lipid profile, except for LDL-C and triglycerides, ↓Lp(a).	[86]
Randomized, double-blinded, and placebo-controlled trial	Overweight/obese type 2 diabetic patients (n = 50 placebo n = 50 curcuminoids)	Curcuminoids/300 mg/day/3 months	Significant difference (15%)	↓ Fasting blood glucose and glycosylated hemoglobin, ↓ HOMA index, ↓total fatty acids, ↓ triglycerides, ↑ lipoprotein lipase activity	[161]
Randomized, double-blinded placebo-control add-on clinical trial	Type-2 diabetic patients, with conventional antidiabetic therapy (n = 35 nanocurcumin group, n = 35 placebo group)	Curcumin nano-micelle/80 mg/day/3 months	Significant difference (11%)	↓fasting blood glucose and glycosylated hemoglobin, improved lipid profile,	[165]
Non controlled before and after study	Patients with type 2 diabetes and diabetic kidney disease, some of them taking conventional medication	Commercial turmeric formulation/500 mg/day/15–30 days	No significant difference	Activation of the Nrf2 system ↓ urinary microalbumin excretion ↑ antioxidant enzymes ↓ LDL-cholesterol	[166]
Pilot study (placebo-controlled study)	Patients with diabetic proteinuric chronic kidney disease (n = 23 placebo, n = 28 curcumin) There was another group with nondiabetic proteinuric chronic kidney disease.	Commercial turmeric formulation (80 mg curcumin/g)/320 mg of curcumin/day/8 weeks	No significant difference	Enhancement of the antioxidant capacity of plasma, No improvement of lipid profile, No activation of Nfr2 nor effect on activity of antioxidant enzymes.	[167]
Randomized, double-blinded, and placebo-controlled trial	Patients with overt type 2 diabetic nephropathy, normal kidney function, taking ACE-I and/or angiotensin receptor blockers (n = 20 placebo, n = 20 curcumin)	Encapsulated powdered turmeric rhizomes/1500 mg turmeric (66.3 mg of curcumin)/day/2 months	No significant difference	↑TGF-β and IL-8 in serum, ↓ IL-8 and protein excretion in urine. No significant changes in lipid profile.	[168]
Randomized, double-blinded, and placebo-controlled trial	Individuals with prediabetes (n = 240)	Curcuminoid capsules/1500 mg of curcuminoids/day/9 months.	Significant difference (17%)	Prevention of incident cases of type 2 diabetes, ↓ glucose, ↓glycosylated hemoglobin, ↓HOMA index, ↓ adiponectin, ↓ C-peptide.	[173]

HOMA, homeostatic model assessment; LDL, low-density lipoprotein; Nrf2, nuclear factor E2-related factor 2; TGF-β, transforming growth factor beta.

Regarding the influence of curcumin on drug transporters, it inhibits the OATP (organic anion transporting polypeptide) 1B1, and OATP1B3 in human embryonic kidney 293 (HEK293) cells [184] with the potential of increasing systemic exposure and reducing the clearance of drugs using these transporters. The OATPs are influx transporters expressed on the basolateral membrane of hepatocytes [185]. Among the antidiabetic drugs, repaglinide and nateglinide are transported by OATP1B1 [185]; the last one is also transported by OATP1B3 [186]. This interaction could also be relevant for patients taking curcumin along with other antidiabetic drugs, such as pioglitazone, rosiglitazone, and repaglinide, which inhibit OATP1B1 and OATP1B3 -mediated transport of statins [187,188], given that statins are frequently prescribed for dyslipidemia in diabetes [189].

A study performed in rats [182] showed that curcumin increased the half-life, mean residence time, and the apparent volume of distribution at steady state of glibenclamide; the authors suggested that such effects could be due to decreased metabolism of the drug mediated by the inhibition of intestinal and hepatic CYP3A4 [182]. A similar trend was observed for these parameters in patients with type 2 diabetes mellitus [181], but statistical significance was not reached; however, increased bioavailability of glibenclamide was observed as a consequence of curcumin co-administration [181]. The bioavailability of glibenclamide can be affected by a permeability glycoprotein (P-gp)-mediated efflux mechanism [181]. P-gp is a protein that expels xenobiotics from the intracellular space [190] and whose activity and expression is inhibited by curcuminoids in human cell cultures [191–193]. In addition to the increase in glibenclamide levels and the improvement in glycemia in type 2 diabetes mellitus patients, the combination of this drug with curcumin seems to bring the additional benefit of a better lipid profile [181].

Another sulfonylurea whose interactions with curcumin have studied is gliclazide [194,195]. In a multiple dose scheme of treatment, curcumin and gliclazide displayed an additive reduction of glucose levels in both normal and diabetic rats and no pharmacokinetic interaction was observed in rabbits [195].

It is needed; not only for diabetic patients but for patients in general, that they inform their physician about the natural products they are taking with their conventional treatment, to evaluate the risks and benefits of such combinations.

5. Conclusion and future perspectives

The evidence in relation to the hypoglycemic effect of curcumin is not very consistent; however, curcumin has the potential of improving the metabolic profile of patients with diabetes mellitus, mainly with regard to lipid levels, and reducing the associated complications. In addition, curcumin could have interesting interactions with conventional antidiabetic drugs that can positively affect diabetes treatment. Therefore, the use of curcumin as a coadjutant for diabetes mellitus therapy is a topic that merits to be considered. Also, the biological activity of other compounds in turmeric deserves to be well characterized, because those compounds could also be crucial for the therapeutic effects of *Curcuma longa*.

Finally, considering those clinical trials on curcumin antidiabetic properties are no conclusive and many issues regarding its bioavailability need to be resolved, some questions emerge: despite its pharmacokinetic issues, is curcumin able to produce pharmacological effects at tiny concentrations? Is there a point of convergence for diabetes mellitus and other diseases in which curcumin has been reported to exert a beneficial effect? And if this is true, is that point of convergence a target for curcumin? A plausible candidate is GSK-3β, as it is linked to diabetes, neurodegeneration, cancer and other pathologies; however, it is necessary to improve the lab biological assays related to this molecule to solidly affirm that it represents a good target for curcumin.

Conflicts of interest

The authors of this manuscript declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jnim.2018.05.001.

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