NF-κB pathway as a molecular target for curcumin in diabetes mellitus treatment: Focusing on oxidative stress and inflammation

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Abstract

Diabetes mellitus (DM), a chronic metabolic disorder associated with hyperglycemia and other complications, is one of the five priority non communicable diseases of global interest with unprecedented rise in developing countries. Whereas, the current treatment with insulin and oral hypoglycemic agents is aimed at managing the hyperglycemia and associated complications, there is need to explore other critical pathways in the pathogenesis of DM that can act as potential drug targets with better treatment outcomes. This study comprehensively explains the role of cellular and molecular elements, like hyperglycemia-induced oxidative stress, endothelial dysfunction, and Nuclear Factor Kappa B (NF-κB)'s involvement in inflammation and immune regulation, in the onset of DM. With bioactive compounds from natural products gaining popularity as novel drug molecules due to their diverse pharmacological actions, the study also extensively explores the prospective therapeutic benefits of curcumin (CUR), a bioactive compound known for its antioxidant, anti-inflammatory, and hypoglycemic properties, in addressing diabetic complications, predominantly via the modulation of the NF-κB pathway. The findings reveal that CUR administration effectively lowered blood glucose elevation, reinstated diminished serum insulin levels, and enhanced body weight in Streptozotocin -induced diabetic rats. CUR exerts its beneficial effects in management of diabetic complications through regulation of signaling pathways, such as CaMKII, PPAR-γ, NF-κB, and TGF-β1. Moreover, CUR reversed the heightened expression of inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines like MCP-1 in diabetic specimens, vindicating its anti-inflammatory potency in counteracting hyperglycemia-induced alterations. CUR diminishes oxidative stress, avert structural kidney damage linked to diabetic nephropathy, and suppress NF-κB activity. Furthermore, CUR exhibited a protective effect against diabetic cardiomyopathy, lung injury, and diabetic gastroparesis. Conclusively, the study posits that CUR could potentially offer therapeutic benefits in relieving diabetic complications through its influence on the NF-κB pathway.

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Abstract

Diabetes mellitus (DM), a chronic metabolic disorder associated with hyperglycemia and other complications, is one of the five priority non communicable diseases of global interest with unprecedented rise in developing countries. Whereas, the current treatment with insulin and oral hypoglycemic agents is aimed at managing the hyperglycemia and associated complications, there is need to explore other critical pathways in the pathogenesis of DM that can act as potential drug targets with better treatment outcomes. This study comprehensively explains the role of cellular and molecular elements, like hyperglycemia-induced oxidative stress, endothelial dysfunction, and Nuclear Factor Kappa B (NF-ϰB)'s involvement in inflammation and immune regulation, in the onset of DM. With bioactive compounds from natural products gaining popularity as novel drug molecules due to their diverse pharmacological actions, the study also extensively explores the prospective therapeutic benefits of curcumin (CUR), a bioactive compound known for its antioxidant, anti-inflammatory, and hypoglycemic properties, in addressing diabetic complications, predominantly via the modulation of the NF-ϰB pathway.

The findings reveal that CUR administration effectively lowered blood glucose elevation, reinstated diminished serum insulin levels, and enhanced body weight in Streptozotocin -induced diabetic rats. CUR exerts its beneficial effects in management of diabetic complications through regulation of signaling pathways, such

as CaMKII, PPAR-γ, NF-ϰB, and TGF-β1. Moreover, CUR reversed the heightened expression of inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines like MCP-1 in diabetic specimens, vindicating its anti-inflammatory potency in counteracting hyperglycemia-induced alterations. CUR diminishes oxidative stress, avert structural kidney damage linked to diabetic nephropathy, and suppress NF-ϰB activity. Furthermore, CUR exhibited a protective effect against diabetic cardiomyopathy, lung injury, and diabetic gastroparesis. Conclusively, the study posits that CUR could potentially offer therapeutic benefits in relieving diabetic complications through its influence on the NF-ϰB pathway.

Keywords: Curcumin; Diabetes mellitus; NF-ϰB pathway; Antioxidant, Anti-inflammatory

Significance statement:

This study explores the role of cellular and molecular elements, such as hyperglycemia-induced oxidative stress, endothelial dysfunction, and the involvement of the NF-ϰB pathway in inflammation and immune regulation in the onset of diabetes mellitus (DM).

It extensively investigates the potential therapeutic benefits of curcumin (CUR), a bioactive compound known for its antioxidant, anti-inflammatory, and hypoglycemic properties, in addressing diabetic complications, predominantly via the modulation of the NF-ϰB pathway.

The study highlights the importance of the NF-ϰB pathway as a molecular target for CUR in the treatment of diabetes mellitus, focusing on oxidative stress and inflammation.

Abbreviations:

COX-2: Cyclooxygenase-2

TNF-α: Tumor necrosis factor α

IRS1: Insulin receptor substrate 1

GLUT2: Glucose transporter 2

GLUT4: Glucose transporter 4

STAT: Signal transducer and activator of transcription

MMP-3: Matrix metalloproteinase-3

MMP-9: matrix metalloproteinase-9

IL-1: Interleukin-1

IL-6: Interleukin-6

IL-8: Interleukin-8

IL-12: Interleukin-12

LPS: Lipopolysaccharides

IkB: Inhibitor of nuclear factor kappa B

CYLD: Cylindromatosis

CD40: Cluster of differentiation 40

RANK: Receptor activator of nuclear factor kappa B

BAFF: B-cell activating factor

CaMKII: Calcium–calmodulin (CaM)-dependent protein kinase II

PPAR-γ: Peroxisome proliferator-activated receptor gamma

TGF-β1: Transforming growth factor beta 1

TXA2: Thromboxane A2

PGI2: Prostacyclin

NO: Nitric oxide

PGE2: Prostaglandin E2

iNOS: Inducible nitric oxide synthase

MDA: Malondialdehyde

MPO: Myeloperoxidase

SOD: Superoxide dismutase

GSH: Glutathione

JNK: c-Jun N-terminal kinase

ERK1: Extracellular signal-regulated kinase 1

p38MAPK: p38 mitogen-activated protein kinases are a class of mitogen-activated protein kinase

AMPK: AMP-activated protein kinase

MCP-1: Monocyte chemoattractant protein-1

ICAM-1: Intercellular adhesion molecule 1

NADPH: Nicotinamide adenine dinucleotide phosphate

eNOS: Endothelial nitric oxide synthase

PKCβ: Protein kinase C β

MPTP: Mitochondrial permeability transition pore

FOXO-3a: Forkhead box O3

DOP mouse: Diabetic osteoporosis mouse

SCF: Stem cell factor

ICCs: Interstitial cells of Cajal

OS: Oxidative stress

ROS: Reactive oxygen species

1. Introduction

Diabetes mellitus (DM), a widespread chronic metabolic anomaly, manifests through heightened blood sugar levels (hyperglycemia) accompanied by symptoms including, excessive urination (polyuria), intensified thirst (polydipsia) and pronounced hunger (polyphagia) [1]. The worldwide incidence of DM is surging swiftly, positioning it as a leading metabolic disturbance globally [2]. The World Health Organization predicts that diabetes will ascend to the seventh predominant cause of mortality by 2030 [3]. DM presents in four principal forms. Type 1 diabetes mellitus (T1DM) originates as an autoimmune condition, characterized by the destruction of insulin-producing β-cells in the pancreas [4]. The autoimmune origin of T1DM gains validation from the detection of autoantibodies aimed at pancreatic islet cells, their invasion by T-cells, B-cells, and macrophages, and the presence of abnormalities in cellular immunity [5]. Commonly identified during childhood, this diabetes type constitutes 5–10% of all diabetes instances [2].

Type 2 DM (T2DM) stands as the predominant form of diabetes, resulting from inadequate insulin production and / or insensitivity of insulin receptors, leading to the inability of glucose to enter the cells [6]. T2DM accounts for 90–95% of all the DM cases and mainly affects the adults and elderly [7]. T2DM is renowned for its diverse complications, ranging from additional cardiovascular issues like obesity, hypertension, and an atherogenic dyslipidemia profile typified by high levels of triglycerides and low levels of high-density lipoprotein cholesterol among others to neuropathy [7]. Gestational diabetes mellitus (GDM) manifests exclusively during gestation, affecting roughly 5–15% of gravid females, with incidence rates demonstrating variability across ethnic groups and geographical territories [8]. Monogenic diabetes, commonly misclassified as T1DM or T2DM, originates from a mutation in a singular gene or a gene conglomerate [9]. This type of DM is transmitted through an autosomal dominant fashion, affected individuals present with heterogeneous clinical manifestations, symptomatic profiles, and disease trajectories [10].

The etiology of DM on the cellular and molecular scales entails a multifaceted interaction of elements. Hyperglycemia, a hallmark of diabetes, induces increased reactive oxygen species (ROS) levels, precipitating enduring modifications in the structure and functionality of macromolecules like proteins, lipids, and nucleic acids [11]. This oxidative stress (OS) is implicated in the malfunction of endothelial cells, a prevalent condition in diabetic individuals [12]. The compromise of endothelial cells correlates with disturbances in nitric oxide (NO) synthesis, pivotal for maintaining vascular functional equilibrium [13]. The diacylglycerol (DAG)–protein kinase C (PKC) axis is a pivotal pathway implicated in the augmented generation of ROS within endothelial cells [14]. Furthermore, elevated glucose concentrations stimulate PKC, recognized for its substantial involvement in precipitating diabetic endothelial dysfunction [15]. Such activation of PKC results in the enhanced expression of nuclear factor-ϰB (NF-ϰB) and COX-2, fostering OS and modulating the synthesis of vasoconstrictive prostanoids in diabetes [16]. These Cellular and molecular pathways instigate the emergence of vascular abnormalities correlated with diabetes.

NF-ϰB, a primordial protein transcription factor, is instrumental in orchestrating innate immunity, inflammation, oncogenesis, and neural system operations [17]. NF-ϰB plays various roles in diabetes, particularly in inflammation and immune regulation [18]. This transcription factor regulates gene expression pertinent to immune and inflammatory reactions, cellular viability, and cellular adhesion [19, 20]. Heightened NF-ϰB activity is identified as a pathological element in sustained inflammation seen in autoimmune conditions, including T1DM [21]. Suppression of the NF-ϰB signaling cascade has demonstrated efficacy in mitigating cardiomyocyte hypertrophy and fibrosis associated with T1DM [22]. Additionally, NF-ϰB significantly influences the development of T2DM [23]. Research indicates that activating NF-ϰB can replicate the insulin insensitivity observed in rodents subjected to high-fat diets or obesity [24, 25]. Furthermore, pro-inflammatory cytokines such as TNF-α are linked to enhancing insulin insensitivity by the serine phosphorylation of IRS1 through NF-ϰB activation [26]. Moreover, NF-ϰB is pivotal in gene expression, including GLUT2, which is pivotal for insulin release from β cells [27]. NF-ϰB is crucial in diabetic nephropathy (DN) development. ALTamimia et al. found that NF-ϰB contributes to DN progression by triggering intrinsic cell apoptosis, marked by Bax enhancement, Bcl-2 diminution, and cytochrome-c discharge inducement. Excessive NF-ϰB activity also incites inflammation, fibrosis, and apoptosis in the renal tissues of diabetic patients [28].

Mitigating DM is essential for lessening its global burden. Growing evidence endorses the use of medicinal plant supplements for DM prevention and management, with curcumin (CUR) receiving notable attention as a promising option [29, 30]. CUR is a natural active substance present in the rhizome of the Curcuma longa plant, which is more commonly recognized as turmeric [31]. It exhibits a spectrum of therapeutic properties including antioxidative, cardiac protective, anti-inflammatory, glucose-lowering, and antiarthritic capacities, corroborated through comprehensive *in vitro* and *in vivo*experimental studies [32-34]. In animal studies, CUR extract has demonstrated the ability to postpone diabetes onset, bolster β-cell function, shield β-cells from demise, and lessen insulin resistance [35, 36].

Jiménez-Flores et al. identified curcumin's capacity to suppress NF-ϰB expression in diabetic mice's livers, highlighting its potential as an anti-inflammatory mediator in the context of diabetes contexts. This points to the therapeutic potential of NF-ϰB targeting for managing T2DM's inflammatory aspects and related

complications [30]. Furthermore, ALTamimi et al. observed that curcumin's protective impact in reversing diabetic nephropathy (DN) in rats is linked to NF-ϰB inhibition, underlining NF-ϰB's role in DN pathophysiology and its viability as a therapeutic target [28]. This study aims to scrutinize the available scientific data and synthesize compelling evidence for curcumin's potential therapeutic roles in treating diabetic complications, particularly through modulating the NF-ϰB pathway. The curcumin's effects on different types of DM, liver complications tied to diabetes, and its capability to mitigate inflammation, OS and apoptotic cellular demise in tissues affected by diabetes are fully disccussed.

2. Chemistry and pharmacokinetics of curcumin

CUR (Figure 1), a molecule with the formula $C_{21}H_{20}O_6$ and the structure ((1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-dien-3,5-dione was initially extracted from turmeric in the year 1815 [37].

Figure 1. Curcumin chemical structure [38].

As a polyphenolic compound from the diarylheptanoid class, CUR is characterized by its symmetrically substituted aromatic rings bearing methoxy groups and phenolic OH groups in the ortho position, linked via a conjugated heptadiene chain featuring an enone segment and a 1,3-diketone structure. The molecule's bioactivity stems from its functional groups: two ortho-methoxy and two hydroxyl phenolic groups, a duo of double bonds in the aliphatic chain, and the 1,3-keto–enol structure [39].

CUR maintains stability under heat (<120 °C) and within a pH range of 2.5–6.5, transitioning from yellow in acidic conditions to reddish-brown in alkaline settings. It dissolves well in ethanol, acetone, methanol, and oils, yet exhibits minimal water solubility [40]. Its low bioavailability at 12 g/day in humans is owing to limited intestinal uptake, accelerated hepatic metabolism, and rapid systemic elimination [41]. Predominantly excreted unmetabolized in feces, a minor absorbed fraction undergoes metabolic transformations[42].

Metabolism starts with reductase-driven reduction within enterocytes and hepatocytes, resulting in the synthesis of dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin [42]. This process is catalyzed by enzymes such as the NADPH-dependent reductase and alcohol dehydrogenase, inclusive of a certain unidentified microsomal enzyme [43]. Hassaninasab's team identified the curcumin-reducing enzyme in *Escherichia coli,* noting a two-stage reduction to tetrahydrocurcumin via an intermediate, dihydrocurcumin, facilitated by NADPH [44]. *In vivo* and *in vitro* , CUR, along with its metabolites, easily form conjugates with glucuronic acid and sulfate [45, 46]. Glucuronidation and sulfation, primarily in the hepatic and intestinal regions of both rodents and humans, involve glucuronyl transferase and sulfotransferase, respectively, producing glucuronide and sulfate conjugates detectable in human plasma post-oral administration[42]. Human phenol sulfotransferase (SULT1A1, SULT1A3) and uridine diphosphate-glucuronosyltransferase (UGT) facilitate these processes [47].

However, curcumin's reduction or conjugation generates derivatives with less COX-2 suppression than CUR itself [48]. Tetrahydrocurcumin, hexahydrocurcumin, and CUR sulfate exhibit decreased prostaglandin E2 inhibition, with hexahydrocurcuminol showing no inhibition [49]. Except for tetrahydrocurcumin, these metabolites' biological activities are significantly reduced compared to CUR [50, 51].

Curcumin's limited solubility and absorption, coupled with its rapid conversion to inactive metabolites in the gastrointestinal tract, hinder its effectiveness as a health aid and dietary supplement. To counteract this, recent studies have adopted various nanoformulation strategies to boost curcumin's efficacy. These include employing adjuvants, stabilizers, conjugates/polymer conjugates, lipids/liposomes, and nano-sized hydrogels, microgels, and nanoparticles [52, 53].

3. Pharmacological actions of curcumin

CUR has shown potency against numerous chronic conditions like Alzheimer's disease, T2DM, rheumatoid arthritis, and metabolic syndrome [54-57]. It possesses a broad spectrum of therapeutic properties, including antineoplastic, antimicrobial, anti-carcinogenic, anti-mutagenic, anti-aging, anti-inflammatory, antiproliferative, anti-amyloid, and anti-hypercholesterolemic effects [58, 59]. Mechanistically, CUR inhibits the

initiation of the radical-sensitive transcription factor NF-κB, reduces cytokine production, and impedes vital cellular survival processes [60]. It also inhibits STAT proteins and NF-κB-DNA binding, diminishing the expression of pro-inflammatory molecules MMP-9, MMP-3, and cytokines like TNF-α, IL-1, and IL-8. Furthermore, CUR attaches to the COX-2 protein, curtailing COX-2 expression and the synthesis of prostaglandins and thromboxanes [61].

Clinical trials have consistently affirmed curcumin's assurance, acceptability, and effectiveness in addressing diverse chronic disorders in humans. These trials reported no toxicity when CUR was given by mouth at a daily dose of 6 g for a duration of 4 to 7 weeks [62-64]. Specific studies, like that of Greil et al., determined the maximum safe dosage of liposomal CUR (Lipocurc) for cancer treatment to be 300 mg/m^2 [65]. Saghatelyan et al.'s research on the combined intravenous infusion of CUR and paclitaxel in individuals with progressive breast cancer demonstrated no significant adverse effects or deterioration in life quality after a 12-week regimen [66].

4. Overview of NF-kB

NF-κB, identified in 1986 by David Baltimore's team, is a nuclear factor in B cells binding the kappa light chain immunoglobulin enhancer[67, 68]. In its dormant state, NF-κB is located in the cytoplasm, it becomes active and moves to the nucleus to initiate the transcription of more than 400 genes vital for immunity, growth, apoptosis, and inflammation [68-70]. It modulates a spectrum of crucial genes, encompassing chemokines and pro-inflammatory cytokines, both positively and negatively. Potent activators like IL-1β and TNF-α induce NF-κB, which also tempers inflammation, thereby regulating its own activity [68, 71-73].

NF-κB activation occurs via canonical or alternative pathways [74]. The principal route, crucial for inherent immunity, inflammation, and programmed cell death prevention, is stimulated by factors like TNF-α, IL-1, and LPS [75]. Within this pathway, NF-κB, primarily a p50 and RelA heterodimer, is held inactive within the cytoplasm by ankyrin repeat-containing inhibitors interacting with NF-κB's Rel homology domains, with IkBα being the most common [68, 69, 76]. Activation involves specific IkB kinase (IKK) triggering, resulting in the phosphorylation, polyubiquitination, and ensuing proteasomal breakdown of IkB proteins. This reveals a nuclear positioning indicator, permitting the NF-κB heterodimer to access the nucleus and initiate transcription of target genes [68, 69, 77]. Conversely, the alternative pathway, vital for B-cell maturation, secondary lymphoid organ formation, and high-affinity antibody production, is initiated by NF-κB-inducing kinase (NIK) [75, 78]. NIK phosphorylates IKKa, which subsequently phosphorylates preexisting p100/NF-κB2:RelB heterodimers. This action converts inhibitory p100/NF-κB2 into p52, allowing the active p52:RelB complexes to enter the nucleus and stimulate target genes [68, 79].

In normal conditions, mechanisms exist to regulate NF-κB overactivation, ensuring controlled NF-κB nuclear presence. IkBα, possessing a nuclear export sequence, can bind NF-κB and escort it out of the nucleus. Additionally, proinflammatory signals trigger deubiquitinating enzymes like CYLD, A20, and Cezanne, which inhibit IKK activation by removing polyubiquitin chains from IkBα. This stabilizes newly synthesized IkBα, thus curtailing further NF-κB activation [68, 80].

Figure 2. Illustrates the NF-κB signaling cascade, delineating the canonical pathway on the left and the alternative pathway on the right, with respective agonists listed.

Figure 2. In the canonical pathway, the NF-κB heterodimer, typically consisting of p50 and RelA subunits, plays a pivotal role in innate immunity, inflammation, and apoptosis prevention. Residing in the cytoplasm, this heterodimer is inactivated by an inhibitory molecule, commonly IkBα. Activation occurs when a specific IkB kinase (IKK) phosphorylates two conserved serine residues on the N-terminal domains of IkB proteins, leading to their polyubiquitination and proteasomal degradation. This reveals a nuclear localization signal, permitting NF-κB's migration into the nucleus to trigger target gene transcription. In the alternative pathway, NF-kB-inducing kinase phosphorylates inhibitory IKKa, which in turn phosphorylates preexisting p100/NF-kB2:RelB heterodimers. This process triggers the processing of inhibitory p100/NF-kB2 to p52. The active p52:RelB complexes can then translocate and activate downstream target genes. This pathway is crucial for appropriate B-cell maturation, formation of lymphoid organs, and the production of high-affinity

antibodies. The response element (RE) serves as a binding site for active NF-kB.

5. Effects of curcumin on T1DM and T2DM: Focus on NF-κB pathway

T1DM, primarily identified in children and young adults, is characterized by the body's inability to synthesize and secrete insulin, necessitating lifelong insulin treatment [81, 82]. Streptozotocin (STZ) is a preferred agent to induce experimental T1DM in animals [83], as it selectively destroys insulin-generating beta cells in the pancreas, mimicking T1DM characteristics [4, 84]. Curcumin's beneficial impact on hyperglycemia in STZ-induced diabetic rats is widely reported, yet its underlying mechanisms require further exploration [85]. It's hypothesized that curcumin's cholesterol-lowering, antioxidant properties, and its ability to elevate plasma insulin levels contribute to its potential in managing metabolic syndrome, obesity, and diabetes-related issues [86-88].

Diabetic cardiomyopathy (DCM), a grave complication of diabetes, notably in T1DM, [89] involves heart structure and function alterations, leading to compromised cardiac performance [90]. Despite being a major mortality cause in diabetic patients, DCM lacks specific treatments due to its complex pathogenesis [91]. It's occurrence in T1DM patients is characterized by disrupted lipid metabolism, increased cardiac injury markers, and escalated OS [89]. JM-2, a CUR derivative, exhibited therapeutic benefit in combating DCM in mouse models of STZ-induced T1DM and diet-induced T2DM [92]. Wang et al. reported that JM-2 combats cardiac functional and structural deficits in both T1DM and T2DM models. JM-2 administration curtailed cardiac dysfunction, inflammation, fibrosis, and inhibited the NF-κB pathway in diabetic mouse hearts. Particularly, JM-2 eradicated STZ-induced cardiac issues in T1DM mice, forestalled heart fibrosis in T2DM mice, and mitigated hypertrophy and fibrosis in high glucose-exposed cardiac cells, owing to its NF-κB-mediated anti-inflammatory action [92]. These insights bolster the therapeutic potential of JM-2 for DCM and accentuate the necessity of novel drug development for this condition, positioning JM-2 as a promising candidate for DCM treatment.

CaMKII, a serine/threonine kinase, is pivotal in cardiac pathologies like DCM, regulating cardiac hypertrophy genes, amplifying pro-inflammatory signaling, elevating inflammatory cytokine expression, and modulating cardiac fibroblast growth and collagen production [93, 94]. Its heightened activity in diabetic hearts contributes to pathological cardiac remodeling [95]. PPAR-γ, a nuclear hormone receptor, is instrumental in controlling lipid and glucose metabolism genes [96]. Clinically utilized for T2DM treatment, its activation can ameliorate cardiovascular disorders including DCM, by optimizing myocardial lipid profiles, mitigating endoplasmic reticulum stress, curbing inflammation, and diminishing ROS [97]. PPAR-γ also suppresses myocardial pro-inflammatory markers like NF-κB and TGF-β1 [97, 98]. TGF-β1, a multifunctional cytokine, plays a crucial role in cellular proliferation, differentiation, and immune regulation [99]. It significantly influences myocardial fibrosis in DCM by regulating fibroblast function and extracellular matrix accumulation [100]. Additionally, its link to OS and inflammation highlights its involvement in the onset of cardiac fibrosis [98, 101].

A research conducted by Gbr et al. investigated the cardioprotective attributes of pioglitazone (a PPAR-γ agonist) and CUR in DCM within a T1DM rat model. The findings indicated notable reductions in heart weight, blood glucose levels, lipid and cardiac injury markers, OS, and fibrosis following pioglitazone and CUR treatment. The duo therapy notably outperformed individual treatments, with observed cardioprotective effects tied to modulations in CaMKII, PPAR-γ, NF-κB, and TGF-β1 pathways. Histological analyses corroborated the cardiac structural improvements in the treated groups, suggesting pioglitazone and curcumin's potential in mitigating DCM in T1DM via these signaling pathways [98].

COX-2, an integral enzyme in prostaglandin synthesis, plays a key role in inflammation, pain, and fever. Often upregulated by inflammatory triggers, COX-2 is linked to prostanoid production, like TXA2 and PGI2 which are crucial in vascular tone and inflammation regulation [102]. NF-κB p65, a component of the NF-κB transcription factor, is central in regulating genes pertinent to inflammation, immunity, cell proliferation, and survival. Typically bound to inhibitory proteins in the cytoplasm, it relocates to the nucleus upon activation by stress or inflammation, initiating the expression of related genes [68, 103]. Protein kinase C

(PKC) represents a family of enzymes critical in cellular functions including proliferation, differentiation, and programmed cell death [104].

Rungseesantivanon and colleagues showed that daily supplementation of CUR at 30 and 300 mg/kg notably reduced blood glucose in T1DM rats by 18.73% and 30.26%, respectively. The research also highlighted curcumin's capacity to balance the prostanoid ratio in diabetic mesenteric arteries and decrease average arterial blood pressure. Importantly, CUR therapy significantly diminished COX-2 and NF-ϰB p65 expression in the small mesenteric arterial walls of the rats. Emphasizing PKC's contribution to diabetic vascular complications, the study indicated that elevated glucose levels trigger PKC, resulting in increased ROS production and raised NF-ϰB p65 and COX-2 expressions, elements linked with OS and modified vasoconstrictor prostanoid production in diabetes. These observations endorse curcumin's potential in alleviating diabetes-induced endothelial dysfunction through its antioxidant and anti-inflammatory characteristics[16].

In another study, Zhang et al. explored impacts of CUR on diabetes-induced lung injury in rats. Their findings indicated that CUR not only Diminished blood glucose, triglycerides, and cholesterol levels in diabetic rats but also diminished lung tissue inflammation. CUR significantly decreased Pro-inflammatory mediators like TNF-α, IL-1β, and IL-6 in pulmonary structures. Furthermore, CUR lessened NO and PGE2 levels, crucial inflammatory response effectors during tissue injury, and curtailed inflammatory mediators and enzymes like iNOS and COX-2 in the pulmonary structures. The research also highlighted curcumin's role in reducing OS, evidenced by decreased MDA and MPO levels, and enhancing the antioxidant system, indicated by increased SOD and reduced GSH levels. These results underscore curcumin's potential in ameliorating diabetic lung injury through its antioxidative and counter-inflammatory responses, particularly by inhibiting the NF-ϰB pathway, thus mitigating pulmonary inflammation and OS in the STZ-diabetic rats [105].

C66, a novel derivative of curcumin, has garnered attention for its potential therapeutic properties [106]. Exhibiting anti-inflammatory effects, it curtails high glucose-provoked inflammatory reactions within both laboratory conditions and living organisms, effectively mitigating renal damage in diabetic rat models through its Counter-inflammatory effects [107]. TNF-α, a pivotal pro-inflammatory cytokine, is integral to immune regulation, inflammation, and apoptosis, primarily produced by cells like macrophages [108, 109]. Pan et al. revealed that C66 diminishes NO and TNF-α production in macrophages under high glucose conditions. Moreover, C66 suppresses mRNA transcription of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-12) and inducible enzymes (COX-2, iNOS), offering renal protection. This is evident from the amelioration of histopathological anomalies and fibrosis in diabetic kidneys, marked by decreased glycogen deposition, type IV collagen levels, serum creatinine, and kidney/body weight ratio. Additionally, C66 treatment has been found to result in the dephosphorylation of JNK and inhibition of the activation of NF-kB. This inhibition is associated with the suppression of IkBa phosphorylation and degradation, as well as the nuclear translocation of the p65 subunit of NF-kB. Notably, these therapeutic benefits of C66 manifest without altering blood glucose or body weight, underscoring its promise as a diabetic nephropathy (DN) treatment by targeting inflammation and renal damage [29].

Inflammation is pivotal in both the onset and advancement of T1DM [110]. The progression of T1DM results in the migration of inflammatory cells into pancreatic islets, which triggers the release of proinflammatory cytokines, notably TNF-α, IFN-γ, and IL-1β [111, 112]. These cytokines initiate the degradation of pancreatic β cells by activating intracellular signaling that favors apoptotic pathways [113, 114]. Excessive cytokine release activates NF-ϰB in β cells, further inducing the transcription of proinflammatory cytokines [115]. The existence of T cells that produce IFN-γ in pancreatic islets marks an early sign of T1DM [116]. Elevated levels of cytokines like IL-1β and IL-6 correlate with hampered insulin secretion, diminished β cell multiplication, and heightened cell death, underscoring the vital role of inflammation in β cell destruction and T1DM pathogenesis [117].

Rashid et al. explored the impact of CUR on diabetes-induced OS and related spleen complications. Key findings include: 1) CUR successfully reduced blood glucose, normalized serum insulin levels, and enhanced body weight in STZ-diabetic rats, 2) it countered the heightened expression of inflammatory cytokines (TNF-α,

IL-1β, IL-6) and chemokines (MCP-1), showcasing its anti-inflammatory role in ameliorating hyperglycemia-driven splenic damage, 3) CUR modulated the detrimental impacts of the NF-κB-mediated inflammatory cascade in diabetic spleen tissue, 4) it altered ER-dependent apoptotic proteins and decreased intracellular Ca2+ in the spleen, and 5) CUR significantly raised the GSH/GSSG ratio, indicating its efficacy in attenuating OS in the spleen. Overall, the study posits CUR as a promising agent against diabetes-induced OS, inflammation, and apoptosis in the spleen [118].

In a study by Badr et al., the influence of CUR on STZ-diabetic mice was assessed. Findings reported significant blood glucose reduction. The study underscored the role of NF-κB in T1DM pathogenesis, particularly in β cell dysfunction and apoptosis, driven by cytokines like IL-1β and IFN-γ. They identified phosphorylated p65 as a marker of NF-κB activation. CUR administration, with its anti-inflammatory properties, inhibited NF-κB activation and curtailed the expression of proinflammatory cytokines (TNF-α, IL-1, IL-6). These outcomes highlight NF-κB's involvement in diabetic inflammation and suggest curcumin's therapeutic potential in modulating these responses [119]. In another study, Mojtabavi et al. highlighted that CUR not only reduced blood glucose levels but also demonstrated significant analgesic properties, likely due to its influence on diminishing the expression of inflammatory genes like NF-B, IL6, and TNF-α. Notably, in neuropathy assessments, both CUR and metformin treatment groups exhibited significant improvements compared to the diabetic control group [120].

Inflammation plays a crucial role in insulin resistance, especially in obesity and T2DM contexts [121]. Elevated levels of pro-inflammatory cytokines like TNF-α and IL-6 in these states disrupt insulin signaling, particularly in liver, muscle, and adipose tissues [122]. These cytokines play a critical role in the development of insulin resistance and can impair insulin signaling pathways [122]. These cytokines impede insulin signaling molecules like IRS-1 and GLUT4, leading to reduced insulin receptor signaling and increased insulin resistance [123, 124]. Addressing this inflammatory cascade is thus crucial in managing insulin resistance-related conditions.

3T3-L1 adipocytes, derived from mouse embryonic fibroblasts, are key in adipose and obesity research due to their role in adipocyte differentiation, lipid metabolism, and inflammation studies [125, 126]. Wang et al. reported curcumin's efficacy in countering palmitate-induced insulin resistance in these cells by enhancing insulin-stimulated glucose uptake, blocking NF-B p65 nuclear translocation, and reducing MAPKs activity. The spice also reversed the pro-inflammatory state induced by palmitate, downregulating TNF-α and IL-6 expression and decreasing JNK, ERK1/2, and p38MAPK activities dose-dependently, suggesting its potential in managing obesity-related insulin resistance and inflammation [127].

AMPK, a vital enzyme in cellular energy regulation, is activated during low energy states to stimulate energy production and inhibit energy consumption, thereby managing glucose and fatty acid metabolism [128-131]. Jiménez-Flores et al. explored curcumin's impact on diabetic db/db mice livers, noting increased AMPK and PPARγ expression and reduced NF-κB protein levels post-treatment. These results point to curcumin's therapeutic promise in T2DM by modulating inflammatory pathways and metabolic dysfunctions, as evidenced by its ability to significantly lower NF-κB expression, indicating its anti-inflammatory potential in diabetic contexts. Therefore, the findings of this study support the potential of CUR as a modulator of NF-κB expression, indicating its possible role in managing the inflammatory response associated with T2DM [30].

6. Effects of Curcumin on Diabetic Nephropathy in STZ-induced Diabetic Animal Models: Focus on NF-κB Pathway

Diabetic nephropathy (DN), also termed diabetic kidney disease, is a grave complication of both type 1 and type 2 diabetes, impairing the kidneys' capacity to eliminate waste and excess fluids from the body [132]. It stems from elevated blood sugar levels and hypertension, which may harm the renal blood vessels responsible for filtering waste [133]. Prolonged DN can result into chronic kidney disease culminating in kidney failure.

Inflammation is pivotal in the onset and advancement of DN. Inflammation contributes to DN's pathology at multiple junctures, including the escalation of chemokine production, influx of inflammatory cells into

the kidney, synthesis of pro-inflammatory cytokines, and resultant tissue damage. In diabetic individuals, inflammatory markers such as chemokines (MCP-1), pro-inflammatory cytokines, and cell adhesion molecules intensify in the renal tissues. Moreover, the concentration of these cytokines and cell adhesion molecules in the serum and urine correlates with albuminuria [134]. The modulation of inflammatory signaling pathways has gained attention as a prospective therapeutic avenue for DN. Numerous investigations indicate that anti-inflammatory compounds, like CUR, may mitigate diabetic renal injury and avert kidney deterioration by curbing inflammation [134-136].

NF-kB orchestrates the expression of genes pivotal in renal disease progression, including chemokines like MCP-1. In DN, MCP-1 is instrumental in drawing monocytes/macrophages, and its elevated presence in human DN tubulointerstitial lesions implies its role in advanced DN pathogenesis. In DN, blocking NF-kB activation has emerged as a viable therapeutic approach, curtailing gene transcription and impeding the inflammatory cascade. Numerous investigations reveal that persistent suppression of NF-kB mitigates kidney damage in DN models [137-140]. MCP-1, a pivotal chemokine, orchestrates the recruitment and congregation of monocytes and macrophages in various inflammatory scenarios, DN included [141]. ICAM-1, a 90-kD membrane glycoprotein, crucially moderates interactions with immune cells and is notably elevated at inflammation sites [142].

Soetikno and colleagues demonstrated that CUR therapy mitigated DN in a T1DM rat model, achieved by curtailing macrophage penetration in the glomerulus via its anti-inflammatory properties. Furthermore, CUR hindered NF-kB activity, diminishing the release of proinflammatory and profibrotic cytokines. The study also highlighted curcumin's ability to significantly reduce blood glucose and 24-hour urinary protein, alongside mitigating weight loss and enhancing DN-related biochemical indicators like plasma creatinine, blood urea nitrogen, and creatinine clearance. Histological analysis showed CUR reduced glomerular sclerosis and macrophage presence in diabetic rat kidneys. Moreover, CUR suppressed proinflammatory proteins such as ICAM-1, TGF-β1, and MCP-1, underscoring its potential as an adjunct therapy in DN prevention [143].

Oxidative stress (OS) is central in DN pathogenesis, predominantly fueled by excessive ROS generation due to hyperglycemia, resulting in oxidative damage, inflammation, and fibrosis in the renal system [144]. Mitochondria-derived ROS are pinpointed as key catalysts in DN onset and progression [145]. Diabetic individuals face additional ROS sources, including NADPH oxidase activation and eNOS uncoupling [146]. Notably, hindering mitochondrial ROS production via antioxidant agents or transgenic antioxidant expression has shown efficacy in curbing DN and other microvascular complications [147].

The PKCβ/p66Shc pathway involves PKCβII and p66Shc [28]. Stress conditions like hyperglycemia, hydrogen peroxide (H_2O_2), and UV exposure lead to PKCβII and JNK-mediated Ser36 phosphorylation of p66Shc in the cytoplasm [148]. This phosphorylation is essential for p66Shc's mitochondrial migration, disrupting the electron transport chain, cytochrome-c release, and MPTP opening[149]. These actions trigger extensive mitochondrial ROS production and activate intrinsic cell death mechanisms [28]. The PKCβ/p66Shc axis is implicated in DN's evolution and is a prospective therapeutic target for the disorder [28]. FOXO-3a, a key transcription factor, regulates a spectrum of cellular functions, including OS resistance, apoptosis, cell cycle regulation, and metabolism [150, 151]. It belongs to the FOXO transcription factor family, recognized for regulating genes tied to cellular longevity and survival [152]. Predominantly situated in the nucleus, FOXO-3a modulates the expression of genes linked to antioxidant defense, DNA repair, and cell cycle arrest [153].

ALTamimi and colleagues underscored curcumin's renal protective role in STZ-induced diabetic rats, primarily through thwarting the PKCβ/p66Shc pathway and invigorating FOXO-3a. They observed curcumin's reversal of DN symptoms, encompassing proteinuria, glomerular and tubular deterioration, and interstitial fibrosis. CUR showcased its therapeutic prowess by mitigating OS, inflammation, and fibrosis, thus exhibiting antioxidant, anti-inflammatory, and anti-fibrotic properties. It also safeguarded mitochondrial integrity, obstructed the mitochondrial permeability transition pore, and enhanced mitochondrial function indicators. Notably, CUR impeded NF-ϰB in the renal tissues of both normal and T1DM-induced rats, markedly diminishing TNF-α and IL-6 levels, as well as NF-ϰB P65 nuclear presence and activity in T1DM

+ CUR -treated rats compared to their untreated T1DM counterparts. Further, CUR was found to inhibit cytochrome-c release and downregulate mRNA and protein expressions of collagen I/III in the renal tubules and mitochondria. These insights vindicate curcumin's potential as an efficacious therapeutic agent in DN management [28].

ECM proteins are a set of structural proteins secreted by cells, forming an intricate matrix in the extracellular space [154]. They bolster structural integrity for adjacent cells and partake in various cellular processes including adhesion, migration, differentiation, and proliferation [155, 156].

Chiu et al. observed a halt in the diabetes-prompted surge of vasoactive factors (eNOS and endothelin-1), transforming growth factor-β-1, and ECM proteins (fibronectin and extradomain-B-containing fibronectin) within the kidneys of diabetic rats treated with curcumin. These alterations correlated with escalated OS, mesangial proliferation, and heightened activity of p300 and NF-κB, all of which were subdued by CUR intervention. Furthermore, CUR was shown to diminish OS and avert structural kidney damage linked to DN. The curative impacts of CUR were primarily through the suppression of p300 and NF-κB pathways. Conclusively, the research posited CUR as a promising agent for patients grappling with chronic diabetic complications, especially for the prevention of diabetes-induced renal anomalies [157].

7. Εφφεστς οφ ῦρσυμιν ον οτηερ ςομπλιςατιονς οφ διαβετες: Φοςυς ον ΝΦ-κΒ πατηωαψ

Diabetic osteoporosis (DOP), a diabetes complication, is marked by weakened bone microarchitecture and reduced bone mineral density (BMD) due to elevated glucose levels [158]. Individuals with DOP are significantly more susceptible to fractures, leading to increased disability and mortality [159]. The disorder is linked to hampered bone regeneration and remodeling, along with reduced osteogenic differentiation and angiogenesis capabilities of bone marrow mesenchymal stem cells (BMSCs) [160]. Restoring the compromised osteogenesis and angiogenesis functions of BMSCs is pivotal for treating DOP [161]. Both types 1 and 2 diabetes are associated with an increased risk of osteoporosis and fractures [162]. BMSCs are adult stem cells located in the bone marrow, capable of transforming into various cell types, including osteoblasts (bone-forming cells), chondrocytes (cartilage-forming cells), and adipocytes (fat-storing cells)[163]. NF-κB, a transcription factor, regulates genes involved in inflammation, bone resorption, and bone formation [164]. Inhibiting NF-κB activation has shown promise in enhancing bone formation and alleviating osteopenia in osteoporosis animal models [165]. NF-κB activation is known to exert an anti-anabolic effect on bone formation, suggesting that NF-κB inhibitors might serve as anabolic agents in bone health [166]. Fan et al. noted that CUR might reverse the hindered osteogenic differentiation and proangiogenic capability of BMSCs in hyperglycemic environments. Their studies reveal that CUR fosters bone reconstruction and vascular development in a DOP mouse framework, highlighting its therapeutic potential for diabetic osteoporosis. The research also suggests CUR enhances BMSC-driven bone formation and angiogenesis in high glucose scenarios, possibly by suppressing the hyperactive NF-κB signaling. These insights propose curcumin's effectiveness in counteracting DOP by advancing bone reconstruction and vascular growth [160].

Diabetic gastroparesis, marked by sluggish gastric evacuation in diabetes mellitus patients [167] , is a prevalent complication, impacting 30-50% of individuals with type 1 or type 2 diabetes [168, 169]. Symptoms include premature fullness, weight reduction, stomach swelling, discomfort, nausea, and vomiting [170]. This condition disrupts glycemic regulation and severely affects life quality [171]. Diabetic gastroparesis's origin involves OS, inflammation, and loss of gastric ICCs crucial for modulating gastric movement [172, 173]. ICCs, specialized cells in the gastrointestinal system, regulate gut motility and coordinate smooth muscle contractions [174]. They generate and propagate electrical slow waves, crucial for the digestive system's rhythmic contractions and regulating the digestive tract's food passage [175]. ICC dysfunction or loss is linked to various gastrointestinal motility disorders, including diabetic gastroparesis [176, 177]. SCF, a growth factor, is vital for ICC development and maintenance, while c-kit serves as a receptor for SC [178, 179]. SCF and c-kit signaling are essential for ICC survival, differentiation, and function, crucial for regulating gastric movement and emptying [180].

Jin et al. explored curcumin's impact on diabetic gastric motility in rats, noting improvements in gastric

emptying rates, diminished OS, inhibited NF-κB activation, and increased SCF/c-kit expression in diabetic rat stomach tissues. Curcumin's protective role on ICCs underscores its potential therapeutic application in diabetic gastroparesis. The study also found curcumin's antioxidative and free radical scavenging properties and its ability to restore SCF/Kit protein levels in diabetic rats. Curcumin's supplementation mitigated OS and NF-κB activation, hinting at its protective potential against diabetic gastroparesis. CUR decreased MDA levels, increased SOD activity, inhibited ROS formation, and prevented ROS-induced apoptosis in diabetic rat stomach tissues, demonstrating its beneficial effects on gastric motility and OS [181].

Table 1 and Figure 3 briefly show curcumin effects on NF-κB pathway in diabetes mellitus.

Table 1. Curcumin effects on NF-κB pathway in diabetes mellitus

Figure 3. Targeting of the NF-κB pathway by curcumin in diabetes mellitus: Focusing on oxidative stress and inflammation

Conclusion

The study underscores curcumin's potential as a therapeutic agent in mitigating DM complications, primarily through modulating the NF-κB pathway. By demonstrating anti-inflammatory, antioxidative, and anti-fibrotic properties, CUR has been effective in managing multiple diabetic conditions, including nephropathy, cardiomyopathy, and gastroparesis. The alteration of critical signaling pathways such as CaMKII, PPAR-γ, NF-κB, and TGF-β1 is pivotal in curcumin's beneficial effects. Additionally, its capacity to diminish OS, curb inflammation, and enhance vascular functionality vindicate CUR as a promising candidate molecule for management of DM complication. These findings highlight the necessity to further explore the potential of CUR as a supplementary treatment option in management of DM complications.

Author Contributions Statement

M.Y.Z & M.G: Writing – review & editing, Validation. A.S, H.O.A & A.Y: Writing – original draft, Conceptualization. S.B.O & A.S: Writing – review & editing, funding acquisition. F.K: Validation. A.M.J & M.K.A: Visualization, Methodology. A.J & A.H.A: Methodology. M.Y.Z & A.S: Supervision and Conceptualization. N.S.J & F.K: Data curation and Software.

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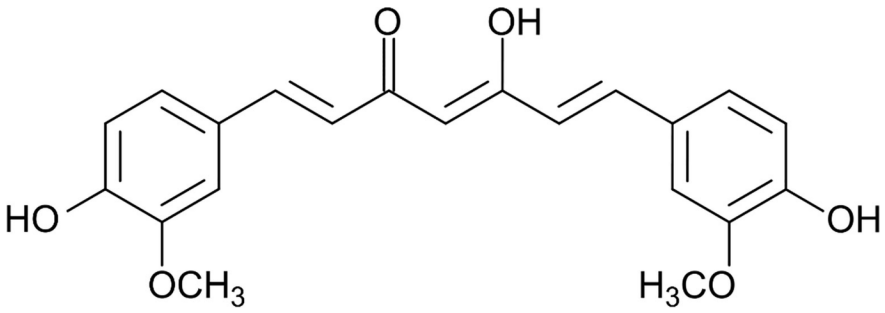

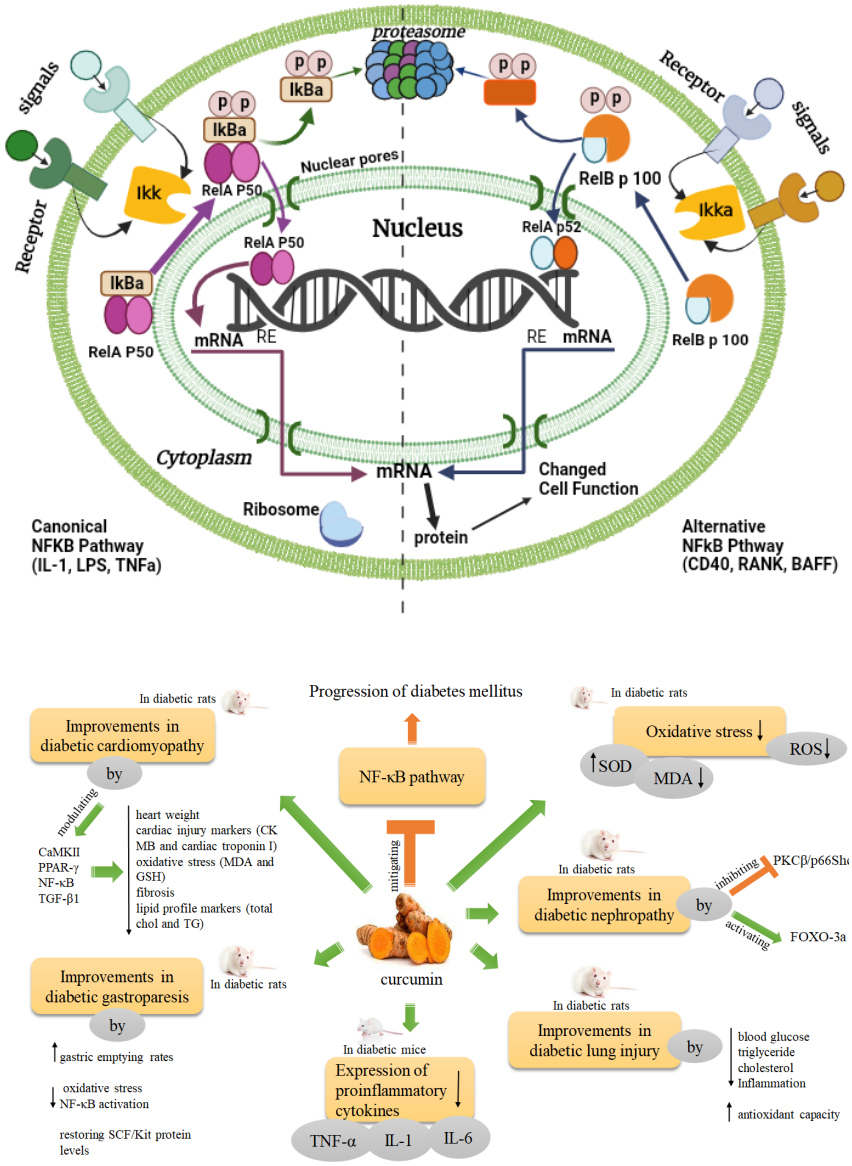

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