

Curcumin-Mediated Regulation of the IKK/NF- κ B Inflammatory Pathway in Diabetes Mellitus: Mechanisms and Therapeutic Implications

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ABSTRACT

Diabetes Mellitus (DM) is one of the fastest-growing diseases around the globe, affecting millions of people each year. In addition to blood glucose levels, this disease is largely driven by chronic inflammation. Although inflammation is vital to the body's immune system, chronic inflammation can lead to the development of diabetes-related complications, such as insulin resistance and damaged pancreatic beta cells. A common inflammatory process, the nuclear factor kappa B (NF- κ B) pathway, regulates the synthesis of inflammatory proteins, which contribute to the pathogenesis of DM. Various bioactive compounds are currently under scientific investigation as a natural remedy for chronic inflammation triggered by prolonged activation of the NF- κ B pathway. One of the most researched bioactive compounds is curcumin, extracted from turmeric (*Curcuma longa*), known for its inhibitory effects on the NF- κ B pathway. Curcumin is known for its potent anti-inflammatory properties, which can improve health conditions by reducing inflammation in the body via suppression of the I κ B kinase (IKK)/NF- κ B pathway. Consequently, the synthesis of inflammatory proteins would be better regulated, while blood sugar regulation and insulin activity would be enhanced. In this article, we examine the impact of curcumin administration on the regulation of the IKK/NF- κ B pathway in patients with DM. We discuss the biological mechanisms, laboratory and clinical trials, and therapeutic implications of curcumin on the NF- κ B pathway. Additionally, we address the current gaps and limitations, highlighting the need for future research on curcumin.

INTRODUCTION

Diabetes mellitus (DM) is among the most significant and fast-growing diseases that are imposing health burdens around the world, as this disease has no viable cure (Aloke et al., 2022). A study by Ogle et al. projected the Type 1 Diabetes (T1D) population for 2040 to be 14.7 million people, which would be a 55% increase from the 2025 estimate of 9.5 million (Ogle et al., 2025). T1D significantly influences lifestyle, including dietary regulations, physical activity, and regular blood glucose monitoring. In contrast, Type 2 Diabetes (T2D) accounts for the vast majority of diabetes cases worldwide, representing

a significant and escalating global health burden. It is a metabolic disorder characterized by systemic insulin resistance, where peripheral tissues fail to adequately respond to circulating insulin, a state frequently exacerbated by lifestyle factors such as obesity and physical inactivity (Banday et al., 2020). Beyond that, T2D is linked to chronic low-grade inflammation, which disrupts signaling pathways and actively furthers disease progression (Obeagu, 2026; Stafeev et al., 2017). Given the rapid increase in prevalence, T2D places immense strain on healthcare systems globally, underscoring the critical need for effective management strategies (Aloke et al., 2022).

Diabetes mellitus is a non-communicable endocrine disease characterized by elevated blood glucose and lipid levels and high oxidative stress (Aloke et al., 2022). These abnormalities culminate in abnormal function of vital organs and tissues, such as the kidneys, nerves, blood vessels, and pancreas (Aloke et al., 2022). The pancreas plays a central role in glucose regulation through the production and secretion of insulin by the beta cells located in the islets of Langerhans. In individuals with diabetes, pancreatic dysfunction impairs insulin production, leading to persistent hyperglycemia and metabolic imbalance (Banday et al., 2020). As breakdowns in these major organs intensify, DM turns into a fatal disease if not treated. Although abnormal glucose metabolism characterizes diabetes, there is considerable evidence indicating that chronic inflammation is an important characteristic of the disease (Obeagu, 2026). The presence of chronic inflammation appears to be central in the initiation and development of insulin resistance and diabetes mellitus complications (Obeagu, 2026).

Among several inflammatory signaling pathways associated with diabetes, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway is one of the most critical in regulating inflammatory gene expression. NF- κ B activation mainly depends on the activity of the inhibitor of the I κ B kinase (IKK) complex, which acts as a key inflammatory pathway regulator (Israel, 2010). The continuous activation of the IKK/NF- κ B pathway is strongly implicated in the pathogenesis of immune-mediated diabetes (Salem et al., 2014). With rising focus on anti-inflammatory therapies, there has been increasing attention towards natural products that have the potential to inhibit the NF- κ B pathway. Bioactive compounds such as resveratrol and quercetin, naturally occurring chemicals that have a profound biological impact on cells and tissues, are being researched for potential therapeutic measures (Israni et al., 2026).

Throughout the extensive field of bioactive compounds, Curcumin, a bioactive polyphenolic compound isolated from turmeric (*Curcuma longa*), has been thoroughly researched and has been found to be a bioactive compound with one of the most inhibitory effects on the NF- κ B pathway. Curcumin has been found to possess antioxidant and anti-inflammatory effects in various experiments and clinical trials (El-Saadony et al., 2023). Studies have revealed that curcumin can inhibit the activation of the IKK/NF- κ B inflammatory pathway, which can lead to inhibition of inflammatory cytokine secretion (Olivera et al., 2012). The inhibition of the NF- κ B signaling system has been shown to mitigate inflammation and normalize glucose metabolism in patients with gestational diabetes mellitus (Khatap et al., 2025). Nonetheless, curcumin's mechanisms, therapeutic efficacy, and bioavailability remain areas requiring further study.

This paper aims to analyze the present scientific data on curcumin-mediated regulation of the IKK/NF- κ B inflammatory pathway in patients with various forms of diabetes mellitus, paying special attention to its molecular mechanisms and therapeutic implications.

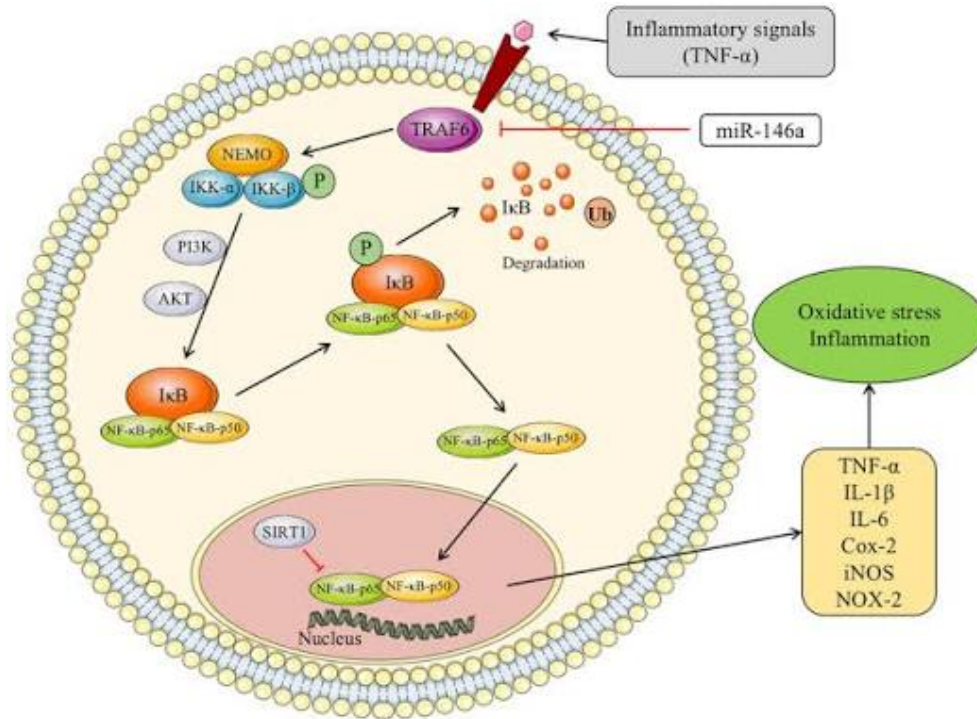
PATHWAY CONTEXT: THE IKK-I κ B-NF- κ B MODULE AS AN INFLAMMATORY PATHWAY

The nuclear factor kappa-light-chain-enhancer (NF- κ B) inflammatory pathway is an inducible signaling complex that is among the most extensively studied regulators of inflammation, immunity, and cell survival. In mammals, the NF- κ B consists of five structurally related members (RelA, ReB, c-Rel, NF- κ B1, NF- κ B2), all of which form a variety of homodimers and heterodimers that convey distinct transcriptional outputs (T. Liu et al., 2017). The most abundant and proinflammatory of the NF- κ B dimers is the p50/RelA (p65) heterodimer, which, in the resting state, is retained in the cytoplasm (Giridharan & Srinivasan, 2018). Activated NF- κ B translocates to the nucleus and acts as a transcription factor for the expression of pro-inflammatory mediators like TNF- α , IL-6, IL-1 β , COX-2, and iNOS. The constant activation of these pro-inflammatory mediators leads to insulin resistance and eventually results in the development of diabetes mellitus (Mao et al., 2025).

One frequent signaling process induced by pattern-recognition receptors (PRRs) is the activation of the canonical NF- κ B signaling pathway that plays a role in the production of pro-inflammatory cytokines, chemokines, and other mediators of inflammation in different types of innate immune cells (T. Liu et al., 2017). As seen in Figure 1 below, the primary mechanism for the canonical activation of NF- κ B involves the inducible degradation of the I κ B α protein resulting from its site-specific phosphorylation by a multi-subunit complex of the I κ B kinase (T. Liu et al., 2017). The IKK complex is made of at least three subunits, specifically the kinases IKK- α (IKK-1) and IKK- β (IKK-2), and the auxiliary subunit IKK- γ (or NEMO) (Zhang et al., 2021). IKK-1 predominantly plays a role in the regulation of non-canonical NF- κ B pathway activity, while the regulation of the canonical NF- κ B pathway, induced by signaling molecules from pro-inflammatory cytokines and microbes, requires the function of IKK β (Zhang et al., 2021).

Now that we have established how the NF- κ B pathway works, in the following section, we will be discussing the NF- κ B pathway in the specific context of DM.

Figure 1
Schematic Diagram of NF- κ B Activation



Note. I κ B kinases phosphorylate and degrade I κ B α , allowing the NF- κ B (p50/p65) complex to move to the nucleus and trigger the expression of inflammatory proteins.

MECHANISMS: WHY IKK/NF- κ B INHIBITION IS IMPORTANT IN DIABETES CONTEXTS

The NF- κ B pathway is a common inflammatory mediator, and its dysregulation can lead to many chronic diseases, including rheumatoid arthritis, neuropathy, and cancer. (T. Liu et al., 2017). The IKK/NF- κ B pathway occupies a central position in both type 1 diabetes (T1D) and type 2 diabetes (T2D), connecting hyperglycemia, chronic low-grade inflammation, oxidative stress, and progressive β -cell destruction or insulin resistance.

In the context of T2D, obesity and dyslipidemia elevate circulating levels of proinflammatory adipokines (TNF- α , IL-6, resistin) and free fatty acids (FFAs), both of which activate IKK β in metabolically active tissues, including adipose tissue, liver, and skeletal muscle. Critically, IKK β can phosphorylate the IRS-1 receptor, present at the cell surface, directly at its inhibitory serine residues (especially serine 307), thereby blocking insulin signaling through the PI3K/Akt pathway and impairing glucose uptake (Choi et al., 2025). This, in turn, increases blood glucose levels. This represents an important link between the inflammatory and metabolic pathways (Stafeev et al., 2017).

In the kidney, liver, and vasculature of a diabetic patient, NF- κ B activation is associated with progression of end-organ complications that are mostly irreversible. For instance, in the case of the urinary system, high-glucose conditions activate NF- κ B in glomerular mesangial cells. This promotes upregulation of ICAM-1, MCP-1, and TGF- β 1, collectively driving macrophage infiltration, fibrosis, and glomerulosclerosis that characterize diabetic nephropathy (Chen et al., 2025). In the diabetic liver, NF- κ B orchestrates macrophage activation, prompting them to release pro-inflammatory cytokines that impair hepatocyte insulin signaling. This cellular disruption establishes hepatic insulin resistance and changes lipid metabolism, furthering the progression of hepatic steatosis (Pourdad & Pourdad, 2026). In the vasculature, it drives endothelial dysfunction by upregulating surface adhesion molecules. This upregulation allows the adhesion of circulating monocytes to the vascular endothelium, furthering chronic plaque inflammation and atherogenesis. At the systemic level, circulating monocytes from diabetic patients exhibit enhanced NF- κ B activation in response to high glucose; hyperglycemia promotes histone acetyltransferase (HAT/p300) activity, which acetylates the p65 subunit and suppresses histone deacetylase 2 (HDAC2), sustaining NF- κ B transcription and amplifying the expression of IL-6 and TNF- α (Baker et al., 2011).

Together, these cell-type and tissue-specific mechanisms establish IKK/NF- κ B as a potential therapeutic target across diabetic pathology. One prominent therapeutic method under current research is the bioactive compound curcumin.

CURCUMIN-MEDIATED INHIBITION: HOW DOES IT AFFECT IKK/NF- κ B MODELS

Curcumin, the primary bioactive compound extracted from *Curcuma longa*, exhibits potent anti-inflammatory effects through the disruption of the IKK/I κ B α /NF- κ B signaling complex (M. Liu et al., 2025). The primary action is the inhibition of IKK β subunit activity. Specifically, curcumin blocks IKK β -mediated phosphorylation of I κ B α , consequently preventing I κ B α degradation and keeping NF- κ B in the cytoplasm (M. Liu et al., 2025), which prevents the synthesis of inflammatory proteins. Additional mechanisms include curcumin's epigenetic modulation of NF- κ B activity: in high-glucose-conditioned monocytes, curcumin induces HDAC2 activity (which actively removes activating acetyl groups from the p65 subunit) and suppresses HAT (p300) activity (which prevents the addition of new acetyl groups), thereby reversing the epigenetic acetylation of p65 that sustains NF- κ B transcription under diabetic conditions (Yun et al., 2011).

Although curcumin suppresses NF- κ B through direct mechanisms, it also does so through indirect mechanisms that converge on the IKK/I κ B α . By inhibiting the c-Jun N-terminal kinase (JNK) pathway, an upstream activator of IKK β , curcumin reduces serine phosphorylation of IRS-1 and simultaneously blocks p65 nuclear translocation and NF- κ B-dependent transcription of proinflammatory genes including TNF- α , IL-1 β , IL-6, COX-2, and iNOS (Hussain et al., 2022). Curcumin further activates PPAR γ , which antagonizes NF- κ B transcriptional activity and activates the Nrf2/Keap1/HO-1 antioxidant pathway. This

reduces ROS-driven IKK activation and thereby diminishes NF- κ B-dependent inflammation through oxidative stress reduction (Jiménez-Flores et al., 2014). Additionally, curcumin has been identified as a direct inhibitor of the 26S proteasome, and since proteasomal activity is required for I κ B α degradation following its phosphorylation, proteasome inhibition by curcumin provides an independent mechanism for maintaining I κ B α levels and NF- κ B cytoplasmic sequestration (Weisberg et al., 2016).

ROLE OF CURCUMIN IN THE IKK/I κ B α /NF- κ B IN DIABETES-RELEVANT SYSTEMS

The inhibitory effects of curcumin on the IKK/I κ B α /NF- κ B cascade have been validated across a range of diabetes-relevant in vitro and in vivo experimental systems, demonstrating functional consequences for glycemic control, β -cell survival, and end-organ protection (Zamanian et al., 2024).

In streptozotocin (STZ)-induced diabetic CD1 mice, a model of T1D, curcumin administration (170 mg/kg, three times per week for 28 days) significantly reduced pancreatic phosphorylated NF- κ B p65, with decreases in proinflammatory cytokines (IFN- γ , IL-6, IL-1 β) and improvement in β -cell histopathology and regeneration. This indicated that NF- κ B pathway suppression in the islet microenvironment is a primary mechanism in curcumin's pancreatic protective effects in T1D (Badr et al. 2020). Similarly, in STZ-induced diabetic rats with gastroparesis, curcumin treatment preserved I κ B α protein levels (preventing its STZ-induced degradation), blocked nuclear NF- κ B translocation as assessed by electrophoretic mobility shift assay (EMSA), and suppressed downstream expression of SCF/c-kit pathway components involved in confirming I κ B α stabilization as the operative mechanism of NF- κ B inhibition in this diabetic complication model (Jin et al. 2013).

In diabetic neuropathy, a self-nano-emulsifying drug delivery system (SNEDDS) formulation of curcumin, designed to improve oral bioavailability, reduced neural tissue levels of NF- κ B, IKK, COX-2, iNOS, TNF- α , and IL-6, with superior efficacy relative to native curcumin, linking improved bioavailability directly to enhanced target engagement within the IKK/NF- κ B cascade (Hussain et al. 2022). These mechanistic findings suggest that curcumin, as a therapeutic agent, can target inflammatory components of diabetes mellitus.

THERAPEUTIC IMPLICATIONS FOR DIABETES MELLITUS

Studies in diabetic nephropathy (DN) models have shown that curcumin can reduce kidney inflammation by preserving I κ B α , which prevents NF- κ B from moving into the nucleus and activating inflammatory genes. As a result, levels of inflammatory cytokines such as TNF- α and IL-1 β decrease, leading to less macrophage infiltration, reduced proteinuria, and improved overall kidney function (Soetikno et al., 2011). Researchers have also developed modified forms of curcumin, such as C66, that appear to suppress inflammation even more effectively by blocking IKK activation and preventing the phosphorylation and

degradation of I κ B α . Notably, these protective effects occur without lowering blood glucose levels, suggesting that curcumin-based therapies may help treat diabetic nephropathy through mechanisms that are independent of glucose control (Pan et al., 2012).

Clinical studies also support the use of curcumin as an adjunct therapy for diabetic nephropathy in patients with type 2 diabetes. In a randomized, placebo-controlled trial involving 40 participants, those who received turmeric supplementation three times daily for two months experienced a significant reduction in proteinuria, with average levels decreasing from approximately 4,329 mg/day to 2,355 mg/day. Treatment also lowered serum levels of TGF- β and IL-8, as well as urinary IL-8, suggesting reduced inflammation and fibrosis (Khajehdehi et al., 2011). Although the study did not directly measure NF- κ B activity, the decline in these inflammatory and fibrotic markers is consistent with the proposed mechanism of curcumin, in which suppression of upstream inflammatory signaling helps protect against the progression of diabetic nephropathy (Khajehdehi et al., 2011).

It was seen through studies on obese mice that when curcumin was delivered specifically to inflammatory myeloid cells, the activity of the NF- κ B pathway was inhibited (Yekollu et al., 2011). Additionally, there was a reduction in the number of NF- κ B active elements like RelA and p65. With the decline in inflammation, insulin sensitivity increased, and this was due to activation of pAKT, which is a key protein in the process of insulin sensitivity in the liver and muscles. There was an improvement in blood glucose levels, glucose tolerance, and general metabolic function of the obese mice (Yekollu et al. 2011). These findings suggest that anti-inflammatory targeting of specific immune cells can improve systemic insulin resistance.

There are many investigations indicating that improvement in the delivery of curcumin, given its poor bioavailability, would be useful. Artificial curcusesomes are liposome-based carriers that enhance the uptake of curcumin by inflammatory cells and show a promising clinical outlook (Sitompul et al., 2026). In addition to this, artificial curcuminoids were found to decrease NF- κ B expression, particularly by decreasing nuclear RelA DNA binding, as well as improving metabolic health in animal trials (Yekollu et al. 2011). There have also been modifications in curcumin, like C66, that seem to be more active than normal curcumin in producing a stronger therapeutic effect in smaller doses (Pan et al., 2012). These observations support the belief that pharmacokinetic optimization is necessary to modulate the NF- κ B pathway in clinical diabetes.

LIMITATIONS AND EVIDENCE GAP

Despite the preclinical evidence supporting curcumin's inhibitory activity on the IKK/I κ B α /NF- κ B pathway in diabetic systems, several critical limitations constrain the translation of these findings into established clinical practice. The most fundamental pharmacological challenge is curcumin's poor oral bioavailability (Marton et al., 2021). This issue arises from its hydrophobicity, instability in alkaline environments, rapid intestinal and hepatic metabolism (primarily glucuronidation and sulfation), and

extensive fecal excretion, leading to very low systemic plasma concentrations following oral ingestion (Marton et al., 2021). At a physiological pH greater than 7, curcumin degrades within approximately 30 minutes, while acidic conditions significantly slow its decomposition; collectively, these properties mean that the in vitro concentrations (typically 5–25 μ M) at which IKK/NF- κ B inhibition is robustly demonstrated are not reliably achieved in vivo with standard oral dosing (Lu et al. 2022). Various formulation strategies, including nanoparticles, liposomes, phytosomes, piperine co-administration, and self-emulsifying delivery systems, have been developed to improve bioavailability and have demonstrated greater pharmacodynamic activity in animal models, but these formulations introduce additional complexity regarding their own safety profiles, stability, and regulatory approval pathways that have yet to be fully addressed in large-scale clinical trials (Lu et al. 2022).

Another major limitation is that the vast majority of evidence for curcumin's inhibitory effects on the IKK/I κ B α /NF- κ B pathway in diabetes comes from in vitro cell culture studies and in vivo rodent models, none of which fully encapsulate the complexity of human diabetes, including its polygenic background, co-morbidities, polypharmacy, and the chronic multi-decade course of end-organ complications (Sivani et al. 2022). For example, the doses used in animal models (100–300 mg/kg/day) are not directly translatable to human therapeutic doses, and the few clinical trials conducted to date have been limited by various factors. These factors include small sample sizes, short intervention periods, single-dose evaluations, variable curcumin formulations, and a failure to directly measure pathway-level biomarkers (e.g., IKK β kinase activity, I κ B α phosphorylation, or NF- κ B p65 nuclear occupancy) in target tissues rather than surrogate circulating inflammatory markers (Basu et al., 2021).

One rigorous ten-week trial noted that high-dose curcumin reduced systemic inflammatory indicators but had no effects on oxidative stress, insulin levels, or HbA1c, underscoring the disconnect between anti-inflammatory effects and clinically meaningful metabolic outcomes that must be bridged by future research (Marton et al., 2021).

CONCLUSION

Chronic inflammation is increasingly recognized as a major contributor to the development and progression of diabetes mellitus. The IKK/NF- κ B signaling pathway serves as a central regulator of inflammatory gene expression. Persistent activation of this pathway promotes the production of pro-inflammatory cytokines and mediators that contribute to insulin resistance, β -cell dysfunction, oxidative stress, and diabetic complications. As a result, targeting the IKK/NF- κ B axis has emerged as a promising therapeutic strategy for reducing inflammatory burden in diabetes-related conditions (Liu et al. 2017).

Curcumin, a naturally occurring polyphenol derived from turmeric, has demonstrated significant anti-inflammatory potential through its ability to modulate the IKK/NF- κ B pathway (El-Saadony et al., 2023). Evidence from in vitro, animal, and clinical studies suggests that curcumin may inhibit IKK

activation, prevent degradation of IκBα, suppress NF-κB nuclear translocation, and reduce transcription of pro-inflammatory genes. These effects have been associated with improvements in inflammatory biomarkers, insulin sensitivity, glycemic control, and protection against diabetic complications (El-Saadony et al., 2023).

Despite these promising findings, several limitations remain, including poor bioavailability, variability in experimental methodologies, and the limited number of large-scale clinical trials. Additional research is needed to better understand the molecular mechanisms of curcumin to enhance its bioavailability, optimize delivery systems and dosing strategies, and determine its long-term therapeutic efficacy and safety in diabetic populations.

Overall, current evidence supports the potential role of curcumin as a complementary anti-inflammatory agent capable of modulating the IKK/NF-κB signaling pathway in diabetes mellitus. Continued investigation into curcumin-mediated regulation of inflammatory signaling may contribute to the development of more effective and accessible therapeutic strategies for the management of diabetes and its associated complications.

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