Mechanisms and Future Perspectives of Curcumin in Diabetes Management

Kamran Javed Naquvi [1*]

Abstract

Background: Diabetes is a chronic metabolic disorder that leads to significant damage to vital organs due to prolonged high blood glucose levels. These complications include cardiovascular disease, peripheral neuropathy, retinopathy (eye damage), nephropathy (kidney damage), myopathy, and foot infections. Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, primarily affecting adults when the body becomes resistant to insulin or when insulin production by the pancreas is insufficient. Turmeric (Curcuma longa), a spice widely used around the world, has been traditionally recognized for its numerous health benefits, including antidiabetic, antioxidant, antibacterial, hepatoprotective, and anticancer properties. Among its active compounds, curcumin, a polyphenolic curcuminoid, has garnered significant attention for its potential role in managing diabetes and its complications. Methods: Data for this review were obtained from databases including PubMed, Elsevier, ScienceDirect, and Google Scholar. Search terms utilized included "diabetes," "type 2 diabetes," "diabetic complications," "turmeric," "curcumin," "oxidative stress and curcumin," "curcumin and nephropathy," "curcumin and retinopathy," "curcumin and neuropathy," "curcumin and cardiovascular diseases," "curcumin and cardiomyopathy," "curcumin and pyroptosis," "curcumin and diabetic foot ulcer," and "curcumin and erectile dysfunction." Results: This review highlights the promising role of curcumin in transforming diabetes treatment and management. The findings demonstrate that curcumin offers protective effects against diabetic complications by modulating key signaling pathways, such as NF-κB, AMPK, MAPK, and AP-1. Its anti-inflammatory properties, inhibition of hepatic gluconeogenesis, and reduction of oxidative stress through antioxidant activity present a strong case for its therapeutic potential in diabetes care. Conclusion: This review provides an in-depth explanation of curcumin's mechanisms of action, detailing its medicinal effects on diabetes-related complications and key outcomes from preclinical and clinical studies supporting its potential benefits. It also outlines future directions for research into curcumin's role in diabetes treatment.

Keywords: Curcumin, Curcuma longa, Diabetes, Diabetic Complications, Oxidative Stress.

Significance | This review emphasizes curcumin's multifaceted roles in managing diabetes and its complications, highlighting the need for improved formulations to enhance efficacy.

*Correspondence. Kamran Javed Naquvi, Pharmacy Department, Tishk International University, Erbil, Kurdistan Region, Iraq.
E-mail: kjnaquvi@gmail.com; kamran.javed@tiu.edu.iq

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1. Introduction

1.1 Diabetes and its complications

Diabetes is a severe, chronic disorder that occurs when the body either produces insufficient insulin or fails to use the insulin it produces effectively. This results in prolonged metabolic dysfunction, which leads to elevated blood glucose levels. Diabetes can be caused by diminished insulin production or selective insulin resistance, a condition in which the body's cells become less responsive to insulin's effects, leading to persistent hyperglycemia (Giacco & Brownlee, 2010). According to the International Diabetes Federation (IDF), approximately 537 million people aged

Author Affiliation.
[1] Pharmacy Department, Tishk International University, Erbil, Kurdistan Region, Iraq.

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20 to 79 live with diabetes globally, representing 10.5% of this demographic. The IDF projects that the diabetic population will reach 643 million by 2030 and increase to 783 million by 2045 (Kumar et al., 2024; International Diabetes Federation, 2021).

In recent years, growing attention has been focused on oxidative stress and its relationship to human health, especially its role in diabetes (Caturano et al., 2023). Oxidative stress is believed to play a pivotal role in both the initiation and progression of diabetes by damaging and dedifferentiating pancreatic β cells, which are responsible for insulin production. This damage is often caused by elevated levels of reactive oxygen species (ROS), a byproduct of insulin resistance-related mechanisms, including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and oxidative damage to insulin production (Eguchi et al., 2021; Darenskaya et al., 2021). Pancreatic β cells are particularly susceptible to oxidative stress due to their high production of ROS and insufficient antioxidant defenses, underscoring the critical role of oxidative stress in the failure of these cells (Gurgul-Convey et al., 2016).

Research indicates that elevated ROS levels can damage blood vessels, trigger inflammation, and impair endothelial function, all of which contribute to the development of diabetic vascular complications, such as diabetic retinopathy, nephropathy, sensory impairments, and cardiovascular diseases (Caturano et al., 2023; Luc et al., 2019). Chronic inflammation, a hallmark of type 2 diabetes (T2DM), exacerbates these complications. The inflammatory response is driven by the activity of macrophages and adipocytes, leading to oxidative stress that damages pancreatic β cells, reduces insulin production, and increases insulin resistance. This, in turn, results in a heightened risk of cardiovascular diseases, which are common in individuals with diabetes.

Diabetes is strongly associated with various complications, including heart disease, stroke, peripheral arterial disease, and microvascular conditions like diabetic kidney disease (DKD, or nephropathy), retinopathy, and peripheral neuropathy (Tomic et al., 2022; Zakir et al., 2023). Alarmingly, approximately 66% of individuals with diabetes die from heart-related diseases, and their risk of cardiovascular death is two to four times higher than that of nondiabetics (Deshpande et al., 2008). Diabetic cardiomyopathy encompasses a range of illnesses that complicate patient care and pose a significant challenge in modern medicine. These complications can lead to structural and functional abnormalities in the heart, increasing the risk of heart failure, arrhythmias, and other severe cardiovascular disorders (Zakir et al., 2023). However, many of these complications can be prevented through proper diabetes management.

Atherosclerosis, the narrowing of arteries due to plaque buildup, significantly reduces life expectancy in diabetic patients. Meanwhile, diabetic nephropathy and retinopathy can lead to end-stage renal disease (ESRD) if not properly managed (Rask-Madsen & King, 2013). Diabetic retinopathy (DR) is one of the leading causes of blindness globally and a well-known microvascular complication of diabetes (Kour et al., 2024). DR damages the blood vessels in the retina and can cause vision loss or blindness if not diagnosed and treated promptly. Early detection and treatment are essential for maintaining visual function in affected individuals (Ashwini & Dash, 2023). Furthermore, diabetes increases the risk of other eye-related conditions such as cataracts and glaucoma. To mitigate these risks, individuals with diabetes are advised to undergo a comprehensive eye examination by an ophthalmologist at least once a year to detect and address any potential complications early (Khan & Shaw, 2023).

Another severe complication of diabetes is diabetic nephropathy (DN), which is a significant cause of ESRD. Early markers of DN include albuminuria (protein in the urine) and hyperfiltration, where the kidneys filter blood at an abnormally high rate. If left untreated, DN can progress, resulting in a significant decline in kidney function and eventually leading to renal failure (Sagoo & Gnudi, 2022). Diabetic neuropathy (DNP) is another devastating microvascular complication that affects millions of people worldwide. This condition is characterized by nerve damage caused by prolonged high blood glucose levels (Strand et al., 2024). DNP is the most common diabetic complication and often presents as a loss of sensory function, particularly in the lower limbs. This leads to a significant reduction in quality of life, accompanied by severe morbidity and, in many cases, chronic pain (Feldman et al., 2019). Given its prevalence and impact, there is an urgent need for increased awareness and improved management of DNP.

Diabetic peripheral neuropathy, which affects as many as half of all diabetes patients, increases the likelihood of developing diabetic foot ulcers (DFUs) and infections (Bragg et al., 2024). DFUs are particularly problematic because they heal slowly and can lead to severe infections, extended hospital stays, and, in extreme cases, amputations (Baig et al., 2022). Patients with peripheral neuropathy often experience chronic symptoms such as numbness, tingling, aching, and burning sensations, along with limb weakness. These symptoms, which can range from mild to severe, are exacerbated at night, affecting sleep and overall well-being. Furthermore, individuals may suffer from hyperalgesia (increased sensitivity to pain) or allodynia (pain from normally non-painful stimuli), making daily life difficult (Landrum et al., 2023; Çakici et al., 2016).

The complications associated with diabetes, including cardiovascular disease, diabetic retinopathy, nephropathy, and neuropathy, highlight the critical importance of effective diabetes management. While these complications are severe and potentially life-threatening, many are preventable with early detection and proper treatment. The growing global prevalence of diabetes necessitates continued research and public health efforts to improve

prevention, diagnosis, and management strategies to reduce the burden of this disease and its associated complications.

1.2 Curcumin

Turmeric (*Curcuma longa*) is a perennial plant belonging to the family Zingiberaceae, native to Southeast Asia and renowned for its vibrant yellow rhizomes. Among its various bioactive constituents, curcumin is the most widely studied and has been used for centuries as a spice, medicine, and food flavoring. Traditional Ayurvedic, Unani, and Chinese medicine practitioners have utilized curcumin for treating a range of conditions, including diabetes, inflammation, liver and lung disorders, and even cancer (Gorain et al., 2022).

Curcumin, the primary bioactive component of turmeric, belongs to the polyphenol class and is also known as diferuloylmethane. It was first isolated in 1815 and chemically described as 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Figure 1). Curcuminoids, a group of polyphenolic compounds found in turmeric, include curcumin, demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin, all of which contribute to turmeric's distinctive yellow color (Tundis et al., 2018). However, curcumin and its related curcuminoids have poor solubility in water and other aqueous solutions, limiting their bioavailability and therapeutic potential.

Curcumin is known by different names around the world: it is referred to as saffron in Arab countries; in India, it is called Haridra in Sanskrit and within Ayurvedic practices; in China, it is known as Jianghuang, meaning "yellow ginger"; and in Japan, it is called Kyoo or Ukon (Sultana et al., 2021).

Extensive research conducted by leading scientists has demonstrated curcumin's potent anti-inflammatory properties (Zamanian et al., 2024; Lin et al., 2024; Wei et al., 2023; Xu et al., 2021; Miao et al., 2021; Ren et al., 2020; Lu et al., 2017; Trujillo et al., 2013) and significant antioxidant activities (Zamanian et al., 2024; Chaudhary et al., 2023; González et al., 2023; Masenga et al., 2023; Bhatti et al., 2022; Juan et al., 2021; Miao et al., 2021; Kao et al., 2020; Xie et al., 2018; Gaschler & Stockwell, 2017; Rashid et al., 2017; Suryanarayana et al., 2007). These properties make curcumin a subject of intense study for its potential therapeutic benefits across various diseases and conditions.

2. Different Modes of Actions of Curcumin

2.1 Anti-inflammatory activity

Curcumin works against inflammation by interacting with Toll-like receptors (TLRs) and modifying essential signaling pathways such as Activator Protein 1 (AP-1), Mitogen-Activated Protein Kinases (MAPK), and Nuclear Factor Kappa-B (NF-κB) (Nunes et al., 2024; Peng et al., 2021). Through the Peroxisome proliferator-activated receptor gamma (PPARγ), it inhibits NF-κB activity and modifies the inflammatory pathways via Janus kinase/Signal transducer and activator of transcription (JAK/STAT). Curcumin also inhibits the production of pro-inflammatory cytokines, including IL-1, IL-1β, IL-6, IL-8, IL-17, and IL-27. Further boosting its anti-inflammatory properties, it also blocks the NF-κB pathway, inhibiting the combination and activation of the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome (Figure 2) (Peng et al., 2021).

2.2 Antioxidant activity

Diabetes and its associated complications are primarily triggered by oxidative stress. Curcumin, a powerful antioxidant, uses a variety of strategies to scavenge free radicals and prevent the activation of enzymes that produce reactive oxygen species (ROS). Its crucial role in stimulating the function of glutathione (GSH), catalase, and superoxide dismutase (SOD) is crucial in maintaining cellular redox equilibrium, thereby protecting diabetes patients' cells and tissues against the oxidative damage induced by increased blood glucose levels (Figure 3) (Chaudhary et al., 2023).

2.3 Modulation of Metabolic Pathways

Regulating AMPK-mediated gluconeogenic gene expression and enhancing glucose absorption in cells improves insulin signaling by activating the AMP-activated protein kinase (AMPK) pathway. This action lowers blood glucose levels by inhibiting the liver's hepatic gluconeogenesis, which produces glucose (Kim et al., 2009). Upregulation of AMPK inhibits stress and cell death in β cells, crucial for preventing type I diabetes development. AMPK can potentially enhance conditions related to neuropathy, nephropathy, liver diseases, and reproductive changes associated with diabetes mellitus (Entezari et al., 2022).

3. Methodology

The research articles were sourced from reputable academic databases, including PubMed, Elsevier, ScienceDirect, and Google Scholar, to ensure a thorough and reliable compilation of data. The search strategy involved the use of multiple keywords, such as "diabetes," "type 2 diabetes," "diabetic complications," "turmeric," and "curcumin," along with specific conditions associated with curcumin, including "nephropathy," "retinopathy," "neuropathy," "cardiovascular diseases," "cardiomyopathy," "pyroptosis," "diabetic foot ulcers," and "erectile dysfunction." Studies focusing on the effects of curcumin on diabetic complications and oxidative stress were selected. Articles published in non-English languages and unrelated animal studies were excluded to maintain the relevance and quality of the review. This methodology ensured a comprehensive and high-quality selection of pertinent studies.

4. Role of Curcumin in Diabetes and its Complications

4.1 Role of Curcumin in Oxidative Stress

All forms of diabetes are marked by chronic hyperglycemia, which can damage multiple organ systems, particularly the neurological, renal, and cardiovascular systems. These complications

significantly contribute to the higher rates of morbidity and mortality in individuals with diabetes, highlighting the critical importance of proper blood glucose management (Alshehri, 2010). The primary mechanisms disrupted in diabetes are insulin action and secretion, which are further impaired by the oxidative stress (OS) induced by hyperglycemia. In addition to increased OS, people with diabetes have diminished antioxidant defenses, exacerbating OS and necessitating its management (Alshehri, 2010; González et al., 2023; Bhatti et al., 2022; Santos et al., 2018; Santos et al., 2019).

Research has increasingly pointed to OS as a key mechanism in the development and progression of diabetes and its associated complications. OS occurs due to an imbalance between the production of free radicals and the body's ability to neutralize them, either by excessive production of free radicals or a reduction in antioxidant defenses. Factors contributing to OS in diabetes include the auto-oxidation of glucose, non-enzymatic protein glycosylation (Masenga et al., 2023; Mullarkey et al., 1990), altered antioxidant enzyme activity, reduced glutathione metabolism (Mclennan et al., 1991), and the formation of lipid peroxides and reduced ascorbic acid levels (Juan et al., 2021). In terms of antioxidant defenses, beyond glutathione (GSH), key enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) play critical roles in neutralizing harmful radicals like superoxide, hydrogen peroxide, and hydroxyl radicals (Gaschler & Stockwell, 2017; Mclennan et al., 1991; Soto et al., 2003; Strain, 1991; Baynes, 1991).

In animal models, curcumin and turmeric have shown protective effects against OS, particularly in streptozotocin (STZ)-induced diabetic rats. For example, Wistar rats were given an intraperitoneal injection of STZ (35 mg/kg body weight) to induce diabetes and were then fed either a standard diet or a diet supplemented with varying concentrations of curcumin or turmeric for eight weeks. Both curcumin and turmeric were found to reduce levels of thiobarbituric acid reactive substances (TBARS), which are markers of lipid peroxidation and red blood cell protein carbonyls, while restoring antioxidant enzyme activity in most tissues, even though hyperglycemia persisted (Suryanarayana et al., 2007). In another study, diabetic Sprague-Dawley rats that were administered a diet containing 1.0% curcumin for 21 days demonstrated a significant reduction in blood glucose, plasma malondialdehyde (MDA), and other OS markers like GSH-Px and CAT, while SOD and insulin levels increased (Xie et al., 2018). These findings suggest that curcumin might enhance antioxidant defense mechanisms by mitigating OS in diabetic rats via the Keap1-Nrf2-ARE pathway.

In STZ-induced diabetic rats (65 mg/kg body weight), daily administration of curcumin (100 mg/kg) for eight weeks reversed elevated intracellular ROS and reduced blood glucose levels. Curcumin's anti-hyperglycemic, antioxidant, anti-inflammatory, and anti-apoptotic properties were proposed as potential mechanisms for preventing diabetes-induced splenic damage (Rashid et al., 2017). Additionally, turmeric aqueous extract (300 mg/kg body weight) administered orally showed some effectiveness in countering OS in diabetic rats, though a decline in antioxidant processes over time may contribute to chronic diabetes (Ali Hussain, 2002).

Further research has explored curcumin's impact on inflammatory pathways, particularly its influence on the NF-κB signaling pathway, which regulates the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). By reducing the expression of these inflammatory mediators, curcumin has demonstrated protective effects in diabetes, improving insulin sensitivity, enhancing pancreatic β-cell function, and reducing OS (Zamanian et al., 2024). Moreover, curcumin and its analog A13 have shown promise in mitigating diabetes-related brain damage by modulating OS and inflammatory pathways, increasing SOD levels, and reducing MDA concentrations in the brains of diabetic rats (Miao et al., 2021).

4.2 Role of Curcumin in Diabetic Retinopathy

There is increasing evidence that oxidative stress (OS) caused by metabolic imbalances induced by diabetes is a key mechanism in the pathophysiology of diabetic retinopathy (DR), affecting both type 1 and type 2 diabetes patients (Wu et al., 2014). DR is a chronic inflammatory condition that primarily affects the retina's blood vessels and photoreceptors. As diabetes progresses, localized hypertension within the retinal vasculature results in the thickening of the basement membrane and breakdown of tight junctions between pericytes, which are essential for maintaining blood-retina barrier integrity (Barber, 2015). This dysfunction leads to the release of angiogenic factors and pericyte apoptosis. The accumulation of advanced glycation end products (AGEs) further triggers the production of reactive oxygen species (ROS), which damages both vascular and extravascular structures and cross-links proteins, exacerbating the complications of DR (Radomska-Lesniewska et al., 2019).

Oxidative stress induced by hyperglycemia plays a pivotal role in diabetic kidney disease (DKD) and abnormal neovascularization. ROS-induced pericyte loss and microaneurysm formation contribute to DR's vascular syndrome, leading to progressive vision impairment (Wan et al., 2015; Wu et al., 2014; Radomska-Lesniewska et al., 2019).

In 2011, Gupta and colleagues explored the impact of oral curcumin (1 g/kg) on DR in streptozotocin (STZ)-induced diabetic Wistar rats. Curcumin supplementation resulted in improved antioxidant enzyme activities, including catalase and superoxide dismutase (SOD), a significant reduction in blood glucose levels, and an increase in retinal glutathione. Additionally, curcumin prevented structural degeneration in the retina, inhibiting capillary basement membrane thickening and suppressing the rise of pro-

inflammatory cytokines, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) (Gupta et al., 2011; Radomska-Lesniewska et al., 2019).

Yang et al. (2018) conducted a study to investigate the protective effects of curcumin on the retina in diabetic rats that were fed a high-energy diet and given a low-dose STZ. For 16 weeks, the oral administration of curcumin (100 mg/kg) led to the prevention of diabetes-induced weight loss, a reduction in blood glucose levels, and the prevention of capillary basement membrane thickening, retinal cell death, and retinal thinning. Curcumin demonstrated significant antioxidant effects by reducing VEGF expression and exhibited anti-apoptotic benefits by upregulating Bcl-2 and downregulating Bax, indicating its therapeutic potential for preventing retinal damage in diabetes (Yang et al., 2018).

Further research demonstrated that curcumin, in combination with KN93 (a Ca^{2+}/calmodulin-dependent protein kinase II, or CaMKII, inhibitor), suppressed the CaMKII/NF-κB signaling pathway, which is activated by hyperglycemia. This suppression led to the downregulation of intercellular adhesion molecule-1 (ICAM-1), VEGF, and inducible nitric oxide synthase (iNOS). By inhibiting CaMKII activity, curcumin protected the retina from early vascular injury caused by diabetes, suggesting its potential in preventing diabetic nephropathy (DN) (Li et al., 2016). Additionally, curcumin was shown to mitigate diabetes-induced retinal neuron apoptosis by downregulating CaMKII and lowering glutamate levels, further supporting its use in preventing DN in diabetic patients (Li et al., 2015).

Curcumin-loaded nanocarriers (CN) have also been found to provide neuroprotective benefits to the retina. These nanocarriers significantly protected retinal cells by decreasing glutamate- and cobalt chloride-induced toxicity, reducing retinal ganglion cell loss, and improving cell viability in retinal neuron cultures. Curcumin's potential as a neuroprotective therapy for glaucoma and other neurodegenerative eye conditions has been proposed, indicating its broader application in retinal and eye disease management (Davis et al., 2018).

Curcumin's antioxidative, anti-inflammatory, and antiproliferative properties make it a promising agent for managing various retinal conditions, including glaucoma, DN, and age-related macular degeneration (AMD) (Wang et al., 2013). Studies have demonstrated that curcumin can slow down or even reverse the progression of proliferative vitreoretinopathy, retinitis pigmentosa, DN, AMD, and retinal tumors (Peddada et al., 2019). In diabetic retinopathy, curcumin (10 μM) has been shown to protect retinal pericytes from high-glucose-induced damage by significantly reducing ROS production and TNF-α release in retinal pigmented epithelium cells and retinal endothelial cells (Platania et al., 2018).

The curcumin metabolite tetrahydrocurcumin (THC) has also demonstrated neuroprotective, anti-angiogenic, antioxidative, and anti-inflammatory effects, with studies highlighting its potential to treat conditions such as DN, AMD, cataracts, and glaucoma (Kao et al., 2020).

Early diabetic retinopathy is often marked by disruption of the blood-retina barrier (BRB) and damage to retinal pigment epithelium (RPE) cells, leading to vision loss. Curcumin has shown strong protective effects on RPE cells by preserving tight junction integrity, enhancing retinoid regeneration, reducing apoptosis, and curbing retinal neovascularization. These findings suggest that curcumin may be a viable treatment for early DR, improving RPE survival and overall retinal health (Cheng et al., 2024).

4.3 Role of Curcumin in Diabetic Nephropathy

Diabetic nephropathy (DN), also referred to as diabetic kidney disease (DKD), is the progressive decline in kidney function associated with diabetes mellitus. Globally, DN is the leading cause of end-stage renal disease (ESRD) and chronic kidney disease (Alicic et al., 2017). DKD is characterized by albuminuria, glomerular hyperfiltration, and a gradual decline in the glomerular filtration rate (GFR). Additionally, it is marked by the proliferation of the mesangial matrix and the overexpression of extracellular matrix (ECM) proteins, including profibrotic factors like connective tissue growth factor (CTGF) and transforming growth factor β (TGF-β), which contribute to kidney fibrosis (Alicic et al., 2017; Suneja, 2021; Hoogeveen, 2022). The metabolic disturbances linked to diabetes result in tubulointerstitial inflammation, fibrosis, glomerular hypertrophy, and glomerulosclerosis, leading to progressive kidney damage (Alicic et al., 2017).

Curcumin, a bioactive compound with multi-targeted properties, has been shown to mitigate many pathological changes in DKD by modulating several molecular pathways. In diabetic rats, curcumin (100 mg/kg/day, orally, for eight weeks) effectively slowed the progression of renal disease by inhibiting the activity of extracellular signal-regulated kinases (ERK1/2) and protein kinase C (PKC-α and PKC-β1) (Soetikno et al., 2011). It also suppressed the production of ECM proteins, such as fibronectin and type IV collagen, and reduced the expression of pro-fibrotic factors like osteopontin, TGF-β1, CTGF, and p300. Furthermore, curcumin decreased the levels of VEGF and its receptor (VEGFR II or flk-1), which are elevated in response to high glucose levels, thereby reducing the deleterious effects of hyperglycemia on the kidneys (Soetikno et al., 2011).

Curcumin's anti-inflammatory effects have also been demonstrated in diabetic rats, where it reduced kidney macrophage infiltration and pro-inflammatory cytokine expression following eight weeks of oral administration (100 mg/kg/day). The treatment decreased the expression of intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and TGF-β1 while inhibiting nuclear factor kappa B (NF-κB) signaling. By preventing the degradation of the inhibitor protein IκBα, curcumin blocked

NF-κB activation, thereby reducing inflammation and kidney damage, underscoring its potential as a therapeutic agent for DN (Soetikno et al., 2011a).

Curcumin's antioxidant properties play a crucial role in its nephroprotective effects. In DN models, curcumin (15 and 30 mg/kg/day for two weeks) reduced oxidative stress and improved renal function, suggesting its protective role in mitigating kidney damage by attenuating oxidative stress (Sharma et al., 2006; Prabhakar, 2017). These findings highlight curcumin's potential to regulate oxidative stress through the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and inhibition of mitochondrial dysfunction, making it a promising candidate for treating renal diseases (Trujillo et al., 2013).

Curcumin also demonstrated a significant reduction in renal inflammation markers such as interleukin-1β (IL-1β), cleaved caspase-1, and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) in diabetic mice and human kidney cells (HK-2) exposed to high glucose concentrations. This suggests that curcumin's renoprotective effects in DN are mediated through the inhibition of NLRP3 inflammasome activation, a critical factor in the inflammatory response (Lu et al., 2017).

In a study involving type 1 diabetes mellitus (T1DM) rats induced by streptozotocin (STZ), curcumin (100 mg/kg/day for 12 weeks) was shown to enhance the expression of antioxidant enzymes like gamma-glutamyl ligase and manganese superoxide dismutase (MnSOD). Curcumin also decreased reactive oxygen species (ROS) levels while increasing glutathione (GSH) and Bcl-2 protein expression. These actions, combined with the suppression of NF-κB activity and upregulation of Nrf2 and forkhead box O3 (FOXO-3a), resulted in a reduction in oxidative stress and kidney tissue damage (ALTamimi et al., 2021).

In another study, curcumin (300 mg/kg/day for eight weeks) mitigated DN in diabetic rats and mouse podocytes by inhibiting autophagy and reversing epithelial-mesenchymal transition (EMT) in podocytes. This was achieved by modulating the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway, leading to an increase in E-cadherin and LC3 protein expression, while decreasing levels of vimentin, TWIST1, and p62. These findings indicate that curcumin can restore podocyte integrity and alleviate kidney damage in DN (Tu et al., 2019).

Furthermore, curcumin (200 mg/kg/day for eight weeks) significantly slowed the progression of DN by inhibiting podocyte apoptosis and promoting autophagy. It achieved this by modulating the Beclin1/UVRAG/Bcl2 signaling axis, which reduced the expression of pro-apoptotic proteins Bax and caspase-3 and increased the levels of anti-apoptotic protein Bcl-2 (Zhang et al., 2020). Additionally, curcumin (80 and 130 mg/kg for 60 days) in rats with T1DM reduced markers of kidney injury, including neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), while ameliorating oxidative stress (Ghasemi et al., 2019).

Newer derivatives of curcumin, such as C66, have shown enhanced bioavailability and therapeutic efficacy. C66 improved DN in mice by upregulating Nrf2 and miR-200a while downregulating miR-21, thereby protecting the kidneys from oxidative damage (Wu et al., 2016). Another derivative, zinc(II)-curcumin, was found to ameliorate diabetes-associated nephropathy exacerbated by cadmium exposure through the regulation of gut microbiota and zinc homeostasis (Sun et al., 2024).

4.4 Role of Curcumin in Diabetic Neuropathy

Diabetic neuropathy (DNP) is a prevalent, costly, and debilitating complication associated with both type 1 (T1DM) and type 2 diabetes (T2DM). It significantly impacts patients' quality of life, making it crucial for healthcare professionals to understand and address its consequences. Neuropathy affects approximately 8% of newly diagnosed diabetes patients and over 50% of those with long-term diabetes (Boulton et al., 2005; Edwards et al., 2008). DNP is defined as a neurodegenerative condition affecting the somatic or autonomic peripheral nervous system without other secondary causes of peripheral neuropathy (Cernea & Raz, 2021).

Peripheral neuropathy manifests in the extremities and is characterized by numbness, tingling, burning sensations, limb weakness, hyperalgesia, allodynia, and pain (Azhary et al., 2010). Autonomic neuropathy, on the other hand, involves the nervous system regulating the heart, genitourinary tract, and gastrointestinal tract (GIT), and it affects multiple organ systems. Common GIT disorders include esophageal enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence, all of which can cause severe discomfort and complications (Vinik et al., 2003).

Recent studies have explored the potential of curcumin, a compound derived from *Curcuma longa*, to treat diabetic peripheral neuropathy. Zhang et al. (2022) investigated curcumin's effects on rats with diabetic peripheral neuropathy induced by streptozotocin (STZ) and a high-fat/high-sugar diet. Doses of curcumin (50, 100, and 150 mg/kg) improved sciatic nerve structure, nerve conduction velocity (NCV), and mechanical withdrawal threshold (MWT) after four weeks of treatment, with 150 mg/kg being the most effective in reducing Schwann cell death and raising nerve growth factor (NGF) levels.

In another study, curcumin (200 mg/kg) was administered intragastrically for 14 consecutive days to Sprague-Dawley rats with STZ-induced diabetic neuropathy. Curcumin alleviated neuropathic pain by reducing the expression of NADPH oxidase subunits (p47(phox) and gp91(phox)), lowering hydrogen peroxide (H_2O_2) and malondialdehyde (MDA) levels, and enhancing

superoxide dismutase (SOD) activity in the spinal cord (Zhao et al., 2014).

Further research showed that eight weeks of curcumin treatment (150 mg/kg/day) improved diabetic spinal cord neuropathy in rats by enhancing NeuN and Nrf2/HO-1 signaling while downregulating markers such as Iba1, GFAP, caspase-3, and NF-kB. This modulation helped alleviate oxidative stress and inflammation, reducing high glucose-induced apoptosis and providing protection against Schwann cell lesions (Elsayed et al., 2023; Lin et al., 2024).

Curcumin derivatives like J147 have also demonstrated potential therapeutic effects in STZ-induced diabetic peripheral neuropathy. J147 increased mRNA expression and reduced the adenosine 5'-monophosphate-activated protein kinase (AMPK) pathway, which improved mechanical withdrawal threshold (MWT). The modulation of the transient receptor potential A1 (TRPA1) channel helped alleviate symptoms of diabetic neuropathy, suggesting J147 as a viable treatment option (Lv et al., 2018).

Moreover, curcumin encapsulated in nanoparticles showed promising results in reducing mechanical and thermal hyperalgesia in diabetic rats. The treatment also downregulated the P2Y12 receptor in dorsal root ganglion satellite glial cells (DRG SGCs), which plays a role in pain transmission (Jia et al., 2018).

Collectively, these studies underscore curcumin's neuroprotective properties, highlighting its ability to reduce oxidative stress, inflammation, and apoptosis while enhancing antioxidant defense in nerve tissues. This makes curcumin a promising candidate for the treatment of diabetic neuropathy, offering potential relief from the debilitating symptoms associated with the condition.

4.5 Role of curcumin on diabetic cardiovascular diseases

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among individuals with type 1 and type 2 diabetes. CVD and diabetes mellitus (DM) are closely linked, with shared risk factors such as obesity, hypertension, and high cholesterol (Leon & Maddox, 2015). These cardiovascular (CV) risk factors contribute significantly to the complications associated with diabetes, particularly type 2 diabetes (T2D). Improving glycemic control and maintaining β-cell function are crucial in reducing insulin resistance and dyslipidemia, both of which lower the risk of developing T2D.

Research has shown that curcumin, in combination with long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA), effectively reduces insulin resistance, triglyceride levels, and the risk of T2D (Thota et al., 2019). Curcumin, when combined with metformin, also decreases dyslipidemia and thiobarbituric acid reactive substances (TBARS), a marker of lipid oxidation, in diabetic rats. This combination offers a promising strategy for preventing diabetes-related cardiovascular complications (Roxo et al., 2019).

Diabetic cardiomyopathy (DM-CMP) is a T2D complication that affects the heart's structure and function without the presence of coronary artery disease (CAD), hypertension, or congenital heart defects (Salvatore et al., 2021). Curcumin has been shown to manage DM-CMP by reducing oxidative stress, apoptosis, and increasing Akt phosphorylation while suppressing Foxo1 acetylation. These findings indicate that curcumin modulates the PI3K-Akt and Sirt1-Foxo1 pathways, which are involved in treating DM-CMP (Ren et al., 2020).

Moreover, oral administration of curcumin (100 or 200 mg/kg/day) significantly improved myocardial function in diabetic rats, reducing cardiac fibrosis, advanced glycation end-product (AGE) formation, oxidative stress, and inflammation, while restoring GSK-3β levels (Yu et al., 2012). Curcumin also demonstrated a protective effect against oxidative stress injury in human umbilical vein endothelial cells (HUVECs) by inhibiting the Notch signaling pathway (Yang et al., 2013). These findings highlight curcumin's potential in managing diabetic cardiovascular complications.

4.6 ***Role of Curcumin on Pyroptosis***

The inflammatory-mediated programmed cell death known as pyroptosis is an essential contributor to the development of diabetes and its complications. Diabetes and prolonged inflammation are frequently linked, and this may worsen the condition and produce further tissue damage by promoting increased pyroptosis. This cell death method is crucial in controlling the inflammatory response, making it essential for developing diabetes and its related complications (Xu et al., 2021). Curcumin exhibited pyroptosis-inhibiting action. Curcumin enhanced the production of Heme Oxygenase-1 (HO-1) and Gamma-Glutamylcysteine Ligase (GCLC), two antioxidant factors, and facilitated the transfer of Nrf2 into the nucleus via the AKT pathway. These actions suppressed pyroptosis caused by DM and decreased the formation of ROS and mitochondrial damage in the diabetic myocardium (Wei et al., 2023). Due to curcumin's low bioavailability, gold nanoclusters (AuNCs) were employed to increase curcumin's effectiveness, leading to the development of a nano-formulation known as curcumin-AuNCs (AuCur). ROS increased, whereas AuCur successfully decreased the intracellular lipid buildup. With a decrease in the expression of the peroxisome proliferator-activated receptors-α subtype (PPARα), there was a reduction in mitochondrial division and apoptosis. When treating the lipotoxicity of cardiomyocytes brought on by DM-CMP, AuCur may be an appropriate alternative (Wei et al., 2021). Curcumin therapy showed a potential function in the management of DM-CMP by promoting nuclear transfer of Nrf2, upregulating the expression of oxidative scavenging factors HO-1, decreasing excessive Gpx4 loss, and preventing glucose-induced ferroptosis in cardiomyocytes (Wei et al., 2022).

4.7 Role of Curcumin on Diabetic Foot Ulcers

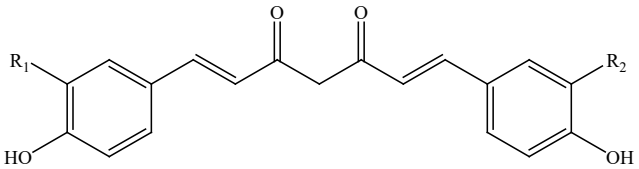

Figure 1. Curcumin (R_1= OCH_3; R_2 = OCH_3); Demethoxycurcumin (R_1 = H; R_2 = OCH_3); Bisdemethoxycurcumin (R_1 = H; R_2 = H)

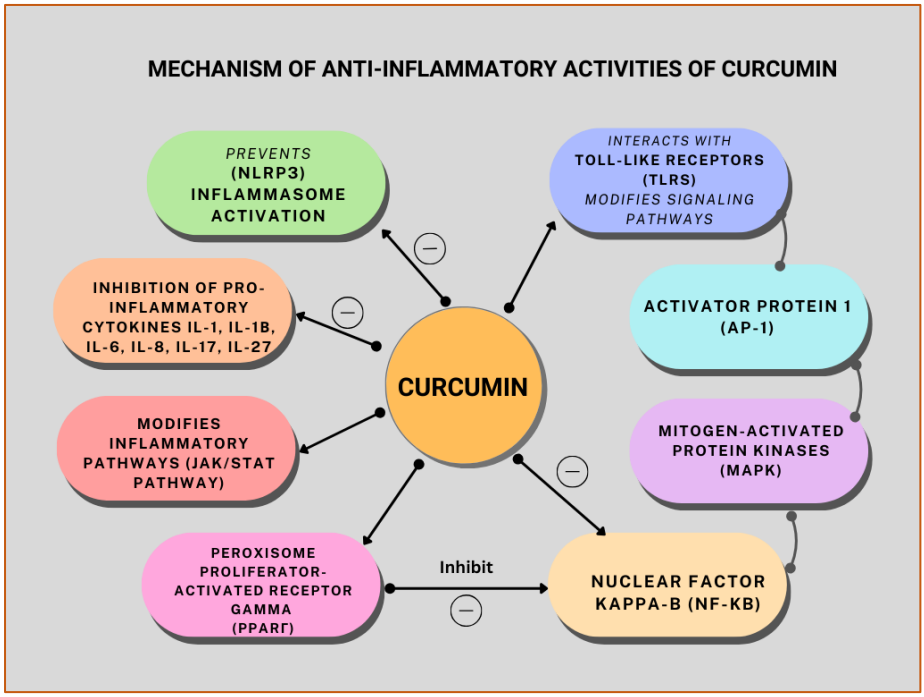

Figure 2. Mechanism of Anti-inflammatory activity of Curcumin

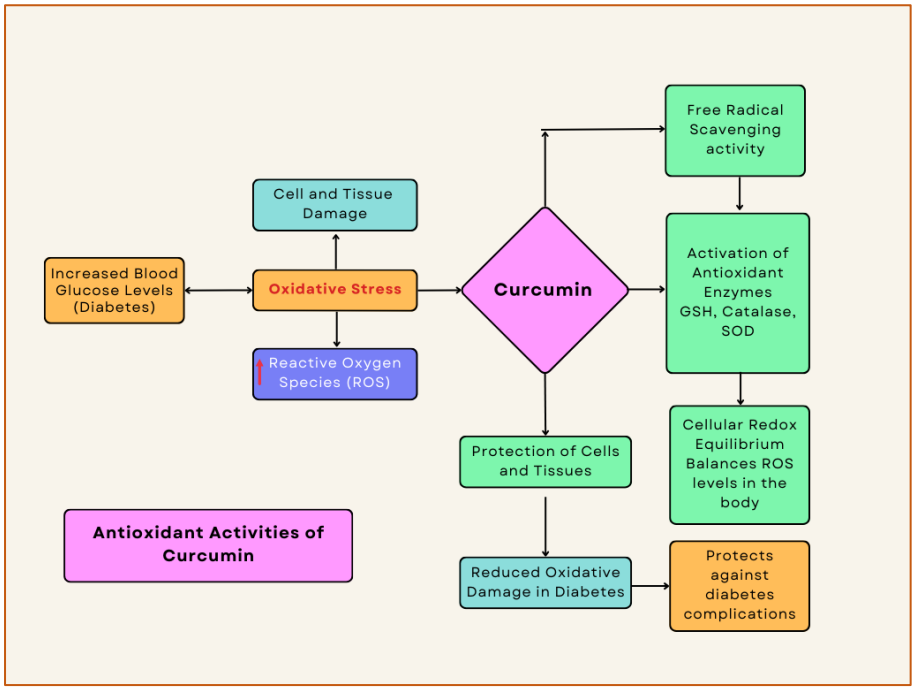

Figure 3. Mechanism of Antioxidant activities of Curcumin

Diabetic foot ulcers (DFU) are a severe consequence of DM that can lead to significant morbidity, mortality, and financial burdens. The causes of DFU include loss of glycaemic control, peripheral neuropathy, peripheral vascular disease, and immunosuppression (Akkus et al., 2022; Aumiller & Dollahite, 2015). Compared to a placebo, topical use of turmeric ointment at five weeks dramatically decreased the size of DFU in clinical research involving patients. Turmeric ointment is indicated to be a potential therapy for DFU (Agharazi et al., 2022). In a study, it was found that curcumin inhibited fibroblast apoptosis, promoted proliferation, migration, and angiogenesis, and accelerated wound healing in DFU rats by reestablishing the FBN1/TGF-β pathway by inhibition of miR-152-3p (Cao et al., 2024). Curcumin was effective in modifying the healing processes of injured skin tissue in a rat model of DFU. It reduced granulation tissue development, angiogenesis, collagen deposition, re-epithelialization, and tissue fibrosis. By lowering CRP expression (Xu et al., 2024). In a clinical study, C3-DiagardTM cream containing (0.05mg of *Curcuma longa* extract) was found effective and well tolerable in reducing the size of DFU and alleviating pain in 50 DM patients (Ruke et al., 2024). A clinical study of 78 participants suggested that the combination of curcumin gel and honey showed a prominent effect on the healing process of DFU (Khalid Ibrahim et al., 2024). In short, curcumin may be a potential treatment therapy for DFU. It is evidenced by clinical research and experimental models that curcumin reduces ulcer size, improves wound healing, and alleviates symptoms, making it a possible treatment choice for DFU.

4.8 Role of Curcumin on Diabetic Sexual Dysfunction

Sexual dysfunction (SD) refers to a variety of conditions that can disturb any stage of the sexual response cycle, including desire, arousal, physical pleasure, and orgasm. Both the mental and physical sides of intimacy may be impacted by these problems, which can make it difficult for a person to have satisfactory sexual relations. Relationships and quality of life can be significantly impacted by SD, which can be caused by psychological, physiological, or hormonal imbalances (Minaz et al., 2019). SD has been linked to DM in both men and women. Those with diabetes have a reported three-fold higher incidence of erectile dysfunction (ED) than those without DM, making DM a recognized risk factor for SD in males (Maiorino et al., 2014). Intracorporal pressure (ICP), which is a marker of erectile function, was enhanced in Zucker diabetic fatty rats by topical treatment of nanoformulated curcumin (Curc-np, 4 mg) every two days for two weeks (ICP/BP). Improved ICP/BP was correlated with a 60% drop in Nkap expression and a 60% rise in heme oxygenase-1 following curc-np therapy. These findings imply that Curc-np controls inflammatory indicators and cures ED effectively (Draganski et al., 2018). In another study, Decreased ICP and changed enzyme and gene expressions were used to confirm ED twelve weeks after diabetes induction. ICP, cGMP, and enzyme levels were all enhanced by the administration of curcumin or its water-soluble form daily for 12 weeks, with the water-soluble form having more pronounced and long-lasting benefits. Zinc protoporphyrin (ZnPP) lowered ICP/mean arterial pressure (MAP) and heme oxygenase-1 enzyme activity. The result suggested that curcumin can enhance erectile function effectively with an extended duration of action (Abdel Aziz et al., 2012).

5 Results

The review brings attention to the alarming increase in the incidence of diabetes, a long-term condition defined by high blood sugar levels caused by either insulin resistance or decreased insulin secretion (Dilworth et al., 2021). The bioactive component curcumin found in turmeric has several beneficial effects, including preventing hyperglycemia, inflammation, oxidative stress, and cell death (Rashid et al., 2017). According to Wei et al. (2023), it successfully decreases oxidative stress by reducing levels of reactive oxygen species (ROS), alleviating stress on the endoplasmic reticulum (ER), and restoring proper functioning of the mitochondria. Potentially via the Keap1-Nrf2-ARE pathway, curcumin improves antioxidant defense mechanisms in diabetes rats (Xie et al., 2018). According to Eguchi et al. (2021) and Darenskaya et al. (2021), it enhances insulin production and treats diabetes-related problems such as peripheral vascular disease, diabetic retinopathy, diabetic nephropathy, neuropathy, erectile dysfunction, and foot ulcers. Peng et al. (2021) and Zamanian et al. (2024) found that curcumin enhances its anti-inflammatory effects by inhibiting pro-inflammatory cytokines like IL-1, IL-6, and IL-8, as well as by blocking the NF-κB pathway and preventing the activation of the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome. By activating Nrf2, lowering inflammation, and preserving antioxidant enzymes, curcumin also protects kidney function (Trujillo et al., 2013). It may have renoprotective benefits because it blocks the activation of the NLRP3 inflammasome (Lu et al., 2017). In addition, curcumin helps treat diabetes problems by modulating the PI3K-Akt and Sirt1-Foxo1 pathways (Ren et al., 2020). The available information indicates that curcumin's antioxidants and anti-inflammatory potential show great potential in treating diabetes and its complications. The relevant clinical and nonclinical data on the possible benefits of curcumin in controlling diabetic complications is given in enormous detail in the corresponding parts on diabetic complications.

6. Discussion

Type 2 diabetes mellitus is a heterogeneous disorder characterized by insulin resistance with varying degrees of insulin secretory defects, followed by reduced insulin secretion from the pancreas

(pancreatic beta-cell dysfunction). Due to constant oxidative stress in diabetic cells, hyperpolarization is responsible for the long-term complications of diabetes (Dilworth et al., 2021). Oxidative stress stimulates the generation of inflammatory mediators, and inflammation, in turn, enhances the production of reactive oxygen species (Oguntibeju, 2019). The exacerbated ROS production can modulate several intracellular signaling pathways that lead to insulin resistance and impairment of β-cell function (Bhatti et al., 2022). In addition, hyperglycemia-induced ROS production contributes to micro- and macro-vascular diabetic complications like diabetic retinopathy, nephropathy, neuropathy, sensory impairments, and cardiovascular diseases (Caturano et al., 2023; Luc et al., 2019). *Curcumin* is a polyphenol that is prominent in controlling inflammatory mediators, oxidative stress, and various pathways related to insulin production. Results showed that curcumin has many valuable functions, including reducing inflammation, lowering blood sugar, preventing cell death, and lowering cholesterol, making it a helpful tool in managing type 2 diabetes (T2DM) (Gu et al., 2024). Based on prior studies, curcumin is known to have strong anti-inflammatory properties (Lin et al., 2024; Xu et al., 2021; Wei et al., 2023); (Trujillo et al., 2013; Lu et al., 2017; Ren et al., 2020; Miao et al., 2021; Zamanian et al., 2024). Based on prior studies, curcumin is known to have strong anti-inflammatory properties. It can alter MAPK and NF-κB, which in turn prevents the production of inflammatory cytokines such as IL-1, IL-1β, IL-6, IL-8, IL-17, and IL-27 (Nunes et al., 2024; Peng et al., 2021; Zamanian et al., 2024). The anti-inflammatory and antioxidant properties of curcumin make it an attractive candidate for treating diabetes and its consequences. However, additional clinical trials are necessary to improve its bioavailability and confirm its efficacy, which will help create better formulations.

7. Diabetes Management with Curcumin: Obstacles and Limitations

The low bioavailability of curcumin limits its medicinal potential, even though it is a potent bioactive chemical. Because of its fast metabolism, poor absorption, and rapid excretion, it cannot remain in the body for long periods, which is the main problem. Because of these issues, its high metabolic conversion rate and poor water solubility diminish its oral effectiveness (Arli & Celik, 2020). Curcumin has a low absorption rate in part because it is lipophilic. Although curcumin has demonstrated potential in the management of diseases such as diabetes, its efficacy is limited by these physicochemical constraints, calling for the creation of more sophisticated formulations to enhance its medicinal advantages (Ugo et al., 2022; Quispe et al., 2022; Ogbonnaya et al., 2023). Nanotechnology-based drug delivery technologies, such as nanoparticles, liposomes, and nanocapsules, have arisen as effective options to address the limited bioavailability of curcumin. These systems markedly improve curcumin's solubility and bioavailability, augmenting its efficacy in therapeutic applications, especially in diabetes treatment. Curcumin nanoformulations, including conjugates, cyclodextrins, micelles, nanospheres, and solid lipid nanoparticles (SLNs), enhance its capacity to regulate blood glucose, diminish inflammation, and mitigate diabetes-related problems (Jabczyk et al., 2021; Quispe et al., 2022). Methods such as PEGylation, which involves the conjugation of curcumin with hydrophilic polymers like polyethylene glycol (PEG), enhance its solubility and guarantee chemical stability (Racz et al., 2022). The co-ingestion of curcumin with lipids boosts its bioavailability and absorption. These enhanced nanoformulations significantly enhance curcumin's therapeutic efficacy, rendering it a more potent medication for treating metabolic illnesses such as diabetes (Ogbonnaya et al., 2023; Quispe et al., 2022). Adjuvants such as piperine, an active ingredient in black pepper, dramatically increase the absorption of curcumin by blocking the enzymes that cause the drug to be rapidly metabolized in the intestines and liver (Tabanelli et al., 2021; Bertoncini-Silva et al., 2024).

8. Conclusion

In conclusion, this review highlights curcumin, a polyphenolic molecule from turmeric, as a therapeutically potential substance in managing diabetes and its related consequences. Diabetes, which is characterized by long-lasting hyperglycemia, risks essential organs and causes cardiovascular disease, peripheral neuropathy, retinopathy, nephropathy, myopathy, and foot infections. Curcumin has gained popularity because of its several modes of action, which include the capacity to control oxidative stress, decrease inflammation, and improve endothelial function. These characteristics have a critical role in reducing the risk of diabetic complications, including retinopathy, neuropathy, nephropathy, cardiovascular disorders, cardiomyopathy, and erectile dysfunction. Because of the compound's ability to reduce oxidative damage and enhance metabolic parameters, diabetes treatment may benefit from an additional tactic. Clinical trials to confirm curcumin's safety and usefulness in broader populations, optimize dosage schedules, and investigate its synergistic effects with traditional medicines should be the main emphasis of future research. As we learn more about the biological effects of curcumin, it may become more significant in addressing diabetes management and its complications.

Author contributions

K.J.N. contributed to the conceptualization, data analysis, and manuscript preparation.

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Competing financial interests

The authors have no conflict of interest.

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