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Curcumin as a Potential Hypoglycaemic Agent for Managing Oxidative Stress

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ABSTRACT

This review outlined the basic mechanisms by which curcumin exerted protective effects in diabetes and discussed its potential as a supportive treatment for oxidative stress-related metabolic disorders. Curcumin, a yellow compound from the rhizomes of *Curcuma longa*, the primary active ingredient in turmeric. It was a lipophilic polyphenol, a bis-a, b-unsaturated b-diphenone, with the chemical formula C21H20O6 and the name (E,E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. This plant had several biological properties like antimicrobial, anti-inflammatory etc and one of which included anti-diabetic property as well. Diabetes mellitus was a metabolic disorder that has reached pandemic proportions world-wide. As the incidence of type 2 diabetes mellitus (T2DM) continues to rise globally, oxidative stress and inflammation have emerged as major drivers of its progression and complications. Oxidative stress plays a crucial role as one of the major causes of diabetes, as it leads to the destruction of pancreatic beta cells and a consequent lack of insulin production. Therefore, curcumin contributed to redox balance by enhancing the activity of endogenous antioxidant systems through the Nrf2-ARE signalling pathway and limiting inflammatory responses via inhibition of NF-κB. Additionally, it supported glucose regulation by improving insulin sensitivity, promoting glucose uptake, and reducing hepatic glucose production. Despite these promising effects, curcumin's therapeutic use was challenged by its poor oral bioavailability, leading to exploration of advanced delivery strategies including nanoparticles, liposomal encapsulation, and phytosome formulations.

KEYWORDS: Antioxidant, curcumin, diabetes, oxidative stress, inflammatory response, signalling pathways

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1. INTRODUCTION

In 2021, the International Diabetes Federation reported that 537 million adults were living with diabetes, which was 10.5% of the adult population. According to IDF projects that by 2045, this number will increase to 783 million, or 1 in 8 adults. Diabetes is one of the fastest growing endocrinal disorder in worldwide (Magliano and Boyko, 2021). Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycaemia, which arises due to either an absolute or relative deficiency of insulin, often in conjunction with insulin resistance. The condition has diverse etiologies and is primarily classified into two distinct forms: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Approximately 80% of diabetes cases are T2DM, while 5–10% develop T1DM. The liver plays a key role in regulating glucose and lipid metabolism and is central to the development and progression of diabetes (Cheng et al., 2025). T2DM is primarily characterized by insulin resistance and elevated blood glucose levels. Persistent hyperglycaemia increases advanced glycation end products (AGEs), triggering inflammation and oxidative stress (Patergnani et al., 2021). Oxidative stress plays a critical role in the development of type 2 diabetes mellitus (T2DM). Increased production of reactive oxygen species (ROS) and reduced antioxidant defences have been consistently observed in individuals with T2DM (Lie et al., 2007). Hyperglycaemia induces oxidative stress by activating the polyol pathway, protein kinase C, eicosanoid metabolism, and glucose auto-oxidation, leading to elevated ROS. These ROS impair insulin secretion, damage glucose transporters, oxidize proteins and DNA, increase free fatty acids, and raise vascular permeability (Shen et al., 2020; Salvatore et al., 2021). Additionally, oxidative stress causes the formation of advanced glycation end products (AGEs), which contribute to endothelial dysfunction and the progression of microvascular and macrovascular complications in T2DM (Chang et al., 2025). Inflammation may contribute to the progression of type 2 diabetes (T2DM), and this effect is amplified by hyperglycaemia, leading to further insulin resistance (Wittwer et al., 2021). Oxidative stress, caused by reactive oxygen species (ROS) like superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO•), damages proteins, nucleic acids, and membranes. It is closely linked to diabetes complications, including insulin resistance and cellular damage (Nielo et al., 2007). Therefore, oxidative stress may get develop due to acute glucose fluctuations (Chong et al., 2004). The rise in cellular glucose levels can contribute to the enhanced production of reactive oxygen species (ROS) (You et al., 2002). Under normal conditions, cells maintain redox balance using antioxidant defenses like superoxide dismutase, catalase, and the glutathione system (GSH, glutathione reductase, peroxidase, and S-transferase). Herbal medicines such as turmeric and bitter melon have long supported diabetes management through antioxidant and glucose-lowering effects.

Curcumin (CUR) exhibits potent antioxidant activity by directly scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS), including $O_2^{\bullet-}$, HO•, NO•, and $ONOO^{\bullet-}$, and indirectly boosting antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1) to protect cells and maintain metabolic balance (Marton et al., 2021). Curcumin is also very popular from ancient era and used as anti-inflammatory herbal medicine. Moreover, Curcumin shows potential in mitigating hyperglycaemia, hyperlipidaemia and associated liver injury induced by high-fat diet and STZ in rats, likely through its antioxidant and anti-apoptotic actions (Xia et al., 2020). Curcumin, the bioactive compound in *Curcuma longa*, offers antioxidant, anti-inflammatory, and hypoglycaemic effects, supporting its role in managing chronic diseases like diabetes. Despite low natural bioavailability, modern formulations have improved its efficacy (Li et al., 2024). This review highlighted curcumin's potential in preventing oxidative stress, reinforcing its value as a safe, natural adjunct to conventional therapies.

2. CURCUMIN

Among different species of curcuma the one which is mostly known to everyone is curcuma longa (Haldi). *Curcuma longae* rhizome, also referred to as "Ezhu" in China and commonly known as "turmeric" in English, is accurately identified as *Curcuma longa* L. [Zingiberaceae; Curcumae longae rhizoma] in pharmacopeia (Zhang et al., 2022). While it is widely used in traditional Chinese medicine, its medicinal uses extend across various traditional medicine systems in Asia, such as and it is now utilized globally (Ayati et al., 2019). Curcuma longa is a plant commonly known as turmeric frequently used as a spice in cooking. It is distinguished by its orange, tuberous rhizomes which is primarily grown and cultivated in Southeast Asia. The plant has gained recognition in the scientific community for its various properties and uses. *Curcuma longa* rhizome is well known for its strong antioxidant activity, primarily due to the presence of curcumin, β-elemene, and other bioactive phytochemicals (Yurasbe et al., 2023). Curcumin, the key component extracted from the rhizomes of the turmeric plant, has been shown to possess anti-inflammatory and antidiabetic properties, making it beneficial for health. This is why the plant has gain popularity from ancient era (Kunnumakkara et al., 2017). Moreover, curcumin has potential in preventing and treating several diseases through its antibacterial, antidiabetic, antiviral, and anticancer effects

(Sultana et al., 2021a). The chemical structure of curcumin is depicted in figure 1.

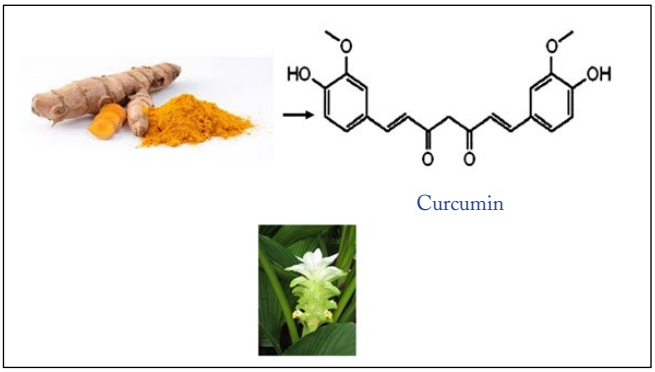

Figure 1: Chemical structure of Curcumin (Den Hartogh et al., 2020)

3. MECHANISMS OF ACTION OF CURCUMIN IN HYPERGLYCAEMIA

Hyperglycaemia leads to excessive free radical production, weakening the antioxidant defences (Catalase, Superoxide dismutase, Glutathione Peroxidase) and activating oxidative pathways along with AGE (Advanced Glycation End-products) formation. These leads to increase lipid peroxidation by disrupting membrane-oxidative disruption (Nowotny et al., 2015). Intake of curcumin enhances insulin sensitivity by activating AMP-activated protein kinase (AMPK), which plays a central role in energy homeostasis and glucose uptake. It also stimulates the expression and translocation of glucose transporter proteins (such as GLUT4), facilitating increased glucose absorption by muscle and adipose tissues (Ghorbani et al., 2014). Furthermore, curcumin suppresses hepatic gluconeogenesis, thereby reducing endogenous glucose production. Its strong anti-inflammatory action, mediated by the inhibition of nuclear factor-kappa B (NF-κB), helps decrease pro-inflammatory cytokines like TNF-α and IL-6, which are commonly elevated in diabetic conditions Figure (Kotha et al., 2019). An illustration of the inhibitory effect of curcumin through ROS scavenging and reduction of blood glucose levels is presented in Figure 2.

4. BIOAVAILABILITY OF CURCUMIN

According to studies, daily intake of curcumin up to 8000 mg over three months was well-tolerated without showing any signs of toxicity (Basnet and Skalko-Basnet, 2011). The overall safety profile of curcumin has been supported by findings from six clinical trials and five preclinical animal studies (Chainani-Wu, 2003). However, despite its non-toxic nature, high oral doses have occasionally been associated with gastrointestinal discomfort in humans and hepatotoxic effects in mice. A major limitation to curcumin's therapeutic use is its poor

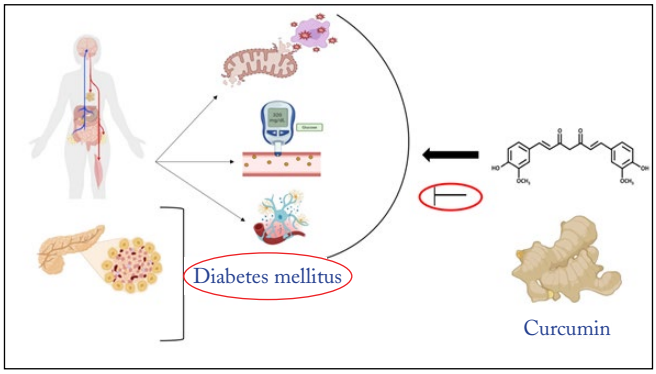

Figure 2: Pictorial representation of curcumin inhibiting hyperglycaemia, oxidative stress, and the inflammatory processes caused by Diabetes Mellitus

oral bioavailability, which is primarily due to low water solubility, limited absorption, rapid metabolism, and swift systemic elimination (Anand et al., 2007). As a result, only a small fraction of orally consumed curcumin reaches systemic circulation, reducing its effectiveness. To overcome these challenges, various approaches are being explored, including modifying the route of administration and structurally enhancing curcumin to improve its bioavailability (Anand et al., 2007).

To enhance the bioavailability, intestinal absorption, and systemic distribution of curcumin, various advanced delivery systems have been explored, including liposomes, micelles, phospholipid complexes, and nanoparticles (Neerati et al., 2014). Among these, the phytosome delivery system has emerged as one of the most promising technologies. Its structural compatibility with oral delivery makes it well-suited for curcuminoids and offers improved pharmacokinetic properties. The effectiveness and safety of phytosomal curcumin have been demonstrated in managing inflammatory conditions such as cancer, cardiovascular diseases, and osteoarthritis (Appendino et al., 2011).

Another strategy to improve the solubility and bioavailability of polyphenols like curcumin involves encapsulation in solid lipid nanoparticles, which has been shown to enhance cellular uptake and anti-tumour activity in vitro, as well as improve in-vivo bioavailability (Sun et al., 2013). Additionally, curcumin encapsulated in camel-casein micelles exhibited over 2000-fold improvement in solubility (Hu et al., 2018). Further, curcumin nano emulsions have also been reported to significantly enhance its oral bioavailability and therapeutic effectiveness (Tabanelli et al., 2021).

5. CURCUMIN AND OXIDATIVE STRESS

Curcumin, the principal curcuminoid derived from the rhizome of *Curcuma longa* (turmeric), has garnered considerable attention for its powerful antioxidant and anti-inflammatory effects, especially in the context of

oxidative stress. Oxidative stress arises due to an imbalance between the excessive production of reactive oxygen species (ROS) and the body's limited capacity to detoxify these reactive intermediates or repair the resulting damage. This imbalance plays a central role in the progression of various chronic conditions, including neurodegenerative diseases, cardiovascular disorders, diabetes, and cancer (Hewlings and Kalman, 2017).

Curcumin exerts its antioxidative effects through multiple mechanisms. It directly scavenges ROS, such as superoxide anions, hydrogen peroxide, and nitric oxide radicals, thereby neutralizing harmful species before they can damage cellular components (Figure 3). Moreover, curcumin enhances the body's endogenous antioxidant defences by activating the Nrf2 (nuclear factor erythroid 2–related factor 2) pathway. Upon activation, Nrf2 translocate to the nucleus and promotes the expression of several cytoprotective and antioxidant genes, including those encoding glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase the key enzymes in neutralizing oxidative stress (Menon and Sudheer, 2007).

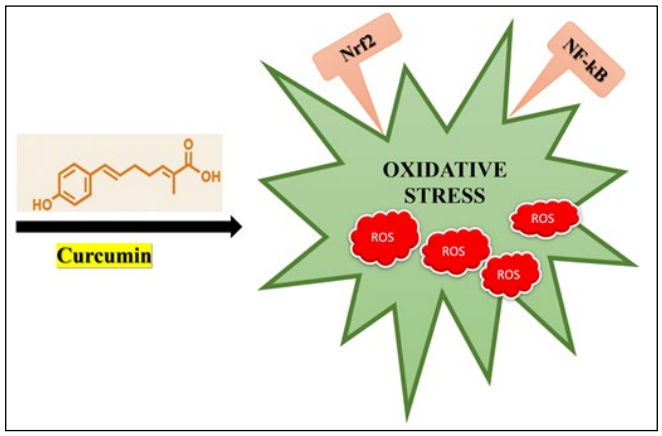

Figure 3: Effect of curcumin in inhibiting oxidative stress (Made by Biorender)

In parallel, curcumin inhibits the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signalling pathway, which is commonly upregulated under oxidative and inflammatory conditions. NF-κB controls the expression of pro-inflammatory cytokines and enzymes that amplify oxidative stress, such as COX-2 and iNOS. By suppressing NF-κB activation, curcumin effectively reduces inflammation-driven oxidative damage (Gupta et al., 2013). These dual actions like enhancement of antioxidant defences via Nrf2 and suppression of inflammation via NF-κB inhibition make curcumin a promising natural compound for the prevention and management of oxidative stress-related diseases (Kim et al., 2005). Effect of curcumin in different pathways has been listed in Table 1.

6. PRE-CLINICAL AND CLINICAL EVIDENCE

6.1. Pre-clinical Evidence

Animal studies consistently show that curcumin exerts antihyperglycemic and antioxidant effects in diabetes models. For example, Xia et al. (2020) found that curcumin markedly attenuated hyperglycaemia, hyperlipidaemia and liver injury in high-fat-diet/STZ diabetic rats. In a streptozotocin (STZ)-induced diabetic rat model, curcumin (50 mg kg^{-1}) reduced fasting blood glucose, improved oral glucose tolerance, and raised circulating insulin levels. Ghorbani et al. (2014) summarize that these effects arise from multiple mechanisms – curcumin lowers hepatic gluconeogenesis and suppresses inflammatory signalling, while upregulating GLUT-2/4 transporters, activating

Table 1: Effect of curcumin in different pathways

Pathway	Effect of Curcumin	Outcome	References
Nrf2-ARE	Activates Nrf2, which translocate to the nucleus and binds to antioxidant response elements (ARE)	Upregulates antioxidant enzymes (e.g., SOD, catalase, GPx); enhances cellular defense	Scapagnini et al., 2011
NF-κB	Inhibits activation and nuclear translocation of NF-κB	Reduces transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and oxidative enzymes (e.g., iNOS, COX-2)	Jobin et al., 1999; Aggarwal and Harikumar, 2009; Gbr et al., 2021
MAPK (p38, JNK, ERK)	Modulates mitogen-activated protein kinases—typically inhibits p38 and JNK, regulates ERK	Decreases inflammation and oxidative damage; promotes cell survival	Zingg et al., 2012; Park et al., 2021
PI3K/Akt	Activates PI3K/Akt signalling pathway, which supports Nrf2 activation	Promotes antioxidant gene expression and cell survival	Fu et al., 2018; Wu et al., 2020
Keap1	Curcumin disrupts Keap1-Nrf2 binding, freeing Nrf2	Enhances antioxidant gene transcription via ARE binding	Guerrero-Hue et al., 2020; Smirnova et al., 2023

AMPK/PPAR pathways and improving β-cell function.

6.1.1. Glycemic control and insulin sensitivity

In diabetic rodents' curcumin consistently lowers blood glucose and improves insulin action. For instance, high-dose curcumin significantly lowered fasting glucose and improved lipid profiles in diabetic rats (Xia et al., 2020). In one study, curcumin treatment (50 mg kg^{-1} day^{-1} for 8 weeks) decreased fasting glucose and increased insulin in STZ rats, also reducing total cholesterol and triglycerides. Pancreatic β-cell studies show that curcumin can reduce cytokine-induced apoptosis and enhance insulin secretion. Overall, these pre-clinical data indicate improved insulin sensitivity and glycaemic control with curcumin (Ghorbani et al., 2014).

6.1.2. Oxidative stress and antioxidant enzymes

Curcumin strongly boosts endogenous antioxidants and reduces lipid peroxidation in diabetic models. In rodent studies, it was found to be increased SOD, catalase activities and raised glutathione levels, while lowering malondialdehyde (MDA) (a marker of lipid peroxidation). For example, Panahi et al. (2017) reported that curcumin reduced serum MDA and increased total antioxidant capacity (TAC) and SOD activity in T2D patients, and Xie et al. (2018) found that curcumin lowered MDA and normalized antioxidant enzymes in STZ-diabetic rats. Mechanistically, curcumin activates the Nrf2 pathway to induce antioxidant genes (e.g. GPx, SOD) and inhibits NF-κB signalling to block oxidative inflammation.

6.1.3. Inflammation and cytokine markers

Although less emphasized in animal models, curcumin also suppresses pro-inflammatory cytokines. Curcumin treatment down-regulated NF-κB and reduced TNF-α/IL-6 expression in diabetic tissues. This anti-inflammatory action complements its antioxidant effects. In some rodent studies, curcumin analogues lowered markers of tissue inflammation and oxidative stress, contributing to improved metabolic outcomes (Hewlings and Kalman, 2017; Xia et al., 2020).

These preclinical findings support curcumin's potential in diabetes: it improves glycemic measures, enhances insulin sensitivity, and lowers oxidative stress in animal models (Asghari et al., 2024). However, translating these results to humans has challenges. Most rodent studies use high curcumin doses and short durations, and differences in metabolism limit direct extrapolation. Thus, while the animal evidence is promising, it primarily provides mechanistic rationale rather than definitive proof for clinical efficacy.

6.2. Clinical evidence

Numerous human trials and meta-analyses have explored curcumin in type 2 diabetes. Overall, curcumin supplementation tends to produce modest improvements in glycemic control, antioxidant status, and inflammation, though results vary. For instance, Mokgalaboni et al. (2024) performed a meta-analysis of 15 randomized trials (n≈1185) and found that curcumin significantly lowered HbA1c by about 0.54 %points compared to placebo. Many clinical trials reported similar trends: e.g. daily curcumin (500–1500 mg) for 8–12 weeks significantly reduced fasting blood glucose and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in T2DM patients (Panahi et al., 2017). In one double-blind trial, 1500 mg day^{-1} curcumin for 8 weeks cut insulin resistance (HOMA-IR) and improved β-cell function (HOMA-β) (Zeng et al., 2023).

6.2.1. Glycemic control

Curcumin treatment generally yields modest reductions in glucose and HbA1c. The aforementioned meta-analysis observed a significant HbA1c decrease (MD ≈ −0.54%) (Mokgalaboni et al., 2024). Individual trials have reported significant drops in fasting glucose with curcumin (with or without piperine) relative to placebo (Panahi, 2017). For example, Dastani et al. (2023) used nanocurcumin and observed a statistically significant FBG reduction. In aggregate, curcumin appears to improve glucose metabolism and insulin sensitivity (e.g. lower HOMA-IR) in T2DM.

6.2.2. Inflammatory and oxidative markers

Consistent with its antioxidant action, curcumin lowers inflammatory cytokines in patients. In T2DM trials, curcumin supplementation significantly reduced TNF-α, IL-6, hs-CRP and MDA, while increasing anti-inflammatory adiponectin and SOD (Zheng et al., 2018). For instance, a curcumin formulation (NCB-02) at 300 mg day^{-1} for 8 weeks decreased serum IL-6, TNF-α and MDA in T2DM patients. Similarly, a study of diabetic retinopathy patients found that curcumin+piperine (1000 mg curcuminoids+ piperine day^{-1}) raised total antioxidant capacity and SOD and lowered MDA versus placebo (Yang et al., 2021; Amini et al., 2024). In the meta-analysis, curcumin significantly lowered CRP (standardized mean difference ≈ −0.59) (Mokgalaboni et al., 2024), indicating reduced systemic inflammation.

6.2.3. Metabolic and lipoprotein profiles

Curcumin also favourably affected lipids in several trials. Randomized studies report that curcumin decreases triglycerides (TG), total cholesterol (TC) and LDL (Low density lipoprotein), and increases HDL (High density lipoprotein) in T2DM patients. For example, Panahi et al., 2017 noted significant TG and TC reductions with 1500 mg day^{-1} curcumin (Zeng et al., 2023) and nanocurcumin (80 mg day^{-1}) for 12 weeks similarly lowered TG, TC, LDL and VLDL (Very low density lipoprotein). These

lipid improvements likely contribute to curcumin's overall metabolic benefits.

6.2.4. Limitations and inconsistencies

Not all trials agree. Some studies found no significant effect of curcumin on glycaemic indices for example Mokgalaboni et al. (2024) observed no change in HbA1c or fasting glucose after curcumin (equivalent to placebo). Meta-analyses caution that many trials have small sample sizes, short durations and variable quality. Heterogeneity is high across studies, and evidence has geographic clustering (few data from high-T2D regions). Thus, while curcumin shows promise in improving blood glucose, insulin sensitivity and markers of oxidative stress/inflammation, the clinical effect sizes tend to be modest and context-dependent.

6.2.5. Bioavailability and delivery challenges

A key limitation for curcumin's clinical use is its poor oral bioavailability. Only about 1% of ingested curcumin is systemically absorbed (Zeng et al., 2023), due to low solubility and rapid metabolism. To overcome this, many trials employ enhanced formulations. For example, co-supplementation with piperine (a bioenhancer) or use of nanocurcumin capsules markedly increases curcumin plasma levels. Such formulations have shown good effects on oxidative stress markers and inflammation (e.g. nano-curcumin trials report greater reductions in CRP). Despite these advances, delivery remains a hurdle: future studies need to optimize dosage and formulation to ensure sufficient tissue exposure (Febriza et al., 2024).

7. POTENTIAL SYNERGIES: CURCUMIN IN COMBINATION WITH OTHER THERAPIES

Several recent studies have explored the co-administration of curcumin with standard antidiabetic drugs, reporting enhanced metabolic and oxidative outcomes. For example, a large randomized trial by Nasri et al., 2023 in women with polycystic ovary syndrome (PCOS) found that adding nanocurcumin to metformin resulted in significantly greater improvements in glycaemic indices, lipid profiles, and weight loss compared to either agent alone. In diabetic animal models, similar synergistic effects have been observed; Elsayed et al. (2022) demonstrated that diabetic rats treated with both curcumin and metformin showed larger reductions in fasting glucose and oxidative stress markers, including malondialdehyde (MDA), and enhanced antioxidant enzyme activities compared to metformin monotherapy. These benefits likely stem from complementary mechanisms (Lu et al., 2022). Curcumin's potent scavenging of reactive oxygen species (ROS) via Nrf2-HO-1 induction reinforces the antioxidant environment, while the glycaemic control achieved by antidiabetic drugs reduces glucose-driven oxidative stress (Elsayed et al., 2022; Nasri et al., 2023).

Curcumin has also shown additive effects when paired with other natural antioxidants or anti-inflammatory agents (Saha et al., 2022). In an in vitro model of oxidative injury in endothelial cells, Zhang et al. (2022) demonstrated that the combination of curcumin and resveratrol (particularly at an 8:2 ratio) synergistically activated the Nrf2/HO-1 pathway, markedly increasing nuclear Nrf2 translocation, HO-1 expression, and SOD activity, while reducing hydrogen peroxide-induced ROS levels more than either compound alone. Mohamed et al. (2023) in his in vivo studies observed that co-supplementation of curcumin with vitamin E significantly amplified antioxidant defences in diabetic rats, leading to a greater decrease in lipid peroxidation and an increase in testicular antioxidant capacity compared to monotherapy. Additionally, a recent 12-week randomized clinical trial by Rahimi et al. (2023) in patients with type 2 diabetes mellitus found that combining nano-curcumin with omega-3 fatty acids (EPA and DHA) produced larger reductions in systemic inflammatory markers and a more significant increase in total antioxidant capacity (TAC) than either treatment alone. Similar synergy has been noted with other nutrients; Li et al. (2022) reported that curcumin co-administered with vitamin D in a rodent arthritis model synergistically suppressed T-cell activation and inflammatory cytokines, providing stronger immune-modulatory effects compared to single treatments.

Collectively, mounting preclinical and emerging clinical evidence suggests that curcumin co-therapy enhances the management of oxidative stress and metabolic dysfunction. Acting through convergent pathways-including Nrf2-mediated antioxidant gene activation, NF-κB inhibition, and improved insulin/PPARγ signalling curcumin often produces additive or synergistic effects when combined with conventional antidiabetic drugs or nutraceutical antioxidants (Elsayed et al., 2022; Nasri et al., 2023). These findings support the rationale for developing integrated therapeutic regimens, such as curcumin combined with metformin or omega-3 fatty acids, to achieve better antioxidant protection, lower ROS levels, and more effective glycaemic control in diabetes and oxidative stress-related disorders.

8. CHALLENGES AND LIMITATIONS

Despite promising preclinical and clinical findings, several challenges limit the widespread therapeutic application of curcumin for oxidative stress and diabetes management. A major obstacle is curcumin's poor oral bioavailability, attributed to its low water solubility, rapid metabolism, and swift systemic elimination (Anand et al., 2007; Hewlings and Kalman, 2017). Studies have demonstrated that following oral ingestion, only trace amounts of curcumin reach systemic circulation, severely

restricting its therapeutic potential (Ghosh et al., 2021).

Efforts to address this limitation have led to the development of novel delivery systems, including nanoparticles, liposomes, micelles, and phytosome-based formulations (Neerati et al., 2014). For example, nano-curcumin formulations have significantly improved solubility and absorption, leading to enhanced antioxidant and anti-inflammatory effects in diabetic and oxidative stress models (Mokgalaboni et al., 2023). Similarly, phytosomal curcumin preparations have been associated with superior pharmacokinetic profiles and more pronounced clinical benefits compared to native curcumin (Panahi et al., 2017).

Another challenge is the variability in clinical outcomes. Although many studies report significant improvements in glycaemic control, oxidative stress markers, and inflammatory cytokines, others have found minimal or no effects (Dastani et al., 2022a; Liang et al., 2023a) These discrepancies likely arise from differences in study designs, curcumin formulations, dosages, treatment durations, sample sizes, and population characteristics. Moreover, optimal dosing regimens for curcumin remain undefined, with clinical trials using a wide range of doses (from 80 mg day^{-1} to 1500 mg day^{-1}) without standardized guidelines (Ghorbani et al., 2014; Panahi et al., 2017).

We all know that safety considerations also warrant attention. Although curcumin is generally recognized as safe (GRAS) and is well tolerated even at high doses (up to 8,000 mg day^{-1}), occasional gastrointestinal discomfort, nausea, and mild hepatotoxic effects have been reported, particularly with long-term or high-dose usage (Basnet and Skalko-Basnet, 2011; Chainani-Wu, 2003). Recent trials confirm a favourable safety profile for nano-formulated and phytosomal curcumin, but emphasize the need for ongoing monitoring, especially in populations with comorbidities (Mokgalaboni et al., 2023).

In addition, the heterogeneity of curcumin products available commercially-ranging from pure curcumin extracts to complex turmeric mixtures poses regulatory challenges and complicates reproducibility in clinical settings (Sultana et al., 2021b). Standardization of curcumin content and rigorous quality control are necessary to ensure consistency in research outcomes and clinical applications.

9. FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

Although significant progress has been made in elucidating curcumin's role in managing oxidative stress and metabolic disorders, several avenues remain for future investigation. One of the most urgent needs is to enhance the bioavailability of curcumin. Despite promising advances with nanoparticle, liposomal, micellar, and phytosomal formulations, further optimization is required to maximize systemic absorption while ensuring safety and scalability (Mokgalaboni et al., 2023; Alrashdi et al., 2024). Future studies should aim to develop novel carriers such as exosome-based systems or hybrid nanocarriers that can further improve curcumin's pharmacokinetics and targeted tissue delivery.

Another critical area is the integration of curcumin with existing pharmacotherapies. Current evidence suggests that curcumin exhibits synergistic effects when combined with antidiabetic agents, antioxidants, and anti-inflammatory compounds (Zhang et al., 2022; Nasri et al., 2023). However, systematic evaluation of optimal combination strategies, dosing schedules, and long-term safety profiles remains lacking. Future clinical trials should focus on testing curcumin as an adjunct therapy, particularly alongside standard antidiabetic treatments like metformin, GLP-1 receptor agonists, or SGLT2 (Sodium-glucose cotransporter 2) inhibitors, to explore potential additive or synergistic benefits.

Moreover, large-scale, multicentre, randomized controlled trials are necessary to validate curcumin's efficacy and safety in diverse populations. Most existing clinical studies are limited by small sample sizes, short durations, and regional bias (Dastani et al., 2022b; Liang et al., 2023b). To generalize findings globally, future trials must include varied demographic groups, including elderly individuals, patients with multiple comorbidities, and high-risk ethnic populations. Extended follow-up periods are also essential to assess the long-term impact of curcumin supplementation on metabolic outcomes, cardiovascular risk, and diabetes-related complications.

Mechanistic studies at the molecular level represent another promising direction. Although curcumin's activation of the Nrf2-ARE pathway, inhibition of NF-κB signaling, and stimulation of AMPK-mediated glucose uptake have been demonstrated (Menon and Sudheer, 2007; Hewlings and Kalman, 2017), the exact upstream regulators, epigenetic modifications, and cross-talk with other redox-sensitive pathways (e.g., MAPK, JNK) require further exploration. Advanced techniques such as transcriptomic profiling, metabolomics, and CRISPR-based gene editing could help unravel novel mechanisms and identify biomarkers predictive of curcumin responsiveness.

In addition, precision medicine approaches should be incorporated into future research. Individual differences in curcumin metabolism, gut microbiota composition, genetic polymorphisms, and oxidative stress status may influence therapeutic outcomes (Ghosh et al., 2021). Personalized dosing strategies and biomarker-driven patient selection could enhance treatment efficacy and minimize variability.

Finally, establishing regulatory standards for curcumin supplements is a pressing need. The heterogeneity of commercially available curcumin products with varying purity, bioavailability, and dosing poses a major challenge to clinical translation (Sultana et al., 2021b). Future research should prioritize developing standardized, clinically validated curcumin formulations and achieving regulatory approvals based on Good Manufacturing Practices (GMP).

10. CONCLUSION

Curcumin, a key bioactive compound from Curcuma species especially *Curcuma longa* showed strong potential as an adjunct therapy for oxidative stress and metabolic dysfunction in diabetes. Preclinical studies supported curcumin's multifaceted actions, including glycemic control, antioxidant enhancement, and inflammation suppression via Nrf2 activation and NF-κB inhibition. Clinical findings, though limited, aligned with these benefits, especially with improved formulations. Despite challenges like poor absorption and inconsistent outcomes, curcumin showed promise as a safe, effective adjunct in managing oxidative stress-related chronic diseases.

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