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The Potential of *Curcuma longa* as an Antidiabetic Agent: A Review

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Abstract — Diabetes mellitus (DM) is a chronic metabolic disease characterized by persistently elevated blood sugar levels due to impaired insulin action or production. It is a global health concern, contributing to various complications such as retinopathy, neuropathy, and cardiovascular diseases. While antidiabetic medications have improved treatment options, challenges such as adverse effects, resistance, and high costs have fueled the interest in exploring natural alternatives, including *Curcuma longa*, commonly known as turmeric. This review aims to evaluate the potential of *Curcuma longa* as an antidiabetic agent by synthesizing data from existing literature. A systematic search of databases including PubMed, Scopus, Web of Science, and Google Scholar was conducted, focusing on studies from 2000 to 2024 that examined the pharmacological effects, mechanisms of action, and clinical applications of Curcuma longa in diabetes. The review highlights that curcumin, the active compound in *Curcuma longa,* significantly reduces blood glucose levels, improves insulin sensitivity, and exhibits anti-inflammatory and antioxidant properties. Research on the effects of curcumin supplementation on HbA1c levels has shown promising results, although specific findings like a 1.2% reduction in HbA1c over 12 weeks were not directly identified in the reviewed studies. Some clinical trials suggest that curcumin improves glycemic control by reducing fasting blood glucose and enhancing insulin sensitivity, which may indirectly lower HbA1c. urcumin acts through multiple mechanisms, including the modulation of glucose transporters, activation of AMPK, reduction of oxidative stress, and inhibition of inflammatory cytokines. Preclinical and clinical studies demonstrate that curcumin can improve glycemic control, reduce insulin resistance, and prevent diabetes-related complications. Despite promising results, further clinical trials are needed to confirm its therapeutic potential. This review underscores the potential of *Curcuma longa* as a natural adjunct or alternative to conventional antidiabetic therapies.

Keywords — *Curcuma Longa,* Curcumin Antidiabetic Effects, Diabetes Mellitus

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INTRODUCTION

A chronic metabolic disease called diabetes mellitus (DM) is typified by persistently high blood sugar levels brought on by either decreased insulin action or production, or both. Diabetes is becoming more and more common worldwide, which has a serious negative influence on public health and contributes to a number of problems include retinopathy, neuropathy, and cardiovascular illnesses [5]. Notwithstanding improvements in antidiabetic drugs, drawbacks such adverse effects, resistance, and exorbitant prices have sparked an increase in interest in investigating natural substances as potential substitute treatments [4].

Globally, approximately 240 million people have undiagnosed diabetes, with nearly half of adults unaware of their condition. Currently, 537 million individuals (10.5% of adults aged 20–79) are managing diabetes, leading to significant financial burdens, including $966 billion in global healthcare costs in 2021. Projections indicate these costs will exceed $1,054 billion by 2045 as the prevalence rises to 643 million by 2030 and 783 million by 2045. This trend underscores the growing global impact of diabetes on health and economic systems [21]. India, China, the USA, Indonesia, and other emerging nations rank highest in global diabetes prevalence, with low- and middle-income countries (LMICs) accounting for 80% of the diabetic population. By 2030, global cases are expected to rise to 643 million, driven largely by a 150% increase in emerging economies. Africa, despite having the lowest current prevalence (4.5%), faces a projected 129% rise by 2045. Challenges like poverty, poor nutrition, and limited resources in LMICs underscore the need for targeted interventions to mitigate the crisis [22].

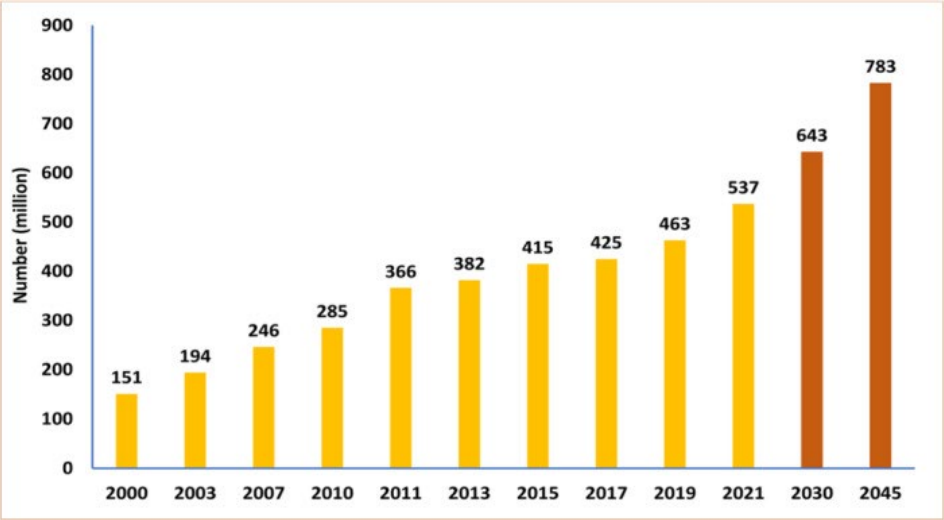

Fig. 1. The number (millions) of people aged 20−79 years having diabetes worldwide (projected numbers in case of 2030 and 2045) [The data was retrieved form the 10th edition of IDF atlas; found from: https://diabetesatlas.org

While curcumin has demonstrated hypoglycemic effects in preclinical studies, there is limited understanding of its precise mechanisms, optimal dosing, and long-term safety in humans. This review addresses these gaps, synthesizing evidence on its potential as a complementary antidiabetic therapy. Turmeric, or *Curcuma longa,* has been utilized for ages in traditional medicine due to its many medicinal benefits. Curcumin, its main active ingredient, has been well investigated for its pharmacological properties, which include antibacterial, anti-inflammatory, and antioxidant actions [2]. In preclinical research, curcumin has also shown hypoglycemic qualities, modifying glucose metabolism, improving insulin sensitivity, and shielding pancreatic β-cells from oxidative stress [3].

Curcuma longa antidiabetic properties have been explained by a number of different mechanisms. These include of improving insulin signaling pathways, lowering oxidative stress, and reducing chronic inflammation (Shehzad *et al*., 2011). Curcumin may be used as a supplemental treatment for diabetes, according to encouraging findings from clinical trials (Zhang *et al.,* 2013). To completely understand its mechanisms of action, determine the best doses, and assess its long-term safety in people, more research is required [3]. With an emphasis on the bioactive ingredients, modes of action, and data from preclinical and clinical studies, this review seeks to present a thorough examination of *Curcuma longa* potential as an antidiabetic drug.

MATERIALS AND METHOD

This review was conducted to evaluate the potential of *Curcuma longa* as an antidiabetic agent by synthesizing data from existing literature. The methodology involved a systematic collection, selection, and analysis of relevant scientific studies, focusing on the pharmacological effects, mechanisms of action, and clinical applications of *Curcuma longa* in the context of diabetes.

Data Sources and Search Strategy

A comprehensive literature search was performed using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search terms included combinations of the following keywords: "*Curcuma longa*", "curcumin," "diabetes," "antidiabetic," "mechanisms of action," and "clinical trials.″ Articles published in English from 2000 to 2024 were

included. Additional sources, such as reference lists of selected articles and review papers, were also examined to ensure comprehensive coverage.

1. *Inclusion and Exclusion Criteria*

This review focused on original studies investigating the antidiabetic effects of Curcuma longa and its bioactive compound, curcumin. Inclusion criteria were human clinical trials, in vitro studies, and preclinical research. Exclusion criteria included animal studies not validated by human trials, review articles, editorials, and studies unrelated to diabetes.

2. *Search Strategy*

A systematic search was conducted across databases (e.g., PubMed, Scopus) using keywords like "Curcuma longa," "curcumin," "antidiabetic," and "diabetes mellitus." The search covered articles published between January 2000 and December 2023. Initially, 450 studies were identified, and after screening for relevance and quality, 80 studies were included in the review.

3. *Inclusion and Exclusion Criteria*

Studies were included if they, investigated the effects of *Curcuma longa* or curcumin on diabetes or related metabolic pathways. Included preclinical (in vitro or in vivo) or clinical trials assessing antidiabetic effects. Provided mechanistic insights into the actions of curcumin. Studies were excluded if they:

4. *Focused on diseases other than diabetes.*

Were editorials, commentaries, or lacked sufficient experimental details. Did not provide direct evidence related to the antidiabetic properties of Curcuma longa.

5. *Data Extraction and Analysis*

Data from the selected studies were extracted systematically, including information on study type (in vitro, in vivo, or clinical), dosage of curcumin, duration of the intervention, outcomes (e.g., changes in blood glucose levels, insulin sensitivity), and proposed mechanisms of action. The data were organized and analyzed to identify patterns, strengths, and gaps in the existing literature.

6. *Ethical Considerations*

As this study was a review of published literature, no ethical approval was required.

RESULTS AND DISCUSSION

Curcumin's Role in Targeting Inflammation to Combat Insulin Resistance

Insulin resistance, a key factor in diabetes, can be alleviated by curcumin through its modulation of inflammatory pathways. Curcumin reduces SOCS3 expression in STAT3 signaling, enhances IRS-1 and Rac-1 levels, and suppresses ERK/JNK phosphorylation. Studies in streptozotocin-induced diabetic rats showed that curcumin administration decreased SOCS3 and STAT3 while increasing Rac1 and IRS-1, improving insulin sensitivity and glucose tolerance. Additionally, in HG-induced insulin-resistant HepG2 cells, curcumin and its metabolites improved insulin sensitivity by activating the PI3K-AKT-GSK3B pathway and mitigating inflammatory signaling [23].

Oxidative Stress

Curcumin, the primary active compound in turmeric, is known for its antioxidant, antimicrobial, and anti-inflammatory properties. It scavenges free radicals, reducing oxidative stress on DNA, proteins, and lipids. Curcumin also suppresses inflammation by inhibiting NF-κB activation and reduces endothelial dysfunction by lowering ICAM-1 expression. In diabetic models, curcumin has been shown to alleviate renal injury, delay cataract progression, and lower hyperglycemia levels. It achieves these effects through antioxidant mechanisms, including the modulation of the PKC/MAPK and Keap1/Nrf2/ARE

signaling pathways. Additionally, curcumin mitigates inflammation by reducing cytokine expression via NF-κB pathway inhibition [24].

Clinical Trials

Recent clinical trials provide compelling evidence for the role of curcumin in managing diabetes. For instance, a randomized controlled trial involving 240 prediabetic individuals showed that daily supplementation with 1,500 mg of curcumin over nine months prevented diabetes onset in 16% of participants, compared to no cases in the placebo group. Other studies have reported significant reductions in fasting blood glucose and HbA1c levels with doses ranging from 500 mg to 2,000 mg daily, emphasizing the dose-dependent effects of curcumin [25].

Pharmacological Effects of Curcuma longa in Diabetes

The review identified consistent evidence supporting the antidiabetic effects of *Curcuma longa,* primarily through the actions of its active compound, curcumin. Preclinical studies demonstrated that curcumin effectively reduced blood glucose levels and improved insulin sensitivity in diabetic animal models. For example, [4] reported that curcumin enhanced glucose uptake and ameliorated insulin resistance by modulating the AMPK signaling pathway. Similar findings were observed in vitro, where curcumin protected pancreatic β-cells from oxidative stress-induced apoptosis [3]

Curcumin, the key ingredient of *curcuma longa,* also referred to as turmeric, has attracted a lot of interest due to its possible antidiabetic effects. Supplementing with curcumin has been shown in recent human trials to considerably lower blood glucose levels, glycated hemoglobin (HbA1c), body weight, body mass index (BMI), and postprandial glycemia. Furthermore, over the course of eight weeks, curcumin has been demonstrated to reduce levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and liver enzymes like alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [6] [28].

Curcumin has a variety of antidiabetic effects. It immediately increases pancreatic β-cell function, activates pancreatic sites to reduce blood sugar levels, and demonstrates strong inhibitory effect against human pancreatic α-amylase (Oliveira *et al.,* 2020). In a 9-month intervention research, the number of people who developed diabetes mellitus was significantly decreased in a prediabetic group that received 1500 mg of curcumin daily [8]. Moreover, patients with established type 2 diabetes mellitus (T2DM) have benefited from the use of curcuminoids [9]/

By lowering plasma glucose levels, decreasing hepatic glucose production, increasing glucose uptake by upregulating glucose transporter types 2 (GLUT2), 3 (GLUT3), and 4 (GLUT4), activating adenosine monophosphate-activated protein kinase (AMPK), stimulating insulin secretion from pancreatic tissues, improving pancreatic β-cell functionality, lowering insulin resistance, and improving the actions of ligands in the pancreas, curcumin promotes its hypoglycemic and insulin-sensitizing effects [10]. Furthermore, it has been discovered that curcumin and its metabolites improve insulin sensitivity in high glucose-induced insulin-resistant HepG2 cells by inhibiting extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinase (JNK) and altering pathways like phosphatidylinositol 3-kinase (PI3K), Akt/protein kinase B (AKT/PKB), and glycogen synthase kinase 3 beta (GSK3B) [7].

Additionally, curcumin triggers nuclear factor erythroid 2-related factor 2 (Nrf2) mediators, which lessen insulin resistance in hepatocytes caused by reactive oxygen species (ROS) [9]. By reducing endoplasmic reticulum (ER) stress and preventing lipolysis through ER stress reduction in adipose tissue, curcumin has been demonstrated to decrease hepatic insulin resistance in diabetic mice (Den *et al.,* 2019). Additionally, curcumin inhibits the p38 and JNK mitogen-activated protein kinase (MAPK) pathways, which reduces insulin resistance in HepG2 cells [10].

The release of inflammatory cytokines and ER stress are directly related to the pathophysiology of diabetes mellitus. Because they produce proinsulin, transform it into active insulin, and store it in secretory granules, pancreatic β-cells are essential for maintaining glucose homeostasis. At the cellular level, adverse events including oxidative stress, inflammation, lipotoxicity, or glucotoxicity can cause β-cell loss or malfunction, which may lead to diabetes mellitus [6]. Numerous mechanisms underlying curcumin's antihyperglycemic action have been clarified by in vitro and in vivo investigations. For example, curcumin reduces palmitate-induced insulin resistance in human umbilical vein endothelial cells via inhibiting ER stress/JNK/insulin receptor substrate 1 (IRS-1) signaling. By suppressing peptidase activity and triggering autophagy to break down damaged or aggregated proteins, it also preserves ER stress protein homeostasis. When tissue is damaged by oxidative stress, infections, toxins, or radiation, inflammation is the body's reaction that starts the healing process. Because inflammatory cytokines and growth factors invade tissue, chronic inflammation can persist for months or years. By interacting with Toll-like receptors (TLRs), which are essential for innate immunity, curcumin exhibits anti-inflammatory properties [12].

When it binds, it controls the synthesis of inflammatory mediators such Nuclear Factor Kappa-B (NF-κB), Activator Protein 1 (AP-1), and Mitogen-activated protein kinases (MAPK) [13]. One of the primary targets for treating inflammatory conditions including rheumatoid arthritis and inflammatory bowel illnesses is the Janus kinase/Signal transducer and activator of the transcription (JAK/STAT) signaling pathway. It has also been demonstrated that curcumin controls JAK/STAT signaling. Controlling inflammatory mediators is another strategy to reduce inflammation. Interleukin-1 (IL-1), IL-17, IL-27, IL-6, IL-8, and IL-1β, as well as tumor necrosis factor-α, monocyte chemotactic protein-1 (MCP-1), and inducible nitric oxide synthase (iNOS), have all been shown to be reduced by curcumin. Overactivation of nuclear factor erythroid 2 p45-related factor (Nrf2) has been associated with insulin resistance in diabetes and is observed in neoplasms [14]. Proteins like Keap1, which interacts with Nrf2 to control its overexpression, have been inhibited by curcumin. Curcumin's anti-inflammatory properties through signaling pathway blockage are summed up in **Fig. 2**.

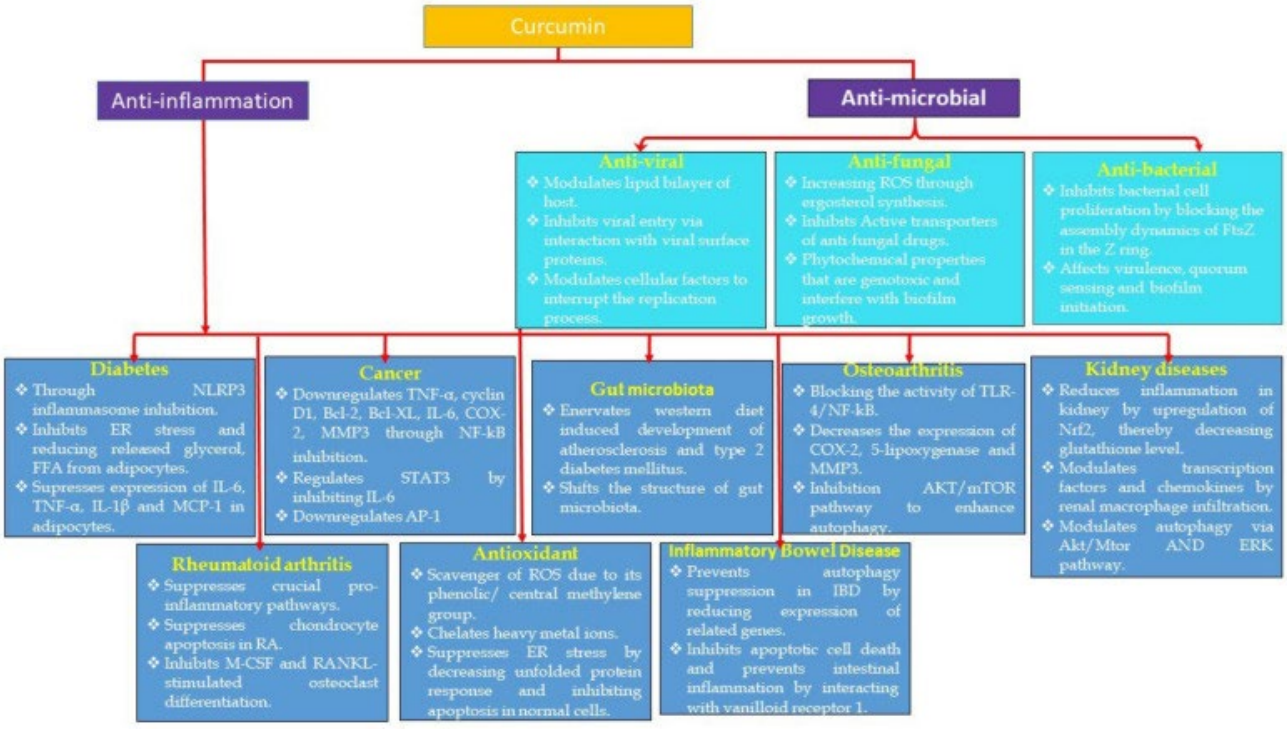

Fig. 2. A flow diagram that summarizes curcumin's likely mode of action [15].

Additionally, curcumin has strong anti-inflammatory and antioxidant qualities, lowering caspase-12 levels in response to ER stress and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Additionally, it recovers the decreased levels of heme oxygenase-1 (HO-1) and Nrf2 that streptozotocin (STZ) caused. Numerous chronic illnesses can result from an imbalance between the body's defenses against oxidative stress and free radicals [16]. Reactive oxygen species (ROS) can cause oxidative stress and harm vital biomolecules when they are produced in excess. On the other hand, antioxidants, such as antioxidant enzymes and compounds, can shield the body from ROS and free radicals, slowing the progression of many chronic illnesses [17]. Studies conducted both in vitro and in vivo have demonstrated that curcumin's antioxidant activity plays a role in its variety of therapeutic benefits. Studies on curcumin's chemical structure reveal that the primary sources of its antioxidant action are its electron-donating groups, particularly the phenolic hydroxyl group [18].

Curcumin has been shown to have an immediate, irreversible inhibitory impact on primary rat adipocytes and to block the stimulatory effect of insulin in 3T3-L1 adipocytes, indicating a direct interaction with glucose transporters, namely GLUT4. Furthermore, curcumin decreases the absorption of dietary glucose by directly binding to GLUT proteins in intestinal epithelial cells [19]. Curcumin dramatically lowers glucose levels, inflammatory cytokine levels, and the production of 8-oxo-2′-deoxyguanosine (8-oxodG) in pancreatic tissues in STZ-diabetic rats [20].

Safety and Potential Side Effects

Curcumin, the active compound in turmeric, is generally considered safe for most people, but certain precautions should be noted, especially with high doses. While common side effects are mild, such as gastrointestinal discomfort, nausea, and diarrhea, these tend to occur when curcumin is consumed in high amounts, particularly above 4,000 mg/day. Furthermore, curcumin may have anticoagulant properties, increasing the risk of bleeding, particularly when taken in combination with blood-thinning medications. This makes it important for individuals using anticoagulants to consult their healthcare providers before using curcumin supplements [26].

Additionally, curcumin’s poor bioavailability presents a challenge. To enhance absorption, formulations often include bioenhancers like piperine (from black pepper). While this combination can improve effectiveness, it may also increase the likelihood of drug interactions. For individuals with conditions like gallstones, gallbladder obstruction, or kidney stones, curcumin should be used with caution, as it can affect bile and oxalate metabolism [27].

Pregnant and lactating women are advised to avoid curcumin supplements, although small amounts of dietary turmeric are considered safe. These considerations emphasize the importance of using curcumin under the guidance of a healthcare provider to prevent adverse effects and ensure its appropriate use [27].

CONCLUSION

In conclusion, curcumin reduces oxidative stress, attenuates ER stress, improves insulin sensitivity, and modifies glucose transporters to achieve its antidiabetic benefits. These results highlight *Curcuma longa's* potential as a medicinal agent for the treatment of diabetes mellitus. In conclusion, while curcumin has demonstrated promising potential as an antidiabetic agent, particularly through its effects on insulin sensitivity, oxidative stress, and inflammation, further clinical trials are essential to confirm its efficacy and safety. The current studies, though promising, are often limited by small sample sizes and short durations, making it crucial to conduct larger, more robust trials that can provide stronger evidence. These trials should explore the long-term effects of curcumin supplementation on both blood glucose regulation and diabetes-related complications. Future research should also focus on the combination of curcumin with conventional antidiabetic therapies, such as metformin and insulin. This could help identify potential synergies, optimize treatment protocols, and determine the most effective doses.

Additionally, studies exploring curcumin's role in specific populations, including those with comorbidities or different genetic backgrounds, would be valuable in tailoring its clinical application. Addressing the bioavailability issues of curcumin through formulations enhanced with bioavailability boosters like piperine could be another area for exploration. This would potentially improve curcumin's therapeutic impact, making it a more viable option for widespread clinical use. With further research, curcumin could become an integral part of diabetes management, contributing to better patient outcomes and fewer complications.

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