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Biochemical and Biological Properties of Curcumin and its Association with Carbohydrate Metabolism: A Review Article

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A B S T R A C T

Introduction: Carbohydrates, popularly known as sugars, are one of three major macromolecules essential for the functioning of living organisms. Altered carbohydrate metabolism can lead to the development of type 2 diabetes mellitus (T2DM). Uncontrolled blood glucose in T2DM is a risk factor for several serious complications, including cardiovascular and cerebrovascular disease, nephropathy, retinopathy, and neuropathy. Synthetic pharmaceuticals are often used by subjects with T2DM to reduce these risks. However, natural compounds from plants might be good candidates for enhancing carbohydrate metabolism and for the improvement of glycemic control.

Aim: The present study was aimed at assessing the biochemical and biological properties of curcumin with special reference to carbohydrate metabolism.

Discussion: Curcumin is the yellow pigment and the most important bioactive component of turmeric, which is obtained from the rhizomes of this medicinal plant. It has unique biological and structural features and variable bioavailability. The positive physiological effects of curcumin depend on the dose and the time of administration. Recently, curcumin nanoformulations have been proposed as novel therapeutic modalities to improve their bioavailability and clinical efficacy. Curcumin has structural properties that allow it to penetrate cells easily and exert beneficial metabolic effects by improving insulin secretion and sensitivity via modulation of glucagon-like peptide-1 (GLP-1), lipid metabolism, and inflammatory signaling pathways. Preclinical studies and randomized controlled trials (RCTs) have shown that curcumin is significantly associated with pathways involved in carbohydrate metabolism.

Conclusion: The available evidence suggests that curcumin may significantly improve carbohydrate metabolism and glycemic control in patients with type 2 diabetes mellitus. Curcumin, with its antioxidant, anti-inflammatory, and insulin-sensitizing properties, may be a promising natural therapeutic agent for the management of impaired glucose metabolism. But we need large clinical trials to prove that it works in the long run, at the right dose, and is safe.

Keywords: Curcumin, Turmeric, Carbohydrate, Glycemic, T2DM, Preclinical, RCT

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Introduction

Carbohydrates, or sugars, are one of three major classes of macromolecules required for physiological functions in living organisms (1). Carbohydrates are important for providing energy so cells can work. They exist in simple forms like glucose and fructose and in complex forms like sucrose and starch (2). Carbohydrate metabolism disorder is the primary cause of type 2 diabetes mellitus (T2DM). It comprises the majority of the cases of diabetes mellitus. This is usually the result of either inadequate insulin secretion or a reduced ability of the body to use insulin effectively (3, 4). Uncontrolled T2DM is associated with several complications such as cardiovascular and cerebrovascular diseases, nephropathy, retinopathy and neuropathy (5-7). Synthetic medications are usually used by subjects with T2DM to attenuate diabetic complications. These medicines have therapeutic benefits, but can also produce a range of adverse effects and may worsen blood glucose levels. Thus, natural compounds obtained from plants are a promising alternative to improve glycaemic control and increase carbohydrate metabolisms.

Curcumin is a yellow pigment and the main active ingredient of turmeric, obtained from the rhizomes of the medicinal plant (8). The present study explored the biochemical and biological properties of curcumin and its role in carbohydrate metabolism. Moreover, it aims to determine whether the results of the current study can be a basis for a systematic review and meta-analysis to explore the association of curcumin and carbohydrate metabolism in future studies.

This article is a narrative review, and the databases used were Google Scholar, PubMed, and Scopus. Most of the studies analysed were published in the period 2010–2025. Articles published before 2010 are less frequently used. The keywords were curcumin, carbohydrate, T2DM, FBS, FPG, insulin, HOMA-IR, FFA, DAG, cholesterol, IRS, PKC, PPAR, AMPK, TNF-α, IL-1β and TLR4. Most of the studies included in this narrative review were mainly research articles of preclinical and randomised controlled trial (RCT) phases. However, only a few review articles were analysed. A total of about 100 articles were screened; similar articles were excluded, and about 76 articles were selected to include in the final analysis.

Biochemical and Biological Properties of Curcumin

Curcumin is a bioactive compound with a specific molecular structure and biological properties as well as excellent bioavailability. The therapeutic effect of the compound is highly dependent on dose and time. The biological actions of curcumin include several physiological processes and chemical reactions in the body. Structurally, curcumin consists of two phenolic rings connected by an aliphatic chain, making it a bis-α,β-unsaturated β-diketone, known as 'diferuloylmethane', and has the chemical formula $C_{21}H_{20}O_6$ (9-11). Curcumin is generally available as a yellow powder; the colour is due to its β-diketone structure. This characteristic hue is significantly contributed by the electron-conjugated system. This yellow pigment can be easily detected at high concentrations (12). Curcumin is soluble in organic solvents like acetone, methanol, ethanol and dimethyl sulfoxide (DMSO). But it is poorly soluble in water. This solubility profile has a major effect on its absorption and bioavailability in the human body (10, 13). Curcumin has been chemically modified in different light, temperature and pH, which can lead to degradation. Therefore, the stability of this theory in different formulations should be carefully examined (14). For example, curcumin's chemical structure can be destabilised by acidic, alkaline or ultraviolet light (15). Moreover, oxidative reactions are also important in the degradation of curcumin, and bicyclopentadione was identified as the major product of oxidative degradation (16). High temperatures favour the degradation of curcumin and thus decrease its therapeutic efficacy (17). The

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presence of excess moisture or water influences the stability of curcumin, and it can be degraded by oxidation and hydrolysis under humid conditions (18). Curcumin can be made more stable in neutral pH, storage in light-protected environments or opaque packaging, low and stable temperature, non-oxidative conditions or vacuum packaging techniques, dry environments and incorporation of nanoparticle technologies. Moreover, curcumin possesses an interesting property of a colour change from yellow in acidic conditions to red-orange in alkaline conditions at a pH of 8.5 or higher. This colour change is due to the protonation of curcumin, which transforms it from the keto (yellow) to the enol (red) form (19). Commercial curcumin contains about 77% diferuloylmethane, 17% dimethoxycurcumin and 6% bisdemethoxycurcumin (20). Curcumin has low bioavailability when taken orally. The bioavailability of substances such as curcumin in oral delivery systems comprising bioactive compounds is restricted by processes such as absorption, metabolism, distribution and excretion. However, the limited bioavailability of curcumin may not be an important issue because daily ingestion of high-dose curcumin may be beneficial to health. However, it is worth mentioning that long-term use of high-dose curcumin may lead to side effects, which can diminish its therapeutic benefits (21). Moreover, curcumin nanoformulation is proposed as a new therapeutic strategy to enhance the clinical effectiveness of curcumin. This method improves the aqueous solubility and can be targeted to specific tissues, which improves bioavailability, increases drug delivery efficiency and accelerates therapeutic outcomes (22). There are various methods of synthesis of nanocurcumin, like the Fessi method, nanoprecipitation, thin film hydration, microemulsion, emulsion polymerisation, ultrasonication, wet milling, spray drying, antisolvent precipitation, ionic gelation, solvent evaporation, coacervation, single emulsion and solid dispersion. These techniques have resulted in the development of different curcumin-based nanoformulations, such as micelles, liposomes, cyclodextrins, conjugates, and nano- or nanosphere structures (23). Piperine is the major bioactive compound of black pepper and accounts for most of its medicinal effects (24). Co-administration of curcumin with piperine improves the intestinal absorption of curcumin and inhibits its rapid hepatic metabolism, thus significantly increasing its bioavailability (25, 26). Hosseini et al. announced that fasting blood sugar (FBS) levels were significantly reduced in patients with T2DM and hypertriglyceridemia with the curcumin-piperine complex (27).

After absorption, curcumin undergoes a series of hepatic biotransformation processes. It is carried to the liver, where it is converted into several derivatives. Phase I and II metabolism of curcumin has been confirmed by both in vivo and in vitro studies. In phase I, the four double bonds of the heptane-3,5-dione system are sequentially reduced, yielding primary metabolites such as tetrahydrocurcumin and hexahydrocurcumin, while dihydrocurcumin and octahydrocuminol (also known as hexahydrocurcuminol) are formed to a lesser extent. The main enzyme in phase I metabolism is alcohol dehydrogenase. In phase II, the conjugation of the reduced metabolites takes place to form monoglucuronide, monosulphate and mixed sulphate/glucuronide derivatives (28) (Figure 1).

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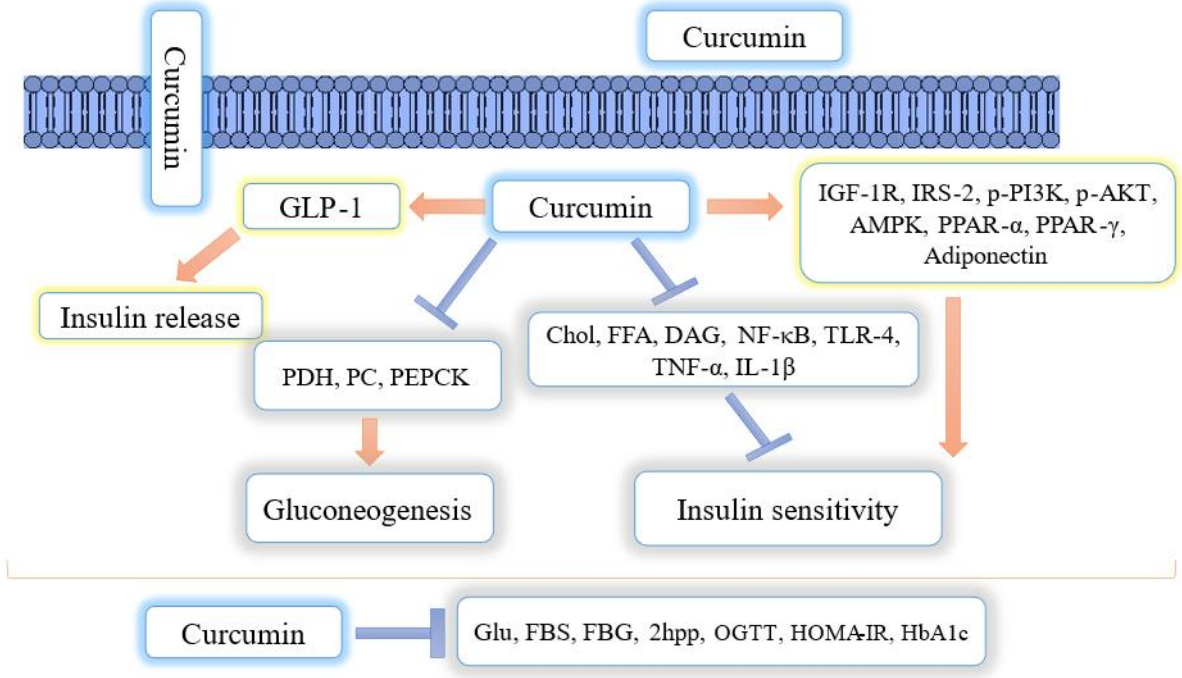

Figure 1. The effects of curcumin on sugar metabolism. Curcumin increases insulin secretion and sensitivity by acting on GLP-1, lipid metabolism, and inflammatory factors, thereby improving metabolism and glycemic indices. GLP-1: glucagon-like peptide-1, IGF-1R: insulin-like growth factor-1 receptor, IRS: insulin receptor substrate, PPAR: proliferator-activated receptor, PDH: pyruvate dehydrogenase, PC: pyruvate carboxylase, PEPCK: phosphoenolpyruvate carboxykinase.

Discussion

Curcumin's Relationship with Carbohydrate Metabolism

The interlinked metabolic pathways are aggravated by carbohydrates, as mentioned earlier, causing diabetic complications. Elevated glucose levels and accumulation of secondary and advanced products of carbohydrate metabolism result from impaired insulin secretion and signalling (29). The following sections discuss the mechanisms and agents that influence curcumin's effects on carbohydrate metabolism.

Curcumin effects on carbohydrate metabolism with involvement of lipids

The influx of pancreatic β-cells is caused by an increase in serum low-density lipoprotein cholesterol (LDL-C). These molecules accumulate intracellularly and interfere with insulin secretion (30). Curcumin has a significant effect on cholesterol and LDL-C reduction (31, 32). Curcumin may therefore stimulate the secretion of more insulin. Increased cellular cholesterol levels lead to accumulation of cholesterol in the cell membrane and attenuation of membrane fluidity. This leads to mislocalisation of insulin receptor subunits and associated adaptor proteins, resulting in impaired insulin signalling (33). Increased triglyceride (TG) levels are associated with increased free fatty acid (FFA) and metabolite synthesis rates, including diacylglycerol (DAG). These FFAs and DAGs impair the function of the insulin receptor substrate (IRS) and decrease insulin sensitivity by activation of protein kinase C (PKC) (34, 35). PKC activation is a major contributor to insulin resistance in diabetic states. Su et al. demonstrated that curcumin significantly decreased FBG, LDL-C, and FFAs in rat models of T2DM (36). Furthermore, Wang et al. also demonstrated that curcumin enhanced insulin signalling by up-regulating the expression of proteins like insulin-like growth factor-1 receptor (IGF-1R), IRS-2, phosphoinositide 3-kinase (PI3K), phosphorylated

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PI3K (p-PI3K), Akt, and phosphorylated Akt (p-Akt) in the brains of APPswe/PS1dE9 mice (37).

The insulin signalling pathway influences cholesterol metabolism. Insulin suppresses FoxO1 activity in the liver, reduces the amount of 12α-hydroxylated bile acids, disrupts cholesterol absorption, and thus reduces plasma cholesterol levels in mice with hepatic deletion of the insulin receptor (38), as reported by Semova et al. Shao and colleagues showed that curcumin can improve insulin signalling in adipose tissue and hepatocytes. In addition, it downregulated hepatic lipogenic genes in C57BL/6J mice fed with either a low-fat or high-fat diet (HFD) (39).

Peroxisome proliferator-activated receptor gamma (PPARγ) is highly expressed in macrophages in adipose tissue (40). Activation of PPARγ increases insulin sensitivity by increasing the secretion of adiponectin (41). Thus, PPARα, PPARγ and adiponectin stimulate β-oxidation of FFAs (42, 43). Also, they greatly reduce the activation of PKC. Zhao et al., in their study, showed that curcumin improved insulin resistance in HFD rats by upregulation of PPARα and PPARγ (44). Demir et al. observed that curcumin at a 50 mg/kg/day dose increased the transcript levels of PPARα and PPARγ in Wistar albino rats (45). Moreover, Gao et al. demonstrated that the expression of PPARγ was enhanced in mouse Raw264.7 macrophages treated with curcumin (46). Adenosine monophosphate-activated protein kinase (AMPK) is an important regulator of fatty acid oxidation. Kim et al. (47) showed that curcumin increased glucose uptake in rat L6 myotubes through the activation of the AMPK-p38 MAPK signalling pathways.

Curcumin has been shown in studies to suppress glucose production. Wang et al. found that curcumin suppressed mitochondrial oxidation, thereby restricting the uptake of FFAs and inhibiting the accumulation of acetyl CoA, leading to reduced lipid accumulation. Therefore, curcumin preserved the activity of pyruvate dehydrogenase (PDH) but inhibited the activity of pyruvate carboxylase (PC) (48). Fujiwara et al. (49) reported that curcumin inhibited the hepatic gluconeogenesis by activating AMPK and inhibiting the activities of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK).

Other studies on effects of curcumin on glycaemic indexes

The homeostasis model assessment of insulin resistance (HOMA-IR) is a validated method (50) to quantify insulin resistance. This metric enables the evaluation of metabolic function, particularly in subjects at risk of T2DM and other metabolic diseases (51). Huang et al. (52) reported that curcumin significantly improved HOMA-IR in T2DM rat models. In an RCT by Thota et al. (53), curcumin supplementation (180 mg/day) for 12 weeks in patients with T2DM and Alzheimer's disease resulted in a significant reduction in HOMA-IR. In another RCT reported by Yaikwawong et al., supplementation of curcumin (1500 mg/day) for 12 months significantly decreased the levels of HOMA-IR, FBS and glycosylated haemoglobin (HbA1c) in T2DM patients (54). In an RCT, Karandish et al. showed that supplementation with curcumin (500 mg) significantly increased fasting plasma glucose (FPG), 2-hour postprandial glucose (2-hpp), HbA1c, insulin levels, and total insulin sensitivity in overweight or obese subjects with prediabetes (55). Furthermore, Mokhtari et al. showed that diabetic foot ulcer patients who were supplemented with nanocurcumin (80 mg/day) for 12 weeks had significant reductions in FPG and HOMA-IR levels (56).

Glucagon-like peptide-1 (GLP-1) is a glucoincretin hormone produced in enteroendocrine cells of the gut and released upon food intake. This hormone promotes the secretion of insulin from pancreatic beta cells (57). Kato et al. (58) demonstrated that administration of curcumin (1.5 mg/kg) to Sprague-

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Dawley rats improved glucose tolerance by increasing the secretion of glucagon-like peptide-1 (GLP-1). Moreover, Seo et al. reported that curcumin supplementation (0.02%, w/w) significantly reduced HbA1c and HOMA-IR levels in diabetic db/db mice. Moreover, curcumin suppressed the activities of G6Pase and PEPCK (59). Besides, curcumin was shown to significantly decrease the hepatic mRNA expression levels of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) in diet-induced obese (DIO) mice (60).

Other factors that lead to reduced insulin sensitivity include interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α) (61). NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) upregulates expression of IL-1β and TNF-α (62). One important pathway that leads to NF-κB activation is the toll-like receptor 4 (TLR4) pathway (63). These factors are inhibited by the expression and activity of curcumin (52, 64).

Table 1 presents the relationship between curcumin and carbohydrate metabolism in preclinical studies, whereas Table 2 summarises the RCT studies.

Table 1. Published studies on the relationship between curcumin and sugar metabolism in preclinical phase.

Study	Dosage	Cellular or molecular mechanism	Effects on glycemic variables	Study model
(60)	40 mg/kg 80 mg/kg	G6pase, PEPCK ↓	-	DIO mice
(66)	100 mg/kg	AMPK ↑	Glu ↓	Diabetic rats
(58)	1.5 mg/kg	Glucose tolerance ↑	GLP-1 ↑	Sprague-Dawley rats
(36)	-	α-C, TNF-FFAs, LDL ↓	FBG ↓	T2DM rat models
(37)	100, 200, 400 mg/kg	R1-IGF, IRS-2, PI3K, p-PI3K, Akt, p-Akt ↑	-	APPswe/PS1dE9 mice
(52)	200 mg/kg	B, TLR4κ-NFα, -TNF ↓	Glu, HOMA-IR ↓	T2DM rats
(44)	100 mg/kg	γPPARα, PPAR ↑ Bκ-NFα, -TNF ↓	Glu ↓	HFD rats
(64)	-	Bκ-NF, IL-1β, α-TNF ↓	Insulin ↑ Glu ↓	Diabetic rats
(47)	10 μM	p38, AMPK, Glucose absorption ↑	-	Rat L6 myotubes
(48)	50 mg/kg	PC, cAMP/PKA Gluconeogenesis ↓ PDH ↑	FBG ↓	HFD mice
(49)	25 μM	G6pase, PEPCK, Gluconeogenesis ↓ AMPK ↑	-	Liver of C57/BL6J mice

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(59)	0.02% w/w	G6pase, PEPCK, FFAs, cholesterol ↓	HOMA-IR, HbA1c ↓	Diabetic db/db mice

DIO: diet-induced obesity, T2DM: type 2 diabetes mellitus, HFD: high-fat diet

Table 2. Published RCT studies on the relationship between curcumin and sugar metabolism.

Study	Dosage	Cellular or molecular mechanism	Effects on glycemic variables	Study model
(67)	500 mg	-	FBG ↓	PCOS patients
(68)	250 mg	Adiponectin ↑	HOMA-IR, FBG, OGTT ↓ HbA1c	T2DM patients
(69)	200 mg	-	HOMA-IR ↓	Subjects with suboptimal values of FPG
(70)	1000 mg	-	FBG ↓	PCOS patients
(71)	500 mg	-	HOMA-IR ↓	Rheumatoid arthritis patients
(54)	1500 mg	Adiponectin ↑	HOMA-IR, FBS, HbA1c ↓	T2DM patients
(55)	500 mg	-	FBG, 2hpp, HbA1c ↓ insulin ↑	Overweight or obese prediabetic subjects
(72)	500 mg	FFAs ↓	FBS, HbA1c ↓	Patients with nonalcoholic simple fatty liver disease
(73)	500 mg	PPARγ ↑	FBG, HOMA-IR ↓	PCOS patients
(74)	400 mg	-	FBG ↓	Individuals with obesity
(75)	70 mg	-	FBS, HbA1c ↓	NAFLD patients
(76)	250 mg	Adiponectin ↑	HOMA-IR ↓	T2DM patients
(77)	80 mg	-	FBG ↓	Patients with diabetes

PCOS: polycystic ovary syndrome, NAFLD: non-alcoholic fatty liver disease

Conclusion

Curcumin is a bioactive compound with unique molecular structure, biological properties and bioavailability. Its therapeutic efficacy varies with the dose and duration of administration. Curcumin is also prone to decomposition under different conditions such as light, temperature and pH variations. Furthermore, the curcumin nanoformulation is suggested as a novel therapeutic strategy to enhance the clinical efficacy of

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curcumin. Preclinical studies and RCTs have demonstrated that curcumin is associated with mediators that influence carbohydrate metabolism. These studies showed that this compound improves glycaemic control and metabolic indices through its effects on GLP-1, lipid metabolism and inflammatory mediators. Preclinical studies have laid a basis for understanding the effects of curcumin on human glucose metabolism. In human studies, oral curcumin doses ranging from 70 to 1500 mg/day have been used to improve glucose metabolism. It is unlikely that the poor bioavailability of curcumin will be of much concern. However, it should be noted that the long-term administration of high doses of curcumin may cause adverse effects, which could potentially reduce its therapeutic efficacy.

Long-term use of high-dose curcumin may be associated with impaired wound healing, decreased cell proliferation, increased cellular stress, DNA damage and apoptosis (65). So the possible side effects of high-dose curcumin should be further studied at preclinical and clinical phases. In future studies, animal and human studies can be performed to compare the improvement in carbohydrate metabolism at different doses and side effects of this compound. These findings indicate that future investigations can conduct systematic studies and meta-analyses to investigate the association between curcumin and glucose metabolism.

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CRediT authorship contribution statement

Conceptualization: ANA, MK, Methodology, Validation: NES, Formal Analysis, Investigation, Resources: FB, RD, Software, Data Curation: DQ, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: ANA, DQ.

Declaration of Generative AI and AI-assisted technologies in the writing process

No artificial intelligence tools were used to write the article.

Conflict of interest

The authors declare no competing interests.

Ethical considerations

The work in this paper used only previously published literature and did not involve human participants, animals, clinical data or personally identifiable information. Thus, ethical approval and informed consent were not required for this review study based on the institutional and international guidelines for research ethics.

Data availability statement

This study is a narrative review article that does not have specific data.

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