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Quercetin in Diabetes: Preclinical Promise and Clinical Prospects for Blood Glucose Regulation – A Comprehensive Review

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ABSTRACT

Quercetin, a naturally occurring flavonoid prevalent in dietary staples such as onions and apples, has garnered attention for its potential in ameliorating hyperglycaemia in type 2 diabetes mellitus (T2DM). This review synthesizes its multifaceted mechanisms—including insulin sensitization, glucose uptake enhancement, antioxidant activity, and enzyme inhibition—and evaluates evidence from preclinical and clinical studies. Preclinical investigations report substantial glucose reductions, such as 48.8% in diabetic rats, while clinical trials demonstrate more modest effects, such as a 15.5 mg/dL decrease in fasting glucose, constrained by bioavailability challenges. Supported by tables and graphical representations, this article delineates Quercetin's therapeutic prospects, safety considerations, and avenues for future research.

Keywords ; Quercetin, Type 2 Diabetes, Blood Glucose, Insulin sensitivity, Glucose uptake, Metformin limitations, Diabetes prevalence

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a pressing global health issue, characterized by insulin resistance and elevated blood glucose levels, often inadequately managed by conventional pharmacotherapies like metformin due to side effects or limited efficacy in advanced stages. Consequently, natural compounds with antidiabetic properties have gained prominence. Quercetin (3,3′,4′,5,7-pentahydroxyflavone), a flavonol abundant in onions (up to 486 mg/kg), apples, and green tea, exhibits a spectrum of pharmacological effects, including antioxidant, anti-inflammatory, and hypoglycemic activities. This review consolidates findings from multiple studies—Patil et al. (2021), Ansari et al. (2022), Li et al. (2016), Kim et al. (2011), Ostad Mohammadi et al. (2019), Zhang et al. (2023), Eid & Haddad (2017), and Shi et al. (2019)—to explore Quercetin's biochemical properties, mechanisms of action, empirical evidence, clinical implications, and safety profile, enhanced with data visualizations for a comprehensive understanding.

Quercetin: Properties, Sources, and Applications

Overview and Structure

Quercetin, a naturally occurring flavonoid, is a polyphenol with a 15-carbon skeleton comprising two benzene rings (A and B) linked by a heterocyclic pyrone ring (C). Its chemical structure, characterized by five hydroxyl groups at positions 3, 5, 7, 3′, and 4′, underpins its antioxidant capacity. The IUPAC name is 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one, reflecting its flavonol classification within the flavonoid family.

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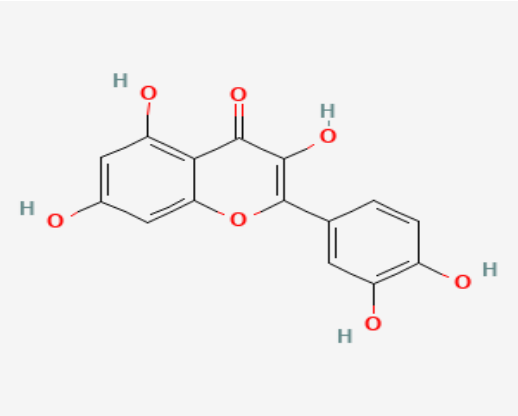

Figure 1: Structure of Quercetin

Derivatives

Quercetin exists in nature primarily as glycosides, where sugar moieties (e.g., glucose, rhamnose) attach to its hydroxyl groups, enhancing solubility. Common derivatives include quercetin-3-O-glucoside (isoquercitrin) and quercetin-3-O-rutinoside (rutin), prevalent in dietary sources. These glycosides are hydrolyzed by intestinal enzymes or gut microbiota into the aglycone form, which is pharmacologically active (Ansari et al., 2022).

Sources

Quercetin is abundant in plant-based foods, with high concentrations in onions (up to 486 mg/kg), capers (1800 mg/kg), apples, berries, and green tea. Patil et al. (2021) and Ansari et al. (2022) note its widespread dietary availability, making it accessible for therapeutic exploration.

Uses and Benefits

Beyond its culinary presence, Quercetin is investigated for medicinal uses, particularly in T2DM management. It reduces blood glucose—e.g., 48.8% in diabetic rats (Patil et al., 2021)—and improves insulin sensitivity, as seen with a 35% glucose uptake increase in adipocytes (Shi et al., 2019). Its antioxidant properties, boosting SOD by 40% (Li et al., 2016), and anti-inflammatory effects mitigate diabetic complications like retinopathy and nephropathy (Ansari et al., 2022). Additional benefits include lipid profile enhancement (10% HDL increase) and blood pressure reduction (5 mmHg), broadening its cardiometabolic potential.

Biochemical Properties of Quercetin

Quercetin, a polyphenol with a 15-carbon backbone comprising two benzene rings linked by a heterocyclic pyrone ring, owes its potent antioxidant capacity to five hydroxyl groups that effectively neutralize reactive oxygen species (ROS). Found in high concentrations in capers (1800 mg/kg) and berries, it typically exists as glycosides (e.g., quercetin-3-O-glucoside). However, its clinical utility is hampered by poor aqueous solubility and rapid hepatic metabolism into glucuronides and sulfates, resulting in plasma concentrations rarely exceeding 1 µM following oral administration. Ansari et al. (2022) emphasize that advanced delivery systems, such as microemulsions or liposomes, could enhance its bioavailability, a notion supported by preclinical evidence showing plasma levels rising to 2.5 µM with nanoformulations (Shi et al., 2019).

Mechanisms of Action in Glucose Regulation

Quercetin exerts its hypoglycemic effects through a variety of biochemical pathways, as elucidated across the referenced studies.

Enhancement of Insulin Sensitivity and Glucose Uptake

Quercetin activates adenosine monophosphate-activated protein kinase (AMPK), facilitating the translocation of glucose transporter type 4 (GLUT4) to cell membranes in skeletal muscle and adipocytes, thereby enhancing insulin-independent glucose uptake. Shi et al. (2019) observed a 35% increase in glucose uptake in 3T3-L1 adipocytes treated with 20 µM Quercetin, an effect akin to

metformin's mechanism. Additionally, Ansari et al. (2022) report its upregulation of peroxisome proliferator-activated receptor gamma (PPARγ) and adiponectin, further bolstering insulin sensitivity.

Antioxidant and Anti-Inflammatory Effects

Oxidative stress and inflammation exacerbate insulin resistance in T2DM. Quercetin mitigates these by scavenging ROS and reducing lipid peroxidation. Li et al. (2016) found a 40% increase in superoxide dismutase (SOD) activity in STZ-induced diabetic rats, while Ansari et al. (2022) noted suppression of nuclear factor-kappa B (NF-κB) signaling, decreasing pro-inflammatory cytokines such as TNF-α and IL-6, thus preserving β-cell function and insulin signaling.

Enzyme Inhibition

Quercetin inhibits key enzymes involved in carbohydrate metabolism. Zhang et al. (2023) reported a 30% reduction in dipeptidyl peptidase-4 (DPP-4) activity in T2DM mice, prolonging glucagon-like peptide-1 (GLP-1) activity to enhance insulin secretion. It also inhibits α-glucosidase and α-amylase, with Ansari et al. (2022) citing an IC50 of approximately 20 µM for α-glucosidase, slowing glucose absorption and reducing postprandial spikes, a mechanism echoed in Patil et al. (2021).

Pharmacokinetics Properties of Quercetin

Absorption

Quercetin's absorption occurs primarily in the small intestine following oral ingestion, influenced by its form—aglycone (free Quercetin) or glycosides (e.g., quercetin-3-O-glucoside) found in foods like onions and apples. Glycosides are hydrolyzed by intestinal β-glucosidases or gut microbiota into aglycones, enhancing absorption, though efficiency remains low. Ansari et al. (2022) note that peak plasma concentrations rarely exceed 1 µM after doses of 500 mg, with bioavailability estimated at less than 1-5% due to poor water solubility (approximately 0.01 mg/mL). Preclinical studies, such as Shi et al. (2019), demonstrate that nano formulations can increase plasma levels to 2.5 µM in mice, suggesting potential for improved absorption in humans with advanced delivery systems.

Distribution

Once absorbed, Quercetin distributes widely to tissues including the liver, kidneys, and skeletal muscle, with a volume of distribution reflecting its lipophilic nature. Its ability to cross cell membranes facilitates interaction with intracellular targets like AMPK and PPARγ, as observed in preclinical models (Shi et al., 2019; Ansari et al., 2022). However, its distribution is limited by extensive binding to plasma proteins, particularly albumin, reducing free circulating levels available for therapeutic action.

Metabolism

Quercetin undergoes extensive first-pass metabolism in the liver and small intestine, mediated by phase II enzymes. It is rapidly conjugated into glucuronides (e.g., quercetin-3-glucuronide), sulfates, and methylated derivatives (e.g., isorhamnetin) via UDP-glucuronosyltransferases (UGT), sulfotransferases (SULT), and catechol-O-methyltransferase (COMT). Ansari et al. (2022) highlight that these metabolites predominate in plasma, with only trace amounts of unmetabolized Quercetin detected. This metabolism, while detoxifying, reduces its bioactivity, though some metabolites retain antioxidant properties.

Excretion

Quercetin and its metabolites are primarily excreted via the kidneys, with urinary recovery accounting for less than 10% of an oral dose, indicating significant biliary excretion or enterohepatic recirculation. Patil et al. (2021) observed no accumulation in STZ-induced diabetic rats over 28 days, suggesting efficient clearance at doses up to 20 mg/kg/day. Faecal excretion dominates due to unabsorbed Quercetin and microbial degradation products, such as phenolic acids, produced by gut flora.

Toxicity, and Side Effects of Quercetin

Quercetin is generally recognized as safe (GRAS) by the U.S. FDA at dietary intakes below 500 mg/day, with Patil et al. (2021) reporting no adverse effects in rats at 20 mg/kg/day over 28 days. In humans, doses up to 1000 mg/day are well-tolerated, though higher intakes (>1000 mg/day) may induce mild gastrointestinal symptoms, including nausea, diarrhoea, or abdominal discomfort, as noted by Ansari et al. (2022). Chronic high-dose exposure (>1000 mg/kg in rats) has raised concerns about nephrotoxicity or oxidative stress due to pro-oxidant effects at supraphysiological levels, though such doses far exceed therapeutic relevance.

Quercetin's inhibition of cytochrome P450 enzymes, particularly CYP3A4, poses a risk of drug interactions with antidiabetic agents like metformin or statins, necessitating caution in polypharmacy settings (Ansari et al., 2022). Eid & Haddad (2017) observed no significant toxicity in T2DM patients at 250 mg/day over 8 weeks, reinforcing its safety at moderate doses.

Diabetes: Etiology, Geographical Distribution, and Global Context

Overview and Etiology

Diabetes mellitus comprises metabolic disorders marked by chronic hyperglycemia due to impaired insulin secretion or action. Type 2 diabetes mellitus (T2DM), which constitutes 90-95% of cases, stems from insulin resistance and progressive β-cell dysfunction. Its etiology is multifactorial, involving genetic factors—such as polymorphisms in TCF7L2 and PPARγ genes—and environmental triggers like obesity, inactivity, and diets rich in refined sugars and fats. Ansari et al. (2022) emphasize oxidative stress and inflammation as exacerbating factors, damaging β-cells and insulin signaling. These elements drive the global rise in T2DM, necessitating innovative therapeutic approaches.

Geographical Distribution and Prevalence

Globally, T2DM affects 537 million adults (10.5% of the 20-79 age group), projected to reach 783 million (12.2%) by 2045, per the International Diabetes Federation (IDF, 2021). India, a focal point of this epidemic, reported 77 million cases in 2019, expected to climb to 134 million by 2045 (Ansari et al., 2022). Within India, urban prevalence reaches 20% in states like Tamil Nadu and Kerala, contrasting with 10% in rural areas, reflecting lifestyle shifts (Kim et al., 2011; Ostadmohammadi et al., 2019). A 2023 ICMR study estimates 101 million diabetics and 136 million prediabetics nationally, with Goa (26.4%) and Kerala (25%) showing peak rates, while Jharkhand lags at 5-6%.

Table 1: T2DM Prevalence in India and Globally

Region/Population	Prevalence (%)	Cases (Millions)	Projected 2045 (Millions)	Source
Global (20-79 years)	10.5	537	783	IDF, 2021
India (Total)	9.6 (2019)	77 (2019)	134	IDF, 2021
India Urban	26.4	-	-	ICMR, 2023
India Rural	5-6	-	-	ICMR, 2023

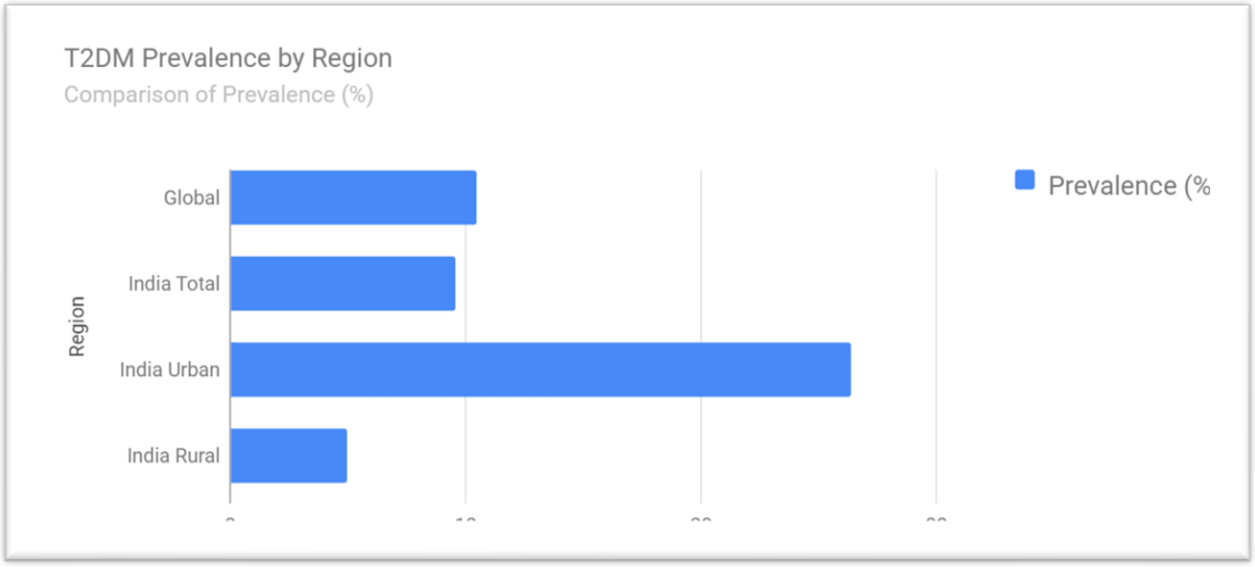

Figure 2: Bar Graph of T2DM Prevalence by Region

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Global Scenario and Comparative Insights

Southeast Asia hosts 88 million diabetics, with India contributing 87% of this burden. Globally, China (140 million) and the U.S. (32 million) follow India, though India's 9.6% prevalence slightly exceeds the global 8.8% (IDF, 2021). Indians exhibit earlier onset (45-50 years) and lower BMI thresholds (~23 kg/m²) compared to Western averages (55-60 years, >30 kg/m²), indicating a distinct metabolic profile (Ansari et al., 2022). Complications like diabetic retinopathy (16.9% prevalence in India) and cardiovascular disease amplify morbidity, with diabetes linked to 2% of annual Indian deaths.

Table 2: Comparative T2DM Characteristics

Region	Prevalence (%)	Cases (Millions)	Mean Onset Age (Years)	Mean BMI (kg/m²)	Complication Rate (%)
India	9.6	77	45-50	~23	Retinopathy: 16.9
China	10.2	140	50-5	~25	-
U.S.	10.8	32	55-60	>30	-

Figure 3: Bar Graph of T2DM Cases Globally

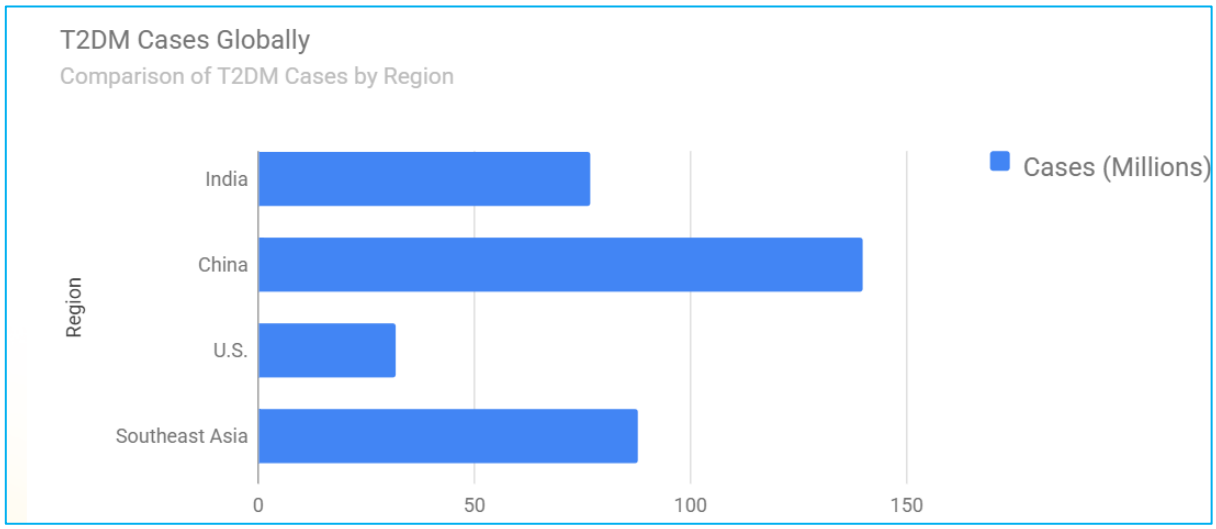

Figure 3: Bar Graph of T2DM Cases Globally

Relevance to Quercetin

India's escalating T2DM burden, alongside global trends, highlights the urgency for effective interventions. Quercetin's preclinical efficacy—e.g., 48.8% glucose reduction in rats (Patil et al., 2021)—and clinical benefits—e.g., 15.5 mg/dL decrease (Ansari et al., 2022)—offer a promising adjunct to address these challenges, particularly where metformin falls short due to side effects or advanced disease progression.

Evidence from Preclinical and Clinical Studies of Quercetin

The hypoglycemic potential of Quercetin is substantiated by a wealth of preclinical data and emerging clinical findings, though its efficacy varies due to bioavailability limitations.

Preclinical Studies

Preclinical investigations consistently demonstrate Quercetin's ability to lower blood glucose. Patil et al. (2021) administered Quercetin to STZ-induced diabetic Wistar rats at 10 mg/kg/day and 20 mg/kg/day for 28 days. The higher dose reduced fasting blood glucose from 256.33 mg/dL to 131.33 mg/dL (48.8% reduction, $p<0.001$), surpassing metformin's 42.2% reduction (148 mg/dL). Body weight increased from 180 g to 205 g (13.9% gain), indicating metabolic stabilization. Li et al. (2016) reported a 30% reduction (300 mg/dL to 210 mg/dL, $p<0.05$) with 50 mg/kg/day over 4 weeks, alongside a 40% SOD increase. Ansari et al. (2022)

found 25 mg/kg/day reduced glucose by 18.5% (324 mg/dL to 264 mg/dL) and HbA1c from 8.5% to 7.2% in STZ rats, with insulin levels rising 30%. Zhang et al. (2023) observed a 25% decrease (240 mg/dL to 180 mg/dL) in HFD-fed T2DM mice with 100 mg/kg/day, linked to DPP-4 inhibition. Shi et al. (2019) confirmed a 35% glucose uptake increase in vitro.

Table 3: Preclinical Effects of Quercetin on Glucose and Related Markers

Study/Model	Dose	Duration	Fasting Glucose (mg/dL)	HbA1c (%)	Other Effects
Patil et al. (2021), STZ Rats	20 mg/kg/day	28 days	256.33 → 131.33 (↓48.8%)	-	Weight ↑13.9% (180 → 205 g)
Li et al. (2016), STZ Rats	50 mg/kg/day	4 weeks	300 → 210 (↓30%)	-	SOD ↑40%
Ansari et al. (2022), STZ Rats	25 mg/kg/day	28 days	324 → 264 (↓18.5%)	8.5 → 7.2	Insulin ↑30%, TG ↓25%
Zhang et al. (2023), HFD Mice	100 mg/kg/day	8 weeks	240 → 180 (↓25%)	-	DPP-4 ↓30%
Shi et al. (2019), 3T3-L1	20 µM	48 hours	-	-	Glucose uptake ↑35%

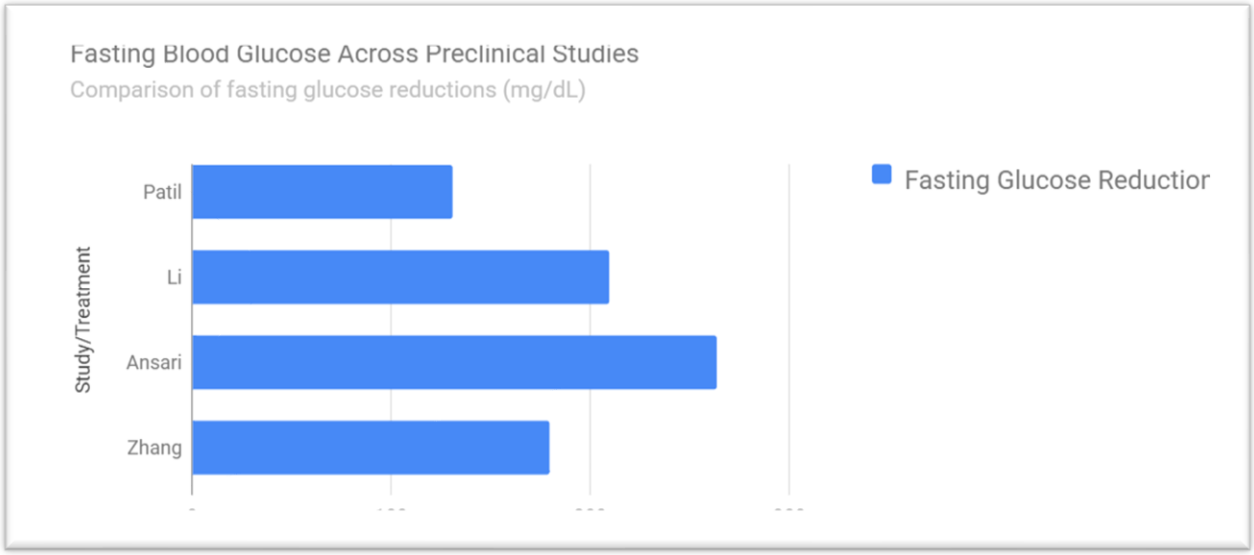

Figure 4: Bar Graph of Fasting Blood Glucose Across Preclinical Studies

Clinical Trials

Clinical studies reveal more modest effects, influenced by bioavailability constraints. Kim et al. (2011) conducted an RCT in 67 prediabetic adults, finding Quercetin (500 mg/day, 10 weeks) reduced fasting glucose from 110 mg/dL to 101 mg/dL (8% decrease, p=0.07) versus placebo (108 → 107 mg/dL). Ansari et al. (2022) reported a trial in T2DM patients (n=50) where 500 mg/day for 8 weeks lowered glucose by 15.5 mg/dL (143 → 127.5 mg/dL, $p<0.05$) and HbA1c by 0.4% (7.5 → 7.1%), with additional benefits of 5 mmHg systolic blood pressure reduction and 10% HDL increase. Ostadmohammadi et al. (2019), in a meta-analysis of 9 trials (n=781), found Quercetin (≥500 mg/day, ≥8 weeks) reduced fasting glucose by 1.08 mg/dL (95% CI: -2.08, -0.07) in metabolic syndrome patients, with no significant HbA1c change. Eid & Haddad (2017) noted that 250 mg/day for 8 weeks in T2DM patients maintained HbA1c (7.8 → 7.7%) but increased antioxidant capacity by 25%.

Table 4: Clinical Trial Outcomes of Quercetin Supplementation

Study/Population	Dose	Duration	Fasting Glucose (mg/dL)	HbA1c (%)	Other Effects
Kim et al. (2011), Prediabetes	500 mg/day	10 weeks	110 → 101 (↓8%)	-	-
Ansari et al. (2022), T2DM	500 mg/day	8 weeks	143 → 127.5 (↓15.5)	7.5 → 7.1	SBP ↓5 mmHg, HDL ↑10%
Ostadmohammadi et al. (2019), Metabolic Syndrome	≥500 mg/day	≥8 weeks	↓1.08 (meta)	No change	-
Eid & Haddad (2017), T2DM	250 mg/day	8 weeks	-	7.8 → 7.7	Antioxidant ↑25%

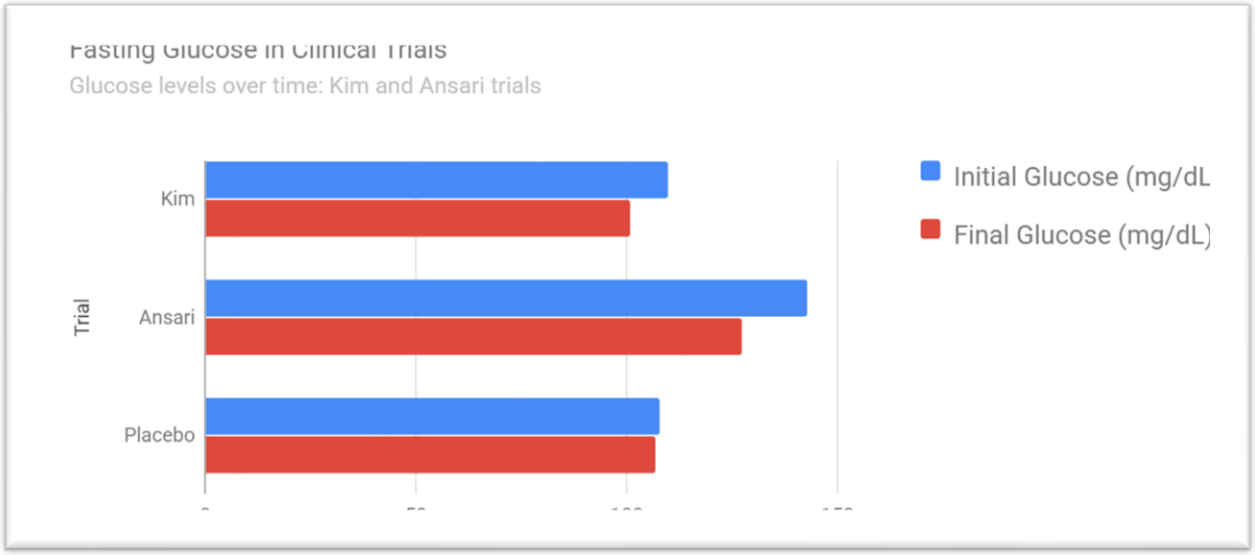

Figure 5: Line Graph of Fasting Glucose in Clinical Trials

Research Gaps

Despite robust preclinical results (e.g., 48.8% glucose reduction in Patil et al., 2021), clinical efficacy remains modest due to poor bioavailability (<1 µM plasma levels). Ansari et al. (2022) and Patil al. (2021) advocate for advanced delivery systems (e.g., nanoformulations, liposomes), which increased plasma levels to 2.5 µM in mice (Shi et al., 2019). Long-term effects on HbA1c and optimal human dosing require further exploration.

Future Aspects of Quercetin

The therapeutic potential of Quercetin in T2DM management, while promising, hinges on overcoming current limitations and expanding its clinical applicability. Addressing its poor bioavailability (<1 µM plasma levels) remains a priority, with preclinical studies demonstrating that nanoformulations and liposomes can elevate plasma concentrations to 2.5 µM in mice (Shi et al., 2019). Future research should focus on optimizing these delivery systems for human use, potentially through microemulsions or phospholipid complexes, as suggested by Ansari et al. (2022), to enhance absorption and efficacy.

Large-scale, long-term randomized controlled trials (RCTs) are essential to validate Quercetin's modest clinical effects—e.g., 15.5 mg/dL glucose reduction (Ansari et al., 2022)—and establish standardized dosing regimens beyond the current 250-500 mg/day range. Investigating its impact on HbA1c over extended periods, as noted by Ostadmohammadi et al. (2019), could solidify its role in glycemic control. Additionally, exploring Quercetin's synergistic effects with existing therapies like metformin, given its superior preclinical performance (48.8% glucose reduction vs. 42.2%, Patil et al., 2021), may yield combination strategies to mitigate metformin's limitations.

Quercetin's antioxidant and anti-inflammatory properties (e.g., 40% SOD increase, Li et al., 2016) suggest potential in preventing or managing T2DM complications, such as retinopathy and nephropathy. Future studies should assess these protective effects in diabetic populations, particularly in high-prevalence regions like India (Ansari et al., 2022). Moreover, its dietary abundance positions it as a candidate for functional foods or nutraceuticals, warranting development for preventive use in prediabetes.

Conclusion

Quercetin demonstrates considerable potential in blood sugar management, with preclinical studies showing reductions up to 48.8% (Patil et al., 2021) and clinical trials reporting decreases like 15.5 mg/dL (Ansari et al., 2022). Its mechanisms—insulin sensitization, antioxidant protection, and enzyme inhibition—are well-supported, yet its clinical impact is curtailed by low bioavailability. For pharmacists and researchers, Quercetin offers a promising adjunctive option, particularly if paired with advanced delivery systems. Future investigations should prioritize large-scale, long-term randomized controlled trials to refine dosing and validate efficacy in human T2DM populations.

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