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Flavonoids as Antidiabetic Agents, Challenges and Future Directions

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Editorial

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Diabetes is a global health concern, affecting hundreds of millions of people worldwide. The number of adults living with diabetes has risen dramatically, from approximately 200 million in 1990 to nearly 589 million in 2024. Type 2 diabetes (T2DM) accounts for 90% of all cases. The incidence is increasing more rapidly in low- and middle-income countries than in high-income countries. By 2050, the number of people with diabetes is likely to reach over 853 million. Diabetes was the ninth leading cause of death globally in 2020, contributing to over 2 million deaths annually. In 2021, diabetes and kidney disease due to diabetes were responsible for more than 2 million deaths, and approximately 11% of cardiovascular deaths were associated with high blood glucose (International Diabetes Federation, 2025).

Antidiabetic drugs play a vital role in managing blood glucose levels in individuals with diabetes mellitus, particularly Type 1 and Type 2 diabetes. These medications act through various mechanisms including enhancing insulin secretion, improving insulin sensitivity, reducing glucose absorption, and promoting glucose excretion. Insulin therapy is essential for individuals with Type 1 diabetes and those with advanced Type 2 diabetes. It is typically administered through injections, insulin pumps, or inhalers, using formulations such as rapid-acting, short-acting, intermediate-acting, and long-acting insulin. For oral medications, different drug classes offer distinct mechanisms and effects: Biguanides (Metformin) improve insulin sensitivity but may cause gastrointestinal issues; Sulfonylureas stimulate insulin secretion but can lead to hypoglycemia and weight gain; Dipeptidyl peptidase-4 (DPP-4) inhibitors enhance insulin release while posing risks of joint pain and respiratory infections; Sodium-glucose cotransporter-2 (SGLT2) protein inhibitors work by inhibiting the SGLT2 protein in the kidneys, which prevents the reabsorption of glucose back into the blood, allowing excess glucose to be excreted in urine but may result in dehydration and urinary infections; Thiazolidinediones increase insulin sensitivity but carry risks of fluid retention and heart failure; and Glucagon-like peptide-1 (GLP-1) receptor agonists slow digestion, assisting with appetite control, though they may trigger nausea and pancreatitis. Given the potential side effects of current treatments, research is ongoing to find safer and more effective drug alternatives (Lai et al., 2019).

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Flavonoids are a diverse group of polyphenolic compounds found abundantly in plants. These compounds are known for their antioxidant, anti-inflammatory, antidiabetic, and antimicrobial properties. Structurally, flavonoids share a C6-C3-C6 backbone, comprising two aromatic rings (A and B) connected through a three-carbon bridge (C-ring). Based on structural differences, they are typically classified into several subgroups, including flavonols (e.g., quercetin, kaempferol), flavones (apigenin, luteolin), flavanones (hesperidin, naringenin), flavanols (catechins) (epicatechin, epigallocatechin), anthocyanins (cyanidin, pelargonidin), and isoflavones (genistein, daidzein). These flavonoids play essential roles in both plant defense mechanisms and human health, with regular consumption contributing to disease prevention (Ahmed et al., 2020; Nur Farisya et al., 2022).

Flavonoids are abundantly found in medicinal plants and a wide variety of foods, including berries, citrus fruits, apples, grapes, onions, parsley, broccoli, green and black tea, red wine, soybeans, and cocoa beans. Their absorption and bioavailability vary depending on various factors such as gut microbiota composition, food processing techniques, and individual metabolism. Upon ingestion, flavonoids undergo metabolism in the liver, where they are modified into active metabolites that exert beneficial health effects (Martin and Ramos 2021).

Flavonoids are increasingly recognized as potential antidiabetic agents, with a growing body of preclinical evidence demonstrating their efficacy through multiple mechanisms, including modulation of glucose transporters, enhancement of insulin secretion, and protection of pancreatic β cells from damage caused by oxidative stress and inflammation (Al-Ishaq et al., 2019). By influencing metabolic pathways, flavonoids contribute to better glucose homeostasis while decreasing complications associated with diabetes. Studies on various flavonoids such as quercetin, kaempferol, luteolin**,** rutin, naringenin, fisetin and epicatechin (Fig. 1,

Table 1) have demonstrated significant antidiabetic effects in animal models and *in vitro* experiments, often showing better outcomes than conventional drugs like metformin (Ansari et al., 2022; Yang et al., 2022; Ke et al., 2023). Among different flavonoids possessing antidiabetic properties, the quercetin has been reported to demonstrate antidiabetic activity through at least

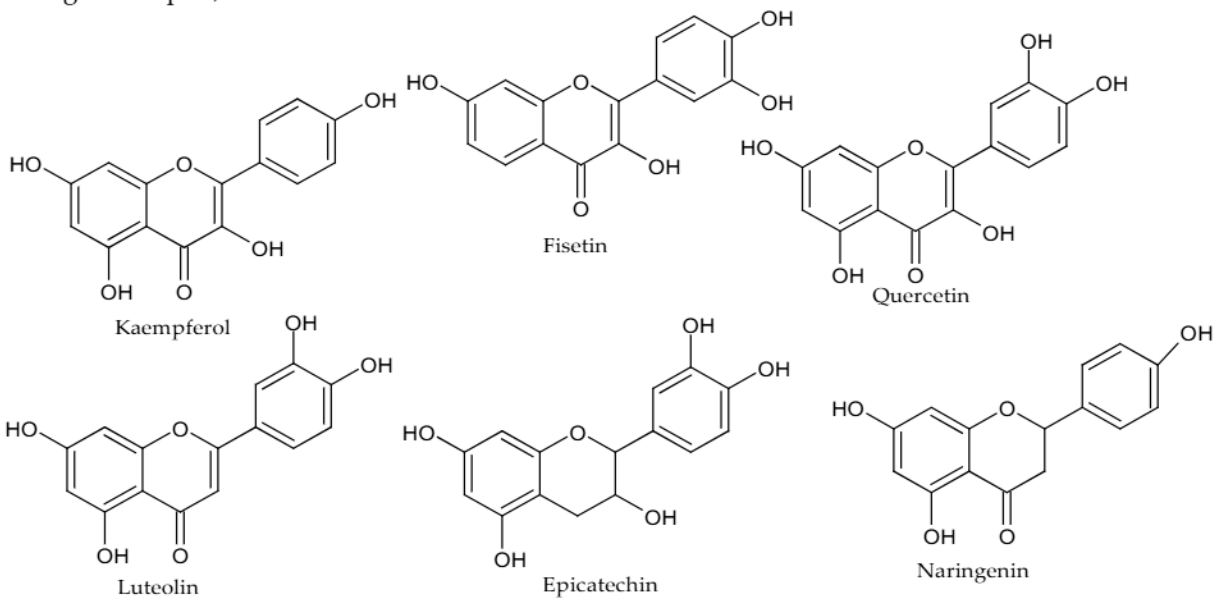

Fig. 1: Structure of key flavonoids demonstrating antidiabetic activities

8 distinct mechanisms, making it a multifaceted candidate for diabetes management. For instance, quercetin inhibits α-amylase and α-glucosidase, slowing starch breakdown and reducing postprandial glucose spikes (Günal-Köroğlu et al., 2025). It stimulates pancreatic β-cell function, promoting insulin release and improving glucose tolerance (Dhanya & Kartha, 2021). Quercetin activates the AMPK pathway, enhancing glucose uptake in muscle cells and reducing insulin resistance (Dhanya et al., 2017). By interacting with intestinal transporters, it limits glucose entry into the bloodstream (Spínola et al., 2020). Quercetin reduces oxidative stress, which is a major contributor to β-cell dysfunction and insulin resistance. It suppresses pro-inflammatory cytokines like IL-1β, IL-6, TNF-α, and blocks NF-κB signaling, helping mitigate diabetic complications. By inhibiting DPP-IV enzyme, it prolongs the half-life of GLP-1 and GIP, enhancing insulin secretion and glucose regulation. Lastly, quercetin inhibits advanced glycation end products (AGEs) formation, which contributes to vascular and tissue damage in diabetes. These mechanisms work synergistically to regulate blood glucose levels, protect pancreatic cells, and reduce complications associated with diabetes (Ansari 2022). Though human studies remain limited, existing evidence suggests flavonoids can serve as effective, natural alternatives for blood sugar regulation, offering potential benefits without the adverse effects linked to synthetic medications. Furthermore, flavonoids may complement conventional diabetes treatments, acting as adjunct therapies to improve patient outcomes and lower long-term health risks (Caro-Ordieres et al., 2020). With continued research, flavonoids hold promise as an essential component in diabetes management and prevention.

Despite their promising pharmacological properties, flavonoids face significant challenges in becoming effective therapeutic agents. A key obstacle is their low bioavailability and limited absorption, primarily due to poor water solubility and rapid metabolic degradation. These factors significantly diminish their systemic availability and therapeutic efficacy (Hu et al., 2025). Innovative solutions such as nanoparticle formulations, liposomal delivery, and prodrug modifications are being explored to improve their bioavailability (Stevens Barrón et al., 2023). Moreover, flavonoids face metabolic instability and rapid clearance, with extensive liver metabolism changing their structure and weakening their therapeutic efficacy (Kozłowska 2025). Researchers associated with medicinal chemistry are investigating structural or molecular modifications and enzyme inhibitors to improve stability. Another stern challenge is their poor target specificity, as broad-spectrum activity can lead to unintended biological interactions, demanding computational approaches like molecular docking and targeted drug design for precision (Fan et al., 2019; Shamsudin et al., 2022; Nur Farisya et al., 2022). Drug formulation and delivery present further hindrances, as conventional methods may not ensure sustained release or efficient tissue penetration, prompting advancements in encapsulation techniques using micelles, liposomes, and polymer-based carriers (Qian et al., 2023). In spite of promising *in vitro* and animal studies, flavonoids lack sufficient clinical validation, posing regulatory obstacles that necessitate standardized formulations, toxicity evaluations, and pharmacokinetic studies before approval (Davies and Yáñez, 2012).

Table 1: Key Flavonoids with Antidiabetic Properties (Shamsudin et al., 2022)

Flavonoid	Mechanisms of Action	Sources
Quercetin	Enhances insulin sensitivity, reduces oxidative stress	Onions, apples, berries
Kaempferol	Stimulates insulin secretion, protects pancreatic β-cells	Kale, spinach, tea
Rutin	Inhibits α-glucosidase, reduces blood glucose spikes post-meal	Buckwheat, citrus fruits
Naringenin	Improves insulin signaling, reduces inflammation	Grapefruit, oranges
Fisetin	Modulates glucose metabolism, protects against diabetic complications	Strawberries, cucumbers

Their structural intricacy further complicates synthetic modifications and chemical stability under physiological conditions, driving researchers toward bioengineering and semi-synthetic derivatives to optimize their pharmacological potential. Future strategies will focus on nanotechnology-based drug delivery, structural modifications for stability, targeted drug design, and rigorous clinical trials to confirm their efficacy and safety, paving the way for their integration into modern therapeutic applications (Wang et al., 2025).

In conclusion, the flavonoids hold promise as future antidiabetic agents, owing to their multifaceted mechanisms of action and potential benefits in managing diabetes and its complications. However, their successful application as therapeutic compounds is hindered by challenges such as low bioavailability, poor absorption, and rapid metabolism. These limitations necessitate innovative formulation strategies, advanced drug delivery systems, and rigorous clinical validation. Furthermore, identifying new flavonoids with antidiabetic properties and exploring their synergistic and antagonistic effects represent vital directions for future research. Continued investigation through well-designed clinical trials will be crucial to fully harness their therapeutic potential and overcome current barriers to their effective use.

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