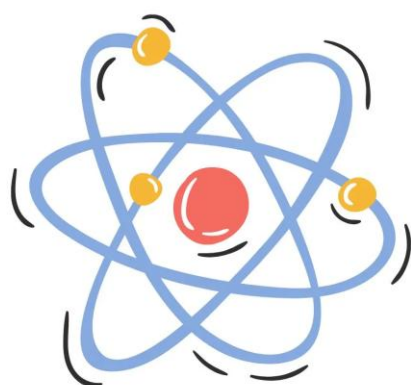




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TARGETING α -AMYLASE AND α -GLUCOSIDASE IN DIABETES: MECHANISTIC AND THERAPEUTIC INSIGHTS INTO APIGENIN AND QUERCETIN

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Abstract: Diabetes mellitus is a fast-growing metabolic disease marked by progressive β -cell dysfunction, insulin resistance, and persistent hyperglycemia. Inflammation, oxidative stress, the production of advanced glycation end products, and vascular problems are all encouraged by persistent hyperglycemia, especially postprandial hyperglycemia. Two important enzymes involved in the breakdown of carbohydrates and the release of glucose are α -amylase and α -glucosidase. Dietary starch is hydrolyzed by α -amylase into oligosaccharides and dextrins, which are then transformed into absorbable glucose by intestinal α -glucosidase. As a result, blocking these enzymes is a crucial tactic for postprandial glucose excursions and postponing the digestion of carbohydrates. For this aim, conventional inhibitors such acarbose, miglitol, and voglibose are used clinically; nevertheless, their use is often linked to gastrointestinal side effects, such as diarrhea, bloating, flatulence, and abdominal discomfort. These restrictions have prompted researchers to look into naturally occurring substances that have better tolerance and multitarget action. The α -amylase and α -glucosidase inhibitory, antioxidant, anti-inflammatory, and insulin-sensitizing characteristics of flavonoids, a significant class of dietary polyphenols, have garnered significant interest. The naturally occurring flavonoids apigenin and quercetin, which have different flavone and flavonol structures, respectively, are the main subjects of this review. There includes discussion of their pharmacological actions, chemical properties, natural sources, and possible methods against α -amylase and α -glucosidase. In addition to influencing oxidative stress, inflammatory signaling, insulin sensitivity, glucose transport, and pancreatic β -cell protection, both substances may decrease the hydrolysis of carbohydrates and the absorption of glucose. The information that is now available suggests that apigenin and quercetin could be useful natural lead molecules for a multitarget strategy to control diabetes. To determine their effectiveness, safety, bioavailability, and therapeutic potential, more mechanistic, pharmacokinetic, preclinical, and clinical research is necessary.

Keywords: Diabetes mellitus; α -Amylase; α -Glucosidase; Apigenin; Quercetin; Flavonoids; Postprandial hyperglycemia; Antidiabetic activity.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent elevation of blood glucose resulting from inadequate insulin secretion, impaired insulin action, or a combination of both. Prolonged hyperglycaemia progressively damages blood vessels, nerves and several vital organs. The major forms of diabetes include type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM). T1DM is primarily associated with autoimmune destruction of pancreatic β -cells, resulting in little or no endogenous insulin production and a lifelong requirement for insulin therapy. In contrast, T2DM is characterized by insulin resistance accompanied by progressive impairment of pancreatic β -cell function and accounts for more than 95% of diabetes cases globally. GDM develops during pregnancy and is associated with an increased future risk of T2DM in both mothers and, potentially, their offspring.¹ Due to factors like population aging, urbanization, sedentary lifestyles, obesity, and dietary changes, the prevalence of diabetes has significantly increased globally in recent decades. The International Diabetes Federation (IDF) Diabetes Atlas, 11th edition, estimates that 589 million persons between the ages of 20 and 79 had diabetes in 2024—roughly one in nine adults globally. By 2050, this figure is predicted to rise to over 853 million, with low- and middle-income nations accounting for the majority of the growth.²

Because uncontrolled diabetes is linked to serious microvascular and macrovascular consequences, the rising prevalence poses a significant public health concern. Diabetic foot ulcers and lower limb amputation, peripheral neuropathy, diabetic retinopathy and vision loss, diabetic nephropathy and kidney failure, cardiovascular disease, myocardial infarction, and stroke are among the major consequences. Through a number of interconnected processes, persistent hyperglycemia increases morbidity and early mortality by causing vascular and neural damage.³

Crucially, in people with diabetes, postprandial hyperglycemia significantly increases total glycemic exposure. Digestive enzymes, especially α -amylase and α -glucosidase, work sequentially to hydrolyze dietary carbohydrates into absorbable glucose. In order to slow down the quick digestion and absorption of dietary carbohydrates and regulate postprandial blood-glucose excursions, inhibition of these enzymes is a crucial therapeutic approach. This has led to a great deal of interest in naturally occurring bioactive substances as possible inhibitors of α -amylase and α -glucosidase, especially flavonoids as apigenin and quercetin.⁴

2. Role of hyperglycemia in issues related to diabetes

One of the main metabolic abnormalities associated with diabetes is hyperglycemia, which can happen both while fasting and after meals. While postprandial hyperglycemia is mostly caused by insufficient insulin response to carbohydrate consumption and is especially significant in early disruptions of glucose homeostasis, fasting hyperglycemia mostly reflects defective basal insulin action and increased hepatic glucose synthesis.⁵ Frequent postprandial glucose fluctuations can exacerbate oxidative stress, inflammatory reactions, and endothelial dysfunction. Persistent hyperglycemia raises the generation of reactive oxygen species (ROS) in the mitochondria, which causes oxidative stress and cellular damage.⁶

Additionally, non-enzymatic glycation of proteins, lipids, and nucleic acids is accelerated by hyperglycemia, leading to the production of advanced glycation end products (AGEs).⁷ Oxidative stress and inflammation are increased when AGEs interact with their receptor RAGE, activating NF- κ B, MAPK, and other signaling pathways.⁸ Vascular and metabolic dysfunction are further exacerbated by chronic low-grade inflammation. Furthermore, insulin signaling pathways are disrupted and insulin resistance is encouraged by oxidative stress and inflammatory signaling.⁹ In addition to impairing pancreatic β -cell function, prolonged metabolic stress also reduces insulin production and release, which exacerbates hyperglycemia. Therefore, hyperglycemia, oxidative stress, AGE buildup, inflammation, insulin resistance, and β -cell dysfunction all play a significant role in the onset and progression of diabetic microvascular and macrovascular problems.¹⁰

2.1 The need for innovative anti-diabetic methods

Even though traditional antidiabetic medications successfully lower blood sugar, long-term use of them may be linked to side effects, treatment load, expense, and, in certain situations, secondary treatment failure.¹¹ In particular, there is a need for safer and better-tolerated therapeutic choices because several glucose-lowering medicines may result in gastrointestinal problems, hypoglycemia, weight gain, or other drug-specific side effects. Furthermore, even with medication, long-term glycemic control in T2DM may be jeopardized by growing β -cell malfunction and insulin resistance. Because of their multitarget antioxidant, anti-inflammatory, and glucose-lowering qualities, naturally generated bioactive compounds particularly flavonoids and other polyphenols have drawn more attention.¹² Natural substances like apigenin and quercetin have shown promise in controlling glucose metabolism and inhibiting enzymes that hydrolyze carbohydrates, such as α -amylase and α -glucosidase, to lower postprandial glucose rise.¹³

3. α -Amylase and α -Glucosidase's Function in Diabetes and Carbohydrate Digestion

3.1 Digestion of carbohydrates and absorption of glucose

In the human diet, dietary carbohydrates especially starch and other complex polysaccharides—are a significant source of glucose and energy. The hydrolysis of α -1,4-glycosidic linkages inside starch molecules is started in the oral cavity by salivary α -amylase. Maltose and maltotriose are among the shorter oligosaccharides and dextrans that are produced in the small intestine by pancreatic α -amylase after gastric passage. Enzymes on the intestinal brush-border membrane then hydrolyze these intermediate products, especially α -glucosidase, which catalyzes the last stage of carbohydrate digestion and releases absorbable monosaccharides, mostly glucose.¹⁴

The small intestine epithelium is the primary route of absorption for the released glucose. The sodium-dependent glucose cotransporter SGLT1 on the apical membrane allows glucose and galactose to enter enterocytes, while GLUT2 primarily allows glucose to depart the basolateral membrane and enter the bloodstream. Therefore, the pace at which glucose becomes accessible for intestinal absorption is directly influenced by the rate of enzymatic carbohydrate digestion, which in turn effects postprandial blood-glucose concentrations.¹⁵

3.2 α -amylase The first enzymatic breakdown of dietary starch is mostly caused by α -amylase, a calcium-dependent glycoside hydrolase that is a member of the amylase family. The two main types in humans are pancreatic α -amylase, which is secreted into the small intestine, and salivary α -amylase, which is secreted by the salivary glands. Internal α -1,4-glycosidic bonds in starch and similar polysaccharides are randomly hydrolyzed by the enzyme, producing smaller carbohydrates such maltose, maltotriose, and α -limit dextrans.¹⁶ The activity of α -amylase affects the availability of substrates for intestinal α -glucosidases because it starts the breakdown of complex carbohydrates. Postprandial hyperglycemia can result from an abrupt rise in glucose availability following meals caused by excessive or quick starch breakdown. As a result, α -amylase inhibition can decrease the rate of glucose release and absorption and impede the digestion of carbohydrates.¹⁷

3.3 α -glucosidase A class of enzymes that hydrolyze carbohydrates and are connected to the small intestine's brush-border membrane includes α -glucosidase. α -glucosidase catalyzes the terminal hydrolysis of oligosaccharides and disaccharides to liberate glucose and other monosaccharides, in contrast to α -amylase, which mainly operates on internal α -1,4 connections of starch. In order for intestinal epithelial cells to absorb partially digested dietary carbohydrates, this last stage of

digestion is crucial. Intestinal α -glucosidase inhibition slows intestinal glucose absorption and lessens the size of the postprandial glucose surge by delaying the conversion of oligosaccharides and disaccharides into absorbable glucose. As a result, α -glucosidase has emerged as a key therapeutic target for managing type 2 diabetes's postprandial hyperglycemia.¹⁸

3.4 The importance of dual enzyme inhibition in therapy

A mechanistically complementary strategy for managing postprandial hyperglycemia is to target both α -amylase and α -glucosidase. While simultaneous α -glucosidase inhibition can restrict the final release of glucose from these digestive products, α -amylase inhibition can decrease the initial breakdown of starch into smaller carbs. This combined impact can lessen postprandial glucose excursions, slow down the rate of glucose absorption, and delay the digestion of carbohydrates.¹⁹ Because regulating postprandial glucose is a crucial part of total glycemic management, the therapeutic justification for dual inhibition is especially pertinent. Reductions in postprandial glucose responses have been shown in clinical studies using α -glucosidase-inhibiting medications, indicating that carbohydrate-digestive enzymes are important targets. Finding dual α -amylase/ α -glucosidase inhibitors from natural and synthetic sources has thus been the focus of recent research, with flavonoids and other polyphenolic compounds of particular interest due to their potential multitarget activity.²⁰

4. Traditional inhibitors of α -amylase and α -glucosidase

4.1 Inhibitors currently in use

One well-established pharmaceutical strategy for managing postprandial hyperglycemia in individuals with type 2 diabetes mellitus is the inhibition of intestinal carbohydrate-digesting enzymes. The three main α -glucosidase inhibitors used in clinical practice are voglibose, miglitol, and acarbose. These substances slow down the process by which dietary carbohydrates are transformed into absorbable monosaccharides, mainly in the gastrointestinal system. Acarbose is a complex oligosaccharide that inhibits both pancreatic α -amylase and intestine α -glucosidases. Miglitol is an iminosugar that primarily inhibits intestinal α -glucosidases and shares structural similarities with glucose. Another strong iminosugar that inhibits intestinal disaccharidases, such as maltase, sucrase, and isomaltase, is voglibose. These medications lessen the quick appearance of glucose in the bloodstream after meals by postponing the breakdown of carbohydrates.²¹

4.2 Conventional inhibitors' limitations

Conventional α -glucosidase inhibitors have significant drawbacks that may impact patient acceptance and long-term compliance despite their clinical efficacy. Because these medications change how carbohydrates are digested in the gut, undigested carbohydrates may enter the colon and be fermented by bacteria, leading to gastrointestinal side effects, including diarrhea, flatulence, and pain and distension in the abdomen. These side effects are typically dose-dependent and could be especially problematic when starting treatment. Therefore, in certain individuals, gastrointestinal discomfort may limit the practical use of these medicines and decrease drug adherence.²²

Finding safer, more tolerable, and multitarget carbohydrate-digestive enzyme inhibitors—especially those derived from natural sources—is therefore still of interest. Because they may concurrently affect oxidative stress, inflammatory pathways, and the digestion of carbohydrates, plant-derived flavonoids and other polyphenolic chemicals are being studied more and more. Among these substances, apigenin and quercetin have garnered significant interest due to their documented ability to inhibit α -amylase and α -glucosidase, as well as more general antioxidant and metabolic effects.²³

5. Flavonoids as Potential Antidiabetic Substances

A vast and structurally varied class of naturally occurring polyphenolic chemicals, flavonoids are found in a wide range of foods derived from plants, including fruits, vegetables, grains, tea, and herbs.²⁴ Their fundamental structure is a C6–C3–C6 skeleton made up of two aromatic rings (A and B) joined by a heterocyclic pyran ring (C). Flavonoids are generally divided as flavones, flavonols, flavanones, flavan-3-ols, anthocyanidins, isoflavones, and chalcones based on differences in the oxidation pattern, hydroxylation, and substitution of the middle ring. Their biological actions are significantly influenced by structural features such the quantity and location of hydroxyl groups, glycosylation, and methoxylation.²⁵

The widespread presence of flavonoids in the human diet, along with their metabolic and antioxidant properties, have sparked a great deal of interest in their possible use in the management and prevention of metabolic diseases, such as type 2 diabetes. Flavonoids are particularly interesting candidates for managing postprandial hyperglycemia because of their capacity to interact with enzymes that breakdown carbohydrates.²⁶

5.1 Mechanism of Flavonoids

Instead of operating through a single molecular target, flavonoids demonstrate antidiabetic benefits through a variety of complimentary pathways. Inhibition of α -amylase and α -glucosidase is a significant mechanism that slows down the breakdown of carbohydrates and lessens the quick release and absorption of glucose following meals.²⁷ Numerous flavonoids were found to be able to inhibit both enzymes in a systematic review of in-vitro research, indicating their potential as dual-target medicines for postprandial glucose management. Flavonoids have significant antioxidant action in addition to inhibiting digestive enzymes, which allows them to lessen oxidative stress linked to long-term hyperglycemia. Their polyphenolic hydroxyl groups can help modulate cellular antioxidant mechanisms and scavenge free radicals. By affecting inflammatory signaling pathways, flavonoids may also have anti-inflammatory actions. This could lessen insulin resistance linked to inflammation and diabetic tissue damage.²⁸ Additionally, flavonoids have been shown to enhance insulin signaling and glucose homeostasis by influencing glucose transport mechanisms and modulating pathways including AMPK and PPAR- γ . Improved insulin sensitivity and increased cellular glucose absorption may result from the regulation of glucose transporters, especially GLUT4. Additionally, their anti-inflammatory and antioxidant qualities may shield pancreatic β -cells from oxidative and inflammatory damage, possibly maintaining insulin secretory activity. Therefore, flavonoids may offer a multitarget strategy to diabetes management due to the combined effects of enzyme inhibition, antioxidant protection, anti-inflammatory activity, enhanced insulin signaling, and modulation of glucose transport.²⁹

5.2 Why quercetin and apigenin

Because of their well-characterized polyphenolic structures, natural abundance, and variety of biological actions, apigenin and quercetin stand out among the many naturally occurring flavonoids. Two structurally different flavonoid frameworks are available for studying the inhibition of carbohydrate-digestive enzymes: apigenin is a flavone and quercetin is a flavonol. Both substances have a number of hydroxyl groups that can interact with enzyme residues by hydrogen bonding and other means, which may contribute to their inhibitory activity.³⁰

Crucially, systematic research demonstrates that both substances can interact with α -amylase and α -glucosidase. Although reported potency varies significantly depending on the enzyme source and testing approach, apigenin has generally shown higher activity toward α -glucosidase than α -amylase. Numerous in-vitro studies have shown that quercetin exhibits particularly significant α -

glucosidase inhibitory action. PubMed Central (PMC) Apigenin and quercetin are appropriate representatives for investigating multitarget natural therapies to postprandial hyperglycemia due to their documented enzyme inhibition, antioxidant, anti-inflammatory, and metabolic activities. However, when converting these results into therapeutic applications, differences in assay settings, bioavailability, and biological models should be taken into account.³¹

6. Apigenin: Sources, Chemistry, and Potential for Diabetes

6.1 Chemical composition and physical properties

Apigenin is a naturally occurring flavone (5,7,4'-trihydroxyflavone) with a C6–C3–C6 flavonoid skeleton. It has hydroxyl groups at positions 5, 7, and 4', which enhance its biological activity and ability to form hydrogen bonds. Apigenin's low water solubility and relative lipophilicity may affect its absorption and bioavailability.

6.2 Organic sources

Many edible and therapeutic plants contain apigenin. Parsley, chamomile, celery, onions, and a variety of fruits and vegetables are important food sources. One well-known source of apigenin and its glycosides is chamomile. Apigenin is a significant dietary flavonoid with significant pharmacological relevance due to its extensive presence in food plants.

6.3 Pharmacological actions

Apigenin has a variety of biological activities, including as cardioprotective, anti-inflammatory, antidiabetic, antioxidant, and anticancer properties. Reactive oxygen species scavenging and endogenous antioxidant defense regulation are linked to its antioxidant action. Additionally, it can affect signaling pathways and inflammatory mediators including MAPK and NF- κ B. Apigenin's potential to enhance glucose metabolism, lower oxidative stress and inflammation, and affect insulin-related signaling pathways has been studied in diabetes-related studies.

6.4 Inhibition of α -amylase and apigenin

Apigenin may disrupt the first breakdown of dietary starch since it has shown inhibitory effect against α -amylase. Its hydroxyl groups and flavone structure may promote hydrophobic and hydrogen bonding interactions with amino acid residues in the substrate-binding region of the enzyme. Catalytic activity and substrate accommodation may be hampered by such interactions. However, the dose of the inhibitor, the assay conditions, and the source of the enzyme all affect how much inhibition occurs.

6.5 Inhibition of α -glucosidase and apigenin

Additionally, apigenin has been shown to block α -glucosidase, which may lessen the amount of oligosaccharides and disaccharides that are ultimately hydrolyzed into absorbable glucose. Hydrogen bonds and hydrophobic interactions with catalytic or substrate-binding residues may be involved in the binding of apigenin within or close to the enzyme active site. Apigenin may reduce postprandial glucose rise by delaying the digestion of carbohydrates by inhibiting α -glucosidase.

6.6 Additional methods of preventing diabetes

Beyond inhibiting digestive enzymes, apigenin has antidiabetic properties. Apigenin may affect insulin signaling, glucose absorption, and glucose metabolism, according to experimental research, and its antioxidant qualities may help prevent oxidative stress linked to long-term hyperglycemia. Additionally, altering inflammatory pathways may lessen pancreatic β -cell damage and insulin resistance linked to inflammation. Together, these metabolic, anti-inflammatory, antioxidant, and enzyme-inhibitory properties suggest that apigenin may function as a multitarget natural antidiabetic drug.³²

7. Quercetin: Sources, Chemistry, and Potential for Diabetes

7.1 Chemical composition

The C6–C3–C6 flavonoid skeleton of quercetin, a naturally occurring flavonol, has hydroxyl groups at positions 3, 5, 7, 3', and 4'. Its antioxidant and enzyme-interacting characteristics are mostly attributed to the catechol group in the B-ring and hydroxyl substitution pattern. These structural characteristics are also crucial for its structure–activity relationship (SAR), especially when it comes to interactions with enzymes that break down carbohydrates.

7.2 Organic sources

Both medicinal plants and plant-based diets contain quercetin. Onions, apples, cherries, grapes, tea, and a variety of vegetables are important food sources. Plants frequently contain it as the aglycone or in glycosylated forms like quercetin and rutin glycosides. Quercetin is one of the most studied flavonoids for metabolic diseases due to its dietary abundance and structural diversity.

7.3 Pharmacological actions

Numerous pharmacological characteristics of quercetin include antioxidant, anti-inflammatory, antidiabetic, cardioprotective, and neuroprotective effects. Its many hydroxyl groups allow it to interact with reactive species in an efficient manner and may strengthen the antioxidant defenses of cells. Additionally, quercetin can reduce inflammation linked to metabolic dysfunction by

modulating inflammatory pathways such as NF- κ B and MAPK signaling. These characteristics support its possible defense against oxidative and inflammatory damage brought on by diabetes.³³

7.4 Inhibition of α -amylase and quercetin

Quercetin may lessen the enzymatic breakdown of dietary starch since it has shown inhibitory effect against α -amylase. Through hydrogen bonding, hydrophobic contacts, and π -related interactions, its hydroxyl groups and planar flavonol structure may promote interactions with amino acid residues in the catalytic or substrate-binding area of the enzyme. Starch digestion may be slowed by such binding, which can obstruct substrate accommodation and enzyme catalytic activity.³⁴

7.5 Inhibition of α -glucosidase and quercetin

It has also been shown that quercetin effectively inhibits α -glucosidase. Its aromatic rings can take part in hydrophobic and π - π interactions, and its hydroxyl groups can create hydrogen bonds with residues around the enzyme active site. These interactions may result in conformational alterations that lower catalytic effectiveness and modify the location or flexibility of active-site residues. Therefore, quercetin's inhibition of α -glucosidase can postpone the final conversion of oligosaccharides and disaccharides into glucose, thereby lowering postprandial glucose increase.³⁵

7.6 Other methods to prevent diabetes

Quercetin's antidiabetic properties go beyond inhibiting the enzymes that break down carbohydrates. According to experimental data, quercetin may enhance insulin sensitivity and glucose absorption in part via modifying GLUT4-related and insulin signaling pathways. Its anti-inflammatory properties may lessen insulin resistance linked to inflammation, and its antioxidant activity may shield pancreatic β -cells from oxidative damage. When taken as a whole, these actions imply that quercetin may have a multitarget antidiabetic impact that includes protecting β -cell function, reducing oxidative stress, improving insulin sensitivity, modulating glucose transport, and inhibiting α -amylase/ α -glucosidase.³⁶

8. Conclusion

Persistent hyperglycemia, especially postprandial glucose elevation, significantly contributes to oxidative stress, inflammation, advanced glycation end-product formation, insulin resistance, β -cell dysfunction, and subsequent diabetic complications in diabetes mellitus, a rapidly growing metabolic disorder worldwide. Postprandial glycemic excursions are significantly influenced by the absorption and digestion of dietary carbs. In this regard, sequential inhibition of α -amylase and

α -glucosidase can delay the digestion of carbohydrates, decrease the release of glucose, and lessen postprandial hyperglycemia, making them significant therapeutic targets.

Conventional α -glucosidase inhibitors, such as acarbose, miglitol, and voglibose, offer a well-established pharmacological approach, but their gastrointestinal side effects, such as diarrhea, flatulence, and abdominal discomfort, may limit their clinical utility and negatively impact treatment adherence. The hunt for safer and more tolerable substitutes has been prompted by these restrictions. Due to their structural diversity and capacity to affect many pathogenic processes associated with diabetes, naturally occurring flavonoids have become attractive possibilities.

Because of their polyphenolic structures, natural occurrence, and documented inhibitory effect against α -amylase and α -glucosidase, apigenin and quercetin stand out among these substances. Antioxidant and anti-inflammatory qualities, regulation of insulin signaling and glucose transport, and potential defense of pancreatic β -cells against metabolic stress further bolster their potential. Although the stated potency can vary depending on the enzyme source, test circumstances, and experimental models, the interaction of their hydroxylated flavonoid structures with the active-site and substrate-binding areas of the enzyme may contribute to the inhibition of carbohydrate-digestive enzymes.

Dual α -amylase/ α -glucosidase inhibition in conjunction with antioxidant, anti-inflammatory, and insulin-sensitizing properties is a potential multitarget strategy for managing diabetes, according to the existing data. Thus, apigenin and quercetin offer useful lead compounds for additional research. However, the majority of the information that is currently available is still primarily in vitro or preclinical, and it is necessary to address issues with bioavailability, metabolism, pharmacokinetics, dose optimization, and clinical efficacy. To determine their therapeutic value, future research incorporating enzyme kinetics, molecular docking, molecular dynamics, cellular and animal models, pharmacokinetic evaluation, and carefully planned clinical investigations will be crucial. The development of natural flavonoid-based treatments that can effectively and more tolerably manage postprandial hyperglycemia and related diabetic problems may be aided by such multidisciplinary approaches.

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