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REVIEW

FOOD SAFETY AND HEALTH

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Quercetin: Potential antidiabetic effects through enzyme inhibition and starch digestibility

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Abstract

Diabetes mellitus involves high blood sugar levels due to insufficient insulin action. Furthermore, enzymes such as α-amylase and α-glucosidase break down carbohydrates into glucose, leading to postprandial hyperglycemia. Flavonoids, particularly quercetin, inhibit these enzymes, slowing carbohydrate digestion and reducing glucose absorption. Quercetin has significant hypoglycemic effects with inhibitory concentration (IC_{50}) values comparable to acarbose, a standard inhibitor, suggesting its potential as a natural alternative for diabetes management. *In silico* models, including molecular docking, molecular dynamics (MD) simulations, and quantitative structure-activity relationship (QSAR) approaches, help researchers understand the molecular interactions of therapeutic agents. These techniques identify potential inhibitors, determine enzyme-inhibitor structures, and calculate binding energies, correlating findings with *in vitro* or *in vivo* data. Molecular docking predicts molecular orientations, MD simulations offer insights into enzyme–inhibitor dynamics, and QSAR models predict inhibitory potential based on structural properties. Studies have shown that quercetin effectively inhibits α-glucosidase and α-amylase by forming hydrogen bonds with specific amino acid residues. Quercetin interacts with starches and reduces their digestibility, increases the formation of resistant starch, lowers the glycemic index, and inhibits digestive enzymes. Studies show that the effects of quercetin on starch digestion vary with concentration and type of starch, and its incorporation into foods such as bakery products, pasta, etc. can significantly decrease starch hydrolysis. The incorporation of quercetin into starch matrices may aid in the development of functional foods aimed at improving glycemic control.

KEYWORDS

α-amylase, α-glucosidase, digestion, glycemic index, molecular docking, resistant starch

1 | INTRODUCTION

Quercetin has a flavonoid backbone consisting of two aromatic rings (A and B) linked by a three-carbon bridge (C ring) with multiple hydroxyl (-OH) groups and a ketone moiety (C4 carbonyl) attached to the C ring (Figure 1) (Singh et al., 2021). The presence of hydroxyl groups located at positions 3, 5, 7, 3′, and 4′ of the A and B rings enhances its antioxidant capacity, as well as the presence of a double bond between the second and third carbons and the carbonyl group at the fourth carbon contributes to its stability and reactivity (Ozgen et al., 2016).

Flavonoids are secondary metabolites that play crucial roles in plant–environment interactions, contributing to physiological activities, such as coloration, taste, and protection against pests, as well as aiding in pollination and seed dispersal (Singh et al., 2021). Quercetin is widely distributed in nature and can be found in various fruits, vegetables, grains, herbs, and beverages commonly consumed in the human diet. Rich dietary sources of quercetin include apples, berries (such as cranberries, blueberries, and strawberries), onions, and tea (Al-Ansari et al., 2023; Kandemir et al., 2022; Lavefve et al., 2020). Quercetin, a hydrophobic flavonoid, influences plant physiology by regulating auxin transport, enhancing antioxidant enzyme activities, and modulating root growth, demonstrating its significant impact on plant health and development. Quercetin has attracted considerable interest in scientific research and nutraceutical development due to its diverse biological activities and potential health benefits. The beneficial physiological properties of quercetin, including its anti-obesity, antimicrobial, anti-cancer, and anti-inflammatory effects, have been summarized in the literature (Azeem et al., 2023; Sato & Mukai, 2020). Despite the documented positive health effects of quercetin, its native form has low bioavailability in the digestive system and poor stability within food matrices and under digestive conditions. As a result, research has explored various carrier systems to enhance quercetin's bioavailability and stability. Relatively improved bioavailability of quercetin has been reported in bigel (Xie et al., 2023), soy protein-stabilized microgel emulsions (Yang et al., 2023) or nano complex (Lin et al., 2023), starch-based nanoemulsions (Wang et al., 2023), inulin microparticles (Quintriqueo-Cid et al., 2024), and whey protein isolate/hyaluronic acid emulsion gel (Wang et al., 2023). These are model studies, and further research should focus on the application of these systems within functional food matrices, together with the investigations on the effects of storage and digestion. For instance, innovative and sustainable approaches could include using quercetin-loaded systems such as oleogels as fat replacers, microparticles, or emulsion systems in beverages.

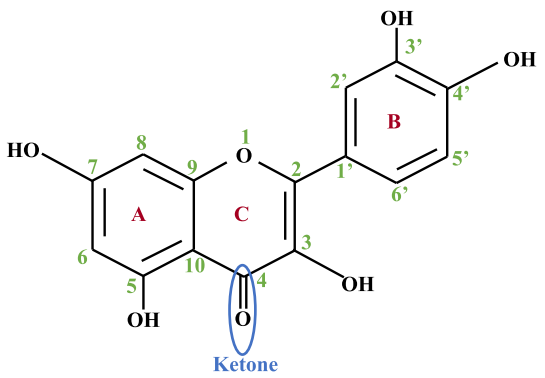

FIGURE 1 The structure of quercetin.

Diabetes is characterized by high blood sugar levels resulting from impaired insulin secretion, resistance to insulin's effects on insulin-sensitive tissues, or both. It is primarily classified into type 1 diabetes, type 2 diabetes, gestational diabetes, and specific types associated with exocrine pancreas diseases (such as cystic fibrosis) or drug-related conditions (Fernandes et al., 2022). Type 2 diabetes, the most common metabolic disorder, involves oxidative stress, pancreatic β-cell dysfunction, and insulin resistance. Hyperglycemia increases reactive oxygen species, which impair cellular function and exacerbate insulin resistance, leading to diabetic complications (Azeem et al., 2023). The most effective treatments for type 2 diabetes are insulin injections or oral antidiabetic medications. However, these treatments can cause side effects, including hypoglycemia, gastrointestinal issues, infections, weight gain, and cardiovascular risks (Fernandes et al., 2022). In regard to diabetes, traditional treatment methods alone are not sufficient. There is increasing emphasis on the importance of a healthy diet, particularly the consumption of phenolics, which have numerous proven health benefits. These bioactive components can serve as alternatives to conventional treatments, such as drugs, which work in similar ways to these medications (Fernandes et al., 2022; Li, Tian et al., 2023).

Quercetin exerts antidiabetic effects through multiple mechanisms, including enhancing β-cell proliferation and insulin secretion, inhibiting α-glucosidase and DPP-IV enzymes, prolonging the half-life of GLP-1 and GIP, and increasing glucose uptake via GLUT-4 expression and AMPK pathway activation by reducing glycogen breakdown. Quercetin mitigates diabetic complications by reducing oxidative stress and suppressing pro-inflammatory cytokines such as IL-1β, IL-4, IL-6, and TNF-α, blocking NF-κB cells, and lowering biomarkers of nephropathy (Ansari et al., 2022; Hamid & Obaid, 2021; Yan et al., 2023). A meta-analysis of 13 studies by Bule et al. (2019) investigated the effects of quercetin at doses of 5, 10, 25, and 50 mg/kg on serum glucose levels, finding significant reductions at 10, 25, and 50 mg/kg, but not at 5 mg/kg, with a dose–response relationship showing a 1.63 mg/dL decrease per 1 mg/kg increase in dose. Studies in the literature indicate that phenolic compounds, including stilbenes, phenolic acids, and flavonoids (anthocyanins, flavanols, flavanones, and isoflavones), regulate type 2 diabetes by inhibiting carbohydrate-digesting enzymes (Fernandes et al., 2022; Li, Tian, et al., 2023).

This study specifically discusses the specific interaction of quercetin with carbohydrate-digesting enzymes to slow down glucose release, highlighting its therapeutic potential for diabetes through various *in vitro* enzyme inhibition, starch digestibility, and *in vivo* studies. The various physiological mechanisms of quercetin are excluded, and the review focuses solely on its impact on carbohydrate absorption and digestion through interactions with enzymes (α-

amylase and α-glucosidase) and starch during gastrointestinal digestion.

2 | *IN VITRO* ENZYME INHIBITION

2.1 | *In vitro* enzyme activity

Diabetes mellitus is characterized by hyperglycemia due to insufficient insulin secretion or action (Abdelli et al., 2021; Ruivo Da Silva et al., 2020; Shen et al., 2023). Starch is initially hydrolyzed by human salivary α-amylase in the mouth and then by human pancreatic α-amylase in the intestine, producing glucose, maltose, maltotriose, and a variety of branched oligosaccharides. Although α-amylase hydrolyzes α-D-1,4-glycosidic bonds, it cannot hydrolyze α-1,6 bonds from amylopectin and α-1,4 bonds adjacent to α-1,6 bonds. α-Glucosidase acts on these smaller carbohydrates by hydrolyzing α-1,4 glycosidic linkages and releasing glucose from the nonreducing ends. These enzymes are essential for contributing to postprandial hyperglycemia (Altuner, 2022; Kikiowo et al., 2023; Li et al., 2022; Lim et al., 2022; Liu et al., 2020; Nabil-Adam et al., 2023; Patil et al., 2022; Shen et al., 2023; Tshiyoyo et al., 2022).

Polyphenols are significant inhibitors of these enzymes, slowing carbohydrate digestion and reducing glucose absorption. Phenolic compounds influence enzyme activity by altering enzyme conformation or stability. The specific effects of phenol–enzyme interactions depend on factors such as the phenolic compound's structure, concentration, and the enzyme's biochemical properties. These compounds can bind to the active or allosteric sites of the enzyme and affect substrate binding or catalysis. The inhibition may be reversible or irreversible based on the strength and nature of the interaction between the phenolic compound and the enzyme (Abdelli et al., 2021; Ruivo Da Silva et al., 2020; Shen et al., 2023; Tshiyoyo et al., 2022). Quercetin shows hypoglycemic effects by inhibiting α-glucosidase and α-amylase (Kikiowo et al., 2023). Figure 2 shows the inhibitory action of quercetin on α-glucosidase and α-amylase.

Table 1 provides a summary of the *in vitro* inhibition of α-glucosidase and α-amylase by quercetin. The half-maximal inhibitory concentration (IC_{50}) is an important parameter for evaluating the efficacy of an inhibitor. The IC_{50} value represents the concentration of an inhibitor required to inhibit the activity of an enzyme or biological target by 50%. A lower IC_{50} value indicates that the inhibitor is more potent and effective at lower concentrations (Li, Yang, et al., 2023).

Quercetin exhibited comparable α-glycosidase and α-amylase inhibition activities with IC_{50} values lower than those of acarbose, a commercial glucosidase inhibitor (Fu et al., 2021; Li, Yang et al., 2023; Liu et al., 2020). Li, Yang, et al. (2023) selected 16 flavonoids, including flavonols, flavones, flavanones, and flavanols, to investigate their effects on α-amylase and α-glucosidase. The IC_{50} values (μg/mL) of acarbose were 85.53 μg/mL for the inhibition of α-glucosidase and 156.7 μg/mL for α-amylase. In comparison, among the 16 flavonoids, quercetin had the lowest IC_{50} values with 13.34 μg/mL for α-glucosidase and 48.09 μg/mL for α-amylase, and this was comparable with the lowest values observed for myricetin and lutein. In a similar study, Fu et al. (2021) investigated the inhibitory effects of 11 flavonoids at a concentration of 1 mg/mL against α-glucosidase. Five flavonoids, myricetin, myricetrin, quercetin, catechin, and gallocatechin, showed significant inhibitory effects. The IC_{50} values were then determined for these five compounds over a range of concentrations (0.001–10 mg/mL). Quercetin had an IC_{50} of 0.0657 ± 0.010 mg/mL, indicating that it could be a potent natural alternative to acarbose, which had an IC_{50} of 0.691 mg/mL. Furthermore, Liu et al. (2020) reported that among the main flavonols of Chinese bayberry, quercetin (IC_{50} = 46.91 μmol/L) inhibited α-glucosidase more strongly than

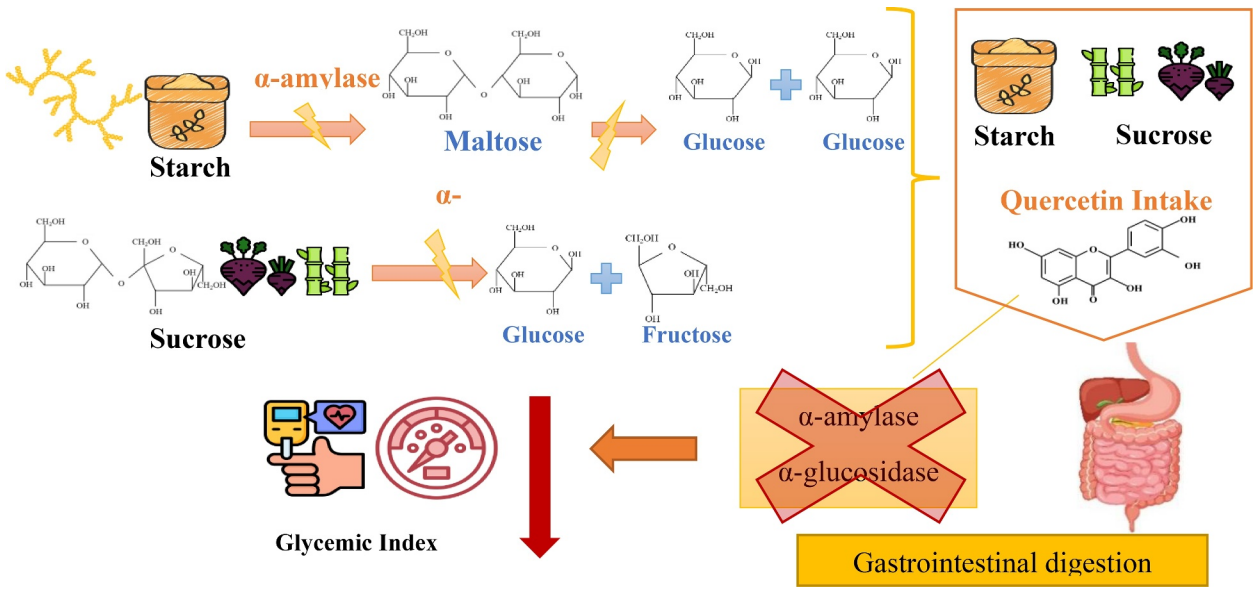

FIGURE 2 Inhibitory effect of quercetin on α-amylase and α-glucosidase activity.

TABLE 1 Summary of the *in vitro* enzyme inhibitory effect of quercetin.

Enzyme inhibitory potential	IC_{50} values	References
α-glucosidase activity ↓	544 ± 9.01 μg/mL	Zhou et al. (2021)
α-amylase activity ↓	270 ± 3.1 μg/mL	
α-glucosidase activity ↓	13.34 μg/mL	Li, Yang, et al. (2023)
α-amylase activity ↓	48.09 μg/mL	
α-glucosidase activity ↓	46.91 μmol/L	Liu et al. (2020)
α-glucosidase activity ↓	0.0657 mg/mL	Fu et al. (2021)
α-amylase activity ↓	0.325 mg/mL	Shen et al. (2023)

Note: ↑: upregulated, ↓: downregulated.

acarbose (IC_{50} = 381.27 μmol/L), and myricetin (IC_{50} = 33.20 μmol/L) was the strongest, but kaempferol was the least effective among them (IC_{50} = 65.36 μmol/L).

Lim et al. (2022) reported that the loss of OH groups on quercetin's A and B rings and differences in C-ring structures influence the degree of inhibition. Quercetin and luteolin, which have a double bond between C2 and C3, strongly inhibit α-amylase. Quercetin and 3′,4′-dihydroxyflavonol exhibited significantly greater inhibition of α-glucosidases than did luteolin. Moreover, Zhou et al. (2021) reported that quercetin and acarbose effectively inhibited α-amylase with IC_{50} values of 270 and 32.3 μg/mL, respectively, while decreasing the inhibition of α-glucosidase with IC_{50} values of 544 and 47.23 μg/mL, respectively. Quercetin at 1.4 mg/mL inhibited α-amylase by approximately 75.89%. The essential structural features for α-glucosidase inhibition include a 4′-OH substitution and a keto group at the C-4 position, particularly at specific positions on ring C and ring B, which could interact with positively charged groups on both enzymes. However, an additional hydroxyl group at the C-3′ position of the B ring in quercetin diminishes its inhibitory effect on α-glucosidase, while this effect is not observed with α-amylase. Although quercetin exhibits lower inhibitory potency than acarbose, it remains an effective inhibitor of both enzymes.

Furthermore, Shen et al. (2023) reported that both hyperoside and quercetin had significant α-amylase inhibitory effects with IC_{50} values of 0.491 mg/mL and 0.325 mg/mL, respectively. Compared to acarbose (IC_{50} = 0.622 mg/mL), both hyperoside and quercetin had stronger inhibitory effects, with quercetin being the most potent α-amylase inhibitor.

Previous studies have suggested a potential link between quercetin and antidiabetic effects through the inhibition of α-amylase or α-glucosidase. Quercetin may be converted into different valuable products, such as a food supplement or nutraceutical that can serve as an antidiabetic agent. It shows promise as a functional compound for inhibiting these enzymes and alleviating diabetes symptoms. Essentially, the relative effectiveness and potential advantages or limitations of quercetin on these digestive enzymes can be studied by comparing it to other natural phenolics and synthetic inhibitors. These more comprehensive comparative studies would help to establish a clearer picture of the effect of quercetin. Nonetheless, specific concentrations of quercetin have been studied, but its bioavailability and effective concentration in a biological system could vary. Information on dose–response relationships, absorption, metabolism, and bioavailability could aid in better understanding how quercetin performs in practical applications.

2.2 | *In silico* models and molecular docking studies

In silico models and molecular docking studies have become invaluable tools for understanding the interaction mechanisms of potential therapeutic agents at the molecular level. With *in silico* studies, it is possible to identify potential inhibitors, determine the conformational structure of the inhibitor–enzyme complex, calculate the binding energy of the inhibitor, elucidate the interactions and specific amino acid residues involved in inhibition, and correlate these findings with *in vitro* or *in vivo* data (Zhang et al., 2020). These computational techniques provide insights into the binding affinity and specific interactions between polyphenols, such as proanthocyanidins (Vazquez-Flores et al., 2018), anthocyanins (Zhang et al., 2019), and flavonoids (Kulkarni et al., 2021), and target enzymes relevant to diabetes management. *In silico* studies include molecular docking, molecular dynamics (MD) simulation, and quantitative structure–activity relationship (QSAR) approaches. Molecular docking is a computational technique used to predict the preferred orientation of one molecule (typically a small ligand) when it binds to another molecule (usually a larger macromolecule, such as a protein) to form a stable complex. It is particularly valuable in studying enzyme inhibition, as it helps predict how potential inhibitors interact with enzyme-active sites. Understanding these interactions at the molecular level provides valuable insights into the mechanisms of inhibition (Agarwal & Mehrotra, 2016). MD simulation is a powerful computational technique used to study the physical movements of atoms and molecules as a function of time. In the context of enzyme inhibition, MD simulations provide a detailed understanding of the dynamic behavior and conformational stability of enzyme–inhibitor complexes (Shukla & Tripathi, 2020). QSAR is a method that correlates the chemical structure of compounds with their biological activity using statistical models. With respect to enzyme inhibition, QSAR models help predict the inhibitory potential of new compounds based on their structural properties (Mitra et al., 2024; Tropsha, 2010).

In silico studies help identify the following key interactions between inhibitors and enzyme-active sites. These interactions include hydrogen bonding, hydrophobic interactions, electrostatic interactions, and π–π interactions (Ben Mustapha et al., 2023; Hua et al., 2018). Furthermore, common mechanisms of enzyme inhibition include competitive inhibition, where the phenolic compound competes with the substrate for binding to the active site, and noncompetitive inhibition, where the phenolic compound binds to an allosteric site, altering the enzyme conformation and reducing its activity (Figure 3) (Şöhretoğlu et al., 2018). Among the flavonoids, quercetin has been extensively studied for its inhibitory effects on

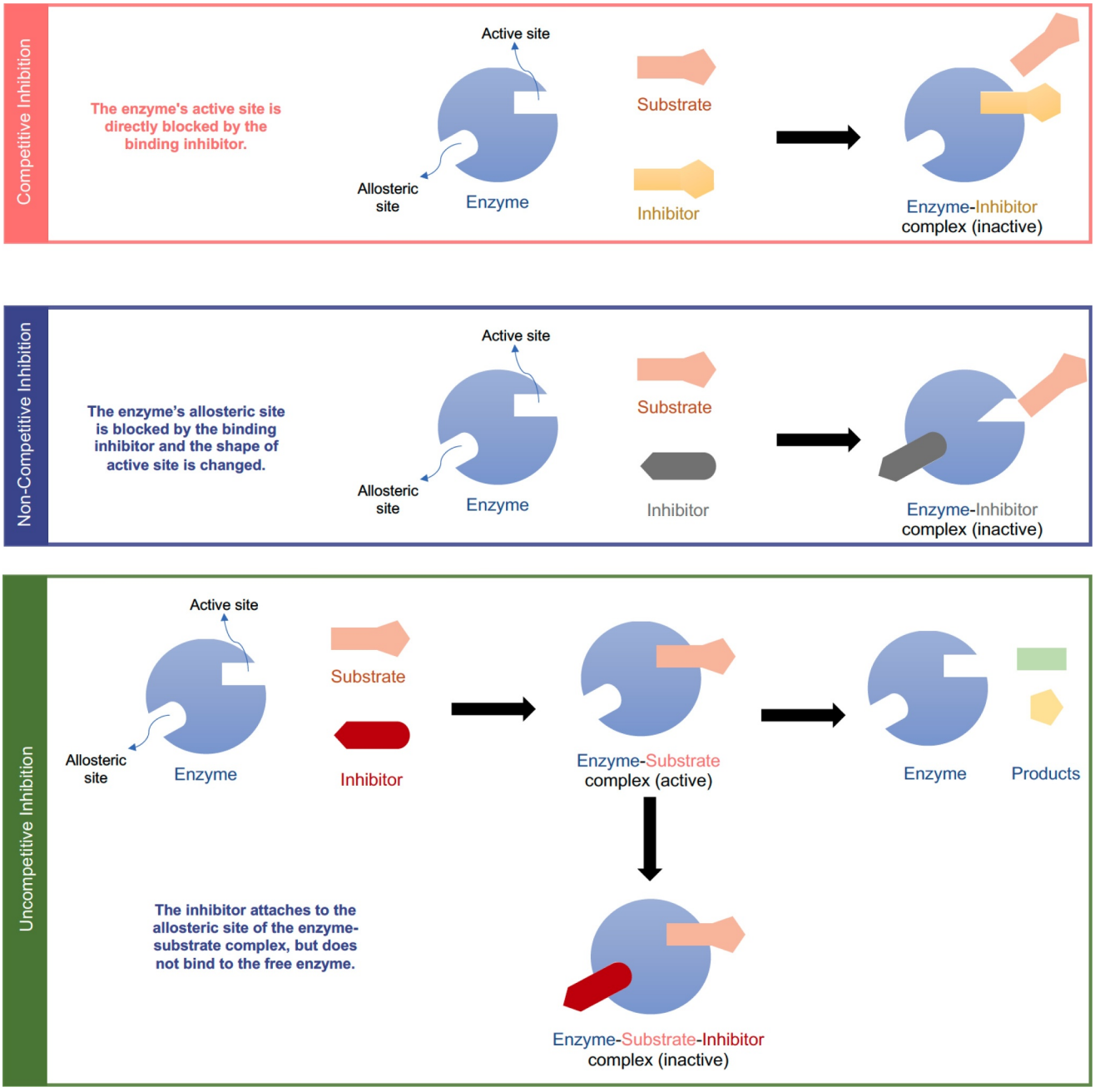

FIGURE 3 α-Amylase and α-glucosidase inhibition mechanisms.

key enzymes involved in carbohydrate metabolism. Molecular docking studies have demonstrated that quercetin binds effectively to the active sites of enzymes such as α-glucosidase and α-amylase (Table 2). These enzymes play a crucial role in the breakdown of complex carbohydrates into glucose, thus influencing postprandial blood sugar levels (Zhang et al., 2017).

A recent study by Shen et al. (2023) examined the inhibitory effects of quercetin and hyperoside on α-amylase activity using molecular docking and MD simulations. The findings indicated that quercetin, with an IC_{50} value of 0.325 mg/mL, demonstrated better inhibitory activity than hyperoside, which had an IC_{50} value of 0.491 mg/mL. The inhibition mechanisms were determined to be competitive for hyperoside and noncompetitive for quercetin. Additionally, quercetin formed hydrogen bonds with the Gln63, Glu233, Asp197, and Asp300 residues of α-amylase. Similar results were obtained when quercetin, umbelliferone, and their commercial counterpart acarbose were evaluated for their inhibitory effects on human salivary α-amylase. Among the three ligands, quercetin demonstrated the lowest binding energy, indicating that it binds to the enzyme's active site more easily than the other compounds. Moreover, the amino acid residues involved in the interaction with quercetin were Ala310, Arg303, Arg346, Asp353, Asp356, Gln302, Gly304, His305, Ile312, Thr314, Trp316, Trp344, and Lys352 (Altuner, 2022). In another study, the inhibitory effects of quercetin

TABLE 2 Summary of the in silico enzyme inhibitory effect of quercetin.

Enzyme inhibitory potential	Driven inhibitory action	*In silico* method	References
Quercetin-α-amylase docked complexes had good stability Hydrogen bonds formed with Gln63, Glu233, Asp197, and Asp300	Noncompetitive inhibitor hydrogen bonding and the π–π stack interaction	Molecular docking and MD simulation	Shen et al. (2023)
Quercetin–human pancreatic α-amylase complex had a root mean square deviation of 2.54 Å and root mean square fluctuation of 1.25 Å ΔG_{bind} of quercetin- α-amylase complex: −41.42 ± 5.57 kcal/mol	Hydrogen bonding	MD simulation	Kikiowo et al. (2023)
ΔG_{bind} of quercetin- α-amylase complex: −10.92 kcal/mol Hydrogen bonds formed with Ala310, Arg303, Arg346, Asp353, Asp356, Gln302, Gly304, His305, Ile312, Thr314, Trp316, Trp344, and Lys352	Hydrogen bonding	Molecular docking	Altuner et al. (2022)
α-amylase and α-glucosidase activity decreased	Competitive inhibition for α-amylase–quercetin complex; mixed inhibition for α-glucosidase–quercetin complex	Molecular docking	Tshiyoyo et al. (2022)
Quercetin formed two H-donor interactions with Asp69, Asp215 and H-acceptor interaction with His351 residues of α-glucosidase	Hydrogen bonding	Molecular docking	Abdelli et al. (2021)
Binding energy of quercetin- α-glucosidase: −8.45 kcal/mol Π-stack interactions formed with fluorescent residues Trp58, Tyr72, and Phe159	Competitive inhibition hydrogen bonding, π- π conjugation	Molecular docking	Fu et al. (2021)
ΔG_{bind} of quercetin- α-amylase complex: −8.8 kcal/mol Arg398, Pro332, Arg421, and Arg252 formed standard hydrogen bonds with α-amylase. Asp402 formed a carbon–hydrogen bond, and Pro332 exhibited π-alkyl and π-sigma interactions.	Hydrogen bonding, carbon–hydrogen bond, π-alkyl and π-sigma interactions	Molecular docking	Nabil-Adam et al. (2023)
Binding energies of quercitrin, quercetin-3-O-rutinoside, quercetin-7-O-glucoside and quercetin to α-amylase were −11.14, −10.87, −9.30, −7.81 kcal/mol, respectively and to α-glucosidase were −11.01, −9.57, −8.80, −8.86 kcal/mol, respectively. Quercetin formed 7 hydrogen bonds with Phe276, Asn277, Lys242, Lys7, Val269, Glu271 and Trp318 of α-glucosidase	Hydrogen bonding	Molecular docking	Li, Yang et al. (2023)
Quercetin glycoside (floralpanasenoside A) has hydrophobic interactions with ASP357, ASP232, PHE476, and LYS506 of α-glucosidase	Hydrogen bonding	Molecular docking	Li, Li et al. (2020)
Binding energy of quercetin- α-glucosidase: −9.0 kcal/mol Quercetin and α-glucosidase interacted at Asp215, His280, Phe303, Asp307, Asp352, and Arg442 residues Quercetin– α-glucosidase complex had a root mean square deviation of 0.3 nm after 10 ns simulation and the binding pattern remained unchanged	Mixed type inhibition, hydrogen bonding	Molecular docking and MD simulations	Liu et al. (2020)

TABLE 2 (Continued)

Enzyme inhibitory potential	Driven inhibitory action	*In silico* method	References
ΔG_{bind} of quercetin– α-glucosidase complex: −8.4 kcal/mol Quercetin– α-glucosidase complex had a root mean square deviation of 0.3 nm and remained stable after 10 ns simulation Quercetin formed hydrogen bonds with Asp214, Glu276, Arg312; electrostatic bonds with Arg 439, Asp349; hydrophobic bonds with Phe300 and Ala278	Hydrogen bonds, electrostatic bonds, and hydrophobic bonds	Molecular docking and MD simulations	Patil et al. (2022)
Tartary buckwheat starch digestion decreased by a dual mechanism of enzyme inhibition and quercetin–starch complexation Binding energy of quercetin– α-glucosidase: −8.7 kcal/mol The binding energy of quercetin– α-amylase: −7.6 kcal/mol Quercetin was surrounded by 12 and 16 amino acid residues of α-amylase and α-glucosidase, respectively.	Hydrogen bonds, π–π stacking, π-alkyl and π-sigma interactions, van der Waals interactions	Molecular docking	Wang et al. (2022)

and ombuin on human pancreatic α-amylase were assessed using MD simulations. The findings revealed that quercetin is strongly bound to human pancreatic α-amylase, primarily through hydrogen bond interactions with the Asp197 residue. Additionally, the compactness of the quercetin–human pancreatic α-amylase complex remained stable over a 100 ns simulation, with a radius of gyration (RGyr) value of 3.79 Å (Kikiowo et al., 2023). Furthermore, quercetin exhibited a greater binding affinity to pancreatic α-amylase than to intestinal α-glucosidase, as determined using both Glide and AutoDock software. The inhibition mechanism for the α-amylase–quercetin complex was determined to be competitive, while for the α-glucosidase–quercetin complex, the inhibition mechanism was mixed (Tshiyoyo et al., 2022). In contrast, Abdelli et al. (2021) reported that the binding affinity of quercetin to α-glucosidase was greater than that of the quercetin–α-amylase complex. In addition, Fu et al. (2021) showed that quercetin forms a complex with α-glucosidase in a competitive manner with a binding energy of −8.45 kcal/mol. In another study, Nabil-Adam et al. (2023) conducted a molecular docking analysis using α-amylase as the target protein to investigate the activities of *Junia rubens* polyphenols based on their predicted binding modes. Among the 12 phenolic compounds tested, molecular docking analysis demonstrated a good affinity score, with quercetin showing a particularly high affinity at −8.8 kcal/mol. The analysis revealed that the amino acid residues Arg398, Pro332, Arg421, and Arg252 formed standard hydrogen bonds with α-amylase. Additionally, Asp402 was involved in a carbon–hydrogen bond, and Pro332 exhibited π-alkyl and π-sigma interactions. The glycosylation of quercetin has been found to enhance its binding affinity for α-amylase and α-glucosidase. According to Li, Yang, et al. (2023), the binding energies of quercitrin, quercetin-3-O-rutinoside, and quercetin-7-O-glucoside to α-amylase and α-glucosidase were notably lower than that of quercetin aglycone, indicating a stronger affinity for these enzymes. A novel quercetin glycoside, namely floralpanasenoside A, was evaluated for its inhibitory effects on α-glucosidase. After molecular docking simulation, the authors found that floralpanasenoside A forms a complex with α-glucosidase via hydrogen bonding at its active site pocket. Additionally, they observed that floralpanasenoside A has hydrophobic interactions with ASP357, ASP232, PHE476, and LYS506 (Li, Li et al., 2020). The inhibition of these digestive enzymes by quercetin also has a significant impact on starch digestibility. Wang et al. (2022) modeled the interaction between quercetin and starch granules, suggesting that quercetin can embed within the starch matrix, further obstructing the access of α-amylase and α-glucosidase to their substrates. This two-way mechanism not only delays carbohydrate digestion but also reduces the glycemic index of starchy foods, making quercetin a potential agent for managing diabetes through dietary interventions.

3 | STARCH DIGESTIBILITY AND GLYCEMIC CONTROL

Starch is one of the basic energy sources for humans, especially in the gastrointestinal tract. The extent and rate of *in vitro* starch digestion in the gastrointestinal tract produce different fractions of starch, including rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS) (Klostermann et al., 2024). A recent study has conducted a meta-analysis to assess the impact of SDS on postprandial glycemic responses. Consuming SDS tends to digest slowly throughout the small intestine, and a more prolonged and stable release of glucose during digestion is positively associated with higher extended glycemic index, glycemic profile levels, and managing blood sugar levels (Y. Wang et al., 2023). Besides, RS is fermented in the colon to produce beneficial short-chain fatty acids and shows promising but inconclusive

effects on improving intestinal health, glycemic balance, lipid metabolism, and body weight (Bojarczuk et al., 2022).

Recent studies have explored how this compound interacts with starches, potentially altering their digestion rate and, consequently, their impact on blood glucose levels. Several studies revealed that quercetin interacted with quinoa starch and maize starch nanoparticles (Jiang et al., 2022), Tartary buckwheat starch (Gao et al., 2021; Li, Gao et al., 2020; Zhou et al., 2021), and canistel seed starch (He et al., 2023) mainly via hydrogen bonds without forming new covalent bonds. Jiang et al. (2022) explained that quinoa starch nanoparticles, due to their higher amylopectin content, exhibit higher quercetin loading rates, more uniform particle sizes, better storage stability over 21 days, and slower enzymatic degradation compared to corn starch nanoparticles. Gao et al. (2021) observed that quercetin made Tartary buckwheat starch granules smoother and more compact and improved thermal stability with no significant changes to the crystalline structure. Li, Gao et al. (2020) noted that quercetin formed rod-like crystals that cross-linked and stabilized Tartary buckwheat starch, reducing amylose leaching.

Quercetin interacts with starch and digestive enzymes (Figure 4) (Ombra et al., 2022). Interactions between polyphenols and starch, particularly amylose, can form complexes that reduce starch digestibility and resist rapid digestion. These complexes include both noninclusion and V-type inclusion complexes. They may slow digestion by preventing starch from swelling and creating a denser starch structure that enzymes cannot access easily (active side of the starch) (Yang et al., 2023).

Overall, quercetin–starch interaction reduced starch digestibility by altering its structure and limiting enzyme access. The details about the inhibitory effect of flavonoids on the starch digestion rate, glycemic index, and starch fractions are provided in Table 3.

Quercetin interaction with Tartary buckwheat starch (Wang et al., 2022) and corn starch (Zhou et al., 2024) increased the resistance to digestion by converting RDS into SDS and RS. This effect is also observed in the presence of ethanol, which further restricts starch gelatinization and contributes to higher SDS and RS content (Wang et al., 2022). A notable effect was observed for higher quercetin content with 1.25%, 2.5%, and 5% (Zhou et al., 2024) and 5.20 and 5.83 mg GAE/g (using a free radical grafting method) (Wu et al., 2022) in the corn–starch complex. The higher quercetin levels lead to a more substantial reduction in starch digestibility, so lower RDS and higher RS were obtained in a dose-dependent manner of quercetin (Wang et al., 2022; Wu et al., 2022; Zhou et al., 2024). The increased resistance of the quercetin–starch complex to amylolytic digestion is likely due to the formation of internal bonds, enhanced structural stability, and a greater ability to compete with starch molecules for α-amylolytic enzyme-active sites (Wu et al., 2022). It was also examined that the addition of quercetin to pregelatinized Tartary buckwheat starch significantly reduced the starch hydrolysis rate and RDS and increased RS content. This indicated that quercetin forms a stable complex with pregelatinized starch, enhancing the starch's resistance to enzymatic digestion and altering its physicochemical properties through hydrogen bonding (Gao et al., 2021; Li, Gao et al., 2020). A similar study by Maibam et al. (2023) stated that the addition of ferulic acid or quercetin to pregelatinized *Euryale ferox* kernel starch significantly decreased the RDS and increased the SDS and RS fractions in a dose-dependent manner. This transformation reflects enhanced resistance to enzymatic digestion, attributed to increased starch crystallinity, reduced granule swelling, and polyphenol interactions with starch and digestive enzymes. Despite the improvements, the added polyphenols do not fully restore the RS content lost during gelatinization but do result in a starch structure

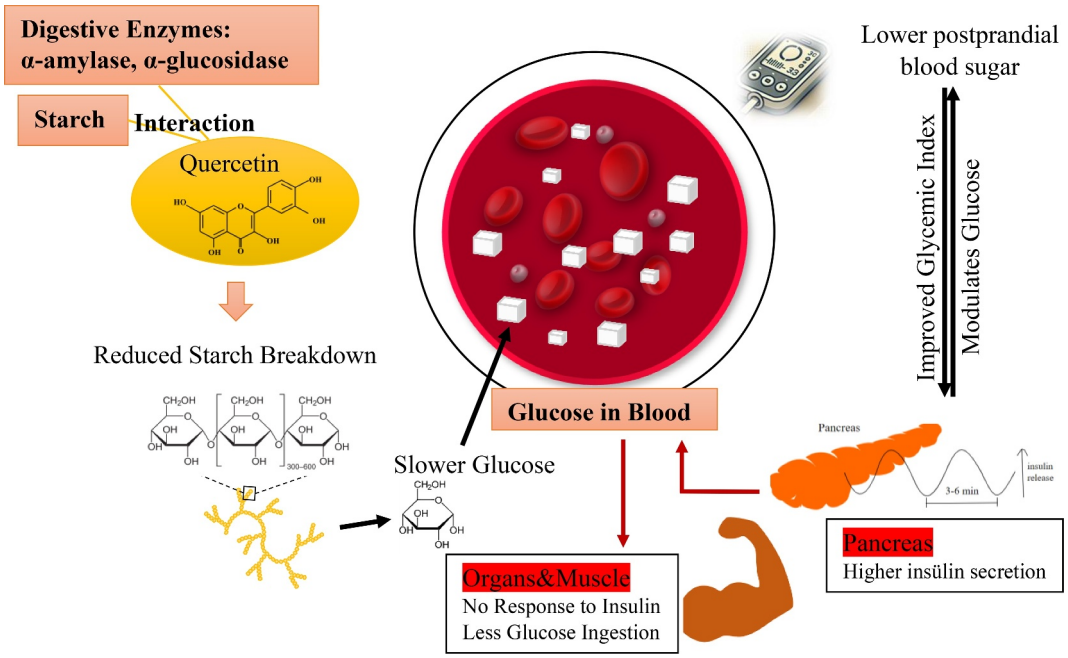

FIGURE 4 Relationship between quercetin intake and glycemic control.

TABLE 3 Summary of the impact of quercetin on starch digestion rate and glycemic index.

Sample	Starch source	Starch digestion results	References
Quercetin or rutin complexes (ethanol modified)	Tartary buckwheat starch	RDS↓ SDS↑ RS↑	Wang et al. (2024)
Quercetin (1.25%, 2.5%, and 5%) complex	Tartary buckwheat starch	RDS↓ RS↑ SDS↑, only for 1.25%–2.5%	Zhou et al. (2024)
Gallic acid or quercetin (5.20 and 5.83 mg GAE/g) complex via the free radical grafting method	Corn starch	RS↑	Wu et al. (2022)
Quercetin (2.5%, 5%, 7.5%, and 10%) complex	Pregelatinized Tartary buckwheat starch (70°C)	Hydrolysis rate and hydrolyzed ratio of starch↓ RDS↓ SDS ↔ RS↑	Li, Jiang, et al. (2020)
Quercetin (10%) complex	Pregelatinized Tartary buckwheat starch (70, 80, and 100°C)	Hydrolysis rate and hydrolyzed ratio of starch↓ RDS↓ SDS↑ RS↓	Gao et al. (2021)
Ferulic acid and quercetin complex	Euryale ferox kernel starch	Hydrolysis rate and hydrolyzed ratio of starch↓ hydrolysis index and the estimated glycemic index↓ RDS↓ SDS↑ RS↑	Maibam et al. (2023)
Quercetin, pre-incubated with enzymes or starch	Tartary buckwheat starch	Hydrolysis index and the estimated glycemic index↓ RDS↓ SDS↑ RS↑, preincubation with enzyme was more efficient	Zhou et al. (2021)
Quercetin or rutin complex	Tartary buckwheat starch	Hydrolysis rate and hydrolyzed ratio of starch↓ hydrolysis index and the estimated glycemic index↓ SDS↓ RDS↓ RS↑ superior to rutin	Wang et al. (2022)
Phenolic acids: *p*-coumaric acid, ferulic acid; flavanones: Hesperidin, naringenin; flavanols: (+)-catechin, epigallocatechin gallate; flavonols: quercetin, kaempferol; anthocyanins: Cyanidin-3-O-glucoside, delphinidin-3-O-glucoside.	Wheat starch gel	RS↑ Lower effect than epigallocatechin gallate, higher effect than kaempferol	Kwaśny et al. (2022)
Dried onions	Wheat pasta	Hydrolysis index and the estimated glycemic index↓ reducing sugar↓	Ombra et al. (2022)

Note: ↔: no obvious change; ↑: upregulated; ↓: downregulated.

Abbreviations: GAE, gallic acid equivalent; RDS, rapidly digestible starch; RS, resistant starch; SDS, slowly digestible starch.

that behaves more like raw starch, offering potential benefits for managing blood sugar and satiety.

An interesting study by Zhou et al. (2021) showed that higher quercetin concentrations (2%–4%) enhance the formation of RS through interactions with starch chains, but when quercetin levels reach 4%, the effect plateaus due to the saturation of interactions. Further, it was noted that quercetin, especially when added to the mixture before the enzyme, reduced RDS and increased RS more than when added after the enzyme.

Quercetin showed a stronger inhibition of starch digestion than rutin, particularly when added in its free form, due to its lower molecular weight and direct inhibition of digestive enzymes, whereas both free and bound forms of phenolics similarly increased RS and decreased starch digestibility (Libo Wang et al., 2022). Kwaśny et al. (2022) compared the different phenolic acids, flavanols, flavonols, and anthocyanins on the digestibility of wheat starch gel. Quercetin's addition to wheat starch gels significantly influences RS content, with varying effectiveness based on the dose. At doses of 5 mg, 10 mg, and 20 mg, quercetin leads to RS contents ranging from 0.34 to 3.4 g/100 g dm, with the highest RS observed at the 5 mg dose. Quercetin is notably less effective than some other polyphenols, such as epigallocatechin gallate, in increasing RS but is more effective than certain compounds like kaempferol. Overall, quercetin contributes to a higher RS content and lower digestibility of starch, though its impact is not as pronounced as the most effective polyphenols tested.

The inhibitory effects of polyphenols or flavonoids on starch digestion were investigated via kinetic studies. The Lineweaver–Burk curve is a kinetic analysis of the polyphenol inhibition of digestive enzymes and the reversibility of inhibition based on crossover (Cui et al., 2022). The other digestion kinetics method used was Goni's method. The authors suggested that starch hydrolysis kinetics be calculated using equations for the percentage of starch hydrolyzed at the time and area under the hydrolysis curve, and in the last step, the kinetics depend on the specific formula for the glycemic index and starch rate (Li, Gao et al., 2020; Maibam et al., 2023; Yusufoğlu et al., 2022). The first-order kinetic and logarithm of slope models both show that quercetin slows down the rate of starch digestion, but the extent of digestion (C_∞) and the digestion rate (K) are influenced by quercetin's interaction with starch and its inhibitory effects on enzymes. The kinetic analysis reveals that pregelatinized Tartary buckwheat starch (Li, Gao et al., 2020) or plasma-modified pregelatinized Tartary buckwheat starch (Gao et al., 2021) with added quercetin exhibits a slower hydrolysis rate, particularly with 10%

quercetin, which results in the lowest hydrolysis rate. Higher quercetin levels lead to more compact starch structures, and this reduction in the hydrolysis rate correlates with a significant increase in RS. Thus, the quercetin–starch complexation limits enzyme access and enhances the resistance to enzymatic digestion (Gao et al., 2021; Li, Gao et al., 2020). Quercetin exhibited a stronger inhibitory effect on starch digestion compared to rutin and ferulic acid, with lower C_{∞}, hydrolysis index, and estimated glycemic index values, particularly in its free form (Maibam et al., 2023; Wang et al., 2022).

Quercetin can alter the glycemic potential of fortified bread by inhibiting carbohydrate digestive enzymes, demonstrating its potential to modify the starch digestion process and enhance glycemic control (Wu et al., 2022). Adding 3% onion flour (which contains mainly quercetin) to pasta significantly lowered the glycemic index from 72% to 54%, indicating a 25% decrease in starch hydrolysis. The onion-enriched pasta exhibited a plateau in glucose release after 120 min of digestion, reflecting slower starch breakdown. The reduction in starch breakdown was associated with the inhibitory effects of onion polyphenols on α-amylase activity.

The incorporation of quercetin into diets, particularly through fortified foods or dietary supplements, could be a promising approach for managing diabetes and preventing related metabolic disorders. Future research should focus on optimizing quercetin formulations to maximize their benefits and evaluate the long-term effects of dietary quercetin on metabolic health.

4 | *IN VIVO* STUDIES

Research on the antidiabetic effects of quercetin involves both *in vitro* studies and animal model investigations. *In vitro* studies have elucidated molecular interactions, while animal models have provided insights into physiological outcomes. Integrating these approaches offers a comprehensive understanding of quercetin's potential as a therapeutic agent for diabetes. Table 4 presents a summary of *in vivo* studies investigating the antidiabetic effects of quercetin consumption. Zhou et al. (2024) demonstrated that mice orally consuming sucrose and maltose with quercetin (at doses of 18.75, 37.5, and 75 mg/kg bw) exhibited delayed and lower peak glucose levels. Compared to acarbose (at a dose of 75 mg/kg bw), quercetin led to a greater initial glucose peak after half an hour but lower levels between 1 and 3 h. Li, Jiang, et al. (2020) reported a 2.3-fold increase in serum insulin levels in diabetic mice following quercetin intervention, accompanied by a reduction in blood glucose levels from 19.76 mmol/L to 15.22 mmol/L.

TABLE 4 In vivo antidiabetic effects of quercetin consumption.

Daily dosage	Treatment	Animal model	The antidiabetic effect	References
30, 60, 120 mg/kg bw	4 Months diet	Streptozotocin (65 mg/kg)-induced type 1 diabetes wistar rats	Blood glucose level ↔	Dong et al. (2022)
1.5 mg/kg bw	4 Months diet	C57BL/6J mice	Insulin resistance ↑ serum glucose level ↓ protective effect on size and structure of pancreatic β-cells insulin intensity per islet cell ↑	Li, Jiang et al. (2020)
18.75, 37.5 and 75 mg/kg bw	Postprandial consumption of sucrose and maltose (0.25 g/mL)	Sprague–Dawley rats	Blood glucose level ↓ blood glucose peak time ↑	Zhou et al. (2024)
50 mg/kg bw	8 Weeks diet	Albino wistar rats	Protective effect on size and structure of pancreatic β-cells	Korkmaz and Dik (2024)
50 mg/kg bw in nanoemulsion form	21 Days diet	Streptozotocin (40 mg/kg)-induced Albino wistar rats	Blood glucose level ↓ 7 days pretreatment of quercetin nanoemulsion: more effective protective effect on size and structure of pancreatic β-cells	Mahadev et al. (2022)
0.25 g/mL of quercetin (1.25%, 2.5% and 5% in) starch complex	Postprandial consumption	Sprague–Dawley rats	Blood glucose level ↓ blood glucose peak time ↑	Zhou et al. (2024)
1 g in 5 mL water (corn starch-gallic acid or quercetin complex)	Oral gavage after fasting for 12–14 h	Sprague–Dawley rats	AUC values for blood glucose levels ↓ quercetin at higher level were more effective	Wu et al. (2022)
50 and 100 mg/kg bw of sertiamarin from *Enicostemma axillare* and quercetin	28 Days diet	Streptozotocin (50 mg/kg)-induced type 2 diabetes Albino wistar rats	Blood glucose level ↓ protective effect on size and structure of pancreatic β-cells	Jaishree and Narsimha (2020)

Note: ↔: no obvious change, ↑: upregulation, ↓: downregulation.

Abbreviation: Bw, body weight.

In contrast, Dong et al. (2022) reported no significant decrease in fasting blood glucose levels in diabetic rats following quercetin intervention, suggesting that its beneficial effects on seminal vesicles are not linked to reduced blood glucose. This discrepancy may stem from the type of diabetes studied; streptozotocin-induced type 1 diabetes involves selective destruction of islet β-cells, and quercetin may not fully reverse the damage caused by high-dose streptozotocin. The differing results between these studies suggest that quercetin's effectiveness may vary with the diabetes model used. Future research should explore how quercetin performs in both type 1 and type 2 diabetes and consider combining it with other therapies to improve its efficacy across different diabetic conditions.

The poor solubility of quercetin (0.17–7 μg/mL) in gastric fluids (5.5 μg/mL) and intestinal fluids (28.9 μg/mL) has been reported in the literature (Cai et al., 2013; Kandemir et al., 2022). Consequently, various studies have explored the consumption of alternative forms of quercetin, such as complexes, emulsions, or combinations with other substances (Jaishree & Narsimha, 2020; Mahadev et al., 2022; Zhou et al., 2024). Mahadev et al. (2022) demonstrated that nanoemulsified quercetin was more effective at reducing blood sugar levels in streptozotocin-induced diabetic rat models, particularly after a 7-day pretreatment, while also preserving the structural integrity of pancreatic β-cells and hepatocytes. While alternative formulations, such as nanoemulsions and quercetin–starch complexes, have shown promise in enhancing bioavailability and efficacy, these solutions need further optimization to assess their effectiveness in human trials. Further, novel research on *in vivo* trials should address quercetin-loaded different delivery systems in food matrices or their co-digestion with food. Moreover, Zhou et al. (2024) showed that a quercetin–starch complex decreased the maximum glucose level in mice from 7.9 mmol/L to 6 mmol/L compared to that in controls, and prolonged the time to reach peak glucose levels by up to 1 hour. Wu et al. (2022) reported an increase in resistance correlated with a notable reduction in glucose production, particularly with the high quercetin compared to gallic acid showing a significant decrease in the blood glucose levels, indicating that high doses of quercetin enhance corn starch's resistance to digestion. To the author's knowledge, no further research exists on how quercetin–starch complexes behave in the digestive system.

Nonetheless, Jaishree and Narsimha (2020) reported that a combination of quercetin (at doses of 50 or 100 mg/kg bw) with a swetiamarin-rich extract from *Enicostemma axillare* significantly reduced blood glucose levels in streptozotocin-induced type 2 diabetic rats after 14 days, with the higher dosage being more effective. Although quercetin has beneficial effects, it may need to be used in conjunction with or as part of a broader therapeutic strategy. Further comparative studies are required to evaluate how effective quercetin is compared to standard diabetes treatments, and to identify optimal dosing regimens and combinations for quercetin.

Pancreatic β-cells, located in the islets of Langerhans within the pancreas, are responsible for secreting insulin, a hormone that regulates blood sugar levels and enables cells to utilize glucose for energy. The relationship between pancreatic β-cells and insulin is crucial for maintaining proper blood sugar regulation in the body. Flavonoids enhance the ability of the pancreatic islets of Langerhans to produce and secrete insulin and glucagon into the bloodstream. In addition to affecting postprandial glucose levels in normal animal models, quercetin consumption mitigates hyperglycemia in type 2 diabetic rats by promoting the regeneration of pancreatic tissue, thus exerting a protective effect on the size and structure of islets (Jaishree & Narsimha, 2020; Korkmaz & Dik, 2024; Li, Jiang et al., 2020; Mahadev et al., 2022). Furthermore, researchers have shown that quercetin may help reduce cell death caused by the oxidative stress in the seminal vesicles of diabetic rats by blocking Nrf2 in type 1 diabetes (Dong et al., 2022) and ferroptosis in renal tubular epithelial cells by modulating the Nrf2 signaling pathway in type 2 diabetic mice with diabetic nephropathy (Feng et al., 2023; Zhang et al., 2024). More detailed mechanistic studies are needed to clarify these pathways and to determine how quercetin's effects might vary with different forms of stress and cellular damage. Long-term studies are necessary to confirm these benefits and to monitor any potential adverse effects.

5 | CONCLUSION AND FUTURE PERSPECTIVES

Polyphenols, particularly flavonoids such as quercetin, have been demonstrated to significantly inhibit α-amylase and α-glucosidase enzymes, thereby slowing carbohydrate digestion and reducing glucose absorption—key factors in managing postprandial hyperglycemia. The enzyme-inhibiting properties of quercetin suggest its potential as a functional compound for diabetes treatment. However, the low bioavailability of quercetin, due to its poor solubility in water and digestive fluids, presents a challenge. Further research may focus on improving the stability and efficacy of quercetin by developing its complex forms with other macro-compounds, creating nanoemulsions, or combining it with other compounds to achieve a synbiotic antidiabetic effect. Moreover, comparisons regarding the antidiabetic effects between the pure form of quercetin and the natural extract form will also present a different perspective on the subject.

Future research is needed to find out the optimum levels of quercetin to be used compared to standard treatments, especially as more people look for natural remedies instead of conventional drugs. Studies should also examine how quercetin affects glucose metabolism and its impact on the glycemic index of starchy or high-glucose foods. Indeed, it is important to see how quercetin works when it is consumed with food (co-digestion) or within the food matrix. Future studies in this field are crucial for determining the optimal concentrations of quercetin required to regulate glucose metabolism and lower the glycemic index of starchy or high-glucose foods, particularly for enhancing their antidiabetic effects. This is also vital for covering the studies on functional food development containing quercetin in different forms (nanoemulsions, starch–quercetin complexes). Furthermore, while *in vitro* studies offer a robust scientific foundation, real clinical and animal experiments are needed to

validate these findings, and mechanistic and long-term studies are needed to understand its effects. Future studies should comprehensively describe the effects of quercetin in biological organisms, ensuring similar antidiabetic benefits, and compare these effects with those of existing medications. Since quercetin's effectiveness can vary between type 1 and type 2 diabetes, more studies are needed to understand how it works, if there are any possible side effects, and how its benefits might change with different types of cellular stress.

AUTHOR CONTRIBUTIONS

Deniz Günal-Köroğlu: Conceptualization; investigation; supervision; writing—original draft. **Gizem Catalkaya**: Investigation; writing—original draft. **Büşra Yusufoğlu**: Investigation; writing—original draft. **Gizem Kezer**: Investigation; writing—original draft. **Tuba Esatbeyoglu**: Supervision; writing—review & editing. **A. M. Abd El-Aty**: Writing—review & editing. **Esra Capanoglu**: Conceptualization; supervision; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors report that there are no competing interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

None declared.

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REFERENCES

Abdelli, I., Benariba, N., Adjdir, S., Fekhikher, Z., Daoud, I., Terki, M., Benramdane, H., & Ghalem, S. (2021). *In silico* evaluation of phenolic compounds as inhibitors of A-amylase and A-glucosidase. *Journal of Biomolecular Structure and Dynamics*, *39*(3), 816–822. https://doi.org/10.1080/07391102.2020.1718553

Agarwal, S., & Mehrotra, R. (2016). An overview of molecular docking. *JSM Chem*, *4*(2), 1024.

Al-Ansari, M., Al-Humaid, L., Aldawsari, M., Abid, I. F., Jhanani, G. K., & Shanmuganathan, R. (2023). Quercetin extraction from small onion skin (Allium cepa L. var. aggregatum Don.) and its antioxidant activity. *Environmental Research*, *224*, 115497. https://doi.org/10.1016/J.ENVRES.2023.115497

Altuner, E. M. (2022). *In silico* proof of the effect of quercetin and umbelliferone as alpha-amylase inhibitors, which can Be used in the treatment of diabetes. *Kastamonu Üniversitesi Orman Fakültesi Dergisi*, *22*(3), 202–216. https://doi.org/10.17475/kastorman.1215281

Ansari, P., Choudhury, S. T., Seidel, V., Rahman, A. B., Aziz, M. A., Richi, A. E., Rahman, A., Jafrin, U. H., Hannan, J. M. A., & Abdel-Wahab, Y. H. A. (2022). Therapeutic potential of quercetin in the management of type-2 diabetes mellitus. *Life*, *12*(8), 1146. https://doi.org/10.3390/LIFE12081146

Azeem, M., Hanif, M., Mahmood, K., Ameer, N., Chughtai, F. R. S., & Abid, U. (2023). An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review. *Polymer Bulletin*, *80*(1), 241–262. https://doi.org/10.1007/S00289-022-04091-8

Ben Mustapha, M., Lazrag, H., Khemis, E., Kaplan, M., Goren, A. C., Harrath, A. H., & Ben Jannet, H. (2023). Phenolic profile, α-amylase inhibition and molecular docking scrutiny of the trunk bark of Pinus pinea growing in Tunisia. *Plant Biosystems*, *157*(2), 357–366. https://doi.org/10.1080/11263504.2023.2165565

Bojarczuk, A., Skąpska, S., Mousavi Khaneghah, A., & Marszałek, K. (2022). Health benefits of resistant starch: A review of the literature. *Journal of Functional Foods*, *93*, 105094. https://doi.org/10.1016/J.JFF.2022.105094

Bule, M., Abdurahman, A., Nikfar, S., Abdollahi, M., & Amini, M. (2019). Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies. *Food and Chemical Toxicology*, *125*, 494–502. https://doi.org/10.1016/J.FCT.2019.01.037

Cai, X., Fang, Z., Dou, J., Yu, A., & Zhai, G. (2013). Bioavailability of quercetin: Problems and promises. *Current Medicinal Chemistry*, *20*, 2572–2582. https://doi.org/10.2174/09298673113209990120

Cui, J., Zeng, S., & Zhang, C. (2022). Anti-hyperglycaemic effects of Burdock (Arctium lappa L.) leaf flavonoids through inhibiting α-amylase and α-glucosidase. *International Journal of Food Science and Technology*, *57*(1), 541–551. https://doi.org/10.1111/ijfs.15026

Dong, B., Shi, Z., Dong, Y., Chen, J., Wu, Z. X., Wu, W., Chen, Z. S., & Han, C. (2022). Quercetin ameliorates oxidative stress-induced cell apoptosis of seminal vesicles via activating Nrf2 in type 1 diabetic rats. *Biomedicine and Pharmacotherapy*, *151*, 113108. https://doi.org/10.1016/j.biopha.2022.113108

Feng, Q., Yang, Y., Qiao, Y., Zheng, Y., Yu, X., Liu, F., Wang, H., Zheng, B., Pan, S., Ren, K., Liu, D., & Liu, Z. (2023). Quercetin ameliorates diabetic kidney injury by inhibiting ferroptosis via activating Nrf2/HO-1 signaling pathway. *American Journal of Chinese Medicine*, *51*(4), 997–1018. https://doi.org/10.1142/S0192415X23500465

Fernandes, I., Oliveira, J., Pinho, A., & Carvalho, E. (2022). The role of nutraceutical containing polyphenols in diabetes prevention. *Metabolites*, *12*(2), 184. https://doi.org/10.3390/metabo12020184

Fu, M., Shen, W., Gao, W., Namujia, L., Yang, X., Cao, J., & Sun, L. (2021). Essential moieties of myricetins, quercetins and catechins for binding and inhibitory activity against α-Glucosidase. *Bioorganic Chemistry*, *115*, 105235. https://doi.org/10.1016/J.BIOORG.2021.105235

Gao, S., Liu, H., Sun, L., Cao, J., Yang, J., Lu, M., & Wang, M. (2021). Rheological, thermal and *in vitro* digestibility properties on complex of plasma modified Tartary buckwheat starches with quercetin. *Food Hydrocolloids*, *110*, 106209. https://doi.org/10.1016/j.foodhyd.2020.106209

Hamid, H. K., & Obaid, M. A. (2021). Role of quercetin flavonoid as antidiabetic: A review. *International Journal of Drug Delivery Technology*, *11*(4), 1495–1500. https://doi.org/10.25258/ijddt.11.4.65

He, R., Pan, Y. gui, Shang, W. T., Zhong, G., Huang, W. Y., Xiang, D., Pan, F., & Zhang, W. min (2023). Ultrasonic-assisted binding of canistel (Lucuma nervosa A.DC) seed starch with quercetin. *Ultrasonics Sonochemistry*, *96*, 106417. https://doi.org/10.1016/j.ultsonch.2023.106417

Hua, F., Zhou, P., Wu, H. Y., Chu, G. X., Xie, Z. W., & Bao, G. H. (2018). Inhibition of α-glucosidase and α-amylase by flavonoid glycosides from Lu'an GuaPian tea: Molecular docking and interaction mechanism. *Food & Function*, *9*(8), 4173–4183. https://doi.org/10.1039/c8fo00562a

Jaishree, V., & Narsimha, S. (2020). Swertiamarin and quercetin combination ameliorates hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced type 2 diabetes mellitus in wistar rats. *Biomedicine and Pharmacotherapy*, *130*, 110561. https://doi.org/10.1016/J.BIOPHA.2020.110561

Jiang, F., Du, C., Zhao, N., Jiang, W., Yu, X., & Du, S. kui (2022). Preparation and characterization of quinoa starch nanoparticles as quercetin carriers. *Food Chemistry*, *369*, 130895. https://doi.org/10.1016/j.foodchem.2021.130895

Kandemir, K., Tomas, M., McClements, D. J., & Capanoglu, E. (2022). Recent advances on the improvement of quercetin bioavailability. *Trends in Food Science and Technology*, *119*, 192–200. https://doi.org/10.1016/j.tifs.2021.11.032

Kikiowo, B., Ahmad, I., Alade, A. A., T. Ijatuyi, T., Iwaloye, O., & Patel, H. M. (2023). Molecular dynamics simulation and pharmacokinetics studies of ombuin and quercetin against human pancreatic α-amylase. *Journal of Biomolecular Structure and Dynamics*, *41*(20), 102312–110395. https://doi.org/10.1080/07391102.2022.2155699

Klostermann, C. E., Endika, M. F., Kouzounis, D., Buwalda, P. L., de Vos, P., Zoetendal, E. G., Bitter, J. H., & Schols, H. A. (2024). Presence of digestible starch impacts *in vitro* fermentation of resistant starch. *Food & Function*, *15*(1), 223–235. https://doi.org/10.1039/d3fo01763j

Korkmaz, Y., & Dik, B. (2024). The comparison of the antidiabetic effects of exenatide, empagliflozin, quercetin, and combination of the drugs in type 2 diabetic rats. *Fundamental and Clinical Pharmacology*, *38*(3), 511–522. https://doi.org/10.1111/FCP.12975

Kulkarni, S., Dwivedi, P., Danappanvar, A. N., Subhash, B. A., & Patil, B. M. (2021). Identification of α-amylase inhibitors from flavonoid fraction of Feronia elephantum and its integration with in-silico studies. *Silico Pharmacology*, *9*(1), 50. https://doi.org/10.1007/s40203-021-00099-6

Kwaśny, D., Borczak, B., Sikora, M., & Kapusta-Duch, J. (2022). Preliminary study on the influence of the polyphenols of different groups on the digestibility of wheat starch, measured by the content of resistant starch. *Applied Sciences*, *12*(21), 21. https://doi.org/10.3390/app122110859

Lavefve, L., Howard, L. R., & Carbonero, F. (2020). Berry polyphenols metabolism and impact on human gut microbiota and health. *Food and Function*, *11*(1), 45–65. https://doi.org/10.1039/C9FO01634A

Li, D., Jiang, C., Mei, G., Zhao, Y., Chen, L., Liu, J., Tang, Y., Gao, C., & Yao, P. (2020). Quercetin alleviates ferroptosis of pancreatic β cells in type 2 diabetes. *Nutrients*, *12*(10), 2954. https://doi.org/10.3390/nu12102954

Li, K., Li, S., Xu, F., Cao, G., & Gong, X. (2020). A novel acylated quercetin glycoside and compounds of inhibitory effects on α-glucosidase from Panax ginseng flower buds. *Natural Product Research*, *34*(18), 2559–2565. https://doi.org/10.1080/14786419.2018.1543685

Li, N., Yang, J., Wang, C., Wu, L., & Liu, Y. (2023). Screening bifunctional flavonoids of anti-cholinesterase and anti-glucosidase by *in vitro* and in silico studies: Quercetin, kaempferol and myricetin. *Food Bioscience*, *51*, 102312. https://doi.org/10.1016/j.fbio.2022.102312

Li, X., Bai, Y., Jin, Z., & Svensson, B. (2022). Food-derived non-phenolic α-amylase and α-glucosidase inhibitors for controlling starch digestion rate and guiding diabetes-friendly recipes. *LWT*, *153*, 112455. https://doi.org/10.1016/j.lwt.2021.112455

Li, Y., Gao, S., Ji, X., Liu, H., Liu, N., Yang, J., Lu, M., Han, L., & Wang, M. (2020). Evaluation studies on effects of quercetin with different concentrations on the physicochemical properties and *in vitro* digestibility of Tartary buckwheat starch. *International Journal of Biological Macromolecules*, *163*, 1729–1737. https://doi.org/10.1016/j.ijbiomac.2020.09.116

Li, Z., Tian, J., Cheng, Z., Teng, W., Zhang, W., Bao, Y., Wang, Y., Song, B., Chen, Y., & Li, B. (2023). Hypoglycemic bioactivity of anthocyanins: A review on proposed targets and potential signaling pathways. *Critical Reviews in Food Science and Nutrition*, *63*(26), 7878–7895. https://doi.org/10.1080/10408398.2022.2055526

Lim, J., Ferruzzi, M. G., & Hamaker, B. R. (2022). Structural requirements of flavonoids for the selective inhibition of α-amylase versus α-glucosidase. *Food Chemistry*, *370*, 130981. https://doi.org/10.1016/j.foodchem.2021.130981

Lin, J., Yong, K. Y. A., Zhou, Y., Wang, Y., & Zhou, W. (2023). Improved *in vitro* bioaccessibility of quercetin by nanocomplexation with high-intensity ultrasound treated soy protein isolate. *Food Chemistry*, *406*(December 2020), 135004. https://doi.org/10.1016/j.foodchem.2022.135004

Liu, Y., Zhan, L., Xu, C., Jiang, H., Zhu, C., Sun, L., Sun, C., & Li, X. (2020). α-Glucosidase inhibitors from Chinese bayberry (Morella rubra Sieb. et Zucc.) fruit: molecular docking and interaction mechanism of flavonols with different B-ring hydroxylations. *RSC Advances*, *10*(49), 29347–29361. https://doi.org/10.1039/D0RA05015F

Mahadev, M., Nandini, H. S., Ramu, R., Gowda, D. V., Almarhoon, Z. M., Al-Ghorbani, M., & Mabkhot, Y. N. (2022). Fabrication and evaluation of quercetin nanoemulsion: A delivery system with improved bioavailability and therapeutic efficacy in diabetes mellitus. *Pharmaceuticals*, *15*(1), 70. https://doi.org/10.3390/ph15010070

Maibam, B. D., Nickhil, C., & Deka, S. C. (2023). Preparation, physicochemical characterization, and *in vitro* starch digestibility on complex of Euryale ferox kernel starch with ferulic acid and quercetin. *International Journal of Biological Macromolecules*, *250*, 126178. https://doi.org/10.1016/j.ijbiomac.2023.126178

Mitra, S., Chatterjee, S., Bose, S., Panda, P., Basak, S., Ghosh, N., Mandal, S. C., Singhmura, S., & Halder, A. K. (2024). Finding structural requirements of structurally diverse α-glucosidase and α-amylase inhibitors through validated and predictive 2D-QSAR and 3D-QSAR analyses. *Journal of Molecular Graphics and Modelling*, *126*, 108640. https://doi.org/10.1016/j.jmgm.2023.108640

Nabil-Adam, A., Ashour, M. L., Tamer, T. M., Shreadah, M. A., & Hassan, M. A. (2023). Interaction of jania rubens polyphenolic extract as an antidiabetic agent with α-amylase, lipase, and trypsin: *In vitro* evaluations and in silico studies. *Catalysts*, *13*(2), 443. https://doi.org/10.3390/CATAL13020443

Ombra, M. N., Nazzaro, F., & Fratianni, F. (2022). Lowering the predicted glycemic index of pasta using dried onions as functional ingredients. *International Journal of Food Sciences & Nutrition*, *73*(4), 443–450. https://doi.org/10.1080/09637486.2021.2025211

Ozgen, S., Kilinc, O. K., & Selamoğlu, Z. (2016). Antioxidant activity of quercetin: A mechanistic review. *Turkish Journal of Agriculture - Food Science and Technology*, *4*(12), 1134–1138. https://doi.org/10.24925/TURJAF.V4I12.1134-1138.1069

Patil, S. M., Martiz, R. M., Ramu, R., Shirahatti, P. S., Prakash, A., Kumar, B. R. P., & Kumar, N. (2022). Evaluation of flavonoids from banana pseudostem and flower (quercetin and catechin) as potent inhibitors of α-glucosidase: An in silico perspective. *Journal of Biomolecular Structure and Dynamics*, *40*(23), 12491–12505. https://doi.org/10.1080/07391102.2021.1971561

Quintriqueo-Cid, A., Giménez, B., Romero-Hasler, P., Soto-Bustamante, E., Lozano-Sánchez, J., & Robert, P. (2024). Influence of the crystallinity on the physicochemical properties of spray-dried quercetin-inulin microparticles and their performance during *in vitro* digestion. *Food Chemistry*, *434*, 137325. https://doi.org/10.1016/j.foodchem.2023.137325

Ruivo Da Silva, M. G., Skrt, M., Komes, D., Poklar Ulrih, N., & Pogačnik, L. (2020). Enhanced yield of bioactivities from onion (Allium cepa L.) skin and their antioxidant and anti-α-amylase activities. *International*

Journal of Molecular Sciences, *21*(8), 2909. https://doi.org/10.3390/IJMS21082909

Sato, S., & Mukai, Y. (2020). Modulation of chronic inflammation by quercetin: The beneficial effects on obesity. *Journal of Inflammation Research*, *13*, 421–431. https://doi.org/10.2147/JIR.S228361

Shen, H., Wang, J., Ao, J., Hou, Y., Xi, M., Cai, Y., Li, M., & Luo, A. (2023). Structure-activity relationships and the underlying mechanism of α-amylase inhibition by hyperoside and quercetin: Multi-spectroscopy and molecular docking analyses. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *285*, 121797. https://doi.org/10.1016/J.SAA.2022.121797

Shukla, R., & Tripathi, T. (2020). Molecular dynamics simulation of protein and protein-ligand complexes. In D. B. Singh (Ed.), *Computer-aided drug design* (pp. 133–161). Springer. https://doi.org/10.1007/978-981-15-6815-2_7

Singh, P., Arif, Y., Bajguz, A., & Hayat, S. (2021). The role of quercetin in plants. *Plant Physiology and Biochemistry*, *166*, 10–19. https://doi.org/10.1016/J.PLAPHY.2021.05.023

Şöhretoğlu, D., Sari, S., Barut, B., & Özel, A. (2018). Discovery of potent α-glucosidase inhibitor flavonols: Insights into mechanism of action through inhibition kinetics and docking simulations. *Bioorganic Chemistry*, *79*, 257–264. https://doi.org/10.1016/j.bioorg.2018.05.010

Tropsha, A. (2010). Best practices for QSAR model development, validation, and exploitation. *Molecular Informatics*, *29*(6–7), 476–488. https://doi.org/10.1002/minf.201000061

Tshiyoyo, K. S., Bester, M. J., Serem, J. C., & Apostolides, Z. (2022). In-silico reverse docking and in-vitro studies identified curcumin, 18α-glycyrrhetinic acid, rosmarinic acid, and quercetin as inhibitors of α-glucosidase and pancreatic α-amylase and lipid accumulation in HepG2 cells, important type 2 diabetes targets. *Journal of Molecular Structure*, *1266*, 133492. https://doi.org/10.1016/J.MOLSTRUC.2022.133492

Vazquez-Flores, A. A., Martinez-Gonzalez, A. I., Alvarez-Parrilla, E., Díaz-Sánchez, Á. G., de la Rosa, L. A., González-Aguilar, G. A., & Aguilar, C. N. (2018). Proanthocyanidins with a low degree of polymerization are good inhibitors of digestive enzymes because of their ability to form specific interactions: A hypothesis. *Journal of Food Science*, *83*(12), 2895–2902. https://doi.org/10.1111/1750-3841.14386

Wang, L., Huang, Y., Ren, Y., Wang, H., Ding, Y., Ren, G., Wang, T., Li, Z., & Qiu, J. (2024). Effect of ethanol addition on the physicochemical, structural and *in vitro* digestive properties of Tartary buckwheat starch-quercetin/rutin complexes. *Food Chemistry*, *451*, 139350. https://doi.org/10.1016/J.FOODCHEM.2024.139350

Wang, L., Wang, L., Wang, T., Li, Z., Gao, Y., Cui, S. W., & Qiu, J. (2022). Comparison of quercetin and rutin inhibitory influence on Tartary buckwheat starch digestion *in vitro* and their differences in binding sites with the digestive enzyme. *Food Chemistry*, *367*, 130762. https://doi.org/10.1016/j.foodchem.2021.130762

Wang, L., Zhan, J., Ma, R., & Tian, Y. (2023a). Preparation of starch-based nanoemulsion for sustained release and enhanced bioaccessibility of quercetin. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *665*, 131218. https://doi.org/10.1016/j.colsurfa.2023.131218

Wang, N., Zhang, K., Chen, Y., Hu, J., Jiang, Y., Wang, X., & Ban, Q. (2023b). Tuning whey protein isolate/hyaluronic acid emulsion gel structure to enhance quercetin bioaccessibility and *in vitro* digestive characteristics. *Food Chemistry*, *429*, 136910. https://doi.org/10.1016/j.foodchem.2023.136910

Wang, Y., Zhou, X., Xiang, X., & Miao, M. (2023c). Association of slowly digestible starch intake with reduction of postprandial glycemic response: An update meta-analysis. *Foods*, *12*(1), 89. https://doi.org/10.3390/foods12010089

Wu, T. Y., Sun, N. N., Chan, Z., Chen, C. J., Wu, Y. C., & Chau, C. F. (2022). Enhancement of digestion resistance and glycemic control of corn starch through conjugation with gallic acid and quercetin using the free radical grafting method. *Processes*, *10*(12), 2610. https://doi.org/10.3390/pr10122610

Xie, D., Hu, H., Huang, Q., & Lu, X. (2023). Influence of oleogel/hydrogel ratios and emulsifiers on structural and digestion properties of food-grade 3D printed bigels as carriers for quercetin and catechin. *Food Hydrocolloids*, *144*, 108948. https://doi.org/10.1016/j.foodhyd.2023.108948

Yan, L., Vaghari-Tabari, M., Malakoti, F., Moein, S., Qujeq, D., Yousefi, B., & Asemi, Z. (2023). Quercetin: An effective polyphenol in alleviating diabetes and diabetic complications. *Critical Reviews in Food Science and Nutrition*, *63*(28), 9163–9186. https://doi.org/10.1080/10408398.2022.2067825

Yang, J., Zhu, B., Lu, K., Dou, J., Ning, Y., Wang, H., Li, Y., Qi, B., & Jiang, L. (2023a). Construction and characterization of Pickering emulsions stabilized by soy protein hydrolysate microgel particles and quercetin-loaded performance *in vitro* digestion. *Food Research International*, *169*, 112844. https://doi.org/10.1016/J.FOODRES.2023.112844

Yang, Z., Zhang, Y., Wu, Y., & Ouyang, J. (2023b). Factors influencing the starch digestibility of starchy foods: A review. *Food Chemistry*, *406*, 135009. https://doi.org/10.1016/j.foodchem.2022.135009

Yusufoğlu, B., Yaman, M., & Karakuş, E. (2022). Glycemic evaluation of some breads from different countries via *in vitro* gastrointestinal enzymatic hydrolysis system. *Food Science and Technology*, *42*, 139350. https://doi.org/10.1590/fst.34920

Zhang, B. W., Li, X., Sun, W. L., Xing, Y., Xiu, Z. L., Zhuang, C. L., & Dong, Y. S. (2017). Dietary flavonoids and acarbose synergistically inhibit α-glucosidase and lower postprandial blood glucose. *Journal of Agricultural and Food Chemistry*, *65*(38), 8319–8330. https://doi.org/10.1021/acs.jafc.7b02531

Zhang, J., Sun, L., Dong, Y., Fang, Z., Nisar, T., Zhao, T., Wang, Z. C., & Guo, Y. (2019). Chemical compositions and α-glucosidase inhibitory effects of anthocyanidins from blueberry, blackcurrant and blue honeysuckle fruits. *Food Chemistry*, *299*, 125102. https://doi.org/10.1016/j.foodchem.2019.125102

Zhang, L., Wang, X., Chang, L., Ren, Y., Sui, M., Fu, Y., Zhang, L., & Hao, L. (2024). Quercetin improves diabetic kidney disease by inhibiting ferroptosis and regulating the Nrf2 in streptozotocin-induced diabetic rats. *Renal Failure*, *46*(1), 2327495. https://doi.org/10.1080/0886022X.2024.2327495

Zhang, Y., Aryee, A. N., & Simpson, B. K. (2020). Current role of in silico approaches for food enzymes. *Current Opinion in Food Science*, *31*, 63–70. https://doi.org/10.1016/j.cofs.2019.11.003

Zhou, J. F., Xu, H. X., Yin, Z. P., Chen, J. G., & Zhang, Q. F. (2024). The combination effects of quercetin on starch and digestive enzymes reduce postprandial blood glucose in rats. *European Food Research and Technology*, *250*(4), 1189–1199. https://doi.org/10.1007/s00217-023-04455-y

Zhou, Y., Jiang, Q., Mak, S., & Zhou, X. (2021). Effect of quercetin on the *in vitro* Tartary buckwheat starch digestibility. *International Journal of Biological Macromolecules*, *183*, 818–830. https://doi.org/10.1016/J.IJBIOMAC.2021.05.013

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