International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 17, No. 1, 2026

Quercetin in Functional Foods: Properties, Applications, Challenges, and Strategies to Improve Bioavailability

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Abstract: The growing interest in functional foods has increased attention to plant-derived bioactive compounds with potential health benefits. Quercetin, one of the most abundant dietary flavonols in fruits and vegetables, has attracted particular interest because of its antioxidant and anti-inflammatory activities. However, its incorporation into functional foods remains limited by poor aqueous solubility, chemical instability, limited gastrointestinal bioaccessibility, and low oral bioavailability. This review examines the physicochemical properties, natural sources, and major application barriers of quercetin, with particular emphasis on recent multi-strategy approaches, ranging from food-grade biopolymer nanoparticles and excipient emulsions to glycosylation and cyclodextrin inclusion complexation. Rather than treating improved bioaccessibility as equivalent to improved bioavailability, the review compares how these strategies affect gastrointestinal solubilisation, epithelial absorption, and systemic exposure. Current evidence indicates that these approaches can improve quercetin dispersibility, formulation stability, intestinal solubilisation, or systemic bioavailability through different mechanisms. However, evidence from human studies remains limited. Further research should therefore validate these strategies through human pharmacokinetic studies and evaluations of their application in real food products.

Keywords: Quercetin; Functional Foods; Bioavailability; Bioaccessibility; Delivery Systems.

1. Introduction

Among the bioactive compounds and ingredients used in functional foods, polyphenols have attracted considerable attention because of their antioxidant, anti-inflammatory, and metabolic properties.

Flavonoids constitute one of the largest subclasses of polyphenols [1]. Quercetin is widely distributed in plant-derived foods, including onions, apples, berries, broccoli, peppers, grapes, citrus fruits, and tea [2,3].

Quercetin's phenolic hydroxyl groups can donate hydrogen atoms or electrons, allowing quercetin to neutralise free radicals and reactive oxygen species and thereby contribute to antioxidant protection [2]. Quercetin also exhibits anti-inflammatory activity, which has been associated with reduced production of pro-inflammatory cytokines [4]. In food systems, quercetin can interact with plant proteins through covalent and non-covalent mechanisms and influence their functional properties [5]. Together, these biological activities and food-system interactions make quercetin a promising bioactive ingredient for functional food development, with potential benefits for oxidative balance, metabolic health, and chronic disease prevention.

Nevertheless, the poor aqueous solubility, chemical instability, and low oral bioavailability of quercetin restrict the extent to which these potential benefits can be realised and limit its direct application in functional foods [2].

This review is organised into four sections: the physicochemical properties and biological activities of quercetin; the major challenges limiting its application; recent food-processing and delivery strategies designed to improve its bioaccessibility and bioavailability; and its current applications and future directions in functional food development.

2. Properties and Potential Applications of Quercetin in Functional Foods

2.1. Quercetin's Chemical Structure and Physical Properties

Quercetin belongs to the flavonol subclass of flavonoids and is one of the most abundant dietary flavonols in plants [2]. The flavonoid skeleton consists of 15 carbon atoms, which are arranged into aromatic rings named A and B and connected by a heterocyclic C ring (C6–C3–C6 structure) (Frenț et al., 2024). Quercetin possesses the typical flavonoid structure but contains five additional hydroxyl groups located at positions 3, 5, 7, 3′, and 4′, together with a C2=C3 double bond and a C4 carbonyl group [2].

These structural features of quercetin determine its properties and biological activities.

Quercetin's chemical structure determines its antioxidant activity. Its phenolic hydroxyl groups are electron donors and contribute to the capture of free radicals. This ability is particularly strong in the 3′,4′-dihydroxyl group on the B ring because its two hydroxyl groups occupy neighboring positions. This group, together with the 3- and 5-hydroxyl groups conjugated with the 4-oxo group, supports the stability and antioxidant activity of quercetin [6].

Even though quercetin has five polar hydroxyl groups, it has a conjugated aromatic structure that determines its hydrophobic property. In plants, quercetin occurs mainly as glycosides, which release quercetin aglycone—the form of quercetin without sugar—after the hydrolysis of their glycosidic bonds. According to Carrillo-Martinez et al. [6], quercetin aglycone is poorly soluble in cold water but has some solubility in alcohol and lipids. This lipophilic tendency

is supported by a reported octanol–water partition coefficient (log P_oct) of 2.06 [7].

2.2. Natural Sources of Quercetin

Quercetin is widely distributed in plant-derived foods; however, its concentration varies among different sources. Dabeek and Marra [8] summarized average quercetin concentrations on a fresh-weight basis: 79.0 mg/100 g in dill, 46.8 mg/100 g in fennel leaves, 45.0 mg/100 g in onions, 32.6 mg/100 g in chili peppers, 14.7 mg/100 g in lettuce, and 13.7 mg/100 g in broccoli. Quercetin is also present in apples at 4.01 mg/100 g, while red wine and black tea contain approximately 3.16 and 2.50 mg/100 mL, respectively.

3. Challenges in the Development of Quercetin-Based Functional Foods

3.1. Low Oral Bioavailability

The low oral bioavailability of quercetin does not result from a single limitation. Instead, it reflects a sequence of barriers involving gastrointestinal solubilisation, intestinal absorption, and presystemic metabolism. In this review, bioaccessibility refers to the fraction of ingested quercetin that is released from the food matrix and remains solubilised in gastrointestinal fluids, making it potentially available for absorption. Bioavailability refers more specifically to the extent to which quercetin or its metabolites appear in the systemic circulation after absorption and metabolism.

3.1.1. Solubility and Bioaccessibility Barrier

The first barrier occurs before intestinal absorption. Because quercetin aglycone is poorly soluble in water, only a limited fraction can dissolve or remain solubilised in gastrointestinal fluids. Quercetin that remains crystalline or precipitates during digestion is less available for contact with the intestinal epithelium. Therefore, poor aqueous solubility directly restricts gastrointestinal bioaccessibility [2]. An increase in dissolved or mixed-micelle-associated quercetin demonstrates improved bioaccessibility, but it does not by itself confirm intestinal absorption or systemic bioavailability.

3.1.2. Intestinal Absorption and Epithelial Transport Barrier

After becoming bioaccessible, quercetin must cross the intestinal epithelium. This process depends partly on its chemical form. In plant-derived foods, quercetin is mainly present as glycosides, and some of these compounds must be hydrolysed by lactase-phlorizin hydrolase or other intestinal enzymes before the released aglycone can enter epithelial cells. The type and position of the attached sugar can influence both the site and extent of absorption [8]. Consequently, the amount of quercetin recovered in gastrointestinal fluids may be greater than the amount that crosses the epithelium, meaning that improved solubilisation cannot automatically be interpreted as improved absorption.

3.1.3. Metabolism Barrier

Quercetin that enters intestinal epithelial cells is rapidly metabolised before reaching the systemic circulation. Phase II metabolism in the intestine and liver converts quercetin mainly into glucuronidated, sulfated, and methylated conjugates. Consequently, only small amounts of unchanged quercetin aglycone are normally detected in plasma, while most circulating compounds are quercetin metabolites [8]. This does not mean that quercetin has not been absorbed; instead, it means that systemic exposure cannot be evaluated from the concentration of unchanged quercetin alone.

Overall, the low oral bioavailability of quercetin results from three sequential barriers: insufficient gastrointestinal solubilisation, incomplete epithelial absorption, and extensive presystemic metabolism. These distinctions provide the basis for evaluating whether the strategies discussed in Section 3 improve only bioaccessibility or also increase systemic bioavailability.

3.2. Poor Stability

Chemical instability is another major barrier to the application of quercetin in functional foods. During food processing and storage, its degradation can be influenced by oxygen, pH, temperature, metal ions, and interactions with other food components [9]. Under neutral-to-alkaline conditions, deprotonation of the phenolic hydroxyl groups facilitates oxidation involving the catechol structure of the B ring and the heterocyclic C ring. The resulting oxidation intermediates can subsequently undergo structural rearrangement and ring cleavage. After an aqueous quercetin solution was heated at 90°C for 50 min, LC–MS/MS analysis identified protocatechuic acid and phloroglucinol carboxylic acid as characteristic degradation products, supporting the breakdown of the original flavonoid structure [10].

The effects of pH and temperature have also been quantified. At 37°C, increasing the pH from 6.0 to 7.5 increased the first-order degradation rate constant of quercetin from 2.81×10^{-2} to 0.375 h^{-1}. At pH 6.8, increasing the temperature from 37 to 65°C increased the rate constant from 7.99×10^{-2} to 1.42 h^{-1} [11]. Although these values were obtained from aqueous model systems rather than actual food products, they demonstrate the strong sensitivity of quercetin to near-alkaline conditions and elevated temperatures. Such degradation reduces the amount of intact quercetin retained in a food product and may alter its antioxidant performance. Therefore, delivery systems should be evaluated not only for their ability to improve bioaccessibility but also for their ability to preserve quercetin during processing and storage.

4. Strategies for Improving the Bioavailability of Quercetin

The strategies reviewed below address different stages of the barriers identified in Section 2. Food-grade biopolymer nanoparticles mainly improve aqueous dispersibility, gastrointestinal release, and the physical stability of quercetin-containing particles. Excipient emulsions primarily enhance intestinal solubilisation and potentially facilitate absorption through mixed-micelle formation. Glycosylation and cyclodextrin inclusion mainly improve molecular hydrophilicity or apparent solubility and have also produced evidence of increased systemic exposure. These effects should be distinguished from protection against the chemical degradation of quercetin during food processing and storage, which requires separate stability measurements.

4.1. Food-Grade Biopolymer Nanoparticles

Food-grade biopolymer nanoparticles mainly address the poor aqueous dispersibility and limited gastrointestinal bioaccessibility described in Section 2.1, while also improving the physical and colloidal stability of the delivery system. Protein-based hydrophobic domains provide sites for quercetin loading, whereas polysaccharide-based interfacial layers reduce particle aggregation and regulate

gastrointestinal release. Consequently, combinations of food-derived proteins and polysaccharides have attracted considerable attention as carrier materials for quercetin [12]. At the molecular level, quercetin can associate with food proteins through non-covalent interactions.

In soybean protein isolate, thermodynamic analysis indicated that hydrophobic interactions were the primary driving force for quercetin binding, while molecular docking identified additional hydrogen bonds with the 11S and 7S protein fractions. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) showed no evidence of covalent bond formation, indicating that the SPI–quercetin complexes were mainly stabilised by non-covalent interactions [13]. This study therefore explains the molecular basis by which a food protein can bind and carry quercetin. However, molecular binding alone does not establish whether the resulting carrier will remain colloidally stable under changes in pH, temperature, or other conditions relevant to food processing. To address this formulation-level challenge, different biopolymers can be combined to construct composite nanoparticles with additional interfacial protection. Zou et al. [14] demonstrated this approach using quercetin-loaded zein nanoparticles coated with sodium caseinate and κ-carrageenan. In this system, particle aggregation and precipitation occurred near the isoelectric point of casein because electrostatic repulsion between the particles was reduced. The addition of an outer κ-carrageenan layer introduced negatively charged sulfate groups, which increased electrostatic and steric repulsion and consequently improved colloidal stability over a broader pH range [14]. The resulting nanoparticles were smaller than 150 nm and achieved a quercetin loading efficiency of approximately 75.7%. X-ray diffraction indicated that encapsulated quercetin was present in an amorphous state rather than its original crystalline state [14]. Because an amorphous solid lacks the long-range molecular order and stable crystal lattice of a crystalline material, this structural change may facilitate the dissolution and release of quercetin. The composite nanoparticles remained resistant to aggregation over the pH range of 2.0–8.0 and after heating at 90°C for 120 min, indicating their potential stability under environmental conditions relevant to food systems [14]. During simulated gastrointestinal digestion, quercetin was released mainly during the intestinal phase, and its encapsulation within the composite nanoparticles enhanced its in vitro bioaccessibility compared with unencapsulated quercetin [14]. Overall, coating quercetin-loaded zein nanoparticles with caseinate and κ-carrageenan improved aqueous dispersibility, colloidal stability, gastrointestinal release, and in vitro bioaccessibility [14]. Therefore, this strategy mainly addresses the solubility and bioaccessibility barrier, as well as the physical stability of the carrier particles. However, because the study used simulated gastrointestinal digestion, it does not establish epithelial absorption or systemic bioavailability.

4.2. Excipient Emulsion-Based Delivery Systems

Excipient emulsions primarily address the gastrointestinal solubility and bioaccessibility barrier identified in Section 2.1, rather than the long-term chemical stability of quercetin during food storage. They improve quercetin delivery without requiring it to be encapsulated before consumption. Instead, a digestible oil-in-water emulsion is co-ingested with quercetin or quercetin-containing foods. During intestinal digestion, the lipid droplets are hydrolysed to generate mixed micelles that maintain quercetin in a solubilised form, thereby increasing the fraction potentially available for epithelial absorption.

Lin et al. [15] prepared excipient emulsions containing medium-chain triglycerides (MCTs), long-chain triglycerides (LCTs), or a 1:1 mixture of the two oils. Their effects on quercetin, kaempferol, and apigenin were examined using in vitro digestion, in situ intestinal perfusion, and pharmacokinetic experiments in rats. Across the three flavonoids, in vitro bioaccessibility was highest with LCT emulsions at 17.9–22.8%, followed by the MCT/LCT mixture at 12.1–13.7% and MCT emulsions at 9.2–12.6%. The authors attributed the higher bioaccessibility of the LCT formulations to the larger hydrophobic domains of the mixed micelles formed during LCT digestion, which provided a greater capacity for flavonoid solubilisation. Although co-ingestion with excipient emulsions increased overall flavonoid bioavailability and antioxidant activity, serum concentrations did not differ significantly among the three carrier-oil formulations [15].

In addition to oil type, the interfacial emulsifier affects the gastrointestinal behaviour of excipient emulsions. Lin et al. [16] found that Tween 80 produced smaller droplets that were more resistant to simulated oral and gastric conditions than emulsions stabilised by whey protein isolate or modified starch. This indicates that emulsifier selection can affect droplet stability and subsequent flavonoid bioaccessibility.

More direct evidence was reported by Ke et al. [17], who investigated a food-grade excipient nanoemulsion with spinach. Compared with spinach administered without the nanoemulsion, quercetin bioaccessibility increased by 1.73-fold, while its in vivo bioavailability in rats increased by 46.6%. Together, these studies show a progression from improved mixed-micelle bioaccessibility in vitro to increased systemic exposure in rats. Excipient emulsions therefore mainly overcome the gastrointestinal solubilisation barrier and may subsequently facilitate epithelial absorption. Nevertheless, the available pharmacokinetic evidence was obtained from animal models, and human studies are required to determine whether these improvements produce comparable increases in human bioavailability.

4.3. Glycosylation and Cyclodextrin Inclusion Complexes

Glycosylation and cyclodextrin inclusion primarily address the poor hydrophilicity and limited apparent solubility of quercetin. In contrast to nanoparticle and emulsion systems, which mainly alter the environment surrounding quercetin, glycosylation modifies its chemical form by attaching glucose residues. This increases molecular hydrophilicity and facilitates dispersion in gastrointestinal fluids. Enzymatically modified isoquercitrin (EMIQ), which contains additional α-glucose residues, can subsequently be hydrolysed by intestinal enzymes after ingestion. According to the human pharmacokinetic studies reviewed by Owczarek-Januszkiewicz et al. [18], EMIQ showed approximately 17-fold higher bioavailability than quercetin aglycone. However, this value was summarised from earlier clinical studies rather than obtained from a new experiment.

In addition, cyclodextrin complexation can further improve solubility without covalently modifying the chemical structure of isoquercetin. Cyclodextrins possess a relatively hydrophobic internal cavity and a hydrophilic external surface. The relatively hydrophobic cavity of γ-cyclodextrin

can accommodate part of the isoquercitrin molecule through non-covalent interactions, while the hydrophilic exterior of γ-cyclodextrin maintains the inclusion complex's compatibility with water.

In a crossover study involving eight healthy adults, an isoquercitrin–γ-cyclodextrin complex produced approximately 10.5-fold greater bioavailability than the quercetin aglycone embedded in dextrin, based on plasma concentrations of quercetin and its metabolites [19]. Kapoor et al. [19] measured plasma concentrations of quercetin and its metabolites after oral administration, providing direct evidence of systemic exposure in humans.

Glycosylation and cyclodextrin inclusion can improve both the gastrointestinal availability and systemic exposure of quercetin. Greater hydrophilicity and apparent solubility make more quercetin available for absorption, while the detection of quercetin metabolites in plasma indicates that absorption has occurred. Among the strategies discussed in this review, this approach has the strongest evidence from human studies. However, its effects on quercetin stability during food processing and storage still require further investigation.

5. Conclusion

Quercetin has considerable potential as a functional food ingredient, but its poor water solubility, chemical instability, and low oral bioavailability remain important barriers. The strategies reviewed in this paper address different parts of these problems. Biopolymer nanoparticles mainly improve dispersibility and physical stability, excipient emulsions increase gastrointestinal solubilisation, and glycosylation and cyclodextrin inclusion can improve systemic exposure. However, no single strategy overcomes all the barriers, and improved bioaccessibility should not be treated as direct evidence of improved bioavailability.

The current evidence also remains uneven. Nanoparticle studies are mainly based on simulated digestion, while evidence for excipient emulsions comes largely from animal models. Human evidence is still limited. Future research should therefore focus on larger human pharmacokinetic studies, direct comparisons between delivery strategies, and testing in real food products. Processing stability, sensory acceptability, safety, and scalability should also be considered before these approaches can be widely used in functional foods.

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