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Review

Quercetin and the gut-brain axis: Microbiome modulation, neuroprotection, and therapeutic implications

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Abstract: Quercetin is one of the dietary flavonols found mostlyin fruits and vegetables and is known to modulate the bidirectional communication among the gut microbiota, immune system, and central nervous system. Apart from its antioxidant and anti-inflammatory effects, it modulates gut microbial composition, the intestinal barrier, and neuroimmune pathways. Clinical translation is constrained because of low systemic bioavailability, extensive first-pass metabolism, and inter-individual variability caused by genetics and microbiome diversity. While nano delivery systems, phospholipid complexes, and metabolic co-administration have been proposed to improve absorption, the extent to which these interventions alter microbiota-mediated effects and yield measurable neurological outcomes in humans remains limited and requires further validation in well-controlled human studies. The evidence also supports a hormetic response, whereby moderate doses stimulate the body's adaptive defenses, whereas supra-physiological doses may have adverse effects. Therefore, researchers should focus on standardized human trials that include neurofunctional outcomes, cerebrospinal fluid biomarkers, and multi-omics approaches to clarify the associated mechanisms. In this review, we synthesize molecular, preclinical, and clinical evidence to advance a conceptual framework that elucidates the potential of this compound as a microbiota-modulating agent, principally on mechanistic and preclinical grounds, while clinical confirmation of its therapeutic efficacy in neuropsychiatric and neurodegenerative disorders remains limited. It emphasizes the significance of gut-level interactions and microbiota-derived metabolites rather than systemic bioavailability alone.

Keywords: gut microbiota; quercetin; precision nutrition; gut-brain axis; neuroprotection; neuroinflammation; microbiota modulation

1. Introduction

The gut-brain axis is a bidirectional communication network that includes neural, hormonal, immunological, and metabolic signaling pathways between the gastrointestinal tract and the central nervous system. This concept has transformed the way we understand neurological and psychiatric disorders by demonstrating that the composition and function of intestinal microbiota have a significant impact on brain physiology, behavior, and cognition via microbial metabolites and host signaling pathways (e.g., neurotransmitter precursors, short-chain fatty acids, and secondary bile acids) that affect neuroinflammation, blood-brain barrier integrity, and synaptic plasticity [1]. The gastrointestinal tract is the primary source of peripheral serotonin and substantially metabolizes peripheral dopamine precursors, supporting its recognition as a neuroendocrine organ. Research into therapies that affect the gut-brain axis is increasing; however, most evidence is preclinical, and it is therefore necessary to conduct human clinical trials to demonstrate efficacy in conditions such as depression, anxiety, and neurodegeneration [2,3].

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a polyphenolic flavonoid found in abundance in plant-based foods such as onions, apples, berries, citrus fruits, leafy vegetables, and tea [4]. The structure of quercetin comprises a 15-carbon flavonol backbone with several hydroxyl groups, which mostlyconfer antioxidant and anti-inflammatory properties. The reported daily consumption of quercetin varies widely across populations (10–500 mg/day), with higher levels observed in Mediterranean and plant-based dietary patterns. Beyond its antioxidant properties, quercetin modulates major inflammatory and redox signaling pathways by activating Nrf2-dependent detoxification enzymes and inhibiting pro-inflammatory mediators, including cyclooxygenase and lipoxygenase [5]. Moreover, the findings from ageing models suggest its senolytic potential; however, this aspect is not clearly integrated into the gut–brain axis context, making it secondary to our primary focus of this review [6]. Moreover, while cellular and animal-based studies have demonstrated the neuroprotective effects of quercetin, critical questions remain regarding how quercetin modulates the gut-brain axis. There have been studies on the direct action of quercetin on neurons; hence, its role in altering gut microbial composition and the production of microbiota-derived metabolites that affect brain function has been largely overlooked [7]. Furthermore, quercetin has low oral bioavailability, below 10%, due to limited absorption and extensive first-pass metabolism, which raises significant uncertainty about whether its neurological benefits are attributable to the parent compound, its conjugated metabolites, or microbial biotransformation products formed in the colon [8]. The interplay among microbiome shifts, gut barrier modulation, systemic inflammatory changes, and neural outcomes remains unclear. In addition, variations in study design, quercetin formulations, dosage regimens, and outcome measures complicate the definition of the integrated mechanistic framework and the assessment of limitations in translational potential [9]. In this review, we consolidate the latest evidence of quercetin's role in the modulation of the gut-brain axis, highlighting microbiome-mediated mechanisms and neuroprotective effects. We examine its impact on gut microbial ecology, intestinal barrier integrity, and the generation of neuroactive metabolites; explore the signaling pathways linking the gut to the brain, such as vagal, neuroendocrine, immune, and neurotransmitter-related mechanisms; and consider its therapeutic potential for neuropsychiatric and neurodegenerative disorders. Finally, we highlight the limitations of the methods employed and suggest future research directions in precision nutrition, multi-omics integration, and combination therapeutic strategies to advance the field.

Although quercetin and the gut-brain axis have attracted increasing attention, the available literature remains fragmented. It primarily addresses either the direct neuroprotective effects or broad microbiome changes, without integrating pharmacokinetics, microbial metabolism, and neurobiological outcomes into a single framework. In addition, the differences between preclinical results and the few human studies make it even more difficult to understand the translational aspect. Thus, we to offer a detailed and integrated viewpoint by connecting the metabolic fate of quercetin, its interactions with the microbiome, and neuroprotective mechanisms within the context of the gut-brain axis. A conceptual framework summarizing quercetin-mediated modulation of the gut–microbiome–brain axis is presented in Figure 1.

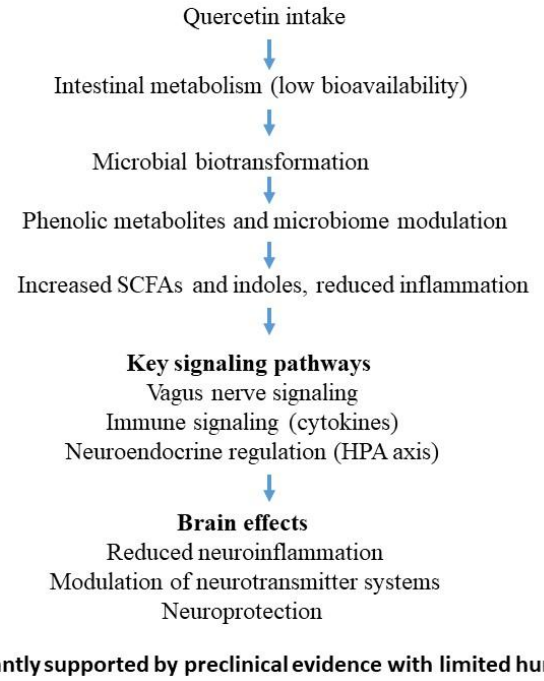

Figure 1. Conceptual framework of quercetin-mediated gut–microbiome–brain axis modulation.

To facilitate better understanding, the evidence covered in this review is organized into three levels: (i) mechanistic studies in cell systems, (ii) preclinical evidence from animal models, and (iii) human clinical studies. Mechanistic and animal studies indicate strong biological plausibility; however, there is limited direct evidence that quercetin-induced modulation of the microbiome affects neurocognitive outcomes in humans.

2. Quercetin bioavailability and metabolic fate

2.1. Intestinal absorption and phase I/II metabolism

Quercetin in the diet is mostly present as glycosides, which must be hydrolyzed by intestinal β-glucosidases and lactase-phlorizin hydrolase to release the aglycone for absorption. The aglycone has limited solubility and low membrane permeability; thus, bioavailability in humans is less than 10%.

The major site of absorption is the small intestine. Absorption occurs primarily via passive diffusion, but carrier-mediated transport via SGLT1 and organic anion transporters is also involved [10].

Once inside the body, quercetin is rapidly subjected to phase II metabolism in intestinal and hepatic cells, mostly by UGTs, SULTs, and COMT. The metabolic routes yield plasma-dominant conjugates, such as quercetin-3-glucuronide, quercetin-3′-sulfate, and isorhamnetin-3-glucuronide, which typically reach their highest levels between 0.5 and 3 hours after ingestion [11]. For example, polymorphisms in the UGT1A1 and COMT genes can greatly contribute to differences in blood metabolite concentrations between individuals, with levels differing by up to 20-fold among individuals taking the same dose. Because the parent compound is subjected to extensive first-pass metabolism, only very small amounts of it reach the systemic circulation with the conjugated metabolites [12].

2.2. Microbial biotransformation: Ring fission and phenolic derivatives

A proportion of quercetin may escape absorption in the small intestine and reach the colon, although the exact fraction varies across studies. At these sites, quercetin undergoes extensive microbial metabolism before being absorbed into the systemic circulation later. This concept is supported by data showing that quercetin glycosides are not efficiently absorbed in the upper gut but are instead released in the colon and metabolized by the microbiota [13].Bacteria from the intestine, such as *Eubacterium*, *Bacteroides*, and *Clostridium*, carry out glycoside hydrolysis and C-ring cleavage, thus producing major phenolic acids like 3,4-dihydroxyphenylacetic acid, 3-hydroxyphenylacetic acid, and hippuric acid. Other compounds are transformed into protocatechuic acid, phloroglucinol, and structurally related compounds. Microbial metabolites derived from phenolic compounds can reach detectable levels in plasma and sometimes remain there longer than the parent compound. On the other hand, their pharmacokinetics vary widely across studies and are influenced by individual microbiota composition and study conditions [14]. Metagenomic research points to enzymes such as quercetinase and flavonol reductase as key factors, whose levels depend on the individual's microbiome. Some phenolic metabolites have better permeability through the blood–brain barrier than quercetin conjugates, which suggests microbial metabolism as an enhancer of neuroactive effects [15].

2.3. Enterohepatic circulation and tissue distribution

Quercetin metabolites undergo enterohepatic recirculation. Hepatic glucuronides and sulfates are secreted into the bile via ABC transporters, mainly MRPs. After that, bacteria in the intestine produce β-glucuronidases and sulfatases that can break conjugates, thus liberating the aglycone, which is then reabsorbed; hence, quercetin’s elimination profile is multiphasic. This recycling process accounts for about 20–30% of total systemic exposure. Studies involving radiolabeled compounds reveal that quercetin metabolites accumulate preferentially in the liver, kidney, and lungs at levels much higher than those in plasma, while the amount in the brain is low due to efflux via P-glycoprotein and BCRP at the blood-brain barrier [16]. However, long-term exposure increases neural tissue levels, indicating that efflux transporters are partially saturated or that certain metabolites penetrate more readily. Metabolites have longer half-lives (11–28 hours) compared to the parent aglycone (1–2 hours), which suggests that conjugated forms predominantly exert biological

effects for a prolonged period [17].

2.4. Critical evaluation: Bioavailability paradox and therapeutic implications

The bioavailability paradox of quercetin highlights the discrepancy between its potent *in-vitro* actions and the very low circulating levels of the parent aglycone. Nonetheless, this apparent inconsistency can be clarified by considering the biological actions of the conjugated metabolites and their deconjugation in specific tissues. After absorption, quercetin is extensively metabolized into glucuronidated, sulfated, and methylated metabolites, which are the major circulating forms in humans. Accumulating evidence indicates that these metabolites are not merely inactive excretion products; they may either contribute to biological activity themselves or serve as reservoirs for the regeneration of the active aglycone.

Most importantly, β-glucuronidase enzymes released from sites of inflammation or expressed by cells or tissues (e.g., macrophages, liver, and kidney) can cleave quercetin glucuronides, release quercetin and enable it to exert its local pharmacological effects. The processes of deconjugation or reconjugation has been demonstrated in inflammatory cells, were quercetin glucuronides, after being converted back to quercetin aglycone, can exert anti-inflammatory effects [18].

Moreover, a growing body of data supports a metabolite-driven pharmacology model, which suggests that circulating conjugates and phenolic metabolites derived from the gut microbiota play important roles in systemic effects. Studies in humans and animals indicate that these metabolites act on endothelial, immune, and metabolic pathways and exhibit biological activities. However, their potency and mechanisms of action may not be entirely the same as those of the parent compound. To further clarify the “bioavailability paradox,” it is important to distinguish systemic exposure and site-specific biological activity. Although circulating levels of the parent aglycone are low due to rapid metabolism, quercetin is predominantly present in plasma as conjugated metabolites, which may retain or modulate biological activity. In addition, tissue-specific deconjugation and microbiota-derived phenolic metabolites may contribute to localized pharmacological effects. Thus, the apparent paradox reflects a shift from parent-compound–centric pharmacology toward a metabolite-driven, context-dependent mechanism of action [11,18,19].

Overall, this evidence indicates that the so-called bioavailability paradox does not entirely disprove the results obtained from *in-vitro* experiments; on the contrary, it underscores the need to re-examine those results, taking into account the body's metabolite profile and the different activation mechanisms in tissues. Nevertheless, a substantial number of *in-vitro* experiments conducted at very high aglycone doses may exaggerate its direct effects. Furthermore, these experimental conditions differ markedly from human physiological conditions, thereby limiting their applicability to human physiology [20]. Three major explanations are proposed: (1) Conjugated metabolites and microbial phenolic derivatives may have biological activity through different mechanisms than the parent compound; (2) transient luminal concentrations during absorption may cause gut-mediated systemic responses; and (3) tissue accumulation and enterohepatic recycling result in longer exposure time even though the circulating aglycone levels are low [21,22].

There is convincing evidence for the metabolite-centered model, which demonstrates that quercetin glucuronides have anti-inflammatory and vascular effects and can be locally deconjugated by tissue β-glucuronidases, thereby regenerating the active aglycone at sites of inflammation or oxidative stress [23]. Additionally, microbiome-derived phenolic metabolites, which typically reach

higher and more sustained plasma concentrations than quercetin, appear to have a major role in systemic and neuroactive effects. These findings collectively indicate that physiologically relevant metabolites, microbial biotransformation pathways, and targeted delivery strategies should be central to future studies aimed at unlocking the therapeutic potential of quercetin [24].

To integrate these findings, quercetin modulation of the gut-brain axis can be conceptualized as an interconnected network involving drug metabolism, microbiome metabolism, and neurobiological signaling. When quercetin is taken orally, it is only slightly absorbed and is mainly transformed by the gut microbiota into phenolic metabolites, which alter microbial composition and metabolic products. As a result, the levels of microbiota-derived signaling molecules, such as short-chain fatty acids and tryptophan metabolites, change, and these molecules then interact with the gut epithelial, immune, and enteroendocrine systems. Further signaling occurs via several interconnected routes, including vagal nerve activation, cytokine-mediated immune modulation, and endocrine regulation via the hypothalamic-pituitary-adrenal axis. These interconnected mechanisms collectively influence brain functions, including neuroinflammation, neurotransmitter levels, and synaptic plasticity. Significantly, these mechanisms form a single network rather than separate processes, even though the available data are mainly preclinical. The differences between *in-vitro* and *in-vivo* relevance underlying the bioavailability paradox are summarized in Table 1.

Table 1. Comparison of *in-vitro* and *in-vivo* relevance underlying the quercetin bioavailability paradox.

Aspect	***In vitro* studies**	***In vivo* (human)**	**References**
Form studied	Quercetin aglycone	Conjugated metabolites	[11]
Concentration	10–100 μM	nM–low μM range	[12]
Biological activity	Direct antioxidant/signaling	Metabolite-driven, indirect	[18]
Mechanism	Direct cellular action	Deconjugation at target tissues	[19]
Relevance	Mechanistic insight	Physiological relevance	[20]

3. Microbiome modulation mechanisms

3.1. Antimicrobial selectivity and prebiotic-like effects

Quercetin exhibits concentration-dependent, species-selective antimicrobial activity that suppresses pathogens while supporting beneficial commensals. It inhibits the growth of Gram-positive pathogens, including *Staphylococcus aureus* and *Clostridium difficile* [25]. The antimicrobial activities include rupture of the bacterial cell membrane, release of intracellular components, and inhibition of quorum sensing [26]. Animal experiments show that quercetin intake reduces *Enterobacteriaceae* and *Desulfovibrio,* resulting in increased microbial diversity and strengthened intestinal barrier function [27]. These prebiotic-like effects are partially explained by quercetin being metabolized by flavonoid-degrading bacteria [28].

3.2. Microbiome-derived metabolites: SCFAs and phenolic compounds

As described in Section 2.2, quercetin is metabolized by gut microbiota into phenolic compounds and SCFAs, which are discussed here in the context of gut–brain signaling [29]. Butyrate,

through histone deacetylase inhibition, supports colonocyte energy metabolism, while propionate and acetate help maintain neurotransmitter balance and energy homeostasis.

The phenolic biotransformation of quercetin also yields neuroactive acids, including 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), protocatechuic acid, and hippuric acid. These metabolites possess antioxidant, anti-inflammatory, and neuroprotective properties and have better bioavailability than native quercetin [30].

3.3. Microbiome functional capacity and metabolic pathways

Quercetin not only changes the microbial taxonomic composition but also appears to influence microbial metabolic functions, especially tryptophan metabolism, bile acid transformation, and vitamin biosynthesis. It has been reported to increase the formation of indole derivatives and kynurenine pathway metabolites, which, in turn, lead to activation of the aryl hydrocarbon receptor (AhR) signaling and restoration of mucosal integrity [31]. Likewise, quercetin enhances bile salt hydrolase activity, thereby promoting the production of secondary bile acids, which in turn activate FXR and TGR5 signaling pathways linked to lipid metabolism and energy expenditure [32]. Microbiomes treated with quercetin also show elevated biosynthesis of B vitamins and vitamin K2, and increased microbial GABA production, which is essential for neurotransmission and redox balance [33].

3.4. Quercetin as a precision microbiome modulator

A study points to quercetin as a precision microbiome modulator rather than a broadly acting antimicrobial. Its impact appears to depend on the baseline microbial composition. Interventions targeting the abundance of *Akkermansiamuciniphila* have demonstrated substantial effects in animal models, but controlled validation in human populations remains limited. Evidence, largely from preclinical studies, suggests that dietary modulation can elevate *A. muciniphila* levels, but the quantitative magnitude and reproducibility of these changes in human cohorts need to be confirmed by properly controlled trials [34]. The magnitude of SCFA and bile acid modulation also depends on basal metabolic capacity, indicating potential compensatory adaptation within the microbiome. These findings suggest that quercetin influences microbiota composition in preclinical settings; however, well-controlled trials confirming this are limited.

Figure 2 provides a schematic overview of gut-brain signaling pathways affected by quercetin. It highlights the principal pathways documented in literature: (1) Alteration of vagal afferents through microbial metabolites, (2) the role of short-chain fatty acids in neuroinflammation, and (3) the influence of the tryptophan/kynurenine pathway on central neurotransmitter pools. These three pathways are the most commonly reported in preclinical studies and are summarized in Table 2 [35].

Table 2. Quercetin in the gut-microbiome-brain axis: Mechanistic actions, molecular mediators, important biological pathways, and neuroprotective outcomes.

Mechanism	Mediators	Key Action	Outcome	Ref
Microbiome composition	*Bifidobacterium*, A. muciniphila, *Lactobacillus*	↑beneficial bacteria; ↓ pathogens	Better gut barrier, reduced endotoxin	[36]
Immune modulation	NF-κB, NLRP3, ASC	↓ cytokines, ↓ inflammasome	Reduced neuroinflammation	[37]
Neuronal plasticity and survival	SIRT1, PI3K/Akt, Nrf2	PI3K/Akt, CREB, SIRT1	Improved memory	[38]
BBB protection	SIRT1 → Nrf2 → HO-1	Strengthens the blood-brain barrier	Reduced permeability, neuroprotection	[39]
Microbial metabolites production	3,4-DHB, benzoylglutamic acid	Production of phenolic acids	Anti-inflammatory, vascular protection	[40]
Gut barrier integrity	ZO-1, Claudins, TLR4/NLRP3	↑ tight junctions, ↓ LPS	Lower systemic inflammation	[41]

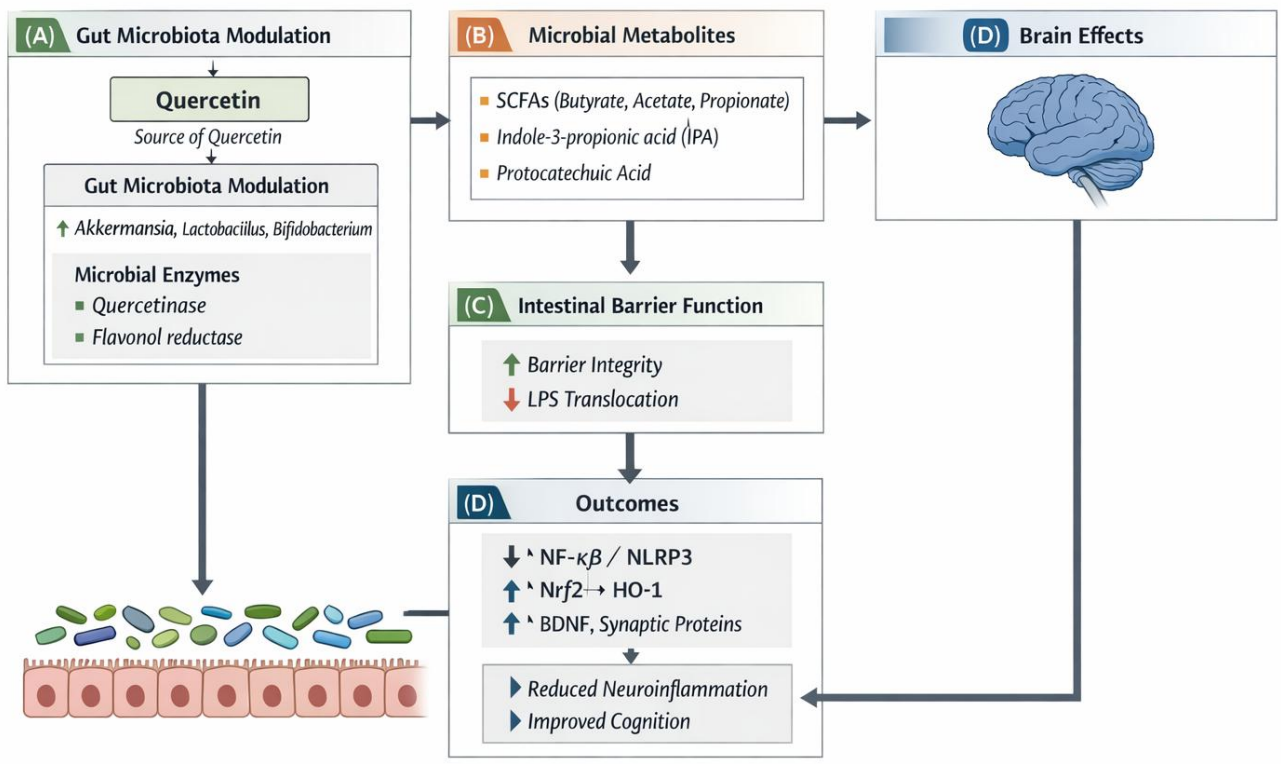

Figure 2. Quercetin regulates the gut–brain axis by modulating microbiota and generating metabolites that enhance barrier integrity, reduce inflammation, and promote neuroprotection.

4. Molecular signaling pathways in gut–brain communication

In this section, we distinguish three levels of evidence: (i) Mechanisms supported by *in-vivo* or human data ("demonstrated mechanisms"), (ii) strong associations mostly backed by animal models ("preclinical correlations"), and (iii)reasonable but as yet untested pathways that require direct validation in human studies ("emerging models"). This framework is used to avoid conflating well-supported effects with speculative hypotheses.

4.1. Vagal nerve signaling and neurotransmitter modulation

The vagus nerve is a major pathway for bidirectional communication between the brain and the gut, transmitting signals produced by microbial metabolites to the central nervous system [42]. These pathways operate as an integrated network (see Section 2.4), involving coordinated immune, neural, and endocrine signaling mechanisms. However, most of the data come from animal experiments, and whether these mechanisms translate into clinically significant neurobiological outcomes in humans remains largely uncertain [43].

4.2. Neuroendocrine and immune-mediated pathways

Immune-mediated pathways are key components of gut–brain communication; detailed neuroinflammatory mechanisms are discussed in Section 6.2 [44]. It is known that butyrate can cross the blood–brain barrier and decrease the excitability of hypothalamic CRH neurons, thereby alleviating the stress response. Microbial modulation (for example, increased abundance of beneficial taxa such as *Akkermansiamuciniphila*) has been linked to improved intestinal barrier function and reduced endotoxin (LPS) translocation. However, the extent to which quercetin directly affects these processes in humans remains unclear. These anti-inflammatory actions involve inflammasome pathways described in Section 6.2. In addition, quercetin and its metabolites influence macrophage polarization toward anti-inflammatory M2 phenotypes and coordinate with regulatory T-cell populations, thereby decreasing neuroimmune activation [45].

4.3. Neurotransmitter precursor availability: Tryptophan, tyrosine, and glutamate pathways

Microbiota in the digestive system are important in determining the availability of neurotransmitter precursors, and emerging research indicates that gut microbiota influence tryptophan metabolism and generate indolic compounds as well as other metabolites that are involved in gut-brain axis signaling. However, there is little direct evidence on how quercetin specifically links these metabolic changes in humans [46]. Notably, quercetin has been found to significantly raise levels of indole-3-propionic acid (IPA), a microbial metabolite of tryptophan, which leads to the activation of the aryl hydrocarbon receptor (AhR) in the intestinal tract. Through quercetin-induced microbiota modulation, tryptophan metabolism is shifted toward beneficial indole derivatives instead of diverting to neurotoxic branches of the kynurenine pathway; thus, the ratio of neuroprotective kynurenic acid to excitotoxic quinolinic acid may be altered. However, whether this translates to humans remains unconfirmed.

Certain microbes can generate metabolites from amino acids (e.g., tyrosine and other

precursors), which may theoretically affect neurotransmitter precursors pools. However, there is no controlled evidence demonstrating quercetin's impact on these pathways in humans. Therefore, it has been hypothesized that quercetin might affect dopaminergic signaling via microbiota-derived tyramine. However, no study has confirmed this by measuring tyramine levels in quercetin-treated models [47].

Additionally, quercetin-containing flavonoids have been linked to the proliferation of GABA-producing bacteria. They may influence GABAergic signaling through the gut–brain axis, as described in mechanistic studies [48]. Despite promising findings, it remains unclear whether quercetin directly mediates the bacterial species-dependent increase in GABA production by Lactobacillus brevis and Bifidobacterium dentium in vivo. Overall, current evidence suggests that quercetin may modulate neurotransmitter precursor pathways; however, further in vivo, particularly human, studies are needed to validate these mechanisms [49].

4.4. Deep integration of pathways

The brain mechanisms modulated by quercetin via the microbiome constitute an integrated signaling network involving the interplay among neural, endocrine, and immune pathways [50]. Changes mediated by the HPA axis and the autonomic nervous system directly affect the gut by altering sympathetic and parasympathetic tone. Gut microbiota profiles are affected not only by changes in gut motility, secretion, and perfusion but also by the microbiota, which remodel microbial diversity and metabolic activity, thereby constituting a dynamic gut-brain feedback loop [51].

The immune and neuroendocrine systems also form part of this network and interact with each other. Glucocorticoids can alter immune function, and inflammatory cytokines can affect neural stress pathways; nevertheless, the exact molecular role of quercetin in these intricate feedback circuits in humans remains to be confirmed. Quercetin's anti-inflammatory and antioxidant activities appear to disrupt this harmful feedback cycle that drives stress-induced neuroinflammation and HPA hyper reactivity [52]. These interconnected systems operate over different time scales. Vagal signaling occurs within seconds; neurotransmitter precursor fluxes take several hours; immune modulation may take several days; and microbiome compositional remodeling takes weeks, enabling rapid adaptation and long-term stabilization of brain function. Together, these pathways can be conceptualized as a sequential and interconnected cascade rather than independent mechanisms.

Individual variability in microbiota composition, host genetic variation, and environmental exposures are factors that create unique pathway configurations that determine responsiveness to quercetin supplementation [53]. The significant mechanisms and their comparative levels of evidence are summarized in Table 3. In fact, these pathways are better viewed as parts of a unified, hierarchical signaling network that works together, rather than as separate mechanisms. Here, microbiome-derived metabolites serve as the primary upstream regulators that coordinate neural, immune, and endocrine responses along the gut-brain axis.

Table 3. Summary of significant mechanisms underlying quercetin-mediated modulation of the gut–brain axis and their corresponding levels of evidence.

Category	Key Mediators	Evidence Level	Ref
Microbial metabolism	Phenolic metabolites	Preclinical-dominant	[13–15]
Microbial metabolites (CNS signaling)	SCFAs, Indoles	Preclinical-dominant	[1,31]
Immune signaling	Cytokines, Inflammasome	Mixed (animal + limited human)	[37,45]
Neuroendocrine	HPA axis	Limited human	[42,51]

5. Blood-brain barrier dynamics

5.1. Structural integrity and transporter-mediated permeability

As discussed in Section 2, quercetin exhibits limited blood–brain barrier permeability; accordingly, in this section, we focus on transporter-mediated modulation and inflammation-related changes that influence CNS uptake. Importantly, numerous in vitro studies have examined the effects of quercetin at concentrations ranging from 10 to 50 μM, which are much higher than levels achievable in human plasma from normal intake. Pharmacokinetic studies in humans have shown that even very large oral doses (e.g., 1000 mg) yield plasma concentrations in the low-micromolar or sub micromolar range. As a result, these experimental conditions should be regarded as supra-physiological, and caution is warranted when applying such results to human biological systems [54].

ATP-binding cassette (ABC) efflux transporters (mainly P-glycoprotein/ABCB1 and BCRP/ABCG2) are responsible for pumping foreign compounds out of the brain. Quercetin affects them in two ways: At low (~1–10 μM) concentrations, it is a substrate, and at higher (>25 μM) concentrations, it impairs their function, thereby potentially facilitating its own entry into the brain. Long-term treatment with quercetin may also lead to downregulation of P-glycoprotein via Nrf2. In addition, on the influx side, GLUT1 and OATPs are transporters that enable certain metabolites to enter; thus, quercetin glucuronides can utilize OATPs for brain penetration and avoid efflux [55].

5.2. Inflammation &endothelial activation

Neuroinflammation affects the blood-brain barrier (BBB), which leads to increased expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and degradation of tight junction proteins, thereby enabling leukocytes and toxins to penetrate the CNS. As part of its broader anti-inflammatory action (see Section 6.2), quercetin reduces leukocyte infiltration and endothelial adhesion molecule expression [56].

5.3. Quercetin penetration: Parent compound vs metabolites

In humans, most quercetin is found in plasma as conjugated metabolites (e.g., glucuronides and sulfates), and the free parent quercetin is often not detectable; this suggests that the biological effects observed *in-vivo* may be due to these metabolites rather than the unchanged aglycone. Therefore, it is

essential to distinguish the effects of the parent compound from those of its metabolites, as the metabolite profiles and their biological activities differ from those of quercetin and are more representative of human exposure. In high-dose studies (50–200 mg/kg), only very small amounts of quercetin have been detected in brain tissue, suggesting that the BBB crossing is limited. On the other hand, metabolites such as methylated derivatives (e.g., isorhamnetin) or glucuronides may reach higher concentrations in the brain, in part because they have a lower affinity for efflux transporters and can be taken up via OATPs. Some microbial metabolites (e.g., protocatechuic acid) have been demonstrated to cross the BBB efficiently and accumulate in the brain, thus supporting the concept of a "metabolite-mediated" mechanism of action [57].

5.4. Critical evaluation &methodological caveats

Understanding quercetin BBB studies from the perspective of the methodologies used has been a major challenge. For example: If perfusion is not properly performed before tissue collection, brain levels may be overestimated due to residual blood; several researchers use excessively high doses (much higher than dietary exposure), so transporters are saturated and the results are misleading; most determine brain levels at only one time point, so dynamic kinetics are not taken into account; and differences between species in the transporter expression make it more difficult to extrapolate the results to humans. To resolve the issue of quercetin bioavailability to the CNS and its mechanism, researchers should employ physiologically relevant doses, strict perfusion protocols, metabolite profiling, and human models (e.g., CSF sampling or neuroimaging).

6. Neuroprotective mechanisms

6.1. Oxidative stress &mitochondrial protection

Oxidative stress is a major contributor to neurodegeneration and cognitive deficits. Quercetin helps in this regard by scavenging reactive oxygen species and activating the Nrf2–ARE pathway. In fact, quercetin interferes with the Keap1–Nrf2 interaction, facilitates Nrf2 translocation to the nucleus, and enhances the production of antioxidant enzymes like SOD, catalase, GPx, and HO-1 [58].

Quercetin, in neuronal and animal models, is capable of restoring the mitochondrial membrane potential, inhibiting the release of cytochrome c, preventing mitochondrial permeability transition pore opening, and stimulating biogenesis through PGC-1α; thus, it is a protective agent against mitochondrial toxin-induced damage (e.g., from rotenone, MPTP) and reduces apoptosis [59].

6.2. Neuroinflammation and glial modulation

Quercetin alleviates neuroinflammation by blocking NF-κB activation: It impedes IκB kinase activation, maintains IκB integrity, and keeps NF-κB in the cytoplasm, thereby reducing microglial production of IL-1β, IL-6, TNF-α, and iNOS [60].Additionally, the flavonoid blocks microglial NLRP3 inflammasome assembly. Quercetin in aged or diseased animal models (e.g., diabetic encephalopathy) increases the expression of SIRT1 and simultaneously decreases NLRP3, ASC, caspase-1, IL-1β, and IL-18, leading to reduced neuroinflammation and increased synaptic and cognitive markers (BDNF, NGF, PSD95) [61].

6.3. Synaptic plasticity and protein aggregation

Preclinical research indicates that quercetin may influence factors related to synaptic integrity, such as BDNF expression and the antioxidant system, both of which have been associated with synaptic plasticity in animal models; however, there is little direct evidence that quercetin repairs synaptic plasticity in humans [62].

In Alzheimer's disease models, quercetin has been shown to inhibit β-secretase (BACE1), reduce amyloid-β production, shift aggregates toward non-toxic forms, and enhance autophagy, thereby promoting amyloid clearance. Additionally, it prevents tau hyperphosphorylation (via inhibition of GSK-3β/CDK5) and supports proteasomal and autophagic degradation. In Parkinson's disease models, quercetin prevents α-synuclein oligomerization and facilitates aggregate removal [63].

6.4. Hormetic stress &adaptive neuroprotection

Quercetin shows dose-dependent effects typical of hormesis. When used in low doses, it has cytoprotective properties. However, at high doses, it becomes a pro-oxidant or cytotoxic agent. Biphasic behavior is one of the key characteristics of dietary polyphenols, which, in addition to being mild cellular stressors, facilitates the activation of endogenous defense pathways [64]. Studies indicate that quercetin-induced hormetic responses are highly specific to the human body and vary across experimental models [65]. At a broader level, polyphenol hormesis reflects a general adaptive mechanism in which cells, upon low-dose exposure, exhibit greater resilience, whereas higher doses lead to inhibitory or toxic effects. Nevertheless, it should be kept in mind that most data on quercetin-induced hormetic neuroprotection come from *in-vitro* and animal studies, and its clinical efficacy in humans has yet to be confirmed [66,67].

7. Disease-specific applications

7.1. Neuropsychiatric disorders: Depression &anxiety

While quercetin has been demonstrated to reduce depression- and anxiety-like behaviors in rodent models, strong clinical evidence in humans is missing. It has been shown that quercetin (10–50 mg/kg) effectively reduces depressive and anxiety-like behaviors (e.g., forced swimming/tail suspension and sucrose preference) in rodents (subjected to chronic unpredictable stress, corticosterone administration) and restores corticosterone levels and hippocampal BDNF and serotonergic signaling. From a mechanistic perspective, quercetin stimulates hippocampal neurogenesis in mice under chronic stress via the FoxG1/CREB/BDNF pathway.

Moreover, the anxiolytic effect of quercetin might be related to interactions between the lateral habenula and the endocannabinoid (eCB) system: In mice exposed to CUMS, quercetin restored CB_1 receptor activity and alleviated depressive behavior, and inhibition of CB_1 receptors reversed quercetin's effect [68].

7.2. Neurodegenerative diseases: Alzheimer's& Parkinson's diseases

Quercetin has been reported to impact the major pathological components of Alzheimer's

disease (AD) in animal experiments; however, such evidence has not been corroborated by human clinical trials. For example, in 3×Tg-AD mice, long-term treatment with quercetin (25 mg/kg every 48 h) not only reduced levels of β-amyloid, paired helical filament tau, and BACE1 but also improved memory [69]. Furthermore, a systematic review of 14 preclinical AD studies strongly supports quercetin's neuroprotective effects across models [70]. In a model of repeated intranasal Aβ exposure, mice treated with quercetin orally (30 or 100 mg/kg) showed a significant reduction in neuroinflammation, oxidative stress, Aβ accumulation, and phosphorylated tau, along with an improvement in behavior [71]. In Parkinson's disease (PD) quercetin has been shown to promote motor function, safeguard dopaminergic neurons, and reduce neuroinflammation and programmed cell death through mechanisms involving survival signaling pathways (see Section 6) in an MPTP-induced mouse model of PD [72].

7.3. Autism spectrum disorder (ASD): Microbiome &immune modulation

Almost all the literature on quercetin or quercetin-containing formulations for autism spectrum disorder (ASD) originates from preclinical animal studies or small open-label pilot studies, and there are no large, randomized, placebo-controlled clinical trials showing that quercetin alone is efficacious in human ASD populations. Preclinical studies using rodent models of autism have shown that quercetin could reduce oxidative stress, neuroinflammation, and behavioral deficits; however, these results have not been replicated in well-controlled human clinical trials. Open-label studies, which combine quercetin with other flavonoids (such asluteolin), do not have placebos or objective outcome measures [73].

7.4. Critical gaps &challenges

Reported dose ranges of 10-200 mg/kg, in the literature, primarily refer to rodent experimental models. When these doses are converted to human equivalents using body surface area, the resulting doses are significantly lower. For instance, considering the typical Km factors (rat Km≈ 6, human Km≈37), a 50 mg/kg dose in a rat is equivalent to ~8 mg/kg in humans, which is roughly ~560 mg/day for a 70 kg adult. This suggest that the effects seen at very high animal doses may not be directly related to the levels that can be achieved in humans, especially given quercetin poor oral absorption and extensive metabolism, and there is no agreement on the equivalent or safe dose ranges for human ASD studies; a careful pharmacokinetic and safety evaluation is necessary when extrapolating these doses to humans. Moreover, obtaining systemic exposures in humans comparable to those in rodents is difficult, primarily due to quercetin’s rapid metabolism and poor oral bioavailability. This is demonstrated in clinical pharmacokinetic studies of quercetin, in which even a 150 mg/day dose yields only low-μM plasma concentrations. Additionally, biomarkers for target engagement remain poorly established. Reliable methods to accurately quantify quercetin and its metabolite’s levels in the brain are lacking, and approaches to assessing Nrf2 activation or anti-inflammatory effects in humans are not standardized. The therapeutic window also remains uncertain, as most benefits are observed in preventive or early-stage conditions, and only a few studies suggest the possibility of reversing advanced disease.

Neurological disorders are heterogeneous; therefore, it will be necessary to determine which subpopulations (based on genetics, the microbiome, and inflammation) are most likely to benefit

from quercetin. Therefore, there is a need for rigorous clinical trials, and researchers should employ standardized formulations, clearly defined patient groups, use mechanism-based biomarkers, and monitor long-term safety [74].

8. Clinical translation challenges

8.1. Pharmacokinetic barriers: Bioavailability, metabolism, and inter-individual variability

One of the major issues in the clinical translation of quercetin is its oral bioavailability, which is less than 10%. After first-pass metabolism, the biological products are glucuronidated, sulfated, and methylated conjugates with significantly lower biological activity than the aglycone form, which is generally used for mechanistic studies. After normal dietary intakes (10–100 mg), plasma concentrations are often below 0.5 μM, which is 10–100 times lower than the concentration at which *in-vitro* efficacy is observed [75].

Variability between individuals is very high; plasma levels differ by 10–20-fold among individuals receiving the same dose. This variability is mainly due to genetic polymorphisms in UGT1A1 and COMT, as well as variations in gut microbiota composition that influence metabolism and absorption. In addition, quercetin has the potential to influence drug-metabolizing enzymes and transporters by interacting with CYP3A4, OATP, and BCRP, and thus, pharmacokinetics becomes less predictable [76].

8.2. Formulation strategies: Nanoencapsulation, complexation, and co-administration

Advanced drug delivery systems primarily aim to improve quercetin's bioavailability without compromising its biological activity. Phytosome formulations that complex quercetin with phospholipids greatly enhance absorption and plasma exposure in human trials [77]. Polymeric micelles (e.g., Soluplus) and nano cochleates have been shown to improve solubility, stability, and intestinal permeability, resulting in bioavailability levels several times higher than those of free quercetin [78].

The use of metabolic inhibitors, such as piperine, in co-administration strategies can significantly enhance oral absorption by inhibiting glucuronidation and reducing pre systemic metabolism, as demonstrated in nanosuspension formulations. Nevertheless, enhanced systemic bioavailability may lead to changes in metabolite profiles, thus potentially affecting pharmacodynamics and safety profiles [79].

8.3. Dosing and safety: Effective ranges, long-term safety, and drug interactions

Some human supplementation studies have tested different amounts of quercetin (usually between 250 and 1000 mg/day), which are generally well tolerated in short-term interventions. However, quercetin has the potential to interact with drug-metabolizing enzymes and transporters, such as various cytochrome P450s (e.g., CYP3A4) and P-glycoprotein, thereby altering the pharmacokinetics of concomitantly administered drugs. These situations may cause changes in drug exposure levels, either increases or decreases, as has been shown, for example, for drugs such as cyclosporine, anticoagulants, and some chemotherapeutics. At high doses, quercetin may cause

gastrointestinal discomfort and, in laboratory studies, kidney toxicity as well as changes in liver enzyme activity. Most importantly, excessive consumption may affect drug metabolism and transporter systems, especially during chronic use. Hence, caution should be exercised when quercetin is co administered with drugs that have a narrow therapeutic index or are cleared by CYP3A4 or transporter-mediated pathways [80,81].

Initially, animal experiments showed kidney toxicity only at very high intravenous doses (>100 mg/kg). These results have not been confirmed in human studies; however, people with renal impairment are advised to exercise caution [82]. Safety data on human quercetin supplementation remain limited, especially when it comes to long-term use and effects on vulnerable populations like pregnant women, breastfeeding women, children, and people with chronic illnesses. Clinical studies have not defined the safety profiles for these groups, and one should exercise caution when extrapolating animal data to humans.

8.4. Critical evaluation: Enhanced bioavailability vs. altered biological activity

Human clinical pharmacokinetic studies have demonstrated that strategies to improve quercetin bioavailability, such as lipid complexes, phytosomes, glucosylation, and other formulation approaches, can increase systemic quercetin exposure. However, the effects of these tailored delivery systems on gut microbiota composition, microbiota function, and derived metabolites, and hence on gut-brain axis outcomes, have not been thoroughly assessed in controlled human intervention studies [83]. In future studies, researchers should employ mechanism-based drug delivery system design to clarify which therapeutic goals depend on actions in the local gut, on metabolites in the systemic circulation, or on direct tissue penetration (for instance, brain bioavailability in neuroprotective applications) [84].

8.5. Clinical evidence limitations

While limitations in translation have been considered, clinical evidence for quercetin remains heterogeneous and has not been consistently investigated across studies. Some human randomized controlled trials have reported mixed results: On the one hand, some studies have shown mild improvements in inflammatory or metabolic markers; on the other hand, others show no major clinical benefit. For instance, meta-analyses of clinical trials show that effects on lipid profiles and inflammatory markers are quite variable, and changes in IL-6 and TNF-α levels are inconsistent. The same is true of clinical studies looking at body weight or cardiovascular risk factors, which have frequently reported small or insignificant effects. Overall, the human evidence base is limited and heterogeneous and thus remains inadequate to support claims of therapeutic efficacy [85].

9. Methodological considerations and future directions

9.1. Research gaps

The neuroprotective effects of quercetin have mostly been demonstrated *in-vitro* and in animal models, whereas human intervention trials assessing cognitive, mood, or functional brain outcomes are scarce. Additionally, human pharmacokinetic studies reveal high variability in quercetin

absorption and metabolism among individuals, likely influenced by genetic factors (e.g., UGT variants) and by differences in gut microbiota composition [86]. However, it remains unclear how much these factors affect the levels of quercetin and its metabolites in the human bloodstream, or whether the gut-brain axis effects observed in animals translate into truly significant clinical outcomes. Further studies should include not only effect-based biomarkers, but also short-chain fatty acids (e.g., butyrate, acetate, propionate), inflammatory cytokines (e.g., IL-6, TNF-α), and neurocognitive parameters [87].

9.2. Mechanistic and multi-omics approaches

Network pharmacology analyses have suggested that quercetin may affect genes such as DYRK1A, NOS2, and NQO1, which are implicated in AD. However, these findings are largely based on in silico models and cell or animal-based experiments. Human studies combining metagenomics, transcriptomics, and metabolomics, together with targeted biomarker panels, are needed to establish whether these pathways operate *in-vivo*. Highly relevant outcomes would be microbiota-derived metabolites, inflammatory cytokines, and neuroimaging markers, such as functional MRI or PET-based measures of neuroinflammation, that enable connecting microbiome alterations to brain function [88].

9.3. Translational strategies

Quercetin exhibits antioxidant, anti-inflammatory, and metabolic effects in preclinical models; however, data demonstrating its combination with probiotics or known neuroprotective drugs in humans are lacking. So far, there are no rigorously controlled clinical studies confirming the efficacy or safety of such combination approaches in humans [89]. Future trials should incorporate biomarker-based endpoints to strengthen translational interpretation.

9.4. Personalized and precision approaches and future directions

Techniques in personalized nutrition, such as genotyping and microbiome profiling, not only help isolate responsive subpopulations but also hold promise for individualizing quercetin dosing. Nevertheless, there is a lack of controlled prospective human studies stratified by genetic or microbial profiles; to our knowledge, such studies remain limited. Appropriate clinical trials with neurocognitive endpoints, alongside standardized multi-omic analyses and predefined biomarker panels (e.g., short-chain fatty acids like butyrate, acetate, and propionate; inflammatory cytokines like IL-6 and TNF-α and neuroimaging markers like functional MRI or PET), rather than general multi-omic endpoints, should be the focus of future research. Although digital health tools (e.g., wearable monitoring) offer the potential for real-time physiological assessment, their use in gut-brain axis research should be considered preliminary and exploratory, given the lack of empirical evidence [90–92].

10. Conclusions

In this review, we highlight quercetin as a prominent multifactorial modulator of the gut-brain axis, integrating biochemical, microbial, and neurophysiological mechanisms. In addition to its

already known antioxidant and anti-inflammatory properties, quercetin has been proposed as a mediator of microbiota-host interactions, thus altering gut microbial ecology and influencing neural function through vagal, endocrine, immune, and metabolic signaling pathways. Quercetin, therefore, has been proposed as a potential microbiome intervention agent with the prospect of fostering neural resilience and metabolic balance by restoring beneficial commensals such as *Akkermansiamuciniphila, Lactobacillus, and Bifidobacterium,* as well as increasing the production of neuroactive metabolites*;* however, these effects need to be validated in human populations.

The long-term 'bioavailability paradox' of quercetin can be viewed differently by understanding its activity in the gut and metabolite-driven neuroprotection. The results suggest that microbial transformation and local intestinal signaling, rather than systemic aglycone exposure, are the major factors underlying quercetin's neurological effects. However, the extent to which gut microbial transformation, local intestinal signaling, and circulating quercetin metabolites each contribute to neurological outcomes in humans has not been well characterized and, in many cases, remains speculative. Therefore, formulation strategies focused on targeted delivery to the gut microbiome may be conceptually appealing; however, clinical outcomes with clear translational advantages supported by evidence have not been established. Besides that, the hormetic profile of quercetin, which, at moderate levels, is said to initiate adaptive cytoprotective responses in cell models, has not been shown to be clinically relevant in humans, and the optimal therapeutic windows remain to be determined.

To ensure clinical success, researchers should use standardized formulations, mechanism-based biomarkers, and stratified trial designs with microbiome, pharmacogenomic, and inflammatory profiling. It is necessary to carefully define and validate the clinical endpoints and biomarkers that can distinguish true treatment effects from background variability. The use of quercetin as a therapy may be of greater significance for prevention or for very early-stage intervention, but it remains only a presumption and needs to be confirmed by human studies with adequate power. Synergistic approaches combining quercetin with probiotics, pharmacotherapy, or lifestyle interventions require thorough clinical trials to be considered effective, and their efficacy cannot be assumed from preclinical results alone.

Subsequently, rigorous human trials incorporating neuroimaging, cerebrospinal fluid biomarkers, and multi-omics analyses are needed to confirm the preclinical data and identify differences in individual responses. Linking nutritional neuroscience and precision medicine together might, in the future, enable personalized quercetin-based therapies. Nevertheless, the data supporting immediate monitoring or dosage changes through digital health platforms are at a very early stage and are only exploratory. They have not been confirmed in clinical research. Instead, this review's additional value lies in presenting quercetin as a precision microbiome modulator and highlighting the crucial roles of microbiota-driven metabolic pathways and local gut signaling, rather than mere systemic bioavailability.

Author contributions

Vikrant Verma: Conceptualization, literature review, data interpretation and writing original draft. Dharmendra Kumar: Supervision, critical review, editing and Visualization,

Use of Generative-AI tools declaration

The authors declare that no generative AI tools were used in the preparation of this manuscript.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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