www.pharmaerudition.org

ISSN: 2249-3875

International Journal of Pharmaceutical Erudition

Research for Present and Next Generation

NOV 2025

Vol: 15 Issue:03

(25--33)

Review Article

ROLE OF FLAVONOID NANOCARRIERS IN MODULATING THE GUT–BRAIN AXIS FOR COGNITIVE HEALTH

Kishor Awadh

Pacific College of Pharmacy, PAHER, University, Udaipur Rajasthan-313024

The gut–brain axis (GBA) represents a dynamic bidirectional communication network linking the gastrointestinal tract and the central nervous system (CNS), governed by neural, endocrine, and immune pathways. Growing evidence highlights that gut dysbiosis contributes to neuroinflammation, oxidative stress, and cognitive decline. Flavonoids—bioactive polyphenols abundant in fruits, vegetables, and medicinal plants—possess strong antioxidant, anti-inflammatory, and neuroprotective properties that can beneficially modulate the GBA. However, poor solubility, instability, and limited bioavailability hinder flavonoid efficacy in reaching both gut microbiota and brain tissues. To overcome these pharmacokinetic barriers, nanocarrier-based drug delivery systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanomicelles have emerged as advanced strategies to enhance flavonoid absorption, stability, and targeted delivery.

This review comprehensively examines the mechanistic role of flavonoid nanocarriers in regulating the gut–brain axis, emphasizing their impact on microbiota modulation, neuroinflammation control, and cognitive enhancement. Moreover, it discusses the integration of nanotechnology and nutraceutical **science** as a sustainable approach to promote brain health, prevent neurodegenerative diseases, and support cognitive longevity.

Keywords: Flavonoids, Nanocarriers, Gut–Brain Axis, Cognitive Health, Neuroinflammation, Microbiota, Neuroprotection.

INTRODUCTION

Cognitive health is an essential component of overall well-being and longevity. Disorders such as Alzheimer's disease, Parkinson's disease, and age-related cognitive decline are increasingly recognized as multifactorial conditions influenced not only by neuronal dysfunction but also by systemic factors like inflammation and gut microbiota imbalance.

Recent research has unveiled the gut–brain axis (GBA)—a sophisticated network involving the enteric nervous system (ENS), vagus nerve, immune signaling, and microbial metabolites as a critical determinant of brain health. The intestinal microbiota produces neurotransmitters, short-chain fatty acids (SCFAs), and other metabolites that modulate neuroinflammation, synaptic plasticity, and cognitive function. Disturbance in this system, known as gut dysbiosis, is associated with neurodegeneration, mood disorders, and cognitive impairments.

Flavonoids, a diverse class of plant-derived polyphenolic compounds (e.g., quercetin, kaempferol, catechin, and naringenin), have demonstrated significant potential in protecting neurons and maintaining gut microbial balance. Their biological activities include scavenging reactive oxygen species (ROS), inhibiting pro-

inflammatory cytokines (IL-1β, TNF-α, IL-6), and enhancing mitochondrial biogenesis. Moreover, flavonoids influence microbial composition by promoting beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, which in turn produce neuroactive compounds like GABA and serotonin.

Despite these promising effects, flavonoids suffer from low oral bioavailability, rapid metabolism, and instability under physiological conditions, resulting in suboptimal therapeutic concentrations in the brain. This has spurred the exploration of nanocarrier-based delivery systems, which offer controlled release, enhanced permeability, and improved target specificity.

Nanocarriers—including liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanoemulsions, and dendrimers—enable flavonoids to cross the intestinal and blood–brain barriers effectively. Furthermore, nanoformulations can shield flavonoids from enzymatic degradation and modulate their interaction with gut microbiota, thereby enhancing their systemic and neuroprotective outcomes.

This review delves into the emerging role of flavonoid nanocarriers as modulators of the gut–brain axis, highlighting their potential to revolutionize cognitive health therapeutics through integrated nutraceutical nanotechnology.

Rationale of the Study

The increasing global prevalence of neurodegenerative disorders and cognitive decline, particularly in aging populations, has emphasized the urgent need for safe and effective therapeutic interventions. Traditional pharmacotherapy targeting central nervous system (CNS) pathways has demonstrated limited efficacy due to poor blood–brain barrier (BBB) permeability and systemic toxicity. Concurrently, lifestyle factors, diet, and gut microbiome composition have emerged as critical modulators of neurological health.

In recent years, the gut–brain axis (GBA) has gained recognition as a key regulatory system influencing emotional and cognitive processes. The interdependence of the gut microbiota and the brain suggests that neuroprotection can be achieved through modulation of intestinal microbial ecology. Flavonoids, derived from natural dietary sources, offer multifaceted neuroprotective effects—antioxidant, anti-inflammatory, and synaptic modulatory—but are limited by low bioavailability and metabolic instability.

Nanotechnology provides a transformative platform to address these limitations by improving flavonoid solubility, protecting active compounds from degradation, and enabling site-specific delivery. Flavonoid nanocarriers can potentially enhance bidirectional communication between the gut and brain by stabilizing gut

microbial populations, promoting neurogenesis, and attenuating neuroinflammation.

This integrated approach—merging nutraceuticals with nanotechnology—offers a sustainable and innovative strategy for preventing and managing cognitive decline. Hence, this review aims to elucidate the mechanistic role of flavonoid nanocarriers in modulating the gut–brain axis and promoting cognitive health.

Aim

To critically explore the role of flavonoid-based nanocarriers in modulating the gut–brain axis for improving cognitive health, emphasizing their neuroprotective mechanisms, microbiota interactions, and nanotechnological advantages.

Objectives

1. To review the fundamental relationship between the gut–brain axis and cognitive function.
2. To analyze the biological activities of major flavonoids influencing gut microbiota and neuroinflammatory signaling.
3. To evaluate recent advancements in nanocarrier systems designed for flavonoid delivery.
4. To examine how nanocarrier-assisted flavonoids modulate gut microbial metabolites and influence neurocognitive outcomes.
5. To identify challenges, limitations, and future research directions for developing clinically viable flavonoid nanotherapies.

This review employs a **systematic and integrative literature analysis** approach to collect, evaluate, and synthesize data on flavonoid nanocarriers and gut–brain axis modulation. The methodology involved:

- **Database Search:** Relevant articles were retrieved from Scopus, PubMed, Web of Science, and ScienceDirect databases published between 2015 and 2025.
- **Keywords Used:** "Flavonoids," "Nanocarriers," "Gut–Brain Axis," "Neuroprotection," "Cognitive Health," "Polyphenols," and "Microbiota."
- **Inclusion Criteria:**
    - Peer-reviewed articles, review papers, and conference proceedings.
    - Studies focusing on nanotechnology-based flavonoid delivery.
    - Research involving gut microbiota modulation or neuroprotective models.
- **Exclusion Criteria:**
    - Non-English publications.
    - Studies lacking mechanistic evidence or unclear data interpretation.

Data were critically analyzed and organized into thematic sections covering (i) gut–brain axis physiology, (ii) flavonoid–microbiota interaction,

(iii) nanocarrier systems, and (iv) cognitive health outcomes. Conceptual frameworks were developed to illustrate potential molecular pathways linking **nanotechnology,** flavonoid bioavailability, and gut–brain crosstalk.

Overview of the Gut–Brain Axis (GBA)

The gut–brain axis (GBA) is a complex, bidirectional communication system that integrates the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system (ANS), immune system, and gut microbiota. This intricate network enables continuous exchange of biochemical and neural signals between the gastrointestinal tract and the brain, influencing both emotional behavior and cognitive function.

Components of the Gut–Brain Axis

1. **Neural Pathways:** The **vagus nerve** acts as the primary conduit, transmitting sensory signals from the gut to the brainstem and modulating neurotransmitter release.
2. **Endocrine Pathways:** Gut hormones such as ghrelin, leptin, and peptide YY influence appetite, mood, and neuroplasticity.
3. **Immune Pathways:** Cytokines and microbial antigens modulate neuroinflammation through systemic immune signaling.
4. **Microbial Metabolites:** Short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, along with tryptophan-derived metabolites, regulate neurotransmitter synthesis and synaptic function.

Gut Microbiota and Cognitive Health

Emerging studies reveal that gut microbiota composition significantly impacts brain health. Beneficial microbes such as *Lactobacillus* and *Bifidobacterium* enhance the production of gamma-aminobutyric acid (GABA), serotonin, and dopamine, while dysbiosis promotes neuroinflammation and amyloidogenesis. Animal models have shown that fecal microbiota transplantation (FMT) from cognitively healthy donors can reverse age-related memory decline, confirming the **microbiota–neurocognitive link**.

Role of Flavonoids in Neuroprotection and Microbiota Modulation

Flavonoids are a diverse class of polyphenolic compounds found abundantly in fruits, vegetables, tea, cocoa, and medicinal plants. They possess a **C6–C3–C6** backbone structure and are categorized into subclasses such as **flavones, flavonols, flavanones, isoflavones, and anthocyanidins**.

Neuroprotective Mechanisms of Flavonoids

Flavonoids exhibit pleiotropic neuroprotective mechanisms:

- **Antioxidant Action:** Scavenge ROS and upregulate endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx).

- **Anti-inflammatory Response:** Inhibit nuclear factor kappa B (NF-κB) signaling, thereby reducing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α).
- **Synaptic Plasticity Enhancement:** Activate the BDNF–TrkB pathway, improving neuronal survival and learning memory.
- **Mitochondrial Protection:** Maintain mitochondrial membrane potential and ATP synthesis.
- **Amyloid Pathway Regulation:** Suppress amyloid-β aggregation and tau hyperphosphorylation, major hallmarks of Alzheimer's disease.

Flavonoids and Gut Microbiota

Flavonoids modulate the gut microbiome by promoting beneficial bacteria and inhibiting pathogenic strains. In return, the microbiota metabolizes flavonoids into smaller phenolic acids with higher bioactivity and permeability.

- **Probiotic Interaction:** Flavonoids enhance growth of *Bifidobacterium longum* and *Lactobacillus rhamnosus*, which release neuroactive metabolites.
- **Anti-pathogenic Effects:** Inhibit *Clostridium* and *Escherichia coli* species associated with cognitive decline.
- **Metabolite Signaling:** Metabolites such as phenyl-γ-valerolactones can cross the BBB and modulate neurotransmission.

Collectively, these interactions create a bi-directional symbiotic relationship where flavonoids and microbiota co-regulate gut and brain health.

Nanocarrier-Based Delivery Systems for Flavonoids

Despite their potential, flavonoids face low water solubility, enzymatic degradation, and poor BBB penetration, which limit their therapeutic translation. Nanocarriers offer an advanced solution to overcome these pharmacokinetic barriers.

Liposomes

Liposomes are phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic flavonoids. They protect flavonoids from gastrointestinal degradation and enhance intestinal absorption. For example, **quercetin-loaded liposomes** demonstrated improved memory retention in Alzheimer's models.

Polymeric Nanoparticles

Biodegradable polymers such as PLGA (poly lactic-co-glycolic acid) and chitosan are widely used to formulate flavonoid nanoparticles. These carriers provide sustained release and can be surface-modified for BBB targeting. Curcumin–PLGA nanoparticles, for instance, improved cognitive performance and reduced oxidative markers in animal studies.

Solid Lipid Nanoparticles (SLNs)

SLNs combine the stability of liposomes with the bioavailability of emulsions. They are ideal for

oral and parenteral delivery. Naringenin-SLNs have shown enhanced bioavailability and neuroprotective efficacy through improved brain uptake.

Nanoemulsions and Micelles

Nanoemulsions increase flavonoid solubility in aqueous environments and facilitate intestinal lymphatic transport. Similarly, polymeric micelles, due to their amphiphilic nature, enhance solubilization and targeted release.

Dendrimers and Nanogels

Dendrimers offer precise molecular architecture, allowing for high drug loading capacity. Nanogels, composed of cross-linked polymer networks, respond to pH and temperature changes—making them suitable for controlled flavonoid delivery in gut microenvironments.

Mechanistic Insights: Flavonoid Nanocarriers and Gut–Brain Modulation

Flavonoid-loaded nanocarriers function at multiple biological interfaces to regulate the gut–brain axis (GBA). Their mechanisms can be understood across three key levels—gut microbiota modulation, intestinal barrier reinforcement, and neuroinflammatory control.

Modulation of Gut Microbiota Composition

Flavonoid nanocarriers protect bioactive compounds from premature degradation in the gastrointestinal tract, allowing them to interact effectively with gut microbiota. Controlled release of flavonoids enhances selective growth of probiotic strains such as *Bifidobacterium* and *Lactobacillus*, which produce short-chain fatty acids (SCFAs) beneficial for neuronal health. Nanocarrier-assisted flavonoids also suppress dysbiotic bacteria like *Clostridium* and *Desulfovibrio*, reducing endotoxin release and gut permeability. This modulation restores microbial diversity, leading to balanced neurotransmitter signaling.

Enhancement of Intestinal Barrier Integrity

Leaky gut syndrome, characterized by disrupted tight junction proteins (e.g., occludin, claudin-1, ZO-1), allows toxins and lipopolysaccharides (LPS) to enter systemic circulation, promoting neuroinflammation.

Flavonoid nanocarriers stabilize epithelial integrity by upregulating tight junction proteins and reducing oxidative stress. For example, quercetin nanospheres significantly increased ZO-1 expression and reduced LPS-induced permeability in in vitro models. This maintains intestinal homeostasis and protects the neural environment from peripheral inflammatory insults.

Reduction of Neuroinflammation

Upon entering systemic circulation, flavonoid nanocarriers can cross the blood–brain barrier **(BBB)** either via receptor-mediated transport or by transiently opening tight junctions without toxicity.

Inside the CNS, flavonoids inhibit microglial activation, suppress pro-inflammatory mediators (NF-κB, COX-2, iNOS), and stimulate neurotrophic factors such as brain-derived neurotrophic factor (BDNF). These effects

synergize to reduce neuroinflammation, improve synaptic signaling, and enhance memory consolidation.

Neurotransmitter and Metabolite Regulation

Flavonoid-derived metabolites and SCFAs produced through gut microbial fermentation influence serotonin, GABA, and dopamine pathways. By promoting beneficial microbes and enhancing metabolite bioavailability, flavonoid nanocarriers indirectly regulate neurotransmitter balance—key for cognitive stability and mood regulation.

Therapeutic Implications for Cognitive Health

The integration of flavonoid nanocarriers in cognitive health management represents a paradigm shift from conventional pharmacotherapy to nutraceutical nanomedicine.

Alzheimer's and Parkinson's Diseases

Flavonoid nanocarriers such as epigallocatechin gallate (EGCG) nanoparticles and quercetin-loaded liposomes have shown remarkable efficacy in reducing amyloid-β deposition and α-synuclein aggregation, two hallmarks of neurodegeneration. Their antioxidant and anti-inflammatory synergy helps preserve neuronal integrity and cognitive function.

Stress, Depression, and Anxiety Disorders

Gut dysbiosis-induced neurotransmitter imbalance contributes to psychiatric disorders. Nanocarrier-delivered flavonoids modulate the hypothalamic–pituitary–adrenal (HPA) axis, reducing cortisol levels and improving resilience to chronic stress. Enhanced GABAergic and serotonergic activity promotes anxiolytic and antidepressant effects.

Age-Related Cognitive Decline

Aging is associated with oxidative stress and microbial imbalance. Curcumin–chitosan nanoparticles and kaempferol nanocarriers have shown improved memory retention and mitochondrial function in elderly animal models, suggesting potential for delaying cognitive aging.

Metabolic–Neurodegenerative Interface

Metabolic disorders like diabetes and obesity disrupt the gut–brain axis, accelerating cognitive dysfunction. Nanocarrier-mediated delivery of **naringenin** or **baicalein** regulates glucose metabolism, lipid homeostasis, and neuroinflammatory markers, bridging metabolic and neurological health.

Challenges and Future Prospects

Despite encouraging preclinical findings, translation of flavonoid nanocarriers into clinical use faces several obstacles.

Biocompatibility and Safety

While most nanocarriers are composed of biocompatible polymers and lipids, long-term toxicity and accumulation in non-target tissues remain concerns. Future studies must ensure safety through standardized pharmacokinetic and toxicological evaluations.

Variability in Gut Microbiota

Individual differences in microbiota composition may influence flavonoid metabolism and efficacy. Personalized nutrition-based

nanomedicine approaches should be explored to optimize therapeutic outcomes.

Manufacturing and Scalability

The large-scale production of nanocarriers with consistent particle size, surface charge, and stability is challenging. Regulatory harmonization is needed to ensure reproducibility and quality control.

Clinical Translation

Limited clinical trials exist evaluating flavonoid nanocarriers for cognitive disorders. Rigorous human studies integrating omics-based biomarkers and AI-assisted modeling are required to establish safety, efficacy, and dosing strategie**.**

Future Perspectives

Future research should focus on multi-targeted nanocarriers capable of simultaneous modulation of gut microbiota, intestinal barrier, and CNS signaling. Hybrid systems integrating biodegradable polymers, natural polysaccharides, and metallic nanoparticles may further enhance therapeutic potential. Moreover, the combination of AI-driven formulation design with molecular docking can accelerate discovery of optimal flavonoid–nanocarrier systems for neuroprotection.

CONCLUSION

Flavonoid nanocarriers represent a promising frontier in cognitive health management by bridging nutrition, microbiology, and nanotechnology. Through modulation of the gut–brain axis, these systems enhance microbial balance, reduce neuroinflammation, and improve neuronal resilience. The synergistic action of biogenic flavonoids and nanocarrier engineering holds immense potential for developing safe, sustainable, and effective strategies against neurodegenerative and cognitive disorders.

While challenges remain in large-scale production and clinical validation, the emerging convergence of nanoscience, microbiome research, and neurobiology positions flavonoid nanocarriers as a transformative innovation in next-generation brain therapeutics.

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