

NATURAL FLAVONOIDS IN GASTRIC MUCOSAL PROTECTION: FROM BENCH TO BEDSIDE

Jambulingam M.^{1*}, Saravanan V. S.², Sambath Kumar R.³, Veeravel S.⁴, Priyanka V.⁵, Mohamed Hafil H.⁶, Vengatesh R.⁷, Jahith Ahamed A.⁸

¹Associate Professor, Department of Pharmaceutical Analysis, The Erode College of Pharmacy, Veppampalayam, Erode, Tamil Nadu, India.

²HOD, Department of Pharmaceutical Analysis, The Erode College of Pharmacy, Veppampalayam, Erode, Tamil Nadu, India.

³HOD, Department of Pharmaceutics, The Erode College of Pharmacy, Veppampalayam, Erode, Tamil Nadu, India.

^{4,5,6,7,8}Final Year B.Pharm Students, The Erode College of Pharmacy, Veppampalayam, Erode, Tamil Nadu, India.

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*Corresponding Author: Jambulingam M.



Associate Professor, Department of Pharmaceutical Analysis, The Erode College of Pharmacy, Veppampalayam, Erode, Tamil Nadu, India.



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ABSTRACT

Gastric ulcer disease (GUD) continues to impose a substantial global health burden, arising from a disequilibrium between aggressive luminal factors—gastric acid, pepsin, *Helicobacter pylori* (*H. pylori*), non-steroidal anti-inflammatory drugs (NSAIDs), bile reflux, and reactive oxygen species (ROS)—and mucosal defense systems comprising mucus–bicarbonate secretion, prostaglandins, epithelial restitution, tight junction integrity, and mucosal blood flow. While proton pump inhibitors (PPIs) and H₂ receptor antagonists remain the cornerstone of therapy, their long-term use is associated with adverse effects, drug–drug interactions, rebound hyperacidity, and recurrence. Consequently, there is growing interest in multi-targeted, safer alternatives. Flavonoids—ubiquitous plant-derived polyphenols—exhibit potent antioxidant, anti-inflammatory, antimicrobial, cytoprotective, and anti-secretory activities that converge on key ulcerogenic pathways. This review comprehensively synthesizes the chemistry and classification of flavonoids, gastric ulcer pathophysiology, and the molecular mechanisms underpinning flavonoid-mediated gastroprotection, including redox homeostasis, NF-κB/MAPK modulation, prostaglandin biosynthesis, nitric oxide (NO) signaling, mucin regulation, and *H. pylori* inhibition. It further evaluates pharmacokinetics and bioavailability constraints, and outlines advanced formulation strategies (nanoparticles, liposomes, solid dispersions, and gastroretentive systems) to enhance therapeutic performance. Preclinical and emerging clinical evidence are critically appraised, and future perspectives for translation, standardization, and regulatory alignment are discussed. Flavonoids represent promising, multi-modal candidates for next-generation anti-ulcer therapeutics.

KEYWORDS: Flavonoids; gastric ulcer; gastroprotection; oxidative stress; *H. pylori*; nano formulation.

1. INTRODUCTION

Gastric ulcers are lesions in the stomach lining caused by an imbalance between aggressive and protective factors.^[1,2,4,13] Major etiological factors include *Helicobacter pylori* infection, prolonged NSAID use, alcohol consumption, smoking, and stress. These factors lead to excessive acid secretion, oxidative stress, and inflammation, ultimately damaging the gastric mucosa.^[2,4]

Conventional anti-ulcer drugs such as proton pump inhibitors (PPIs), antacids, and H₂ receptor antagonists provide symptomatic relief but are associated with limitations such as tolerance, adverse effects, and recurrence upon discontinuation. Consequently, there is increasing interest in natural compounds with fewer side effects and multiple therapeutic actions.

Flavonoids are naturally occurring polyphenolic compounds widely distributed in fruits, vegetables, and medicinal plants. They have demonstrated significant pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, and cytoprotective effects. Medicinal plants such as *Bryophyllum pinnatum* have shown promising anti-ulcer activity in experimental studies.^[3,8,15,17,20]

2. CHEMISTRY AND CLASSIFICATION OF FLAVONOIDS

Flavonoids possess a C₆–C₃–C₆ skeleton with two benzene rings (A and B) linked by a heterocyclic pyran (C) ring. Structural diversity arises from variations in hydroxylation, methoxylation, glycosylation, and degree of saturation/oxidation of the C-ring, dictating physicochemical properties and bioactivity.^[1,5,18,19]

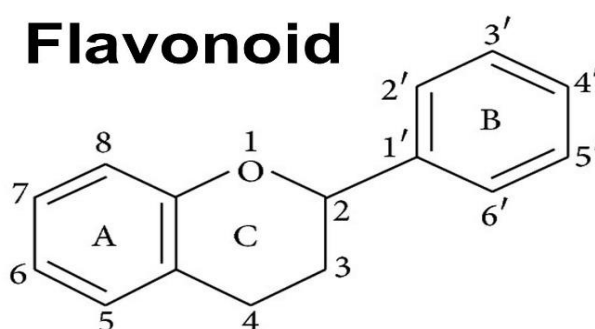


Figure 1

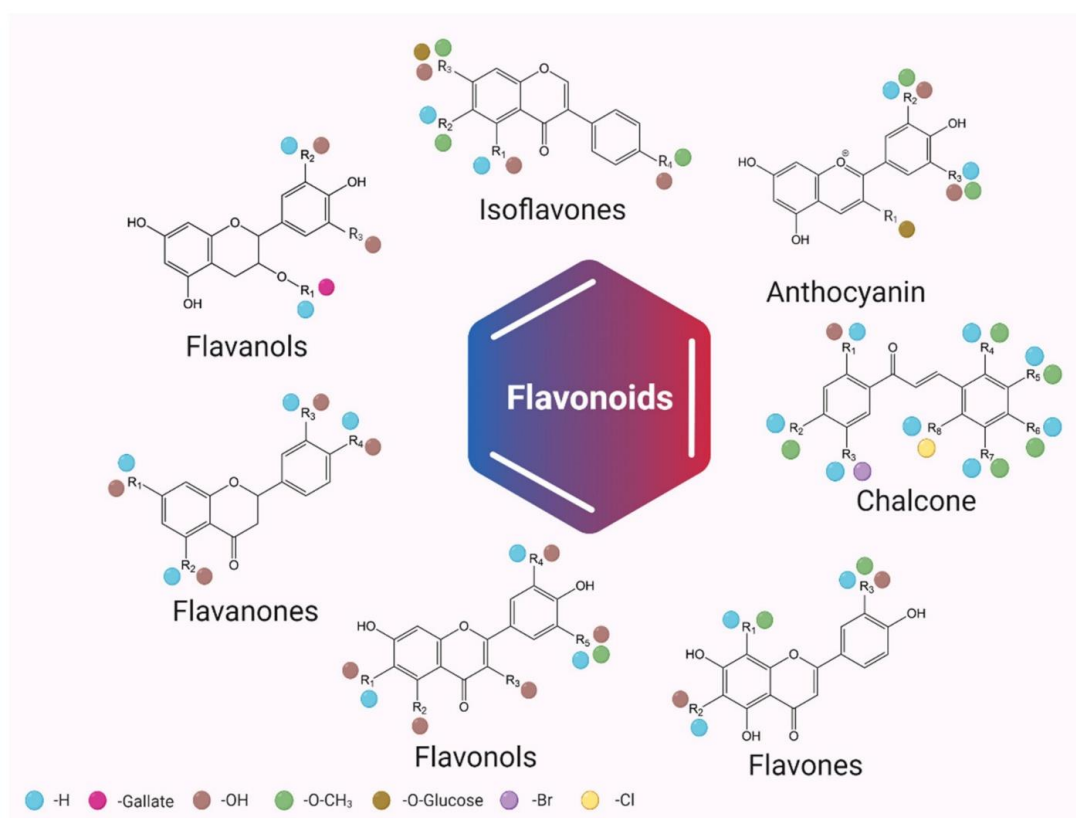


Figure 2

2.1 Flavonols

Characterized by a 3-hydroxyflavone backbone (e.g., quercetin, kaempferol, myricetin), flavonols exhibit strong radical scavenging capacity due to ortho-dihydroxyl groups in the B-ring and conjugation across the C-ring.

2.2 Flavones

Apigenin and luteolin are prototypical flavones lacking a 3-hydroxyl group. They display anti-inflammatory and enzyme inhibitory activities (COX/LOX), with favorable lipophilicity.

2.3 Flavanones

Hesperidin and naringenin (abundant in citrus) possess a saturated C2–C3 bond, influencing stereochemistry and bioavailability; they demonstrate antioxidant and anti-secretory effects.

2.4 Flavanols (Catechins)

Catechin and epicatechin (tea polyphenols) lack the C4 carbonyl and feature a dihydroflavonol structure,

conferring potent ROS scavenging and metal-chelating properties.

2.5 Anthocyanidins

Pigmented molecules (e.g., cyanidin, delphinidin) contribute to antioxidant capacity and vascular effects; stability is pH dependent.

2.6 Isoflavones

Genistein and daidzein have the B-ring attached at C3 of the heterocycle, enabling interactions with estrogen receptors and kinase pathways.

Structure–activity relationships (SAR) indicate that the catechol B-ring, C2=C3 double bond with 4-oxo function, and 3- or 5-hydroxyl groups enhance antioxidant potency and biological efficacy.

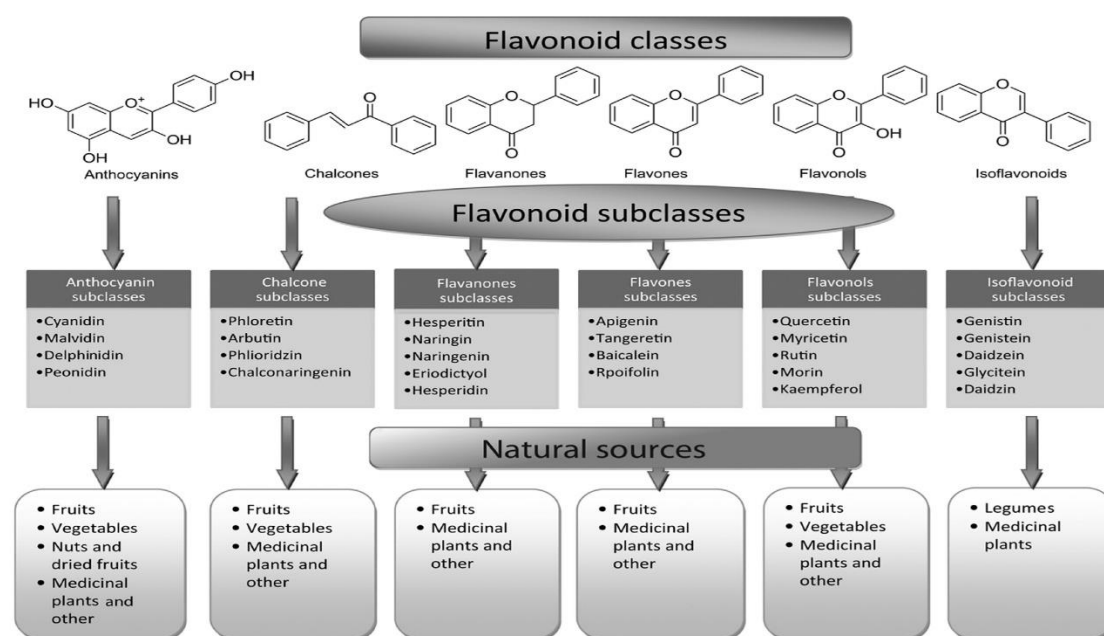


Figure 3

3. PATHOPHYSIOLOGY OF GASTRIC ULCER

Gastric mucosal integrity is maintained by coordinated defense mechanisms. Disruption results from:

- **Acid-pepsin aggression:** Back-diffusion of H⁺ damages epithelial cells.
- **NSAIDs:** Inhibit COX-1/COX-2, reducing prostaglandin (PGE₂), impairing mucus/bicarbonate secretion and blood flow.^[4]
- **H. pylori:** Produces urease, cytotoxins (CagA, VacA), induces inflammation and oxidative stress.
- **Oxidative stress:** Excess ROS (O₂•⁻, •OH, H₂O₂) triggers lipid peroxidation (MDA formation), protein oxidation, and DNA damage.^[13]

- **Inflammation:** Cytokines (TNF-α, IL-1β, IL-6) and transcription factors (NF-κB) perpetuate injury.^[9] Effective gastroprotection requires multi-target modulation—an area where flavonoids excel.

4. MOLECULAR MECHANISMS OF FLAVONOID-MEDIATED GASTROPROTECTION

4.1 Antioxidant and Redox Modulation

Flavonoids directly scavenge reactive oxygen species and enhance endogenous antioxidant defenses such as superoxide dismutase, catalase, and glutathione. Activation of the Nrf2 pathway further enhances cellular protection against oxidative damage.^[15,16]

4.2 Anti-inflammatory Signaling

Flavonoids inhibit NF- κ B activation and reduce pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. They also modulate MAPK signaling pathways, reducing inflammation and tissue injury.^[9,20]

4.3 Prostaglandin and Nitric Oxide Pathways

Flavonoids enhance prostaglandin synthesis and nitric oxide production, improving mucosal blood flow and healing.^[4]

4.4 Enhancement of Mucosal Barrier

They stimulate mucus secretion and strengthen tight junction proteins, preventing gastric mucosal damage.^[17]

4.5 Anti-Helicobacter pylori Activity

Flavonoids inhibit bacterial growth and urease activity of *Helicobacter pylori*.^[10]

4.6 Anti-secretory Effects

Certain flavonoids reduce gastric acid secretion by inhibiting proton pumps and histamine release.^[20]

5. FLOWCHART OF INTEGRATED FLAVONOIDS AS GASTROPROTECTIVE AGENTS

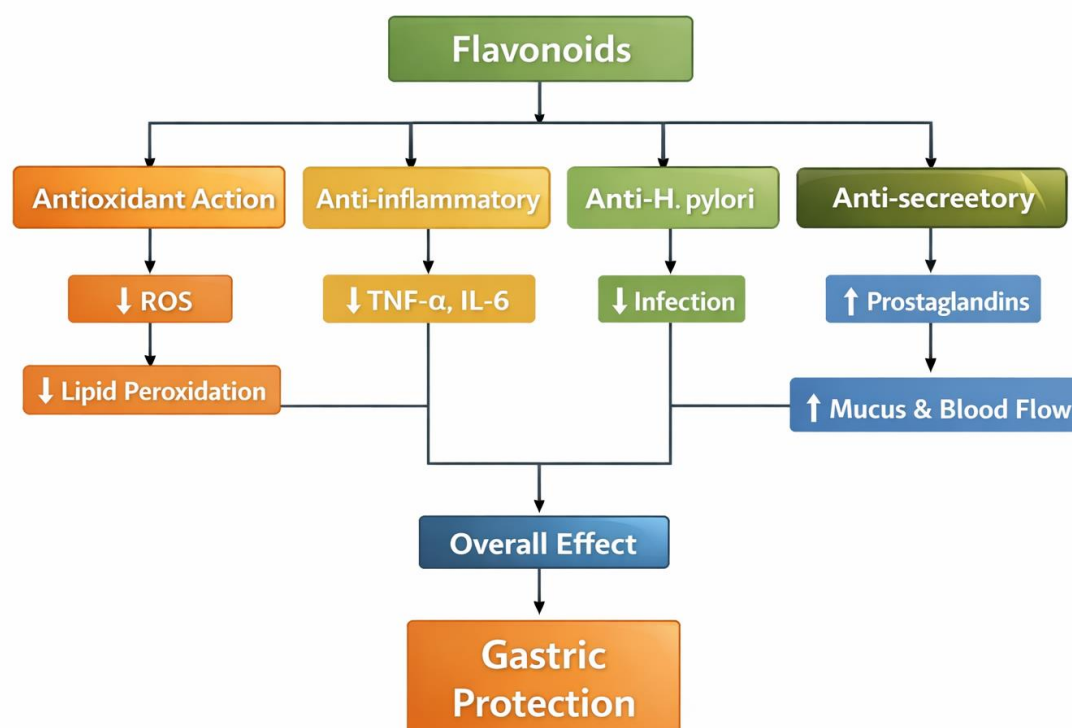


Figure 4

6. PHARMACOKINETICS AND BIOAVAILABILITY

Flavonoids typically exhibit poor oral bioavailability due to low aqueous solubility, instability in the gastrointestinal milieu, extensive first-pass metabolism (glucuronidation, sulfation), and efflux via P-glycoprotein. Aglycones are more lipophilic but less stable, whereas glycosides show variable absorption. Gut microbiota-mediated biotransformation produces phenolic metabolites with distinct activities.

Strategies to improve pharmacokinetics include particle size reduction, amorphization, complexation (cyclodextrins), lipid-based carriers, and enzyme inhibitors to reduce phase II metabolism.^[6,14]

7. FORMULATION STRATEGIES^[11,12]

7.1 Polymeric Nanoparticles

Biodegradable polymers (PLGA, chitosan, alginate) enhance solubility, protect against degradation, and enable controlled release and mucoadhesion.

7.2 Liposomes and Phytosomes

Phospholipid vesicles encapsulate flavonoids, improving permeability and systemic exposure. Phytosomes form complexes that enhance membrane affinity.

7.3 Solid Dispersions and Inclusion Complexes

Amorphous dispersions with carriers (PVP, PEG) and cyclodextrin complexes increase dissolution rate and stability.

7.4 Gastroretentive Systems

Floating and raft-forming systems prolong gastric residence, enabling localized action for ulcer healing. Effervescent matrices and alginate-based rafts are particularly relevant.

7.5 Hydrogels and Mucoadhesive Systems

Hydrogels provide sustained release and intimate mucosal contact, enhancing local bioavailability.

8. PRECLINICAL AND CLINICAL EVIDENCE

Animal models (ethanol-, indomethacin-, stress-, and pylorus ligation-induced ulcers) consistently demonstrate reduced ulcer index, decreased MDA, increased SOD/CAT, elevated PGE₂, and improved histology upon flavonoid treatment (e.g., quercetin, naringenin, catechins). Anti-H. pylori effects have been validated in vitro and in vivo.

Clinical evidence remains limited but encouraging. Dietary flavonoid intake correlates with reduced gastrointestinal inflammation. Small trials and observational studies suggest symptom improvement and mucosal healing with flavonoid-rich extracts; however, standardized, randomized controlled trials are needed.^[7,20]

9. SAFETY, TOXICOLOGY, AND REGULATORY ASPECTS

Flavonoids are generally recognized as safe at dietary levels, with low toxicity profiles. High-dose supplementation may pose risks of drug interactions (e.g., CYP450 modulation) and pro-oxidant effects under certain conditions. Regulatory frameworks require standardization of extracts, quality control (marker compounds), and robust clinical data for therapeutic claims.^[21]

10. LIMITATIONS AND CHALLENGES

- Low and variable bioavailability
- Chemical instability and batch variability in plant extracts
- Limited clinical trials and heterogeneous study designs
- Scale-up and reproducibility issues in advanced formulations

Addressing these requires standardized extraction, validated analytical methods, and well-designed clinical studies.

11. FUTURE PERSPECTIVES

- Rational design of nano-enabled gastroretentive systems
- Systems biology approaches to map multi-target effects
- Microbiome–flavonoid interactions and personalized nutrition
- Combination therapies with PPIs/antibiotics to reduce doses and resistance

- Regulatory harmonization and real-world evidence generation

12. CONCLUSION

Flavonoids offer a compelling, multi-targeted approach to gastric ulcer prevention and therapy, integrating antioxidant, anti-inflammatory, antimicrobial, cytoprotective, and anti-secretory actions. Advances in formulation science can overcome pharmacokinetic limitations, while rigorous clinical validation will be pivotal for translation. Collectively, flavonoids represent a promising class for next-generation, safer anti-ulcer therapeutics.

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