

REVIEW

Flavonoids and Their Influence on the Gut Microbiome: Implications for Cardiovascular Health

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ABSTRACT

Cardiovascular disease (CVD) remains a leading cause of mortality worldwide, necessitating effective preventive and therapeutic strategies. Flavonoids and polyphenols, which are abundant in colourful fruits and vegetables, have emerged as promising bioactive compounds for mitigating CVD. This study elucidates the mechanisms by which flavonoids exert cardioprotective effects through their antioxidant, prebiotic, and mitochondrial restorative properties. Flavonoids function as hydrogen donors, scavenging free radicals such as nitric oxide (NO[•]), superoxide anions (O[•]), and hydroxyl radicals (OH[•]), thereby reducing oxidative stress by decreasing inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS) activity while enhancing endothelial nitric oxide synthase (eNOS) functionality to promote vasodilation and prevent hypertension. Additionally, flavonoids act as prebiotics, fostering the symbiotic gut microbiota (GM), including *Bifidobacteria* and *Lactobacillus*, which produce short-chain fatty acids (SCFAs) and suppress pathogenic trimethylamine-N-oxide (TMAO)-producing bacteria. This enhances gut epithelial barrier integrity, reduces inflammation mediated by lipopolysaccharide (LPS), and protects against heart failure, ischaemia, and atherosclerosis. Under ischemic and heart failure conditions, flavonoids inhibit apoptosis, necrosis, ferroptosis, and fibrosis by restoring hypoxia-damaged mitochondrial function and cardiac energy metabolism. Furthermore, flavonoids prevent arteriosclerosis by inhibiting low-density lipoprotein (LDL) oxidation, reducing cholesterol absorption, promoting bile salt-hydrolysing bacteria, and decreasing vascular cell adhesion molecule (VCAM)-1 expression on coronary vessels. Here, we aim to advance the understanding of flavonoid-mediated cardioprotection by considering their antioxidant, anti-inflammatory, and gut microbiome-modulating effects, offering novel insights into dietary interventions for CVD prevention and management. The findings underscore the potential of flavonoids as accessible, natural agents to address global health disparities in CVD burden.

1 | Introduction

Cardiovascular diseases continue to dominate as the leading cause of mortality worldwide, accounting for 17.9 million

deaths annually (Hussain et al. 2024). While pharmacological interventions have advanced treatment outcomes, their inherent limitations—including adverse effects, prohibitive costs and inconsistent efficacy—have intensified the search for

preventive strategies leveraging dietary bioactive compounds (Teodoro 2019). Among these compounds, flavonoids have emerged as promising candidates, demonstrating multifaceted cardioprotective effects through their unique interactions with the gut microbiome (GM) and host physiology (Zhou, Ma, et al. 2024).

A growing body of evidence underscores the profound influence of the GM on cardiovascular pathophysiology (Witkowski et al. 2020). These findings, including the localisation of bacterial DNA and LPS within arteriosclerotic plaques (Carnevale et al. 2018) and the systemic circulation of gut-derived metabolites such as trimethylamine-N-oxide (TMAO), bile acids and protocatechuic acid (Qian et al. 2022), reveal intricate gut–gut–cardiovascular crosstalk. Epidemiological studies have further established associations between specific pathogens (*Chlamydophila pneumoniae*, *Porphyromonas gingivalis* and *Helicobacter pylori*) and increased CVD risk (Adinolfi et al. 2018; Ahmadi et al. 2023; Feinstein 2021; Joshi et al. 2013). This microbial influence operates through multiple pathways—gut dysbiosis can induce dyslipidaemia and atherogenesis by altering adipocyte factor expression and promoting triglyceride accumulation (Kobyliak et al. 2016; Yoo et al. 2022).

Flavonoids—a diverse class of polyphenols abundant in fruits, vegetables and medicinal plants—exhibit remarkable cardiovascular benefits through three interconnected mechanisms: direct biological activity, microbiome modulation and host-microbiome co-metabolism. Structurally, their benzo- γ -pyrone core enables potent neutralisation of reactive oxygen and nitrogen species, whereas their subclass diversity (flavonols, flavanones and anthocyanins) allows targeted activity against specific CVD pathologies (de Pascual-Teresa et al. 2010; Fardoun et al. 2020; Rudrapal et al. 2023). The cardioprotective mechanisms of flavonoids extend far beyond their antioxidant properties. These compounds demonstrate antimicrobial effects against pathogenic species (*Clostridium*, *H. pylori* and *S. aureus*) through membrane disruption (Bae et al. 2022; Górniak et al. 2019), prebiotic stimulation of beneficial bacteria (*Lactobacillus* and *Bifidobacterium*), anti-inflammatory modulation of the NF- κ B and PPAR pathways (Choy et al. 2019; Enayati et al. 2022), and vasoprotective, antithrombotic and antiapoptotic activities (Bao et al. 2016; Wätjen et al. 2005). Human trials have demonstrated that cocoa polyphenols increase *Lactobacillus* populations while reducing systemic inflammation (Sorrenti et al. 2020), and high flavonoid intake is correlated with improved blood pressure and vascular function (Jennings et al. 2021). The multiherb formulas containing *Salvia miltiorrhiza* (Danshen) and *Pueraria lobata* (Gegen), both rich in flavonoids, have shown potential for mitigating CVD risk (Woo et al. 2013). However, further clinical evidence is needed to fully establish their anti-inflammatory efficacy in humans. Notably, while many polyphenol-rich foods and herbs have traditional uses in cardiovascular support, this review focuses specifically on flavonoids and polyphenols—whether derived from traditional sources or dietary intake—through the lens of GM interactions and cardiovascular effects.

The therapeutic efficacy of flavonoids hinges on the dynamic interplay among host genetics, the GM, and the food matrix. For example, polymorphisms in the metabolic enzymes uridine diphosphate glucuronosyltransferase family 1 Member

A1 (UGT1A1) and catechol-O-methyltransferase (COMT) significantly influence flavonoid processing (Mir et al. 2018; Saracino et al. 2009). Specific bacterial taxa (*Lactobacillus* and *Bifidobacterium*) metabolise flavonoids into more bioactive forms (Pereira-Caro et al. 2018), and whole-food sources often outperform isolated compounds by increasing microbial fermentation (Baky et al. 2022; Egert and Rimbach 2011). Key enzyme families responsible for the microbial metabolism of flavonoids are found in the normal gut flora, including Lactobacillidae, Trichophyceae and Enterococcaceae (Taherkhani et al. 2024). This interdependence explains why individuals respond differently to flavonoid interventions and underscores the limitations of conventional preclinical models. For example, the antihypertensive effects of rutin and the conversion of quercetin to active metabolites depend entirely on an individual's microbial β -glucuronidase producers (Shimoi et al. 2003).

This review examines flavonoid protection against several major CVD pathologies: atherosclerosis, hypertension, myocardial ischaemia and heart failure through the lens of microbiome-mediated mechanisms. Three critical questions guide our analysis: (1) How do microbiota-mediated processes (TMAO reduction, SCFA production) contribute to flavonoid cardioprotection? (mechanistic pathways), (2) What genetic and microbial factors limit the clinical application of preclinical findings? (translational barriers), and (3) Why must human trials with microbiome profiling replace conventional models? (research priorities).

By synthesising evidence from epidemiological studies, clinical trials, and mechanistic research, this review aims to bridge the gap between flavonoid science and clinical practice, offering actionable strategies for personalised cardiovascular prevention and therapy. The complex interplay between flavonoids, the GM and host genetics represents both a challenge and an opportunity for developing more effective, tailored approaches to cardiovascular health maintenance.

2 | Flavonoid Sources and Dietary Intake

Flavonoids represent a diverse group of polyphenolic plant metabolites characterised by a benzo- γ -pyrone core structure synthesised via the phenylpropanoid pathway (Kumar et al. 2024). Their basic molecular framework consists of two benzene rings (A and B) interconnected by a heterocyclic pyran ring (C) (Ohkatsu et al. 2010). These compounds exhibit remarkable chemical diversity stemming from variations in their structural classes (flavones, flavonols, flavanones, etc.), hydroxylation patterns (typically at positions 3, 5, 7, 2', 3', 4' and 5'), substitution types (glycosylation, methylation, acetylation), and polymerisation states (monomeric or oligomeric forms; Alseekh et al. 2020). Structurally, they are categorised into six major subclasses, including flavonols (e.g., quercetin, kaempferol), flavones (e.g., apigenin, luteolin), flavanones (e.g., hesperidin, naringenin), flavan-3-ols (e.g., catechins, epicatechin), anthocyanins (e.g., cyanidin, delphinidin), and isoflavones (e.g., genistein, daidzein; Egbuna et al. 2023; Shen et al. 2022).

Flavonoids are ubiquitously distributed across at least nine principal plant-based food groups, including fruits, vegetables,

legumes, herbs/spices, beverages, nuts/seeds, cereals, medicinal plants and other botanical sources, with their specific occurrence and concentration varying significantly among different plant species and tissues (Tanwar and Modgil 2012; see Table 1). Citrus fruits (containing flavanones at 50–100 mg/100 g; Saini et al. 2022), berries (rich in anthocyanins 50–300 mg/100 g; Kalt et al. 2020), and onions (containing quercetin at 20–50 mg/100 g; Nishimura et al. 2019) are key sources. Beverages such as green tea (catechins 100–300 mg per cup; Catechins and Performance 2006) also contribute significantly. Among legumes, soy (isoflavones 20–50 mg/100 g; Messina 2016) is particularly notable. Food processing impacts the flavonoid content; for example, orange juice retains 81–644 mg/L flavanones (Gil-Izquierdo et al. 2001) after processing and storage (see Table 1).

Meta-analyses have demonstrated a significant inverse association between flavonoid consumption and CVD and coronary heart disease (CHD) risk in humans (Micek et al. 2021). Dose-response analyses revealed that daily intake of 100 mg of flavonoids was associated with a 7% reduction in CVD mortality risk, whereas a daily intake of 200 mg of flavonoids was associated with a 13% reduction in CVD risk. This protective effect becomes more pronounced with higher doses (Micek et al. 2021). A daily intake of 400 mg of flavonoids corresponds to a 21% lower CVD mortality risk, and a daily intake of 500 mg of flavonoids results in a 23% risk reduction. For coronary heart disease specifically, 300 mg daily flavonoid is linked to a 26% lower CHD risk, increasing to a 28% risk reduction at 500 mg/day (Micek et al. 2021). The analyses indicate a nonlinear dose-response relationship, suggesting greater protective effects at higher intake levels. These findings strongly support the cardioprotective role of dietary flavonoids, with optimal risk reduction observed at daily intakes of 300–500 mg. The consistent dose-dependent reduction in risk across multiple cardiovascular outcomes highlights the potential importance of flavonoids in cardiovascular disease prevention strategies (Micek et al. 2021).

Flavonoids are well known for their cardioprotective properties, but their clinical application is limited by poor bioavailability, with only 2%–20% absorption due to low water solubility, chemical instability and rapid metabolism in the liver and gastrointestinal tract (Waheed Janabi et al. 2020).

Decreased bioavailability may result from the entrapment of flavonoids within the food matrix. Digestible carbohydrates, lipids, proteins, vitamins and minerals are typically found in the food matrix, which encases flavonoids in the gastrointestinal tract and can negatively influence their bioaccessibility and bioavailability (Kamiloglu et al. 2021).

To overcome these challenges, advanced delivery technologies such as nanoencapsulation have been developed (Husain 2015). These nanocarriers increase solubility, enable targeted release and protect flavonoids from degradation. Owing to their small size, they efficiently cross the intestinal barrier and can even penetrate the blood-brain barrier while demonstrating minimal toxicity when formulated with biocompatible materials such as biodegradable polymers and lipids (Silva et al. 2018; Trindade et al. 2021). In addition to improving absorption, nanoencapsulated flavonoids also stimulate nitric oxide production by activating endothelial nitric oxide synthase (eNOS), promoting

vasodilation (Silva et al. 2018). They further support cardiovascular health through antioxidant effects, anti-inflammatory modulation, lipid regulation and beneficial interactions with the gut microbiome. Among recent advancements, polymeric nanoparticles (e.g., copolymer of lactic and glycolic acid (PLGA)), liposomes and polymeric micelles (e.g., Pluronic F127) have been designed to protect flavonoids from gastric degradation and enhance their stability (Li, Liu, et al. 2023). Phytosome technology, which involves the binding of flavonoids to phospholipids such as phosphatidylcholine, significantly improves intestinal absorption (Riva et al. 2019). Emerging approaches include synbiotic delivery systems that combine flavonoids with probiotics (e.g., *Lactobacillus* and *Bifidobacterium*) and prebiotics (e.g., inulin) to simultaneously increase flavonoid metabolism and promote beneficial gut bacteria (Hashem et al. 2023; Kvakova et al. 2021). Genetically engineered probiotics have also been developed to express specific enzymes that optimise flavonoid conversion (Al-Ishaq et al. 2021). For precise targeting, ligand-conjugated nanoparticles selectively bind to tissues such as blood vessels (Mukherjee et al. 2020; Vinayak and Maurya 2019). Some advanced systems are pH-responsive, releasing their payload only under optimal intestinal conditions (Barbosa et al. 2019). Hybrid innovations, including gold nanoparticles and plant-derived exosomes, further improve stability and efficacy without compromising biocompatibility (Madhan et al. 2024; Zhao et al. 2024). These advancements demonstrate how nanotechnology can address the limitations of flavonoid bioavailability, paving the way for targeted therapies for cardiovascular disease.

3 | Dietary Sources Versus Supplements

While technological advances have increased the clinical appeal of flavonoid supplements, the debate over whether to prioritise natural dietary sources or supplements remains ongoing. In whole foods, flavonoids are accompanied by essential nutrients—such as vitamins and fibre—that not only increase their effects but also promote balanced absorption (Egert and Rimbach 2011). Foods such as green tea, citrus fruits and berries are recognised as components of a healthy diet. When consumed naturally, flavonoids rarely cause side effects due to their lower, physiologically appropriate doses (Tang and Zhang 2022). However, in some cases—such as high tea or coffee intake—they may inhibit the absorption of nonheme iron, potentially contributing to iron deficiency in sensitive individuals (Gunec 2023; Zijp et al. 2000).

On the other hand, dietary supplements deliver concentrated flavonoid doses and may be beneficial in clinical contexts requiring high bioactivity (Yuan et al. 2024).

For instance, the results of a double-blind, placebo-controlled pilot study suggest that flavonoid supplements could offer a novel therapeutic approach to address premenstrual fluid retention and enhance leg health (Christie et al. 2004). Other randomised, double-blind, placebo-controlled trial results indicate that citrus flavonoids enhanced postprandial glycemia, supported the maintenance of GLP-1 levels, decreased inflammation and oxidative stress, and led to modest enhancements in body composition and blood pressure during the initial management of prediabetes (Cesar et al. 2025).

TABLE 1 | Table of the richest dietary sources of flavonoids based on the U.S. Department of Agriculture database (values expressed in mg per 100g edible portion; Haytowitz et al. 2018).

Food source	Total flavonoids (mg/100g)	Flavonoid class and compounds (mg/100g edible portion)
Parsley, dried	4854.49	Flavones: Apigenin (4503.50), Luteolin (19.75); Flavonols: Isorhamnetin (331.24)
Mexican Oregano, dried	1545.79	Flavones: Apigenin (17.71), Luteolin (1028.75); Flavanones: Eriodictyol (85.33), Naringenin (372.00); Flavonols: Quercetin (42.00)
Celery seed	841.05	Flavones: Apigenin (78.65), Luteolin (762.40)
Black Raspberries, raw	686.79	Anthocyanins: Cyanidin (669.01), Pelargonidin (16.69), Peonidin (1.09)
Elderberries, raw	512.03	Anthocyanidins: Cyanidin (485.26); Flavonols: Quercetin (26.77)
Cocoa, dry powder, unsweetened	271.25	Flavan-3-ols: (–)-Epicatechin (196.43), (+)-Catechin (64.82); Flavonols: Quercetin (10.00)
Capers, canned	303.89	Flavonols: Kaempferol (131.34), Quercetin (172.55)
Carob flour	235.72	Flavan-3-ols: (–)-Epicatechin 3-gallate (30.06), (–)-Epigallocatechin 3-gallate (109.46), (+)-Catechin (50.75); Flavonols: Myricetin (6.73), Quercetin (38.78)
Parsley, fresh	233.16	Flavones: Apigenin (215.46), Luteolin (1.09); Flavonols: Kaempferol (1.49), Myricetin (14.84), Quercetin (0.28)
Bilberry, raw	224.11	Anthocyanidins: Cyanidin (85.26), Delphinidin (97.59), Malvidin (39.22); Flavonols: Quercetin (3.04)
Red Cabbage, raw	209.83	Anthocyanins: Cyanidin (209.83)
Radicchio, raw	166.16	Anthocyanidins: Cyanidin (126.99), Delphinidin (7.68); Flavones: Luteolin (37.98); Flavonols: Quercetin (31.51)
Lovage Leaves, raw	177.00	Flavonols: Quercetin (170.00), Kaempferol (7.00)
Service (Saskatoon) Berries, raw	171.55	Anthocyanins: Cyanidin (110.58), Delphinidin (50.38), Malvidin (10.59)
Black chokeberry, raw	362.60	Anthocyanidins: Cyanidin (344.07); Flavonols: Quercetin (18.53)
Kale, raw	69.38	Flavonols: Kaempferol (46.80), Quercetin (22.58)
Mustard greens, raw	63.30	Flavonols: Isorhamnetin (16.20), Kaempferol (38.30), Quercetin (8.80)
Celery, Chinese, raw	58.89	Flavones: Apigenin (24.02), Luteolin (34.87)
Peppers, hot, yellow wax, raw	57.56	Flavones: Luteolin (6.93); Flavonols: Quercetin (50.63)
Blackberries, raw	103.53	Anthocyanidins: Cyanidin (99.95); Flavonols: Quercetin (3.58)
Eggplant, raw	85.69	Anthocyanins: Delphinidin (85.69)
Radish leaves, raw	78.09	Flavonols: Kaempferol (7.72), Quercetin (70.37)
Onion, red, raw	49.32	Anthocyanidins: Cyanidin (3.19), Delphinidin (4.28), Peonidin (2.07); Flavones: Apigenin (0.24), Luteolin (0.16); Flavonols: Isorhamnetin (4.58), Kaempferol (0.70), Myricetin (2.16), Quercetin (39.21)
Watercress, raw	53.02	Flavonols: Kaempferol (23.03), Quercetin (29.99)
Green tea, brewed	53.60	Flavan-3-ols: (–)-Epicatechin (6.16), (–)-Epicatechin 3-gallate (7.57), (–)-Epigallocatechin (16.02), (–)-Epigallocatechin 3-gallate (26.05); Flavonols: Kaempferol (1.00), Myricetin (1.00), Quercetin (2.77)

(Continues)

TABLE 1 | (Continued)

Food source	Total flavonoids (mg/100g)	Flavonoid class and compounds (mg/100g edible portion)
Black tea, brewed	29.55	Flavan-3-ols: (–)-Epicatechin (2.13), (–)-Epicatechin 3-gallate (5.86), (–)-Epigallocatechin (8.05), (–)-Epigallocatechin 3-gallate (9.36), (+)-Catechin (1.51); Flavonols: Kaempferol (1.41), Myricetin (0.45), Quercetin (2.19)
Strawberries, raw	26.53	Anthocyanins: Pelargonidin (24.85), Cyanidin (1.68)

Nevertheless, they also carry a greater risk of adverse effects (Barenys et al. 2017; Tang and Zhang 2022). Flavonoids such as epigallocatechin gallate (EGCG) and quercetin can form complexes with minerals such as iron, copper and manganese, impairing their absorption (Granda and de Pascual-Teresa 2018; Herman et al. 2022). This is particularly concerning for individuals with anaemia, pregnant women, or those on restricted diets. Furthermore, these compounds can interfere with folate and vitamin C uptake, and some, including isoflavones and catechins, may suppress thyroid function by inhibiting thyroid enzymes—increasing the risk of hypothyroidism or goitre (Dos Santos et al. 2011; Egert and Rimbach 2011).

Another important concern involves drug interactions. Many flavonoids can inhibit cytochrome P450 enzymes, such as CYP3A4 and CYP1A2, which are responsible for metabolising drugs such as warfarin, statins, and certain antihypertensive medications (Bojić et al. 2019; Shimada et al. 2010). This interference may reduce drug efficacy or increase toxicity. Isoflavones such as genistein can also act as oestrogen mimics at high doses, posing risks for individuals with hormone-sensitive conditions such as breast cancer (Doerge and Sheehan 2002; Naaz et al. 2003; Sayaf et al. 2025).

Given these factors, most experts recommend obtaining flavonoids from natural food sources rather than supplements (Egert and Rimbach 2011). Dietary flavonoids are generally safer, better tolerated, and offer added benefits from other accompanying nutrients (Egert and Rimbach 2011). Supplements may be helpful under medical supervision in specific therapeutic situations, but they should not be used indiscriminately (Egert and Rimbach 2011). A balanced diet rich in fruits, vegetables, and tea remains the most effective and safest way to harness the cardiovascular benefits of flavonoids.

4 | The Genetic-Microbial Nexus in Flavonoid Bioavailability and Cardiovascular Health

The genetic makeup of individuals plays a dual role in influencing both flavonoid metabolism and GM composition, thereby affecting cardiovascular health (Dicks 2024; Mansour et al. 2024; McGrail and Garelnabi 2019; Mofrad et al. 2025; Novakovic et al. 2020; Pan et al. 2023; Singh et al. 2024; Yang et al. 2025). While epidemiological studies consistently show associations between flavonoid intake and reduced CVD risk, human clinical trials specifically examining genetic influences remain limited. Most evidence comes from animal models and in vitro studies, which are crucial for identifying mechanistic pathways

that are difficult to study directly in humans. Flavonoids are metabolised through a complex process involving both host and microbial enzymes, with microbial enzymes often playing a more significant role (Chen et al. 2014; Murota et al. 2018). Therefore, genes encoding key metabolising enzymes (e.g., UGTs, COMT, SULTs) and those regulating microbiota colonisation work in concert to determine flavonoid bioavailability and efficacy (Chen et al. 2014; Hall et al. 2017; Figure 1, Table 2).

4.1 | Host Genetic Variations in Flavonoid Metabolic Pathways

Polymorphisms in key metabolic enzymes such as UGT1A1, COMT, SULTs, and transporters such as MRP2 can significantly influence the pharmacokinetics of flavonoids, altering their absorption, metabolism, and eventual bioactivity. For example, the UGT1A1 gene encodes an enzyme responsible for glucuronidation, a process that facilitates the excretion of flavonoid aglycones. While human clinical evidence is still emerging, multiple animal studies have demonstrated that the well-known UGT1A1*28 polymorphism (rs8175347) reduces enzymatic activity via promoter TA repeat expansion, leading to decreased clearance of both bilirubin and flavonoid compounds such as quercetin and genistein (Saracino et al. 2009). This diminished clearance prolongs their systemic presence and may affect their biological effects. Catechol-type flavonoids such as epicatechin harbour the rs4680 polymorphism (Val158Met), which results in a thermolabile enzyme with reduced activity (Mir et al. 2018). Human nutrigenetic studies, although limited in sample size, suggest that individuals homozygous for the Met allele may experience greater and more sustained exposure to active flavonoid forms, potentially enhancing cardiovascular benefits through improved endothelial function and antioxidant activity (Cassidy and Minihane 2017; Figure 1, Table 2).

Sulfotransferase Family 1A Member 1 (SULT1A1), another critical enzyme, sulfonates flavonoids, facilitating their excretion. Variants such as rs9282861 affect sulfotransferase efficiency and, thus, the systemic availability of compounds such as resveratrol and naringenin (Cassidy and Minihane 2017). These findings are primarily derived from in vitro enzymatic assays and animal models, which provide important mechanistic insights but require validation in human clinical trials. Similarly, transport proteins such as MRP2 (encoded by the ABCB2 gene) play a role in the efflux of flavonoid conjugates from enterocytes into the gut lumen. Polymorphisms in MRP2, including rs717620, can alter transporter function and influence the plasma levels of flavonoid metabolites (Chen

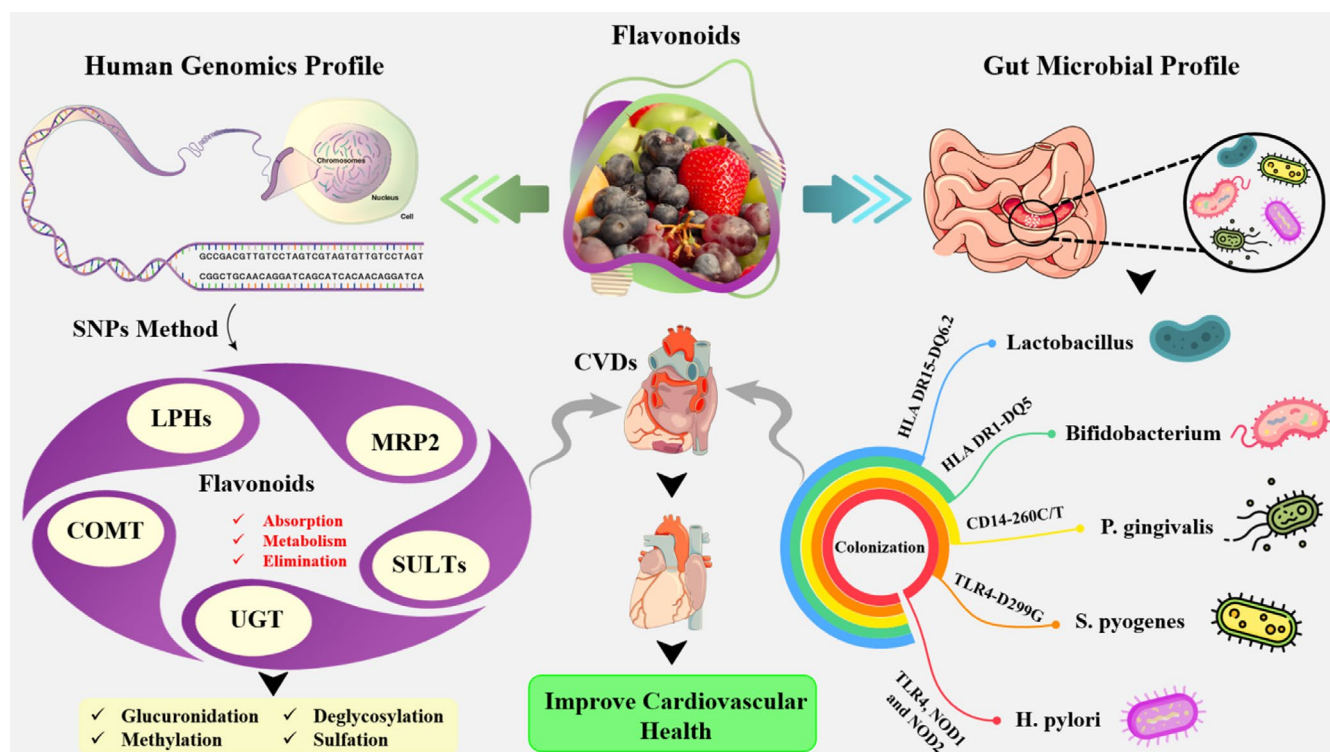


FIGURE 1 | Integrative role of host genomics and the GM in flavonoid metabolism and cardiovascular health. Key polymorphisms in metabolic enzymes (e.g., UGT1A1, COMT, SULTs, and MRP2) affect flavonoid absorption, methylation, glucuronidation, sulfation, and elimination. Simultaneously, host genetics modulate GM colonisation, with certain HLA alleles promoting beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, which are essential for flavonoid biotransformation. In contrast, immune gene variants (e.g., TLR4 D299G and CD14-260C/T) may favour colonisation by pathogens such as *H. pylori* or *P. gingivalis*, potentially impairing flavonoid metabolism and cardiovascular benefits. This gene–microbiome–nutrient axis underscores the importance of personalised nutrition for cardioprotection.

et al. 2014; Halder et al. 2014). Collectively, these genetic differences contribute to significant interindividual variability in flavonoid metabolism and, consequently, their therapeutic potential. Evidence from nutrigenetic studies shows that individuals carrying certain genotypes, such as COMT Met/Met, respond more favourably to flavonoid interventions in terms of vascular reactivity and blood pressure regulation, underscoring the clinical relevance of the host genetic background in determining flavonoid efficacy (Mir et al. 2018; Figure 1, Table 2).

4.2 | Key Polymorphisms Affecting Flavonoid Pharmacokinetics

In addition to shaping enzyme activity, host genetics significantly influence the composition and functionality of the GM, which in turn plays a critical role in the biotransformation of dietary flavonoids (Pan et al. 2023). While human epidemiological studies have identified associations between HLA types and microbiota composition, most mechanistic evidence comes from gnotobiotic mouse models. Certain human leukocyte antigen (HLA) class II alleles, such as DR1-DQ5 and DR15-DQ6.2, are associated with increased colonisation by beneficial bacterial taxa, including *Bifidobacteria* and *Lactobacilli* (Acton et al. 1999; Berryman et al. 2023; Uchida et al. 2006). These genera are particularly important for the

hydrolysis of glycosidic bonds in flavonoids, a prerequisite step for their further microbial metabolism into bioactive phenolic compounds. Individuals carrying these HLA variants may thus harbour a more favourable microbial environment for flavonoid conversion, which could translate into improved cardiovascular protection (Figure 1, Table 2).

Host genetic influence extends to epithelial expression of ABO blood group antigens, which modulate microbial adhesion and colonisation. For example, individuals with B-antigen expression demonstrate increased adhesion of certain *Lactobacillus* strains to intestinal surfaces, potentially enhancing flavonoid metabolism (Uchida et al. 2006). These observations from human cohort studies are supported by in vitro adhesion assays demonstrating strain-specific binding patterns. On the other hand, polymorphisms in immune-regulatory genes, such as toll-like receptor-4 (TLR4) (D299G) and CD14 (rs2569190), and proinflammatory cytokine genes, such as TNF- α and IL-1 β , are linked to altered immune responses and increased intestinal inflammation (Bartosova et al. 2022; Clyne and Rowland 2019). These immune-related genetic variants can disrupt microbial homeostasis, reduce microbial diversity and favour colonisation by opportunistic pathogens such as *Porphyromonas gingivalis*, *Chlamydia pneumoniae* and *Helicobacter pylori* (Novakovic et al. 2020). These pathogens not only contribute to systemic inflammation and atherogenesis but also compromise microbial pathways essential for flavonoid degradation and absorption (Figure 1, Table 2).

TABLE 2 | Human genes influencing GM colonisation and their functional roles.

Gene symbol	Full gene name	Function/effect on microbiota	References
FUT2	Fucosyltransferase 2	Influences the levels of specific gut bacteria, like <i>Bifidobacteria</i>	Wacklin et al. (2011)
MUC2	Mucin 2	Major component of mucus; it affects microbial adhesion and diversity	Yao et al. (2021)
TNF	Tumour Necrosis Factor	Pro-inflammatory cytokine shapes GM composition	Alatawi et al. (2022); Bazin et al. (2018)
IL10	Interleukin 10	Anti-inflammatory cytokine; modulates GM diversity	Maharshak et al. (2013)
NOD2	Nucleotide-binding oligomerisation domain-containing protein 2	Recognises bacterial components; affects microbial diversity and protection	Li et al. (2017)
TLR genes	Toll-like Receptors	Pattern recognition receptors influence gut microbial composition	Burgueño and Abreu (2020); Frosali et al. (2015); Hug et al. (2018)
APOE	Apolipoprotein E	Associated with alterations in microbiota linked to lipid metabolism	Hu et al. (2022); Yu et al. (2019); Zhang, Gu, et al. (2021)
LCT	Lactase	Affects populations' capacity to digest lactose and the composition of the microbiota	Forsgård (2019); Szilagyi et al. (2010)
SLC22A4	Solute Carrier Family 22 Member 4	Involved in the transport of compounds; can impact GM	Del Chierico et al. (2024); Nigam (2018)
CCL2	C-C Motif Chemokine Ligand 2	Chemokine is involved in immune regulation and influences the gut microbiome	Cianci et al. (2022); Luo, Wang, et al. (2023)

Abbreviations: APOE, apolipoprotein E; CCL2, C-C motif chemokine ligand 2; FUT2, fucosyltransferase 2; IL10, interleukin 10; LCT, lactase; MUC2, mucin 2; NOD2, nucleotide-binding oligomerisation domain-containing protein 2; SLC22A4, solute carrier family 22 member 4; TLR, toll-like receptor; TNF, tumour necrosis factor.

Taken together, the genetic regulation of the GM composition plays a fundamental role in determining how effectively an individual can convert flavonoids into absorbable and cardioprotective metabolites (Pan et al. 2023). Human genes that encode flavonoid-metabolising enzymes and shape the composition of the gut microbiota are key determinants of how flavonoids are processed in the body. These genetic factors may, in turn, influence cardiovascular health by modulating the bioavailability and bioactivity of flavonoid-derived metabolites. When host genetic variants favour a diverse and functional microbial ecosystem, the benefits of flavonoid intake are likely to be amplified. In contrast, genetic predispositions that promote dysbiosis may blunt or negate these health effects, highlighting the need to integrate host genomic and microbial information when evaluating flavonoid responsiveness (Figure 1, Table 2).

4.3 | Clinical Implications and Future Directions

The potential cardiovascular benefits of flavonoid-rich interventions show promise but require careful interpretation given the current state of evidence. While preclinical studies have demonstrated compelling mechanisms of action, it is important to note that much of this evidence comes from in vitro and animal (in

vivo) models, with human clinical data remaining limited. The translation of these findings to clinical practice requires further validation through well-designed human trials.

A key consideration is the substantial interindividual variability in the flavonoid response, driven by both genetic and microbial factors. Genetic polymorphisms in metabolic enzymes (e.g., *UGT1A1*, *COMT*, *SULTs* and *MRP2*) significantly influence flavonoid absorption and bioactivity. For example, common variants in *UGT1A1* and *COMT* can alter systemic exposure to active compounds, leading to variable therapeutic outcomes.

Similarly, the gut microbiome—modulated in part by host genetics—plays a pivotal role in flavonoid metabolism. Certain *HLA* genotypes favour the growth of flavonoid-metabolising bacteria (e.g., *Lactobacillus* and *Bifidobacterium*), increasing the production of bioactive metabolites. Conversely, genetic variants in immune-related genes (e.g., *TLR4*, *CD14* and *NOD2*) may predispose individuals to gut dysbiosis, impairing flavonoid activation and diminishing cardioprotective effects. These observations highlight the potential for personalised nutrition strategies, where interventions could be tailored on the basis of genetic or microbial profiling (Figure 1, Table 2).

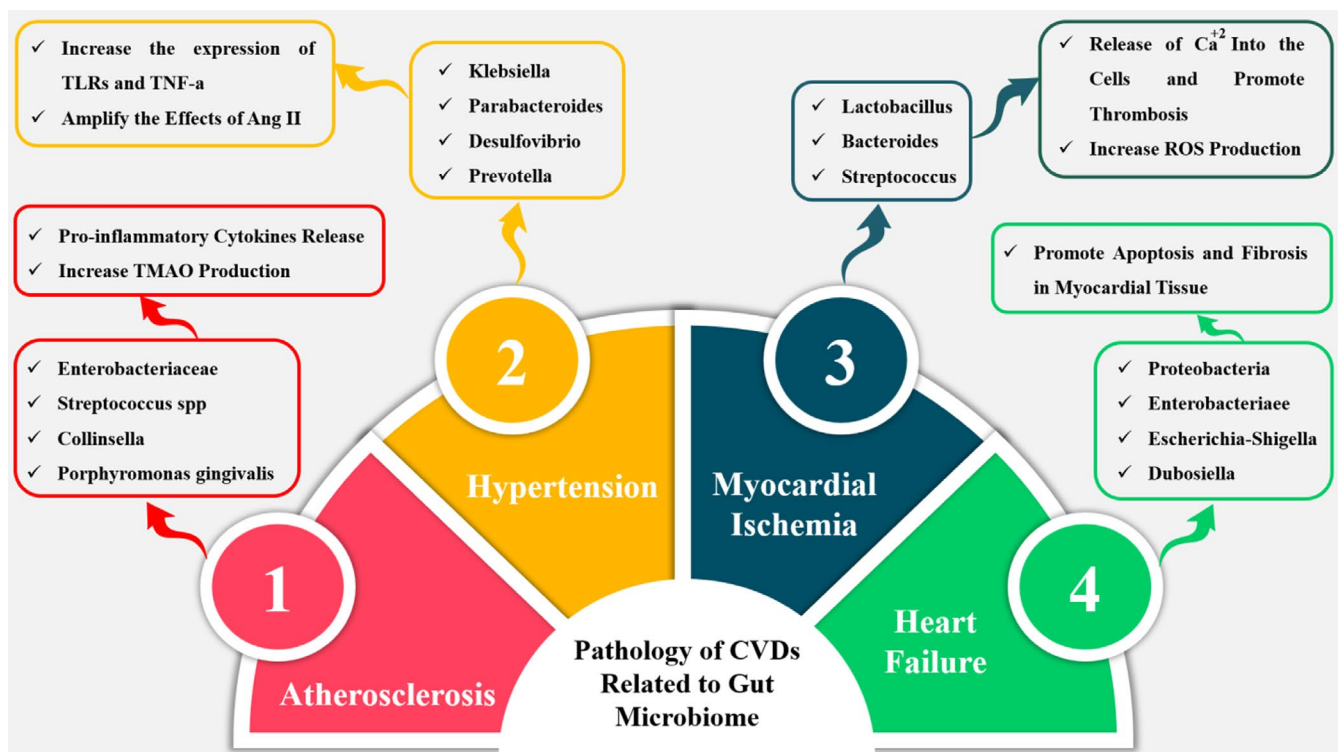


FIGURE 2 | Gut microbiome-mediated mechanisms in cardiovascular disease (CVD) pathology. An imbalance in the GM leads to increased expression of TLRs and TNF- α , which amplifies the effects of Ang II and triggers the release of proinflammatory cytokines. Specific bacterial taxa, such as *Enterobacteriaceae* and *Streptococcus* spp., produce elevated levels of TMAO, promoting oxidative stress and endothelial dysfunction. The overgrowth of pathogenic bacteria, including *Proteobacteria* (e.g., *Escherichia-Shigella*), *Desulfovibrio*, and *Prevotella*, is associated with increased ROS production, dysregulation of intracellular calcium (Ca^{2+}), and increased thrombosis risk. These microbial changes drive apoptosis and fibrosis in myocardial tissue, exacerbating cardiovascular conditions such as hypertension, myocardial ischaemia, and heart failure. Conversely, the depletion of beneficial bacteria such as *Lactobacillus* and *Bacteroides* results in reduced production of short-chain fatty acids (SCFAs) and compromised gut barrier integrity. Dietary flavonoids may counteract these pathological processes through their antioxidant properties, microbiome-modulating effects, and anti-inflammatory actions, potentially offering protective benefits against CVD development and progression.

However, critical gaps remain in our understanding. Most studies have examined genetic or microbial factors in isolation, neglecting their complex interplay. Genetic analyses often focus on a limited set of polymorphisms (e.g., *UGT1A128*, *COMT* rs4680), whereas microbiome studies frequently rely on broad taxonomic classifications rather than functional or strain-specific insights. Environmental factors (e.g., diet, antibiotics, geography) are also underrepresented, limiting the generalisability of the findings.

To advance the field, future research should prioritise the following: (1) Multiomics integration, involving genomics, metagenomics, metabolomics and transcriptomics, enables comprehensive characterisation of the complex interactions between flavonoids, the host, and the microbiome. (2) Longitudinal human studies employing standardised protocols can help establish causal relationships and characterise dose–response effects. (3) Stratifying intervention trials that test personalised flavonoid therapies in genetically or microbially defined subgroups can improve the precision of treatment effects by accounting for patient-specific biological variability.

While the interplay among host genetics, the microbiota, and flavonoids presents challenges, it also opens avenues for precision nutrition in cardiovascular disease (CVD) management.

Larger, diverse human trials are urgently needed to translate these preclinical insights into clinically actionable strategies, ensuring that flavonoid therapies are optimised for individual metabolic and microbial profiles.

5 | Atherosclerosis

5.1 | Microbiota and Atherosclerosis Pathogenesis

Emerging research highlights the significant role of the GM in cardiovascular health, particularly in the development and progression of atherosclerotic plaques (Jonsson and Bäckhed 2017). Specific bacterial species, including *Enterobacteriaceae*, *Streptococcus* spp., *Collinsella*, *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, are strongly associated with plaque formation (Kim et al. 2022; Kurilenko et al. 2021; Zhang, Zhang, et al. 2023; Figure 2). These bacteria can cause atherosclerosis in different ways. Gut dysbiosis increases intestinal permeability, allowing bacterial endotoxins such as LPS to enter systemic circulation (Di Vincenzo et al. 2024; Li, von Ehrlich-Treuenstätt, et al. 2023; Stephens and von der Weid 2020). Upon binding to TLR-4, LPS activates nuclear factor kappa B (NF- κ B), triggering the production of proinflammatory cytokines in antigen-presenting cells (APCs), including macrophages (Ahmadi, Janzadeh, et al. 2025;

TABLE 3 | Microbiome–CVD interactions: Bacterial species influencing cardiovascular disease (CVD) and their mechanisms of action.

Bacteria	Effect on cardiovascular disease	Mechanism	References
<i>Lactobacillus</i> spp.	It may have a protective effect against CVD	Produces SCFAs and reduces cholesterol levels	Zhao, Zhong, et al. (2021)
<i>Bifidobacterium</i> spp.	Associated with lower LDL cholesterol and improved endothelial function	Enhances gut barrier function and reduces inflammation	Tang et al. (2023)
<i>Enterococcus</i> spp.	Can be detrimental in high numbers; linked to increased risk of endocarditis and CVD	Promotes systemic inflammation and bacterial translocation	Dahl et al. (2016); Fernández-Hidalgo et al. (2020)
<i>Bacteroides</i> spp.	Generally, beneficial; associated with reduced inflammation and improved heart health	Produces SCFAs with anti-inflammatory effects	Kun et al. (2020); Zhao et al. (2022)
<i>Prevotella</i> spp.	Context-dependent effects (beneficial or harmful) influence metabolic profiles	Modulates inflammation and glucose metabolism via metabolites	Iljazovic et al. (2021); Kovatcheva-Datchary et al. (2015); Larsen (2017)
<i>Faecalibacterium prausnitzii</i>	Linked to reduced inflammation and lower CVD risk	Produces SCFAs and exhibits anti-inflammatory properties	Leylabadlo et al. (2020); Li, Xu, et al. (2022)
<i>Helicobacter pylori</i>	Associated with increased CVD risk due to chronic inflammation	Promotes systemic inflammation and atherosclerosis	Jamkhane et al. (2016); Sun, Zheng, et al. (2023); Tali et al. (2022)
<i>Clostridium</i> spp. (e.g., <i>C. butyricum</i>)	Certain species are beneficial for cardiovascular health	Improves gut health and reduces pro-inflammatory responses via SCFA production	Luo, Han, et al. (2023); Zhou, Qiu, et al. (2024)

Abbreviations: CVD, cardiovascular disease; LDL, low-density lipoprotein; SCFAs, short-chain fatty acids.

Ahmadi, Mahmoudi, et al. 2025; Javanmardi et al. 2024; Sangaran et al. 2021; Table 3, Figure 2).

Chronic inflammation promotes the upregulation of monocyte adhesion molecules, such as integrins and selectins, on endothelial cells, facilitating monocyte migration into the vessel intima and their subsequent differentiation into foam cells (Angelovich et al. 2015; Čejková et al. 2016; van Gils et al. 2009). In reverse cholesterol transport, apolipoprotein A-1 (Apo A-1), which is synthesised by both the intestine and the liver, accepts cholesterol efflux from macrophages through direct interaction with ATP-binding cassette transporter A1 (ABCA1), a membrane-spanning protein expressed on the macrophage surface (Ahmadi, Doyle, et al. 2025; Ahmadi, Taherkhani, et al. 2025; Chen, Zhao, et al. 2022; Chen et al. 2020; Yin and Fung 2021). These immune cells clear circulating LDL and VLDL particles via three parallel mechanisms: (1) receptor-mediated uptake (SR-A1, CD36 and SR-B1), (2) macropinocytosis, and (3) phagocytosis (Canton et al. 2013; Di and Maiseyeu 2021; Khosravi et al. 2018). However, dysbiosis disrupts lipid metabolism by suppressing fasting-induced adipocyte factor expression, increasing the level of circulating triglycerides, and promoting dyslipidaemia, a key driver of atherosclerosis (Cadena-Ullauri et al. 2024; Oynotkinova et al. 2020; Vourakis et al. 2021).

Additionally, GM-derived TMAO, a metabolite of phosphatidylcholine and L-carnitine, is linked to CVD risk and heart failure (Kanitsoraphan et al. 2018). TMAO impairs hepatic bile acid (BA) synthesis, reduces cholesterol clearance and disrupts

reverse cholesterol transport, exacerbating foam cell accumulation (Ding et al. 2018; Teft et al. 2017). Furthermore, TMAO activates the mitogen-activated protein kinase (MAPK) and NF- κ B pathways, amplifying vascular inflammation and atherosclerosis progression (Wang, Deng, et al. 2022).

Pathogenic bacteria associated with dysbiosis exhibit reduced bile salt hydrolase (BSH) activity, limiting bile acid deconjugation and increasing cholesterol absorption (Bourgin et al. 2021; Gadaleta et al. 2022). Conversely, beneficial microbes such as *Lactobacillus rhamnosus* GG, *Eubacteria*, *Anaeroplasm*, *Roseburia*, *Oscillospira* and *Dehalobacteria* have demonstrated atheroprotective effects by reducing plaque size (Zhao, Oduro, et al. 2021). Moreover, short-chain fatty acids (SCFAs), such as butyrate—produced through bacterial fermentation of indigestible carbohydrates—exert antioxidant effects and downregulate vascular cell adhesion protein 1 (VCAM-1) on monocytes, thereby mitigating endothelial adhesion (Menzel et al. 2004; Figure 2).

This evidence highlights the crucial function of the microbiota in exacerbating or ameliorating atherosclerosis. Therefore, dietary factors such as flavonoids may encourage the beneficial bacteria growth, and mitigate this condition.

5.2 | Flavonoids as Anti-Atherogenic Agents

Flavonoids—including kaempferol, myricetin, rutin, naringenin, catechin, fisetin and gossypetin—have demonstrated

significant potential in reducing atherosclerosis risk factors, suggesting promising avenues for clinical intervention (Salvamani et al. 2014). Other studies on luteolin in celery, parsley, broccoli, onion leaves, carrots, peppers, cabbage, apple and chrysanthemums have shown that it has antiatherosclerotic effects by modulating cells, including endothelial cells, vascular smooth muscle cells, macrophages and neutrophils (Wan et al. 2025) through repression of mitosis (Zhang, Wang, et al. 2024). The anti-atherogenic effects of flavonoids stem from multiple mechanisms, such as inhibition of LDL oxidation, antiplatelet activity, reduction of atherosclerotic lesions, improvement in endothelial function, and enhancement of vascular smooth muscle dilation (Fuhrman and Aviram 2001; Grassi et al. 2010; Grijalva-guiza et al. 2021; Hodgson and Croft 2006; Sharifi-Rad et al. 2022). While epidemiological studies consistently show inverse associations between flavonoid intake and atherosclerosis risk (strongest human evidence), most mechanistic evidence comes from animal models (ApoE^{−/−} mice) and in vitro studies of endothelial cells. Human clinical trials remain limited but show promising results for specific flavonoids, such as quercetin, in improving endothelial function.

These properties make flavonoids valuable as adjunct therapies alongside conventional antiatherosclerotic medications, such as statins or PCSK9 inhibitors, particularly in high-risk patients or those with existing cardiovascular disease. Interestingly, a cross-sectional study of 369 patients with atherosclerotic cardiovascular disease (ASCVD) and 3472 non-ASCVD individuals revealed that the intake of flavan-3-ols, flavones, flavonols and total flavonoids was negatively correlated with ASCVD risk, especially in smokers, non-alcohol consumers, physically inactive individuals, and those with hypertension (Hu et al. 2025). This suggests that flavonoid-rich diets may help mitigate cardiovascular risk even in the presence of adverse lifestyle or clinical factors.

5.3 | Microbiome-Mediated Effects of Flavonoids in Atherosclerosis Management

Flavonoids act as prebiotics, selectively promoting beneficial gut bacteria (e.g., *Lactobacillus* and *Bifidobacterium*) while suppressing pathogenic species, thereby restoring microbial balance and reducing the risk of dyslipidaemia (Plamada and Vodnar 2022). Animal models (particularly germ-free and gnotobiotic mice) have been essential for establishing causal microbiome–flavonoid relationships that cannot be definitively proven in human observational studies. These controlled systems allow the isolation of specific microbial contributions to flavonoid metabolism.

The clinical translation of this effect is exemplified by a study showing that hypercholesterolemic rats fed a combination of soy isoflavones and probiotics (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus gasseri* and *Lactobacillus reuteri*) presented greater reductions in total cholesterol (TC), LDL-C, and LDL/HDL ratios than those fed isoflavones alone (Rababah et al. 2015). This synergy suggests that flavonoid–probiotic co-supplementation could enhance lipid-lowering therapies in humans.

Specific flavonoids exert distinct anti-atherogenic effects via GM modulation. Naringin (a citrus flavonoid) shifts the

microbial composition by increasing Firmicutes and reducing Bacteroidetes and Verrucomicrobia, attenuating atherosclerosis in ApoE^{−/−} mice (Salvamani et al. 2014).

The ApoE^{−/−} mouse model remains the gold standard for pre-clinical atherosclerosis research because it effectively mimics human plaque progression, although notable species differences in lipid metabolism persist. Studies of the human microbiome have revealed similar phylum-level shifts following flavonoid interventions, but these effects exhibit greater interindividual variability. *Ligustrum robustum* enriches BSH-producing bacteria (e.g., *Bifidobacterium*), enhancing bile acid deconjugation and faecal excretion, thereby lowering serum TMAO and cholesterol (Liu et al. 2021). *Helianthus annuus* L. (sunflower) reduces intestinal permeability and increases the abundance of probiotics such as *Akkermansia muciniphila* and *Lactobacillus*, mitigating atherosclerosis in murine models (Wang, Shan, et al. 2021).

Among citrus flavanones, naringin and hesperidin have the strongest anti-atherogenic effects, with naringin primarily acting via gut-mediated bile acid synthesis, while others exert hepatic effects postabsorption (Wang, Zhao, et al. 2021). Quercetin administration in LDLR^{−/−} mice reduces Verrucomicrobia abundance, increases microbial diversity, and diminishes atherosclerotic lesions, highlighting its potential for cholesterol management (Nie et al. 2019).

5.4 | Clinical Applications and Therapeutic Considerations

Emerging evidence from preclinical and limited human studies suggests that flavonoid-rich diets may contribute to atherosclerosis management through multiple pathways, including antioxidant and anti-inflammatory effects, as well as gut microbiota modulation. When combined with standard pharmacological treatments, these dietary approaches may offer complementary cardiovascular benefits, although they should not be viewed as standalone therapies.

Current evidence suggests that luteolin-rich foods (such as celery, parsley, broccoli and apples) may offer vascular protective effects, although existing data are derived primarily from cell culture and animal studies (Wan et al. 2025). Citrus flavonoids such as naringin and hesperidin have been associated with improved lipid profiles and reduced inflammation in select human trials, although their gut-mediated mechanisms require further validation (Wang, Zhao, et al. 2021). Quercetin sources (onions, apples and tea) have potential for endothelial improvement and gut microbiome modulation; however, human clinical data are limited (Nie et al. 2019). Similarly, flavan-3-ols found in green tea, cocoa and berries show particular promise for high-risk groups, although optimal dosing and long-term effects warrant further investigation (Godos et al. 2024). Clinical trials have additionally documented the cholesterol-lowering effects of probiotic-enriched soy products, while certain seeds (e.g., sunflower) may reduce TMAO levels—an emerging cardiovascular risk marker (Rababah et al. 2015).

Epidemiological data support a daily intake of approximately 500 mg of mixed flavonoids from whole food sources, achievable through 5–9 servings of fruits/vegetables, 1–2 cups of tea,

and dark chocolate (Micek et al. 2021; Table 1). Bioavailability can be enhanced through light cooking methods (steaming/saut  ing) and co-consumption with healthy fats (Gonzales et al. 2015; Palermo et al. 2014), with distributed intake throughout the day recommended for optimal absorption. For example, the percentage losses of onion flavonoids when subjected to various cooking methods were as follows: frying resulted in a loss of 33% instead of saut  ing, 21% and steaming, 14%. Interestingly, cooking by microwaving (4%) and baking (0%) are the best (Lee et al. 2008).

Clinically, flavonoid–drug interactions require careful management. For statin-treated patients, while citrus flavonoids may provide complementary benefits, grapefruit juice must be strictly avoided owing to CYP3A4-mediated alterations in drug metabolism (Lee et al. 2016), with high-dose supplements potentially increasing myopathy risk (Zechner et al. 2022). Quercetin supplements may potentiate bleeding risk when combined with antiplatelet agents (e.g., aspirin, clopidogrel), making dietary sources preferable (Mosawy 2015; Stainer et al. 2019). Flavonoid-rich foods may synergise with angiotensin-converting enzyme inhibitors (ACE inhibitors)/angiotensin receptor blockers (ARBs) by enhancing nitric oxide-mediated vasodilation (Balasuriya and Rupasinghe 2011; Stam 2016), whereas concurrent omega-3 fatty acid intake could further improve anti-inflammatory effects and compound absorption.

While flavonoid-rich diets appear beneficial for cardiovascular health, their current role is adjunctive. Rigorous human studies are needed to establish causality, optimal protocols, and long-term outcomes. Until then, a diversified, food-first approach—under clinical supervision—has been recommended.

6 | Hypertension

6.1 | Microbiota and Hypertension Pathogenesis

Gut dysbiosis plays a significant role in hypertension through multiple pathways (Figure 2). It exacerbates oxidative stress, converting LDL into oxidised LDL (ox-LDL), which induces vasoconstriction and elevates blood pressure (Lara-Guzm  n et al. 2018; Pleiner et al. 2003). Foam macrophages absorb ox-LDL, leading to its accumulation and further contributing to hypertension (Cervantes and Kanter 2023). Dysbiosis also promotes LPS penetration, triggering systemic inflammation and increasing blood pressure (Grylls et al. 2021). A compromised gut barrier allows LPS to enter circulation, activating Toll-like receptors (TLRs) and Tumour necrosis factor-   (TNF-  ) in the paraventricular nucleus, which regulates blood pressure, resulting in an elevated heart rate, increased norepinephrine levels, and neuroinflammation (Hao et al. 2024; Masson et al. 2015). Additionally, TMAO, a gut-derived metabolite, is linked to cardiovascular risks, including hypertension and atherosclerosis (Mutengo et al. 2023). Elevated plasma TMAO levels correlate with a greater incidence of cardiovascular events (Qiu et al. 2023), and TMAO may potentiate angiotensin II (Ang II)-induced hypertension (Jiang et al. 2021). Coadministration of TMAO and Ang II in rats significantly increased systolic and diastolic blood pressure, possibly due to increased Ang II receptor activity (Ufnal et al. 2014; Figure 2).

SCFAs, another microbial metabolite, influence blood pressure via receptor-mediated pathways (Pluznick 2013, 2017). Hypertension is associated with reduced SCFA-producing bacteria (e.g., *Bacteroidetes*) and increased lactate-producing species (e.g., *Klebsiella* and *Parabacteroides*; Aguirre-Garc  a et al. 2023). Compared with hypertensive patients, normotensive individuals present greater populations of SCFA-producing bacteria (*Ruminococcaceae*, *Roseburia*, and *Faecalibacterium*; Calder  n-P  rez et al. 2020; Hamad et al. 2022). High salt intake exacerbates hypertension by altering the GM composition, reducing beneficial bacteria such as *Lactobacillus* and *Oscillibacter* (Verhaar et al. 2020). SCFAs, particularly butyrate, exert anti-inflammatory effects by upregulating IL-10 and suppressing proinflammatory cytokines (TNF-  , IL-12, and IFN-  ; Corr  a-Oliveira et al. 2016; Park et al. 2007). Their interaction with G-protein coupled receptors (GPCRs) induces vasodilation, lowering blood pressure (Natarajan et al. 2016; Table 3, Figure 2).

6.2 | Flavonoids in Hypertension Management

Flavonoids have demonstrated significant clinical potential in preventing and treating hypertension. Strong evidence from human clinical studies shows that they enhance vasodilation by activating eNOS (Si et al. 2014). Population-level epidemiological research supports this finding, demonstrating that a Mediterranean diet rich in flavonoids improves systolic blood pressure and arterial stiffness in older adults (Jennings et al. 2019). Moreover, in several human RCTs, flavonoids have shown antihypertensive effects (Maaliki et al. 2019). At the molecular level, these compounds reduce oxidative stress, increase nitric oxide bioavailability, and modulate vascular ion channels (Grijalva-guiza et al. 2021). Mechanistic studies have revealed that genistein, a specific flavonoid, improves endothelial function by activating vascular Akt/eNOS pathways, promoting vasodilation and endothelial protection (Yang et al. 2010). Another study demonstrated that the natural flavonoid scutellarein (Sc) effectively treats pulmonary arterial hypertension (PAH) by targeting mitochondrial dysfunction. Through both in vivo and in vitro experiments, Sc was shown to reduce right ventricular pressure, vascular remodelling and inflammation in PAH models. Mechanistically, Sc activates the sirtuin 1 (SIRT1)/nicotinamide adenine dinucleotide (NAD+) axis, increasing nicotinamide nucleotide transhydrogenase enzyme activity to restore NAD+ homeostasis and mitigate hypoxia-induced damage in pulmonary artery cells (Tang et al. 2025). Another study revealed that isorhamnetin (ISO), a natural flavonoid from sea buckthorn, effectively treats pulmonary arterial hypertension in rats by targeting the p-c-Src/NOX1 pathway. Treatment with ISO significantly reduces pulmonary pressure and prevents heart enlargement and blood vessel remodelling while increasing antioxidant defences and reducing the levels of oxidative damage markers (Chen et al. 2024). Notably, a novel homoisoflavonoid, 7-O-methylpunctatin (MP), prevents harmful changes in small blood vessel cells, suggesting a novel potential treatment for vascular diseases such as hypertension (Fardoun et al. 2019). Rutin, a bioactive flavonoid, has significant vascular protective effects through multiple mechanisms (Negahdari et al. 2021). Its well-characterised anti-capillary fragility properties help prevent and repair haemorrhages resulting from vascular wall instability (Li et al. 2021). Experimental evidence indicates that

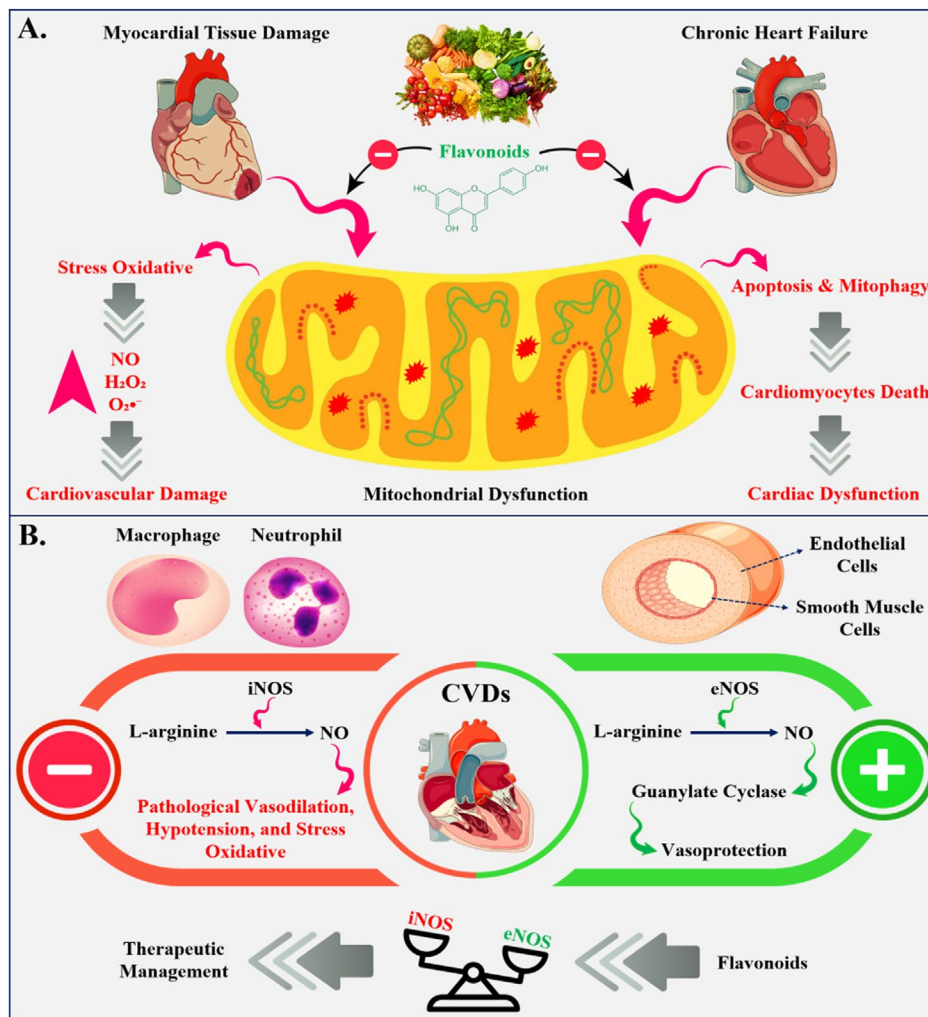


FIGURE 3 | Oxidative stress, nitric oxide dysregulation, and flavonoid-mediated protection in cardiovascular disease; (A) Myocardial Tissue Damage Mechanisms: Panel A illustrates the cascade of oxidative stress-mediated myocardial damage, highlighting key molecular players. Reactive oxygen/nitrogen species (NO, H₂O₂, O₂•⁻) generated from mitochondrial dysfunction drive cardiovascular pathology, leading to damage to endothelial cells, smooth muscle cells, and neutrophils. The panel highlights the dual role of nitric oxide (NO) in cardiovascular diseases (CVDs), where physiological NO production via eNOS from L-arginine supports vasoprotection, whereas pathological overproduction contributes to oxidative stress and hypotension. Therapeutic strategies targeting these pathways through flavonoid interventions have been shown to mitigate these effects by restoring redox balance and enhancing eNOS activity. (B) Cellular Players in Cardiovascular Pathology: Panel B identifies key cellular contributors to CVD progression. Under oxidative stress, macrophages and neutrophils amplify inflammatory responses, whereas endothelial and smooth muscle cells exhibit dysfunction. The panel highlights the central role of the L-arginine-NOS-NO axis dysregulation in CVD pathogenesis, where impaired NO signalling leads to vascular dysfunction. Flavonoids have emerged as multimodal regulators, concurrently addressing oxidative stress (via ROS scavenging), inflammatory cell activity, and endothelial function through eNOS activation, positioning them as promising therapeutic agents for cardiovascular protection.

rutin strengthens capillary integrity by (1) enhancing endothelial cell junctions (Sun et al. 2025), (2) reducing oxidative stress in vascular tissues (Wang et al. 2017), and (3) modulating inflammatory pathways that contribute to capillary brittleness (Lee et al. 2012). Furthermore, these vascular-stabilising effects contribute to the observed antihypertensive activity of rutin, as improved microvascular function reduces peripheral vascular resistance (Ganga et al. 2019; Figure 3A).

The GM-modulating effects of flavonoids in hypertension have been particularly well demonstrated in animal models that mimic human disease. Studies using hypertensive rats fed a high-fructose/high-salt diet, which replicates aspects of human

metabolic syndrome, have shown that *Coriandrum sativum* L. extract (rich in rutin and quercetin) increases the levels of vasodilatory factors (PGI₂, NO and eNOS), reduces the level of serum Na⁺, and enriches beneficial bacteria such as *Bifidobacterium* and *Oscillibacter* (Wang, Liu, et al. 2022). Importantly, the abundance of *Bifidobacterium* is directly correlated with improved Na⁺/H⁺ exchanger 3 (NHE3), NO, and eNOS levels, strongly suggesting microbiota-mediated antihypertensive effects (Wang, Liu, et al. 2022). These findings are supported by translational research showing that flavonoids and polyphenols can restore intestinal barrier integrity, thereby mitigating hypertension (Snelson et al. 2024). Additional preclinical work in hypertensive rat models has demonstrated that *Scutellaria baicalensis*

TABLE 4 | Effects of flavonoids on the composition of the GM and their influence on microbial species.

Flavonoid	Microbiota effect	Microbial species affected	References
Quercetin	Promotes growth of beneficial bacteria	<i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>E. ramulus</i>	Rodriguez-Castaño et al. (2019)
Rutin	Enhances microbial diversity	<i>Bacteroides</i> , <i>E. ramulus</i> , <i>Bifidobacteria</i>	Amaretti et al. (2015); Schneider and Blaut (2000); Shin et al. (2016); Zhao, Yu, et al. (2023)
Catechins	Increases abundance of specific bacteria	<i>Lactobacillus</i> , <i>Enterococcus</i> , <i>L. acidophilus</i> , <i>L. rhamnosus</i>	Alberto et al. (2001); Pacheco-Ordaz et al. (2018); Zhang, Zhou, et al. (2024)
Anthocyanins	Modulates GM composition	<i>Bifidobacterium</i> , <i>Prevotella</i> , <i>Akkermansia</i> , <i>histolyticum</i> , <i>E. coli</i> , <i>Salmonella</i> spp., and <i>Listeria</i> spp	Faria et al. (2014); Liang et al. (2024)
Hesperidin	Supports the growth of beneficial gut bacteria	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Amaretti et al. (2015); Biotechnol et al. (2024); Liu, Lei, et al. (2024)

Abbreviations: *E. coli*, *Escherichia coli*; *E. ramulus*, *Eubacterium ramulus*; *L. acidophilus*: *Lactobacillus acidophilus*; *L. rhamnosus*: *Lactobacillus rhamnosus*; spp., species.

Georgi extract (rich in baicalin) improves gut barrier function while increasing SCFA-producing bacteria (Wu et al. 2019). Similarly, studies on diabetic mice, which develop hypertension similar to that in humans with diabetes, have shown that *Edgeworthia gardneri* and other flavonoid-rich plants expand populations of SCFA-producing bacteria (Hussain et al. 2021; Zhang et al. 2019; Table 4, Figure 2).

These preclinical findings are supported by evidence from human clinical trials. Multiple clinical trials have demonstrated that a polyphenol-rich diet improves gut barrier function, enriches beneficial bacteria such as *Ruminococcaceae* and *Faecalibacterium*, and significantly reduces blood pressure (Del Bo et al. 2021; Suzuki and Hara 2011). Intervention studies with specific flavonoid sources have shown that regular cocoa (2.5 g) and berry (5 g) consumption lowers TMAO levels, enhances vasodilation, and reduces both systolic and diastolic pressure through the promotion of carbohydrate-fermenting bacteria (García-Cordero et al. 2023). Clinical outcome measurements confirmed that flavonoid-rich fruits can reduce systolic blood pressure by more than 4 mmHg over a month (Clemente-Postigo et al. 2013; Jennings et al. 2021; Rees et al. 2018; Warner et al. 2018; Table 4, Figure 2).

6.3 | Clinical Applications and Future Directions

Flavonoid-rich foods show promising but preliminary potential as complementary interventions for hypertension, with current evidence primarily derived from in vitro and animal studies. While these bioactive compounds appear to improve endothelial function through Akt/eNOS pathway activation (soybeans, legumes) and reduce oxidative stress while modulating the gut microbiota (berries, onions, herbs; Snelson et al. 2024; Tang et al. 2025; Wang, Liu, et al. 2022), human clinical evidence remains limited. Traditional medicinal plants such as *Scutellaria*

baicalensis may stabilise NAD⁺ metabolism and support gut barrier integrity via short-chain fatty acid production (Wu et al. 2019), although these effects require further human trials for confirmation.

For clinical implementation, prioritising whole food sources (e.g., incorporating berries at breakfast, legumes in lunches for example) over isolated supplements, conducting baseline and follow-up blood pressure monitoring, assessing gastrointestinal tolerance, and maintaining vigilance for food–drug interactions have been recommended.

Important clinical considerations must be considered when combining flavonoid-rich foods or supplements with cardiovascular medications. Quercetin (abundant in berries and onions) has serum albumin-binding properties that may displace amlodipine, potentially potentiating its hypotensive effects (Vanecková et al. 2019); thus, temporal separation of intake (≥ 2 h) is advised (Lakhanpal and Rai 2007). Grapefruit juice poses dual risks: its CYP3A4 inhibition increases amlodipine/felodipine bioavailability (Sica 2006) while impairing losartan activation (Seden et al. 2010), warranting complete avoidance of these agents. Furthermore, certain flavonoids (e.g., quercetin and apigenin) demonstrate ACE-inhibitory activity that may synergise with pharmacologic ACE inhibitors (Guerrero et al. 2012), necessitating close blood pressure monitoring and the avoidance of high-dose supplements in treated patients. These interactions underscore the necessity for personalised dietary guidance in cardiovascular pharmacotherapy.

7 | Myocardial Ischaemia

Myocardial ischaemia (MI) is a critical cardiovascular event characterised by myocardial necrosis caused by prolonged oxygen deprivation (Yeap et al. 2013). Understanding the

pathogenesis and treatment of MI is supported by a hierarchy of evidence, including strong human clinical studies detecting bacterial DNA in arterial plaques, epidemiological data linking specific gut bacteria to worse outcomes, animal models demonstrating the benefits of probiotics, and in vitro studies elucidating molecular mechanisms.

7.1 | Gut Microbiota and MI Ischaemia

Emerging evidence highlights the pivotal role of gut dysbiosis in myocardial infarction (MI) pathogenesis through multiple mechanisms. The disruption of intestinal mucosal integrity (“leaky gut”) permits the systemic translocation of both microbial metabolites and structural components of the gut microbiota, including bacterial DNA (Compare et al. 2024; Di Vincenzo et al. 2024; Kinashi and Hase 2021). This pathophysiological process provides a plausible explanation for the detection of bacterial DNA, matching both oral and gut microbiome profiles within the arterial plaques of MI patients (Armingohar et al. 2014; Kozarov et al. 2006; Lindskog Jonsson et al. 2017). Importantly, these microbial signatures are strongly correlated with plaque instability and increased cardiovascular risk (Chen, Zhou, et al. 2021; Novakovic et al. 2020). Clinical studies further substantiate these findings, showing poorer outcomes in MI patients with elevated abundances of specific gut bacteria, such as *Lactobacillus*, *Bacteroides*, and *Streptococcus* species (Zhou et al. 2018; Table 3, Figure 2). The therapeutic modulation of the GM presents a promising avenue for MI management. Clinical observations (the highest evidence level) reveal that antibiotic regimens that reduce bacterial translocation effectively attenuate systemic inflammation and myocardial damage post-MI, whereas probiotic supplementation is correlated with improved patient prognosis (Lam et al. 2012; Zhao, Zhang, et al. 2023). The gut-derived metabolite TMAO has emerged as a particularly deleterious factor, with human studies showing its role in promoting thrombotic events through calcium-mediated mechanisms while simultaneously impairing myocardial metabolism (Videja et al. 2021; Xie et al. 2021; Zhu et al. 2016). Conversely, epidemiological and clinical trial data demonstrate that a balanced GM enriched with symbiotic species facilitates cardiac tissue repair and improves clinical outcomes (Oniszczuk et al. 2021; Tang et al. 2017). Preclinical studies (animal models) using probiotic supplementation in antibiotic-pretreated mice before MI induction yielded significant improvements in cardiac function recovery and survival duration, effects attributable to increased production of GM-derived SCFAs (Lam et al. 2012). These animal studies were conducted to model human pathophysiology and suggest potential mechanisms for clinical translation (Figure 2).

7.2 | Flavonoids in the Protection Against Ischaemia–Reperfusion Injury

Flavonoids exert multifaceted cardioprotective effects through diverse molecular mechanisms. The flavonoid quercetin is particularly effective at mitigating ischaemia–reperfusion injury through the inhibition of inducible nitric oxide synthase (iNOS) activity (Chen, Chen, et al. 2023). In the context of myocardial ischaemia–reperfusion (I/R) injury, in vitro and animal studies

have shown that flavonoids effectively modulate critical cellular stress pathways, including endoplasmic reticulum stress and ferroptosis. Resveratrol, a prominent flavonoid found in red grapes, exhibits remarkable cardioprotection in animal models by suppressing ferroptotic cell death through the regulation of transferrin receptor 1, ferritin heavy chain 1, and glutathione peroxidase 4 expression (Chen, Pei, et al. 2022; Hu et al. 2024). Clinical observations (human evidence) with cocoa flavonoids have revealed significant reductions in peroxidative and nitro-oxidative stress markers following acute coronary events (Ahmed et al. 2020), whereas traditional preparations such as Santan Sumtang, which are rich in isovitexin and quercitrin, effectively preserve mitochondrial function and cellular integrity in hypoxic cardiomyocytes (Zhou et al. 2022; Figure 3A).

The vascular effects of flavonoids contribute substantially to their therapeutic value in MI management. Polyphenol-rich persimmon juice induces endothelium-independent vasorelaxation in mesenteric arteries (Sun, Zhou, et al. 2023), whereas moderate consumption of flavonoid-containing beverages such as beer has antioxidant effects on MI-induced oxidative stress (Gallinat et al. 2023). Perhaps most intriguingly, human clinical trials and in vitro studies have shown that flavonoids exhibit bidirectional interactions with the GM, whereas microbial metabolism enhances flavonoid bioactivity (as observed with urolithin B conversion from ellagitannins), and flavonoids simultaneously modulate the microbial composition toward cardioprotective profiles (Trinei et al. 2022). Clinical trials employing flavonoid-rich bilberry and oat interventions have demonstrated significant improvements in lipid profiles and inflammatory markers in MI patients, accompanied by beneficial shifts in GM structure (Bergh et al. 2021).

7.3 | Clinical and Dietary Implementation Strategies

The current evidence suggests that dietary flavonoids may offer cardioprotective benefits, although their clinical application requires careful consideration of both potential benefits and limitations. While preclinical studies in animal models and in vitro systems have demonstrated promising antioxidant, anti-inflammatory, and vascular-protective effects of flavonoids, the translation of these findings to human clinical practice warrants cautious interpretation. Current research supports the incorporation of flavonoid-rich foods such as berries and red grapes into Mediterranean-style dietary patterns for cardiovascular risk reduction (Delgado et al. 2020; Gardener et al. 2011). Specific flavonoids, including quercetin (500 mg/day) and resveratrol (150–300 mg/day), have potential as adjunctive therapies for established cardiovascular disease (Mirza et al. 2023; Teimouri et al. 2022; Ungurianu et al. 2024).

However, important clinical considerations must be addressed regarding flavonoid–drug interactions. Several flavonoids, particularly those found in grapefruit (naringenin), green tea (catechins), and certain supplements (quercetin), can significantly inhibit cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A4 (CYP3A4) enzymes, potentially altering the metabolism of commonly prescribed cardiovascular medications such as beta-blockers, statins, and calcium channel blockers (Bailey and

Dresser 2004; Sica 2006; Su et al. 2012). These interactions may lead to elevated drug levels and increased risk of adverse effects, necessitating careful dietary counselling for patients on these medications. In contrast, soy isoflavones appear to pose minimal risk of such interactions (Su et al. 2012).

The current evidence has several limitations that should be acknowledged. Much of the mechanistic data derives from animal studies, and human clinical trials remain limited in both number and duration. Furthermore, the bioavailability of dietary flavonoids varies considerably among individuals, and the optimal dosing for therapeutic effects requires further clarification. Future research should focus on well-designed human clinical trials to better establish the risk–benefit profile of flavonoid interventions in cardiovascular disease management, with particular attention to individual variability in absorption, metabolism, and potential drug interactions. Clinicians should balance the potential benefits of flavonoid-rich diets with these considerations when making dietary recommendations to cardiovascular patients. Notably, the co-consumption of probiotics and fermented products such as tofu, yogurt, and kefir enhances short-chain fatty acid production and maintains gut barrier function. However, well-designed human clinical trials are needed to confirm these effects.

8 | Oxidative Stress, Nitric Oxide, Flavonoids, and CVD

The major part of this section discusses the role of *flavonoids* in alleviating *oxidative stress* and *vascular nitric oxide*, two common contributing factors of cardiovascular disorders.

8.1 | Oxidative Stress and Its Central Role in Myocardial Damage

Oxidative stress serves as a key factor in myocardial tissue damage and exacerbation of the cardiac microenvironment (Neri et al. 2015). In chronic conditions with inflammatory components—including diabetes, dyslipidaemia, myocardial ischaemia, heart failure, and hypertension—where oxidative stress contributes to disease progression, polyphenol consumption has therapeutic potential for mitigating vascular complications. Chronic heart failure is commonly associated with mitochondrial dysfunction, which generates excessive oxidative stress and accelerates disease progression (Aimo et al. 2020). Reactive oxygen and nitrogen species (RONS), including nitric oxide, hydrogen peroxide (H_2O_2), and superoxide radicals ($\text{O}_2^{\bullet-}$), are produced primarily by damaged mitochondria and significantly contribute to cardiovascular pathology (Aimo et al. 2020; Figure 3A). These mechanisms have drawn researchers' attention to targeted interventions against oxidative stress, particularly through flavonoid supplementation, as potential strategies for prevention and treatment.

The existing evidence regarding the effects of flavonoids on oxidative stress follows a distinct hierarchy. Although human clinical studies in this field are limited yet promising, stronger epidemiological data and more extensive animal and in vitro studies are required to support these findings (Chen and

Zhang 2021; Liu, Luo, et al. 2024). Challenges in controlling dietary variables and long-term follow-up have constrained human studies. However, epidemiological studies have consistently demonstrated an inverse association between flavonoid-rich diets and cardiovascular outcomes. Animal models, particularly those used to study ischaemia–reperfusion injury, provide valuable mechanistic insights that help contextualise potential human applications (Kang et al. 2022; Li et al. 2011; Sopian et al. 2021; Zheng et al. 2022). In vitro studies have been highly effective in identifying molecular targets (Fusi et al. 2017; Scholz et al. 2010), although validation in more complex biological systems remains necessary.

8.2 | Nitric Oxides in Cardiovascular Health and Disease

Nitric oxide plays a dual role in cardiovascular health, acting as both a vasoprotective and a proinflammatory mediator depending on its source. In endothelial cells, eNOS converts L-arginine into NO, promoting vasodilation via guanylate cyclase activation in smooth muscle cells (Tetsuka et al. 2021). However, excessive NO production—particularly by iNOS in macrophages and neutrophils during inflammation—can lead to pathological vasodilation, hypotension, and oxidative stress, exacerbating CVD (Tripathi et al. 2007; Zhang, Hong, et al. 2023; Figure 3B, Table 5). Thus, therapeutic strategies that selectively increase eNOS-derived NO while suppressing iNOS overactivity are crucial for CVD management. This evidence highlights the delicate balance required in NO regulation, where maintaining physiological eNOS activity while controlling pathological iNOS induction represents a key therapeutic target for CVD management (Figure 3B).

8.3 | Antioxidant Properties of Flavonoids

Flavonoids are recognised as bioactive compounds with antioxidant properties that show significant vascular benefits and therapeutic potential in heart failure management (Zheng et al. 2022). The cardioprotective effects of these compounds are attributed primarily to their ability to neutralise reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Rudrapal et al. 2024; Chansiw et al. 2018; García Díaz et al. 2022; Han et al. 2023; Kang et al. 2022; Zhang, Jiang, et al. 2021). Additionally, flavonoids improve vascular function by modulating ion channels in endothelial and vascular smooth muscle cells (Fusi et al. 2017; Scholz et al. 2010). Structurally, the hydroxyl groups in flavonoids act as hydrogen donors, enabling them to effectively neutralise free radicals (Zheng et al. 2022). In smokers, long-term consumption of polyphenol-rich diets (fruits, vegetables, tea, and coffee) can provide protective effects against cigarette smoke-induced oxidative damage (Rudrapal et al. 2022).

Various studies have highlighted specific mechanisms through which flavonoids exert their effects. For example, compared with ascorbic acid, *Flos trollii* extract (often used in traditional Chinese medicine), which is rich in flavonoids, has demonstrated superior ROS scavenging capacity (Li et al. 2011; Zheng et al. 2022). Similarly, isoflavones found in *Astragalus*

TABLE 5 | Effects of flavonoids on the expression and activity of iNOS in macrophages stimulated with LPS.

S.No	Author/ Year/Ref	Cell name	LPS dose	LPS treatment time	Flavonoid treatment	Flavonoid concentration	Flavonoid incubation (time)	Evaluation method	Result
1	Wang/2020/ Wang et al. (2020)	RAW264.7	LPS 10 ng/ mL IFN- γ 20 ng/mL	NG	Luteolin	0, 5, 10, 20, 40 and 80 μ M	24 h	RTQ- PCR	Significant decrease in iNOS expression
2	Li/2016/Li et al. (2016)	RAW 264.7	LPS 50 μ mol/L	24 h	Bergenin (2), norbergenin (3), 11-O- galloylbergenin (4), purpurogallin	5, 25, 50 μ mol/L	ng	RTQ- PCR	Significant decrease in NO and iNOS expression
3	Tsai/2022/ Tsai et al. (2022)	RAW 264.7	50 ng/mL	6 h	Quercetin	1, 5, or 10 μ M	24 h	RTQ- PCR Western blot no	Gradual decrease of NO and iNOS expression
4	Park/2020/ Park et al. (2020)	RAW264.7	1 μ g/mL	24 h	Apigenin quercetin	Apigenin 20, 40, 60, 80, and 100 μ M Quercetin 15 μ M	24 h	Griess reagent RTQ- PCR	Decrease of NO and iNOS expression
5	Liao/2020/ Liao et al. (2020)	BMDM	200 ng/mL	24 h	Isoliquiritigenin	20 and 40 μ M	24 h	RTQ- PCR Western blot	Significant decrease in iNOS expression
6	Lee/2023/Lee et al. (2023)	RAW264.7 cells	200 ng/mL	2 h	<i>Allium cepa</i> L. peel extracts	80 μ g/mL <i>Allium cepa</i> extracted by hot water, 30% EtOH, and 50% EtOH	16 h	Griess reagent RTQ- PCR Western blot	significant decrease in iNOS expression
7	Cuong/2015/ Cuong et al. (2015)	RAW264.7	LPS (1 μ g/ mL)	18 h	Luteolin derived from <i>Scutellaria indica</i>	3,10, 30 μ M	30 min	Griess reagent Western blot	Gradual decrease of NO and iNOS on a concentration basis
8	Cho/2008/ Cho et al. (2008)	RAW264.7	0.1 μ g/mL	6–24 h	Xanthohumol	0.5, 1, 2.5, and 5 μ g/mL	24 h	Griess reagent RTQ-PCR Western blot	Decrease of NO and iNOS

(Continues)

TABLE 5 | (Continued)

S.No	Author/ Year/Ref	Cell name	LPS dose	LPS treatment time	Flavonoid treatment	Flavonoid concentration	Flavonoid incubation (time)	Evaluation method	Result
10	Chen/2023/ Chen, Ma, et al. (2023)	RAW264.7	100 ng/ mL LPS 10 ng/mL IFN- γ	3 h	Calycosin-7- glucoside	100, 50, and 25 μ M	3 h	RTQ-PCR Nitrate reductase method Western blots	Decrease of NO and iNOS
11	Yuasa/2012/ Yuasa et al. (2012)	RAW264	10 ng/ mL LPS	12 h	Sudachitin or Nobiletin	30 mM	24 h	2,3-diaminonaphthalene assay RTQ-PCR	Significant decrease of NO and iNOS
12	Jin/2024/Jin et al. (2024)	RAW264.7	LPS 1 μ g/ mL	24 h	Ficurine E and corylifonol derived from <i>Ficus erecta</i>	2.5, 5, 10, 20, and 30 μ M	1 h	Western blot Griess reagent	Significant decrease of NO and iNOS
13	Wei et al. (2025)	RAW264.7	200 μ g/mL	24 h	Engletin is derived from the <i>Smilax glabra</i> rhizome	0, 5, 10, or 20 μ M	2 h	RTQ-PCR	Significant decrease in iNOS
14	Lin/2021/ Lin, Kao, et al. (2021)	RAW 264.7 and human monocyte- derived macrophages	100 μ g/mL	6, 3, and 6 h	Tellimagrandin II	10, 25, and 50 μ M	30 min	Western blot RTQ-PCR	Pre and post- treatment of Tellimagrandin II dose-dependently decreased iNOS.
15	Tan/2022/ Tan et al. (2022)	RAW264.7	1 μ g/mL	12 h	Daidzin and daidzein	10, 30, 50, and 100 μ M	4 h	Griess reagent Western blot RTQ-PCR	Concentration- dependent decrease of NO and iNOS
16	Wu/2022/ Wu, Chen, et al. (2022)	RAW264.7	100 ng/mL	24 h	Wogonin, prenyl wogonin, geranyl wogonin, and farnesyl wogonin	50 μ M	6, 24, and 48 h	DCFH-DA flowcytometry Griess Test RTQ-PCR	Wogonin dose- dependently decreased NO and iNOS
17	Han/2023/ Han et al. (2023)	RAW264.7	1 μ g/mL	1 h	Gallic acid and rutin derived from <i>Hordeum vulgare</i> L	100, 300, or 500 μ g/mL	24 h	Griess reagent Western blot RTQ-PCR	Concentration- dependent decrease of NO and iNOS
18	Yu/2023/ Yu, Feng, et al. (2023)	RAW264.7	1 μ g/mL	24 h	Gallic acid	50 μ M, 100 μ M, and 200 μ M	24 h	Griess reagents Western blotting	Concentration- dependent decrease of NO and iNOS

(Continues)

TABLE 5 | (Continued)

S.No	Author/ Year/Ref	Cell name	LPS dose	LPS treatment time	Flavonoid treatment	Flavonoid concentration	Flavonoid incubation (time)	Evaluation method	Result
19	L. Li/2015/Li et al. (2015)	BMMs and RAW264.7	LPS (2 ng/ mL)	6, 12, 24 h	Herbacetin (HER)	10, 25, and 50 µM	30 min	Immunoblot analysis Griess reagents	By increasing HER concentration, no and iNOS decreased, but when it was treated with 50 µM HER, by passing over time, iNOS increased
20	Liu/2022/Liu et al. (2022)	RAW264.7	LPS (1 µg/ mL)	18 h	Naringin Cot	(10, 20, 40 µg/ mL) for	18 h	RTQ-PCR	Concentration dependently decreases iNOS

Abbreviations: BMDM, bone marrow-derived macrophages; DCFH-DA, 2',7'-dichlorofluorescein diacetate; EtOH, ethanol; IFN-γ, interferon-gamma; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NG, not given; RT-qPCR, real-time quantitative polymerase chain reaction.

trimestris, including formononetin and genistein, function as superoxide dismutases (SODs) by converting $O_2^{\bullet -}$ into H_2O_2 and O_2 (Yu, Caruso, et al. 2023). Flavonoids such as quercetin, eriodictyol, and naringin effectively reduce H_2O_2 -induced DNA damage and apoptosis (Aimo et al. 2020; Buranasudja et al. 2022; Remigante et al. 2022), confirming their cytoprotective role. Interestingly, extracts from *Sambucus nigra* and blueberries increase the activity of key antioxidant enzymes, including SOD, catalase (CAT), and glutathione peroxidase (Cicek et al. 2023; Wang et al. 2023). Collectively, these findings demonstrate that flavonoids exert comprehensive antioxidant protection through multiple mechanisms, ranging from direct free radical scavenging to the enhancement of endogenous antioxidant systems, making them promising candidates for cardiovascular protection.

8.4 | Flavonoids as Bimodal NO Regulators

Flavonoids exhibit a remarkable capacity to simultaneously modulate multiple NO-related pathways, making them particularly valuable for cardiovascular prevention and management. This bimodal regulation has been demonstrated through a hierarchy of evidence spanning from molecular studies to clinical trials. These plant-derived compounds could improve cardiovascular health through oxidative stress regulation, iNOS inhibition, and eNOS enhancement (Figure 3B, Table 5).

The foundation for understanding flavonoid-NO interactions is derived from cell culture studies, which precisely demonstrate how these compounds can both act as antioxidants and undergo auto-oxidation to generate superoxide radicals that neutralise excessive NO (Chandrasekaran and Karunasagar 2014). Building on these molecular insights, animal models and human studies confirm that specific compounds from *Croton linearis*, quercetin-rich extracts, and gallic acid effectively counteract pathological NO in inflammatory conditions such as LPS-induced macrophage activation (Chansiw et al. 2018; García Díaz et al. 2022; Han et al. 2023; Kang et al. 2022; Zhang, Jiang, et al. 2021; Table 5). Epidemiological data further support these findings, showing consistent cardiovascular benefits from flavonoid-rich diets (Anghel et al. 2024; Farraj et al. 2024; Lim et al. 2024; Olié et al. 2024).

Multiple flavonoid subclasses demonstrate potent suppression of inflammatory iNOS activity, as revealed through integrated research approaches. While in vitro studies first identified this mechanism, murine models have proven especially valuable for investigating how compounds derived from Pollen Typhae, *Allium cepa*, and *Nyctanthes arbor-tristis* maintain the critical balance between protective and inflammatory NO pathways in living organisms (Chen, Chen, et al. 2021; Hada et al. 2021; Lee et al. 2023; Sharma et al. 2024; Tsai et al. 2022; Figure 3B, Table 5). Clinical trials have validated these pre-clinical findings, with randomised controlled studies documenting measurable anti-inflammatory effects in human populations (Jennings et al. 2019). Additional compounds, including fisetin, scutellarein, quercetin, grape seed proanthocyanidin extract and butein, similarly attenuate iNOS activity across experimental models (Chen, Chen, et al. 2021; Hada

et al. 2021; Lee et al. 2023; Sharma et al. 2024; Tsai et al. 2022; Figure 3B, Table 5). The accumulated evidence positions flavonoids as unique therapeutic agents capable of fine-tuning NO homeostasis through simultaneous modulation of both protective and pathological pathways, offering a multifaceted approach to cardiovascular health maintenance. In contrast, another study demonstrated that 5,7-dihydroxyflavone (Chrysin, commonly found in plants, fruit and honey) exerts rapid antihypertensive effects through eNOS activation, as evidenced by both computational and experimental approaches (Shen et al. 2025). Molecular simulations revealed its specific binding to the active site of eNOS, whereas in vivo studies revealed that oral administration (10 mg/kg) significantly reduced blood pressure within 30 min in hypertensive rats, an effect completely abolished by eNOS inhibition (Shen et al. 2025). These findings position 5,7-dihydroxyflavone as a promising fast-acting antihypertensive agent that targets the eNOS pathway, with potential for acute blood pressure management without compromising hemodynamic stability (Shen et al. 2025).

8.5 | Clinical and Nutritional Applications

Several flavonoid-rich foods demonstrate significant clinical benefits through distinct molecular mechanisms. Onions, typhae pollen, and *Croton linearis*, which all contain quercetin, protect against DNA damage while modulating nitric oxide balance by inhibiting proinflammatory iNOS and enhancing endothelial eNOS activity, in addition to their ability to neutralise reactive oxygen and nitrogen species. For optimal effects, a daily intake of 100–200 g of raw or cooked onion is recommended, although caution is warranted in patients taking warfarin due to potential interactions with drug metabolism pathways. Citrus fruits, which are rich in naringin and eriodictyol, exhibit protective effects against endothelial apoptosis induced by oxidative stress, with clinical benefits observed at 2–3 daily servings of oranges, grapefruits, or related fruits.

Rutin, which is abundant in apples and buckwheat, operates through glutathione system activation, specifically increasing GSH-peroxidase activity to increase cellular glutathione levels, making this combination particularly relevant for diabetic patients exhibiting glutathione deficiency. Astragalus-derived compounds formononetin and genistein serve as natural superoxide dismutase mimetics, offering potential therapeutic value for individuals with compromised endogenous SOD activity. Various berries, including blueberries, grapes, and elderberries, demonstrate comprehensive antioxidant effects by simultaneously increasing key enzymes (SOD, catalase, and GPx) while suppressing inflammatory cytokines such as IL-6, representing a multifaceted approach to oxidative stress management.

The therapeutic potential of flavonoids can be maximised through personalised approaches that account for genetic variations in NOS enzymes and gut microbiome composition, which significantly influence individual responses. Genetic testing for polymorphisms in eNOS and other relevant enzymes may enable precise dose adjustments. Clinicians should be aware of potential drug interactions, particularly with anticoagulants

such as warfarin and cytochrome P450 inhibitors, necessitating careful INR monitoring in susceptible patients. Recent advances in drug delivery systems, including nanoencapsulation and liposomal formulations, offer promising solutions to bioavailability challenges; for example, liposomal quercetin demonstrates 50% greater absorption than conventional preparations do.

9 | Heart Failure

9.1 | Flavonoid Interventions in HF

Heart failure (HF), representing the end-stage consequence of myocardial infarction, constitutes a critical medical emergency that demands comprehensive therapeutic strategies. As documented by Minicucci et al. (2011) and Torabi et al. (2014), the complex pathophysiology of HF requires multifaceted treatment approaches (Minicucci et al. 2011; Torabi et al. 2014). Current evidence supporting flavonoid interventions spans multiple research levels, with human clinical data showing promising but limited results, whereas epidemiological studies consistently demonstrate inverse associations between flavonoid-rich diets and HF incidence. Complementary animal studies provide crucial mechanistic insights, and in vitro investigations elucidate fundamental molecular pathways involved. Notably, mouse models of HF have proven particularly valuable for studying cardiac remodelling processes that accurately mirror human pathophysiology within compressed experimental timelines.

Emerging clinical evidence highlights the significant potential of flavonoid supplementation in improving HF outcomes through diverse pathological mechanisms. Research by Li, Zhang, et al. (2022) demonstrated that daidzein, a soy-derived flavonoid, enhances post-HF cardiac function by improving the left ventricular ejection fraction while concurrently reducing cardiac inflammation, oxidative stress, apoptosis, and fibrosis. These beneficial effects appear to be mediated through improved cardiac energy metabolism and restored mitochondrial function (Figure 3A). Other polyphenolic compounds, such as urolithin B, show clinical promise by mitigating NF- κ B-mediated inflammation, whereas gallic acid and resveratrol exert cardioprotective effects via potent antioxidant activities that suppress the production of ROS, including H_2O_2 and $O_2^{\bullet-}$ (Najjar and Feresin 2021). Cyanidin contributes to additional myocardial protection by preventing calcium overload and cytochrome c leakage, thereby inhibiting apoptosis and fibrosis (Najjar and Feresin 2021). The clinical relevance of these findings is underscored by the well-established role of oxidative stress, characterised by excessive free radicals and antioxidant deficiency, in HF progression (Pham-Huy et al. 2008).

The therapeutic applications of flavonoid-rich supplements extend well beyond their direct antioxidant effects. These bioactive compounds demonstrate multifaceted cardioprotective mechanisms that include modulation of the renin–angiotensin system (RAS) through ACE inhibition, potent anti-inflammatory actions, and endothelial protection (Husain 2015). This broad spectrum of activity makes flavonoid supplementation particularly valuable for preventing and managing various cardiovascular conditions, including coronary heart disease, hypertension, myocardial

hypertrophy, and HF, in at-risk populations. Importantly, as highlighted by Li et al. (2021), the bioavailability and efficacy of these compounds are intimately connected to the GM composition, since flavonoid-metabolising enzymes in the intestine significantly influence their absorption and metabolic transformation. This relationship has critical clinical implications, particularly given the established association between GM dysbiosis and HF progression (Bratseth et al. 2025; Matacchione et al. 2024).

9.2 | Gut Microbiota, Flavonoids, and HF

Contemporary research has revealed distinct GM alterations in HF patients compared with healthy individuals, including increased intestinal permeability ('leaky gut'), which is correlated with disease severity (Mahenthiran et al. 2024; Pasini et al. 2016). This pathological gut environment leads to systemic endotoxemia, chronic inflammation, and worsened HF outcomes (Mahenthiran et al. 2024; Pasini et al. 2016). Clinical observations have revealed elevated levels of pathogenic microbes (*Candida*, *Campylobacter*, and *Shigella*) in HF patients, suggesting that GM modulation represents a viable therapeutic target (Pasini et al. 2016). Preclinical studies have demonstrated that specific flavonoid-rich interventions can beneficially reshape the GM composition. For example, Wu, Zhang, et al. (2022) reported that *Arctium lappa* L. polyphenols significantly reduce *Proteobacteria* and *Escherichia-Shigella* populations while increasing beneficial SCFA-producing bacteria such as *Lactobacillaceae* and *Ruminococcaceae* in HF models. Resveratrol exhibits comparable GM-modulating effects, increasing Bacteroidetes while decreasing Firmicutes, changes associated with improved energy metabolism and reduced HF-related fatigue (Sung et al. 2017; Table 4, Figure 2).

From a pathophysiological perspective, HF-induced myocardial hypoperfusion initiates a cascade of detrimental processes, including mitochondrial dysfunction, oxidative damage, apoptosis, and fibrosis (Marín-García et al. 2013; Nojiri et al. 2006; Piek et al. 2016; Shah et al. 2021; Figure 3A). Clinical evidence indicates that flavonoids such as daidzein, cyanidin, gallic acid, and resveratrol, along with flavonoid-rich products such as *Arctium lappa* L can counteract these processes through multiple mechanisms (Gang et al. 2024; Li, Zhang, et al. 2022; Lin, Meng, et al. 2021; Liu, Zhu, et al. 2024; Wu, Zhang, et al. 2022; Yan et al. 2019).

9.3 | Dietary Sources and Their Therapeutic Applications

The current evidence suggests that soy-based foods such as tofu and soybeans, which are rich in daidzein, may offer clinically meaningful cardiovascular benefits by improving the left ventricular ejection fraction while reducing cardiac inflammation and fibrosis (Li, Zhang, et al. 2022; Shu et al. 2022). The optimal daily intake appears to be approximately 40 g of whole soy flour, which can be obtained from various soy products, such as 200 g of tofu, 300 mL of soy milk, or 50 g of tempeh (Liu et al. 2014). Other flavonoid-rich foods, including pomegranate, berries, and walnuts, serve as precursors for urolithin B, a compound that inhibits NF- κ B-mediated inflammatory pathways involved

in heart failure progression (Najjar and Feresin 2021; Selma et al. 2018).

The combination of grapes, green tea, and berries provides resveratrol and gallic acid, which are compounds with demonstrated antioxidant properties and beneficial effects on the composition of the gut microbiota (Iqbal et al. 2022; Shi et al. 2003). Similarly, red-coloured fruits such as blackberries and cherries contain cyanidin, which helps prevent calcium overload in cardiomyocytes and reduces apoptosis (Mattera et al. 2017; Najjar and Feresin 2021; Perveen et al. 2014). Burdock root has shown potential in modulating the gut microbiota by reducing pathogenic bacteria while promoting beneficial SCFA-producing microbes (de Souza et al. 2022).

When these dietary interventions are implemented, a comprehensive "heart-gut axis" approach combining multiple flavonoid sources appears most effective. Patients should adhere consistently to this dietary intervention to achieve observable benefits, as the cardioprotective effects of flavonoid modulation typically require sustained implementation. However, clinicians should be aware of potential interactions with common cardiac medications, including possible hypotension with ACE inhibitors/ARBs and altered absorption with beta-blockers and digoxin.

While promising, much of the supporting evidence comes from preclinical studies, and these dietary approaches should currently be considered adjuncts to guideline-directed medical therapy rather than standalone treatments. Further clinical research is needed to better establish efficacy, optimal dosing, and long-term outcomes in human populations.

10 | Limitations and Future Directions

Flavonoids—widely studied for their anti-inflammatory, antioxidant, and vasodilatory effects—have emerged as promising agents in cardiovascular health. However, the evidence connecting flavonoid intake, gut microbiota modulation, and improvement in CVD outcomes remains fragmented, heterogeneous, and difficult to translate into clinical practice. The following key limitations must be addressed before these compounds can be confidently integrated into cardiovascular treatment protocols. These critical limitations include the following:

- High interindividual variability in the response to flavonoids is a major challenge. Individuals metabolise flavonoids differently, largely due to variations in the gut microbiota composition, genetic polymorphisms such as UGTs and COMT, and differences in diet. This variability makes it difficult to generalise research findings or establish universal effective doses, particularly because patients with different cardiovascular conditions—such as atherosclerosis and heart failure—may have unique microbiota profiles and metabolic capacities.
- Owing to the lack of long-term and high-quality human trials, while short-term trials have shown improvements in surrogate markers such as blood pressure, lipid profiles, and

inflammatory cytokines, robust long-term randomised controlled trials with hard cardiovascular endpoints (e.g., MI, stroke, hospitalisation, death) are still scarce. Many studies rely heavily on animal models (e.g., ApoE^{−/−} and SHR), which do not fully replicate human physiology or microbiota diversity.

- Flavonoids generally have poor oral bioavailability, often less than 20%, because they are rapidly metabolised in the liver and gut. Furthermore, studies have used inconsistent dosing protocols, ranging from isolated, high-purity compounds to whole-food interventions. This variability makes it difficult to develop standardised clinical recommendations.
- Inadequate understanding of drug–flavonoid–microbiota interactions: Patients with cardiovascular diseases frequently take multiple medications (e.g., statins, beta-blockers, and ACE inhibitors). Potential interactions between these drugs and flavonoids—whether competitive, synergistic, or antagonistic—are poorly understood. Moreover, how these combinations influence the gut microbiota and systemic inflammation is virtually unexplored.
- Most studies use 16S rRNA sequencing, which provides information about microbial taxonomy but does not offer functional insights. This approach cannot differentiate between live and dead microbes or determine how flavonoids influence microbial functions such as short-chain fatty acid production or TMAO synthesis. In addition, many studies fail to monitor important microbiota-related biomarkers, including LPS, nitrotyrosine, or microbial-derived metabolites.
- Although preclinical studies in rodents have demonstrated the protective effects of flavonoids against atherosclerosis, hypertension, and ischaemia, significant differences in flavonoid metabolism and microbiota structure limit the translatability of these findings to humans.

11 | Strategic Future Research Priorities

Moving forward, future research in this field must prioritise integrative and personalised approaches that bridge current translational gaps. One critical direction involves the application of multiomics platforms—including metagenomics, metabolomics, transcriptomics, and nutrigenomics—to stratify cardiovascular patients on the basis of individual differences in gut microbiota composition, flavonoid metabolism, and host genetic polymorphisms. This will allow researchers to tailor dietary interventions more precisely, optimising efficacy on the basis of patient-specific characteristics such as being a high- or low-SCFA producer or carrying specific UGT1A1 or COMT genotypes. Emerging evidence suggests that the time of day at which flavonoids are consumed may influence their bioactivity and interaction with the microbiota. Future studies should explore whether timing interventions (e.g., morning vs. evening intake) enhance the cardiometabolic benefits of flavonoids, particularly in conditions such as nocturnal hypertension or heart failure. Most existing research has focused on the gut microbiota, yet the oral microbiome plays a key role in cardiovascular risk via nitrate metabolism, inflammation, and endothelial function.

Investigating whether flavonoids can modulate the oral microbiota may lead to new preventive strategies for atherosclerosis and hypertension.

Another important focus should be the investigation of how flavonoids interact with commonly prescribed cardiovascular medications such as statins, ACE inhibitors, and beta-blockers. By studying the pharmacodynamic and microbiota-mediated effects of such combinations, researchers can determine whether flavonoids enhance, attenuate, or interfere with drug efficacy or safety. These combination studies should ideally be conducted in randomised controlled trials that assess not only cardiovascular parameters but also gut microbial composition and function. Flavonoids may impact not only vascular and immune function but also autonomic nervous system regulation. Given the strong gut–brain–heart axis, future research should examine whether flavonoid intake can reduce anxiety, depression, and autonomic dysfunction in cardiovascular patients, potentially improving both psychological and cardiac outcomes.

Additionally, the development of advanced delivery systems is urgently needed. Since most flavonoids undergo extensive first-pass metabolism and suffer from low oral bioavailability, new formulations such as colon-targeted or encapsulated flavonoid supplements may improve their stability and effectiveness. These delivery methods help maximise the interaction of flavonoids with the colonic microbiota, enhancing the production of beneficial microbial metabolites such as urolithins and phloretin, which have shown independent anti-inflammatory and cardioprotective effects.

Furthermore, researchers should explore microbiota engineering strategies as part of cardiovascular care. For example, combining faecal microbiota transplantation from metabolically healthy donors with flavonoid-rich diets may facilitate long-term microbiota remodelling in high-risk or treatment-resistant patients. In addition, isolating and administering microbial-derived postbiotics could offer a novel, stable, and targeted therapeutic strategy, bypassing the variability in host metabolism.

In parallel, mechanistic studies are needed to better understand the role of the gut barrier and its contribution to cardiovascular diseases, particularly hypertension and heart failure. Flavonoids may play a key role in restoring epithelial integrity, reducing LPS translocation, and thereby attenuating systemic inflammation and sympathetic nervous system overactivity—pathways that are increasingly implicated in the progression of cardiovascular pathology.

Finally, future research must extend beyond current population limitations and include diverse and high-risk cohorts. Most existing studies focus on relatively healthy Western populations, which restricts the generalisability of the findings. There is an urgent need for trials in elderly individuals, non-Western populations with different dietary patterns and microbiota profiles, and patients with comorbidities such as obesity, diabetes, or chronic kidney disease. In these groups, personalised flavonoid-based strategies may offer particularly significant benefits but also pose unique challenges in terms of absorption, metabolism, and drug interactions.

By addressing these research priorities with a coordinated, multidisciplinary approach, the field can move toward establishing flavonoid-based, microbiota-targeted interventions as a meaningful component of comprehensive cardiovascular disease management.

12 | Conclusion

Eating habits, consuming fruits and vegetables, and using some herbal and traditional medicines that are rich in flavonoids and polyphenols are associated with alterations in the composition of the GM, which is an important factor affecting cardiovascular health and disease. Despite bioavailability limitations (2%–20%), epidemiological studies consistently show that the regular consumption of flavonoid-rich foods is associated with significant cardiovascular benefits. This apparent paradox can be explained by multiple mechanisms: (1) microbial transformation of flavonoids into more bioavailable active metabolites, (2) cumulative effects of chronic intake, (3) synergistic interactions with other food components, and, crucially, (4) direct prebiotic effects in the gastrointestinal tract. Even non-absorbed flavonoids can modulate the composition of the gut microbiota by promoting symbiotic bacteria (e.g., *Bifidobacterium* and *Lactobacillus*) while inhibiting pathogens (e.g., *Clostridium* spp.). This microbiota-mediated immunomodulation reduces systemic inflammation and improves metabolic parameters, thereby indirectly supporting cardiovascular health. Thus, while parent flavonoid absorption may be limited, both microbial metabolism and local prebiotic actions contribute to the observed cardioprotective effects. The composition of the gut bacteria and their products, including LPS, TMAO, SCFAs, flavonoid-metabolising enzymes, and bile acids, can affect epithelial barrier integrity and permeability; systemic and local inflammation; and the absorption of flavonoids, lipids, and cholesterol, which could be a determining factor in cardiovascular health. Among the factors that retain the structure of the GM, flavonoids, through their prebiotic function, can expand the population of symbiotic bacteria, including *Lactobacillus* and *Bifidobacterium*, and limit pathogenic bacterial growth. It seems that not only flavonoids but also the microbiota affects the absorption of flavonoids, as they secrete a great extent of flavonoid-metabolising enzymes. The other major factor affecting the metabolism of flavonoids are the host genes, making the gut environment a suitable habitat for either pathogenic or symbiotic bacteria, the dominant flavonoid metabolisers.

Current evidence from preclinical and clinical studies suggests that flavonoids may contribute to balancing the gut microbiota, enhancing intestinal epithelial barrier function, and restoring cardiomyocyte mitochondrial activity through their prebiotic, anti-inflammatory, and antioxidant properties. However, these findings are primarily derived from animal studies and short-term human trials, and their effects are influenced by individual factors such as genetic variability and gut microbiome composition. While flavonoids show promise as potential agents for cardiovascular disease prevention and management, the existing evidence remains insufficient for definitive conclusions about their clinical efficacy across diverse populations. Therefore, future research should focus on long-term human studies and better characterise drug–flavonoid–microbiome interactions.

Author Contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. The individual contributions are as follows: **Parisa Ahmadi**: writing – original draft, writing – review and editing, investigation, and conceptualisation; **Soroush Taherkhani**: visualisation, figure design; **Atousa Janzadeh**: writing – review and editing, manuscript revision; **Maryam Honardoost**: writing – review and editing, manuscript revision, conceptualisation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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