Received: 17 April 2023 | Revised: 19 August 2023 | Accepted: 30 August 2023

DOI: 10.1002/elsc.202300065

Engineering in Life Sciences

REVIEW

# Flavonoids, gut microbiota, and host lipid metabolism

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**Funding information**
Sichuan Science and Technology Programmes, Grant/Award Numbers: 2021JDYZ0001, 2021ZDZX0009; Scientific

## Abstract

Flavonoids are widely distributed in nature and have a variety of beneficial biological effects, including antioxidant, anti-inflammatory, and anti-obesity effects. All of these are related to gut microbiota, and flavonoids also serve as a bridge between the host and gut microbiota. Flavonoids are commonly used to modify the composition of the gut microbiota by promoting or inhibiting specific microbial species within the gut, as well as modifying their metabolites. In turn, the gut microbiota extensively metabolizes flavonoids. Hence, this reciprocal relationship between flavonoids and the gut microbiota may play a crucial role in maintaining the balance and functionality of the metabolism system. In this review, we mainly highlighted the biological effects of antioxidant, anti-inflammatory and antiobesity, and discussed the interaction between flavonoids,

**Abbreviations:** ADRB3, 3-adrenergic receptor; AHR, aryl hydrocarbon receptor; Akt, protein kinase B; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, adenosine monophosphate activated protein kinase; ApoE$^{-/-}$, ApoE-deficient; AST, aspartate aminotransferase; BAs, bile acids; BAT, brown adipose tissue; BSH, bile salt hydrolase; cAMP, cyclic adenosine monophosphate.; CAT, catalase; CCK, cholecystokinin; COX, cyclooxygenase; CREB, cAMP-response element binding protein; CYP1A1, cytochrome P450, family 1, subfamily A, polypeptide 1; *E. coli*, *Escherichia coli*; ERK, extracellular regulated protein kinases; F/B, ratio of *Firmicutes* to *Bacteroidetes*; FGF15, fibroblast growth factor 15; FGF19, fibroblast growth factor 19; FXR, nuclear receptor farnesol X receptor; GLP-1, glucagon-like peptide-1; GPR41, G-protein-coupled receptors 41; GPR43, G-protein-coupled receptors 43; GSH-Px, glutathione peroxidase; GTF-1, glucosyltransferase-1; HO, hydroxyl radicals; HO-1, heme oxygenase-1; HSP90, heat-shock protein90; IL-18, interleukin-18; IL-1$\beta$, interleukin-1$\beta$; IL-6, interleukin-6; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LBPC, larch bark proanthocyanidins; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; LXR, liver X receptor; MDA, malondialdehyde; MRSA, methicillin-resistant *S. aureus*; NA, norepinephrine; NAFLD, non-alcoholic fatty liver disease; NF-$\kappa$b, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain containing 3; NO·, nitric oxide free radicals; NOX4, recombinant nicotinamide adenine dinucleotide phosphate oxidase 4; Nrf2, Nuclear factor erythroid 2-related factor 2; O2·-, superoxide anion free radicals; PCOA, principal coordinate analysis; PGC-1$\alpha$, peroxisome proliferators-activated receptor $\gamma$ coactivator 1 alpha; PI3K, phosphatidylinositol3-kinase; PPARs, peroxisome proliferator-activated receptors; PYY, peptide YY; QS, microbial population sensing; RO·, alkoxy radicals; ROO·, alkyl peroxyradicals; ROS, reactive oxygen species; *S. aureus*, *Staphylococcus aureus*; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; SREBPs, sterol regulatory element-binding proteins; TC, total cholesterol; TG, triglycerides; TGR5, membrane receptor G protein-coupled bile acid receptor 5; Th17, T helper cell 17; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; TLR6, Toll-like receptor 6; TNF-$\alpha$, tumor necrosis factor-$\alpha$; UC, ulcerative colitis; UCP1, uncoupling protein 1; WAT, white adipose tissue; XO, xanthine oxidase.

Research Project of Hunan Provincial Education Department, Grant/Award Number: 20C0950; Postgraduate Scientific Research Innovation Project of Hunan Province, Grant/Award Number: CX20210656

gut microbiota and lipid metabolism, and elaborated the potential mechanisms on host lipid metabolism.

**KEYWORDS**
flavonoids, gut microbiota, lipid metabolism, metabolites, polyphenol

## 1 | INTRODUCTION

In recent decades, with the improvement in living standards, most people's dietary structure and habits have undergone significant changes with the high intake of high sugar, high fat and refined processed foods, sedentary work, and lack of exercise. The physiological processes associated with lipid metabolism encompass the dysregulated synthesis and metabolism of fatty acids and cholesterol [1–3]. Diseases, including, obesity, type 2 diabetes, hyperlipidemia, hyperglycemia, atherosclerosis, nonalcoholic fatty liver disease, asthma, and osteoarthritis arise from disorders in lipid metabolism [4, 5]. More than 2.1 billion adults are estimated to be overweight or obese worldwide; for instance, between 2015 and 2016, the prevalence of obesity in the United States reached nearly 40% (National Health and Nutrition Examination Survey), which was the main health challenge for humans [6, 7]. Disorders of lipid metabolism are accompanied by many abnormal physiological processes, including oxidative stress, chronic inflammation, depression, and microecological destruction. These factors will accelerate the deterioration of the host's metabolic syndrome [8, 9]. Nevertheless, the modulation mechanisms and therapeutic solutions for lipid metabolism are not yet entirely clear; therefore, deeper insight into lipid metabolism modulation methods and their mechanisms is vital to alleviate the risk of incidence and mortality of related diseases.

Flavonoids are a large class of heterocyclic organic compounds produced by natural plant secondary metabolism. It is widely found in fruits, vegetables, and beans in the form of flavonoid glycosides. They play important probiotic effects on antioxidation, antibacterial and anti-inflammatory, antitumor, immune regulation, and gut health [10, 11]. Following intake, flavonoids are metabolized by gut microbiota and host tissues; in particular, hindgut microbiota are able to improve the bioavailability of flavonoids, but individual differences exist [12]. An increasing number of studies have described the ability of flavonoids to inhibit disorders of lipid metabolism and are associated with the correction of oxidative stress, inflammation, and gut microbiota disorders [13–15]. In particular, gut microbiota and host health have been extensively studied, but the mechanism by which flavonoids regulate host lipid metabolism through gut microbiota is unclear.

Growing evidence indicates that the gut microbiota contributes to host metabolism and that dysbiosis is closely associated with metabolic disorders that worsen the pathogenesis process [16, 17]. For example, obese individuals usually have a lower relative abundance of *Akkermansia muciniphila*, *Bacteroidetes*, and *Bifidobacterium,* and a higher abundance of *Firmicutes*, *Fusobacteria*, and *Proteobacteria* [18]. Several studies have also transplanted the gut microbiota from obese mice into the gut of lean mice, resulting in weight gain and an imbalance in lipid metabolism. Conversely, transplanting the gut microbiota from lean to obese mice produced weight loss and reversed lipid metabolism disorders [19]. More interestingly, germ-free mice fed a high-fat diet failed to gain weight [20]. This shows that gut microbiota may play an important role in host lipid metabolism.

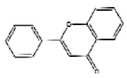
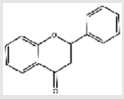
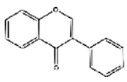
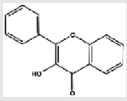
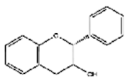
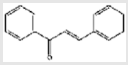
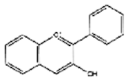
In this review, we highlight the biological effects of flavonoids in terms of antioxidant, antibacterial, and anti-inflammatory properties and describe the current understanding of how flavonoids affect the gut microbiota, discussing how the interaction between dietary flavonoids and the gut microbiota modulates host lipid metabolism.

## 2 | THE PHYSIOLOGICAL FUNCTIONS OF FLAVONOIDS

Flavonoids are a large subclass of polyphenol compounds and more than 8,000 flavonoid molecules. Their basic structure consists of one heterocyclic pyran ring (C) and two aromatic rings (A and B), forming a 15-carbon phenylpropane nucleus with a C6 -C3 -C6 structure [21, 22]. According to the degree of oxidation of the three-carbon bond (C3), whether C3 is cyclized, the connection position of the benzene ring and substituents, and the form of substituents on C3, it is divided into the following subcategories (Table 1): flavone, flavanone, isoflavone, flavonol, flavanol, flavanonol, chalcone, and anthocyanin.

Whereas flavonoids are diverse and exhibit a range of biological activities (Table 2), we focused on three biological effects of antioxidant, anti-inflammatory, and anti-obesity to understand the flavonoids, and they are closely

**TABLE 1** The main basic structures and examples of natural flavonoids.

| Flavonoids subclasses | Structure | Examples | Food source |
|---|---|---|---|
| Flavone |  | Apigenin, luteolin, baicalein, chrysin | Cabbage, wheat sprouts, celery, chamomile, carrot |
| Flavanone |  | Hesperetin, naringenin, holy grass, glycyrrhizin | Naringin, naringenin, eriodictyol, hesperidin |
| Isoflavone |  | Daidzein, genistein, soy isoflavones, glycitein | Soybean, kudzu, alfalfa, red clover |
| Flavonol |  | Quercetin, kaempferol, myricetin | Berries, grapes, tomatoes, onions, kale, broccoli, tea, red wine |
| Flavanol |  | Theaflavins, catechins, epicatechins, theafucins | Red wine, grape skin, tea, apricot, apple, cherry, cocoa |
| Chalcone |  | Licorice Chalcone, phloridin, aureoflocin | Licorice, grapefruit peel, orange peel, eyesight leaves |
| Anthocyanin |  | Anthocyanin, cyanidin, delphinium pigment, anthocyanin | Blueberry, eggplant, cherry, cabbage, elderberry, red onion |

connected to lipid metabolism. Importantly, the physiological functions of flavonoids are mostly governed by their structures; for example, the more phenolic hydroxyl groups there are, the stronger the antioxidant activity, and biological activity is improved by methylation and hydroxylation modification [23, 24].

## 2.1 | Antioxidants

Oxygen atoms, as the final electron acceptors of the electron flow system, are constantly involved in redox reactions in aerobic organisms, but when excess reactive oxygen radicals (such as ROO·, RO·, O2·-, HO·, and NO·

**TABLE 2** Physiological effects of flavonoids.

| Effect | Example flavonoids | Reference |
|---|---|---|
| Antioxidant | Quercetin, xanthohumol, baicalein, catechin, procyanidin | [28, 37, 78] |
| Antibacterial | Procyanidin, quercetin, baicalein, genistein | [35, 79–81] |
| Anti-inflammatory | Xanthohumol, dihydroretrochalcones, quercetin | [82–84] |
| Anticancer | Quercetin, procyanidin | [85, 86] |
| Anti-depression | Epigallocatechin-3-gallate, puerarin, genistein | [87, 88] |
| Anti-obesity | Quercetin, cyanidin, myricetin | [54, 73, 76, 89] |
| Analgesic | Loureirin, cochinchinemin, hesperidin | [90, 91] |
| Antiviral | Apigenin, luteolin, kaempferol | [92] |
| Wound healing | Apigenin, baicalein, quercetin | [93–95] |
| Hair repair | Luteolin, formononetin, epigallocatechin-3-gallate | [96–98] |
| Anti-type 2 diabetes | Hesperetin, quercetin, luteolin | [99, 100] |
| Anti-atherosclerosis | Kaempferol, myricetin, cyanidin | [101–103] |

are produced beyond their own scavenging capacity, disturbing the normal oxidative balance of the organism, damaging cells or tissues, causing oxidative stress, affecting normal life processes and even endangering life and health) [25]. The normal oxidative balance of the organism can be disturbed, destroying cells or tissues, causing oxidative stress, affecting normal life processes, and even endangering life health. In this case, such as disorders of lipid metabolism, although the endogenous antioxidant system can maintain the formation of free radicals and scavenge some of them to a certain extent, there are still some reactive oxygen radicals that are not scavenged and are continuously accumulated, so dietary antioxidants are needed to reduce the cumulative effect of oxidative damage throughout the life cycle as well as to repair damaged tissues [26].

Flavonoids, as a kind of phenolic compound, contain a large number of phenolic hydroxyl groups in their structure, which are a good class of hydrogen-donating antioxidants and scavengers of reactive oxygen species and reactive nitrogen species in vivo and in vitro [27]. Due to the structural uniqueness of flavonoids, their capacity to scavenge free radicals is highly unique and changeable. For example, in comparison to the A ring, the hydroxyl groups in the B and C rings contribute substantially to the antioxidant activity of quercetin and glucoside [28]. Among the five flavonoids (wogonin, baicalin, baicalein, catechin, and procyanidin B2), catechin exhibited the greatest 1,1-diphenyl-2-picrylhydrazyl scavenging activity, followed by procyanidin B2, baicalein, baicalin, and wogonin. Catechin had the greatest superoxide scavenging efficacy, followed by baicalein, procyanidin B2, and baicalin. Only baicalein demonstrated a strong ability to scavenge hydroxyl radicals [29]. Similarly, a study showed that quercetin 7-rhamnoside exhibited strong scavenging effects on 1,1-diphenyl-2-picrylhydrazyl, 2,20-azinobis-(3-ethylbenzthiazolin-6-sulfonate), and ferrous reducing antioxidant power free radicals in vitro [30]. Therefore, group modification may be a new strategy to improve the antioxidant properties of some flavonoids.

Metal ions such as iron and copper can generate reactive free radicals during physiological processes, eliciting redox imbalances to facilitate an increase in ROS. Thus, chelation of transition state ions contributes to antioxidant properties [31]. Nevertheless, some studies show that chelating divalent ions has more favorable antioxidant properties than chelating trivalent ions, which may be related to the inhibition of the Fenton reaction [32]. Flavonoid chelation of metal ions is usually related to the location and amount of hydroxyl and carbonyl groups. For example, quercetin can chelate various divalent metal ions, such as Fe, Cu, Al, Co, Cr, and Pb, thereby reducing the production of reactive free radicals [33, 34]. The chelation state is influenced by a variety of conditions, such as the structure of the flavonoid, the pH of the environment in which the reaction takes place, the solvent, and the stoichiometric relationship, making it difficult to achieve optimal chelation of flavonoids with metal ions [32].

The regulation of process enzymes such as COX, XO, GSH-Px, SOD, and CAT is also an important way in which flavonoids exert their antioxidant properties [22]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master transcriptional regulator of redox homeostasis and influences the expression of downstream antioxidant genes. In a soybean oil-induced oxidative stress model in broiler chickens, quercetin ameliorated oxidized oil–induced oxidative stress by upregulating the transcription of *Nrf2* and its downstream genes, such as *CAT*, *SOD1*, *GSH-Px2*, *HO-1*, and *thioredoxin*, and decreased plasma MDA levels to restore redox balance [35]. Dong et al. administered a high-fat diet to ApoE$^{-/-}$ mice and treated them with alpinetin and found reduced atherosclerotic lesions by increasing nuclear translocation to activate *Nfr2*, promoting thiol-dependent glutathione and thioredoxin antioxidant systems in macrophages to reduce ROS production [36]. Similarly, flavonoids have shown positive antioxidant enzyme modulation in other disease models to restore redox reaction homeostasis [30, 37].

The flavonoid mechanism of action is roughly as follows (Figure 1): (1) supplying electrons to neutralize free radicals; (2) chelating minerals to prevent the generation of reactive oxygen species and free radical production; and (3) activating or upregulating antioxidant signaling pathways to increase the activity and levels of antioxidant enzymes.

## 2.2 | Anti-inflammatory

Disorders of lipid metabolism manifest pathologically as chronic inflammation, causing damage to the organism [38]. Many studies have shown that flavonoids can have an anti-inflammatory effect in many different ways. The anti-inflammatory activity of flavonoids is structure dependent; for example, flavonoids with a 3- or 4-position hydroxyl substituent on the B ring act as selective lipoxygenase inhibitors, whereas flavonoids with five or more methoxy substituents have a greater inhibitory activity against phosphodiesterase [39].

NF-κb (nuclear factor kappa-light-chain-enhancer of activated B cells) is important in the inflammatory response because it activates the release of proinflammatory factors such as IL-6 and TNF-α. In the Salmonella typhimurium infection RAW264.7-cell model, Salmonella typhimurium activated the TLR4/AMPK/NF-κb signaling pathway, increased cellular autophagy, and increased levels of IL-1β, IL-6, IL-8, TNF-α, and ROS, which

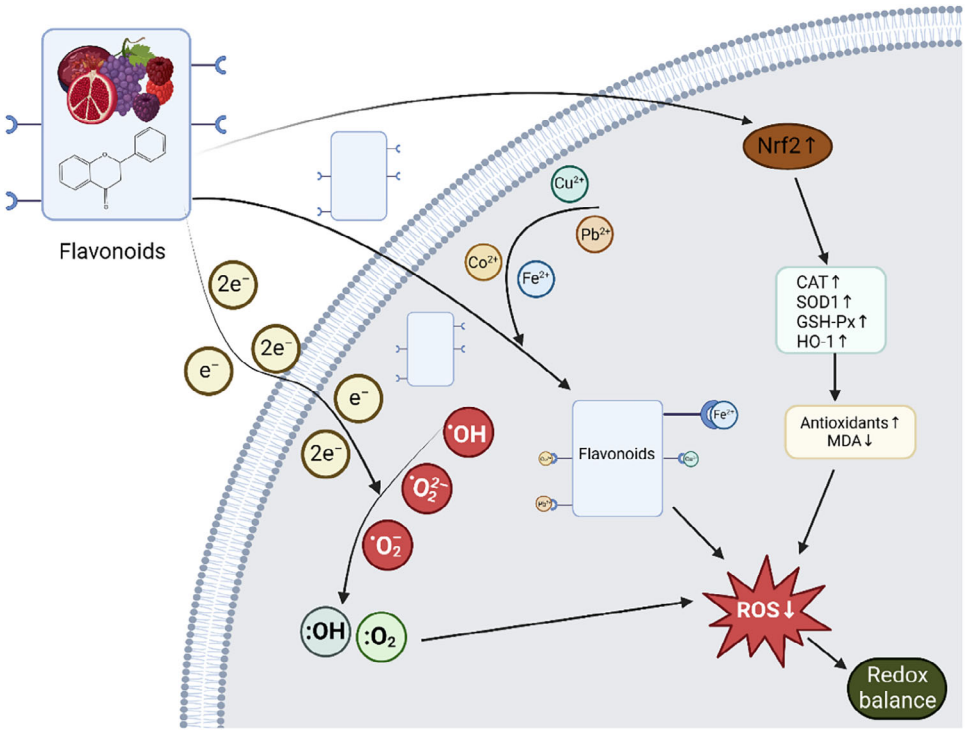



**FIGURE 1** Antioxidant pathways of flavonoids.

were corrected by treatment with baicalein [40]. Cellular autophagy, ROS, and inflammation promote each other. Additionally, baicalin has been shown to relieve mycoplasma fowlis-induced pneumonia in hens by decreasing NF-$\kappa$b-p65 nuclear translocation mediated by TLR6 [41]. While both Th17 and Treg cells are helper T cells, their roles in controlling inflammation are quite distinct. Th17 cells produce proinflammatory cytokines, whereas Treg cells suppress immune responses. In dextran sodium sulfate-induced colitis, sanguinarine, a potential aryl hydrocarbon receptor activator, increased *CYP1A1* expression, promoted dissociation of the AHR/HSP90 complex and induced AHR nuclear translocation to upregulate *CREB* and *Foxp3* promoter region association and Treg differentiation-associated *mDNMT-1* expression in CD4+ T cells, restoring the ratio of Th17 to Treg cells and ameliorating colitis [42]. NLRP3 inflammatory vesicles recruit pro-caspase-1, modulate caspase-1 activity and activate caspase-1. When activated, caspase-1 cleaves the inactive proinflammatory cytokines pro-IL-1$\beta$ and pro-IL-18 to mature body IL-1$\beta$ and IL-18 and mediates apoptosis [43]. Luteolin reduced LPS-stimulated inflammatory damage in H9c2 cells by downregulating *Nlrp3*, decreasing TNF-$\alpha$, IL-1, IL-18, and IL-6 production, and inhibiting iNOS and NOX4 protein expression [44]. Additionally, flavonoids can help reduce inflammation by controlling gut microbiota and altering the metabolism of gut microbiota [45, 46].

## 2.3 | Antiobesity

Obesity is a prevalent and complicated worldwide metabolic illness syndrome marked by an excessive buildup of fat, and its prevalence is increasing year after year as material living standards rise. Obesity can be brought on by a number of things, especially in excessive consumption of sugar and fat, inactivity, and genetics. Patients with obesity are also commonly found to have abnormal physiological conditions such as insulin resistance, chronic inflammation, and oxidative stress, which raises their risk of developing diseases such as diabetes, hyperlipidemia, hyperglycemia, and chronic low-grade inflammation [47]. Numerous studies have demonstrated that flavonoids have an anti-obesity impact with almost no negative effects when compared to pharmaceutical weight loss medications [48, 49]. Additionally, flavonoids are $\alpha$-glucosidase inhibitors and insulin sensitizers that reduce insulin resistance and increase the rate of glucose uptake and utilization by cells [50, 51]. Interestingly, flavonoids also positively influence the hypothalamic regulation of food intake and satiety, such as enhancing GLP-1, CCK, and PYY release [52, 53]. In animal tests, it was discovered that when mice fed a high-fat diet were continuously supplemented with flavonoids, their fecal fat excretion increased, body weight gain decreased significantly, and fat deposition and fat droplet size in the liver, epididymides, groin, and other tissues decreased [54–56].

Moreover, flavonoids regulate biochemical indices and hormone levels associated with lipid metabolism. For example, TC, TG, AST, ALT, ALP, LDL-C, leptin, and the leptin/adiponectin ratio were reduced in mouse serum, and adiponectin and stomach growth hormone-releasing hormone levels were increased [57, 58]. At the microscopic level, the expression of lipid metabolism-related genes such as *FNTA*, *PON1*, *PPARG*, *ALDH1B1*, *APOA4, SREBP-1C*, *ABCG5*, *GPAM*, *ACACA*, *FAS*, *CD36*, *FDFT1*, and *FASN* may be altered by inhibiting key receptors such as PPARs and SREBPs, thereby reducing the accumulation of adipose tissue [54, 59–61].

Continuous adipocyte hypertrophy and an excess of new adipocytes produced by precursor cells are the fundamental causes of obesity, so regulating adipocyte production and hypertrophy is considered a viable tool for preventing and controlling obesity. It was discovered that flavonoids induce apoptosis in precursor adipocytes by activating AMPK signaling, revealing that inhibition of the ERK and JNK pathways induces apoptosis in mature adipocytes [62]. They decrease cellular glucose absorption by activating the Akt and AMPK signaling pathways [63], increase adipocyte mitochondrial number and oxygen consumption rate [64], increase glucose consumption [65], and inhibit adipocyte lipid formation [66]. Flavonoids may limit lipid accumulation in adipocytes by downregulating the mRNA and protein expression of important adipogenic genes, such as *EBPA*, *PPAR*, *C/EBP*, *FABP4*, *AP2, LPL*, and *ApoB* [67–69].

Brown adipose tissue (BAT) and beige adipose tissue in animals produce nonshivering thermogenesis by activating uncoupling protein 1 (UCP1) on the inner mitochondrial membrane, which consumes energy substances such as glucose and fatty acids in the body [70]. Thus, promoting BAT production and WAT browning and increasing its activity are considered promising for intervention in obesity and other metabolic diseases. Flavonoids were observed to increase the expression of *CETED1*, *HOXC9*, *PGC1*, *PRDM16*, and UCP1 and white adipose tissue (WAT) marker genes via a *SIRT1*- or *3AR*-dependent pathway, triggered WAT browning to form beige adipose tissue, increased BAT development, and decreased the amount of WAT. Enhance the weight of brown adipose tissue and beige adipose tissue [65, 71–73]. BAT and beige fat exerted their thermogenic action primarily through the release of norepinephrine from sympathetic nerve terminals. Flavonoid supplementation elevated NA levels and boosted the gene and protein expression of the ADRB3, enhancing NA binding to ADRB3 and upregulating the expression of downstream associated genes [74, 75]. Mitochondria are thermogenic organelles. Flavonoids can activate mitochondrial biogenesis, increase the number of mitochondria in BAT cells, enhance mitochondrial structure and function in BAT cells, upregulate mitochondrial inner membrane UCP1 expression, promote nonshivering thermogenesis, and increase the consumption of energy substances such as glucose and fat [76, 77].

## 3 | THE INTERACTION OF FLAVONOIDS WITH THE GUT MICROBIOTA

Recent research has established that flavonoids and gut microbiota interact and encourage one another. On the one hand, flavonoids influence the composition and relative abundance of the gut microbiota by promoting or inhibiting certain microbes, hence modifying their metabolites. On the other hand, gut microbiota convert and degrade flavonoids via their own enzyme systems, releasing additional active compounds to improve biological effects [104, 105].

### 3.1 | Flavonoids are metabolized by gut microbiota

Flavonoids, the most abundant type of secondary metabolites found in plants, are found in food as glycosides, glucosyl, rutinosyl, neohesperidinyl, and rhamnolipidyl [106]. Low bioavailability is often associated with low bioactivity. A study showed that antibiotic-treated mice had less metabolism of quercetin, kaempferol, lignan, apigenin and naringenin, the concentrations of p-hydroxyphenylacetic acid, protocatechuic acid, p-hydroxybenzoic acid, vanillic acid, hydrocaffeic acid, coumaric acid and 3-(4-hydroxyphenyl) propionic acid were lower in serum [107]. These results indicated that the gut microbiota play an important role in flavonoid metabolism.

The flavonoids that enter the hindgut undergo anaerobic fermentation by gut microbiota, where they undergo dehydroxylation, decarboxylation, demethylation, and glycoside hydrolysis, resulting in the release of more easily absorbed free aglycones and the formation of new metabolites, thereby enhancing the biological activity of flavonoids [108]. Glycosylated flavonoids can operate as the sole carbon source for hindgut microbes, which first digest the glycosidic fraction, thus eliminating the O-glycosylation of flavonoids [109]. The metabolism of naringenin is accompanied by demethylation, C-ring cleavage, and dehydroxylation, with the A-ring metabolized to m-benzotrienol and the B-ring metabolized to 3-(4′-hydroxyphenyl)-propionic acid, as well as the production of sageol [110]. m-Benzotriol can be further metabolized into acetic acid, propionic acid, and caseic acid, and 3-(4′-hydroxyphenyl)-propionic acid is metabolized into small

molecules such as p-coumaric acid, 3-phenylpropionic acid, and 4′-hydroxybenzoic acid, which are thus absorbed by the colon and converted into maleic acid through the portal vein into the liver [111]. Isoflavones are also not well absorbed in the animal intestine but show excellent clinical effectiveness, so it is likely to be related to the metabolites they are converted to, such as estramol. In particular, bacterial strains of *Eggerthellaceae*, a well-known family of bacteria in the gut microbiota, are capable of converting isoflavones into equol [112]. Wang et al. fermented soybean flavonoids anaerobically in rat feces and observed their conversion to dihydrosoybean sapogenins, S-equol and O-desmethylangolensin [113].

Bacterial enzymes such as lactase rhizosphingoside hydrolase, $\beta$-glucuronidase, $\beta$-glucosidase, and $\alpha$-rhamnosidase have been reported as possible key enzyme families for the microbial metabolism of flavonoids, and the main microorganisms of the normal animal intestine contain these enzymes, such as *Lactobacillidae*, *Trichophyceae*, and *Enterococcaceae* [12, 111]. For example, *Casseliflavus* and *Eubacterium ramulus* ferment isoquercitrin [114]. Likewise, microbial metabolites of some flavonoids exhibit greater biological activity than the originals, such as hippuric acid, homovanillic acid, and 5-phenylvaleric acid, which are all metabolites of epicatechin, and the metabolites more effectively enhance glucose-stimulated insulin secretion in $\beta$-cells [115]. In summary, although the metabolic pathways of certain flavonoids vary, available evidence shows that gut microorganisms are essential for flavonoid biotransformation, mostly in terms of improving flavonoid structure and bioavailability.

## 3.2 | Flavonoids alter gut microbiota

The gut microbiota is a large and complicated microbial community composed of bacteria, fungi, viruses, and archaea in the intestine of animals, which is closely related to the metabolism, immunity and other vital life activities of animals. It has been discovered that supplementation with flavonoids is helpful to the dynamic changes in the composition structure, microbial abundance, and microbial metabolites of the animal gut microbiota (Table 3). Notably, in this part, we are equally interested in how flavonoids exert bacteriostatic effects on microorganisms.

### 3.2.1 | How flavonoids inhibit microorganisms

The attachment of bacteria to the mucosal surface of the organism, such as by physical adsorption, is the first step in the initiation of their relationship with the organism, and the pathogenic process can only continue to develop when the bacteria are in contact with certain specific structures of the organism's cells for a certain period of time. Yu et al. reported that sorghum procyanidin tetramers, by binding to a site in the catalytic region of *Streptococcus mutans* GTF-1/CAT protein (GTF-1, also known as water-insoluble glucan synthase, is a control enzyme for bacterial synthesis of adhesion site material glucan and is essential for the expression of virulence factors in *Streptococcus mutans*), alter the GTF-1/CAT secondary structure in the ratio of $\alpha$-helix, $\beta$-sheet, and random helix, thus affecting the normal function of GTF-1 and hindering the adhesion of *Streptococcus mutans* [116]. As a bacterial surface appendage, pili play a critical function in host cell adhesion and biofilm development, which increases bacterial attachment to the host and aids pathogen colonization. Furthermore, it can promote pathogen resistance to host defensive mechanisms and medications. Vasudevan et al. discovered that type A anthocyanin trimers can suppress the expression of pili adhesion-related genes (such as *focA*, *papG*, *fimA*, and *fimH*), reduce biofilm formation by approximately 70% and have synergistic effects with furantoin [117]. The surface hydrophobicity of bacteria is also closely related to the bacterial adhesion process, and appropriate surface hydrophobicity is the basis for the formation of bacterial organisms, which can promote the adhesion and agglutination of pathogens [118]. Flavonoids such as quercetin and myricetin have been shown to drastically reduce the hydrophobicity of urine-derived *Escherichia coli* (*E. coli*) and limit the formation of biofilms, hence preventing bacteria from attaching to the host [119]. The effect of flavonoids on bacterial adherence could be a result of the structure's particular groups. For instance, A-type procyanidins include at least double interflavanyl linkages, and the addition of nitro to the A ring of procyanidins can boost their antibacterial and biofilm-preventive effects [120]. Additionally, the presence of a methyl group at position 6 in the A ring of flavonoids inhibits the formation of biofilms, whereas the presence of methyl groups at positions 6 and 8 stimulates the production of biofilms [121].

Quorum sensing (QS), an intercellular communication process used by bacteria to regulate population behavior, regulates critical invasive processes such as bacterial biofilm formation and virulence factor release and is a key collaborator in chronic infections, with interruption of QS considered one of the most effective ways to control various virulence factors [122]. It was found that flavonoids have inhibitory effects on the expression of major regulatory target genes of microbial QS; for example, baicalin downregulates the expression of *LASI*, *LASR*, *RHLI*, and *RHLR* in *Pseudomonas aeruginosa* and *agrA*,

**TABLE 3** Flavonoids alter gut microbiota.

| Flavonoids | Animal models | Effect on gut microbiota | Reference |
|---|---|---|---|
| Quercetin | Arbor Acre broilers | *Pseudomonas aeruginosaxiang*↓, *Salmonella enterica serotype Typhimurium*↓, *Staphylococcus aureus*↓, *Escherichia coli*↓, *Lactobacillus*↑, *Bifidobacterium*↑. | [35, 80] |
| Flavanol-Enriched Cocoa Powder | 5-mo-old male pigs | *Lactobacillus*↑, *Bifidobacterium*↑. | [148] |
| Procyanidins | Bama mini-pigs | *Firmicutes*↑, *Coprococcus*↑, *Spirochetes*↓. | [149] |
| Baicalin | UC rats | *Firmicutes*↑, *Butyricimonas spp.*↑, *Roseburia spp.*↑, *Subdoligranulum spp.*↑, *Eubacteriu spp.*↑, *Proteobacteria*↓, *Actinomycetes*↓; butyrate↑. | [46] |
| Kaempferol | UC rats | *Prevotellaceae*↑, *Ruminococcaceae*↑, *Proteobacteria*↓. | [45] |
| Puerarin | Depressed mice | *Firmicutes*↑, *Bacillales*↑, *Lactobacillus*↑, *Proteobacteria*↓, *Flexispira*↓, *Desulfovibrio*↓. | [87] |
| Puerarin | UC rats | *Proteobacteria*↓, *Ruminococcus*↓, *Ruminococcaceae*↓; acetate↑, propionate↑, butyrate↑. | [150] |
| Puerarin | Ovariectomized rats as osteoporosis model | *Bacteroidia*↑, *Clostridia*↓, *Bacteroidales*↑, *Peptococcaceae*↑, *Lachnospiraceae*↓, *Melainabacteria*↓, *Prevotellaceae*↑, *Desulfovibrionaceae*↓; acetate↑, butyrate acids↑. | [151] |
| Myricetin | NAFLD rats induced by high-fat diets | *Actinobacteria*↑, *Allobaculum*↑, *Brachybacterium*↑, *Allobaculum spp.*↑, *Lachnospiraceae*↑, *B. paraconglomeratum*↑, *Nocardiaceae*↑, *Tyzzerella 4 spp*↑, *Turicibacter spp.*↑, *Lactobacillus intestinalis*↑, *Lactobacillus spp*↑. | [135] |
| Isoflavone | Postmenopausal women | *Lachnospiraceae*↑, *Pseudoflavonifractor*↑, *Slackia*↑, *Dorea*↑. | [152] |
| Catechin | High-fat diets rats | lithocholic acids↓, hyodeoxycholic acids↓. | [153] |
| Theabrownin | High-fat diets rats | *Lactobacillus*↓, *Bacillus*↓, *Streptococcus*↓, *Lactococcus*↓, ileal conjugated bile acids↑. | [154] |
| Citrus poly-methoxyflavones | Metabolic syndrome induced by high-fat diets | *Bacteroides ovatus*↑, *B. thetaiotaomicron*↑, *B. vulgatus*↑, *B. dorei*↑, *B. caccae*↑, *B. stercoris*↑, *B. uniformis*↑, *Firmicutes Paraprevotella*↓, *Firmicutes Streptococcus*↓, *B. fragilis*↓, *B. finegoldii*↓, *B. coprophilus*↓. | [155] |
| Quercetin | Atherosclerosis induced by high cholesterol diets | *Phascolarctobacterium*↑, *Anaerovibrio*↑. | [156] |

*RNAIII*, *sarA*, and *ica* in *Staphylococcus aureus* (*S. aureu)s*, thus reducing the secretion of signaling molecules (e.g., N-acylhomoserine lactones, furanylboronic acid diesters) that impede the progression of QS and reducing the release of virulence factors such as enterotoxin A, $\alpha$-hemolysin released by *S. aureus*, and pyocyanin, protease, elastase and rhamnolipids released by *Pseudomonas aeruginosa*. Moreover, the formation of biofilms was inhibited, and existing biofilms were disrupted. A significant reduction in biofilms was observed by electron microscopy; biofilm clumps were dispersed, and the extracellular polysaccharide matrix was significantly reduced [123, 124]. Microbial motility is also an important influence on QS and is critical for QS colonization, virulence expression and biofilm formation. Flavonoids such as quercetin, baicalin, and catechin have all been reported to inhibit bacterial swimming and cluster motility and partially exhibit dose dependence [125–127].

As the structural basis for ensuring the stability of the intracellular environment and normal cellular metabolism, the structural integrity of cell membranes is related to the normal life activities of the bacterium. Therefore, modulating the cell membrane structure is also one of the important targets of capturing microorganisms. Wang et al. treated *E. coli* with quercetin and observed the ultrastructure of the bacterium by transmission electron microscopy and found separation of the cytoplasmic membrane from the cell wall, cell wall lysis, inhomogeneous density of the inner cell membrane, leakage and polarization of the cytoplasmic contents as well as cell deformation and cell cavitation in *E. coli*, indicating that quercetin caused a break in the ring of the cell wall and cell membrane of the bacterium and its structural integrity was lost, resulting in significant increases in alkaline phosphatase and $\beta$-galactosidase activities and soluble protein concentrations were observed outside the cell (only

exposed to the cell wall and cell membrane permeability increased) [80]. Kusuda et al. also reported that polymeric proanthocyanidins can cause damage to the cell membrane of methicillin-resistant *S. aureus* (MRSA), decrease its membrane structural stability and tolerance to hypo- and hyperosmotic environments, and inhibit -lactamase activity, thereby significantly lowering the minimum inhibitory concentration of -lactam antibiotics against MRSA [128].

Normal genetic material replication, protein synthesis, and food metabolism are required for optimal microbial life activities, and disruption to any of these processes would impair normal growth and reproduction. Li et al. treated *S. aureus* with LBPC and discovered changes in the total protein content and protein production of *S. aureus*, a decrease in the activity of essential energy metabolizing enzymes (succinate dehydrogenase, malate dehydrogenase, and adenosine triphosphatase ATPase), and LBPC binding to small grooves in the DNA double helix to form complexes that affected genetic material and protein expression systems [129]. Lin et al. discovered using transcriptome technology that when *E. coli* was treated with flavonoids from agastache leaves, the signal pathway and transcription level closely related to the nucleotide metabolic pathway, energy metabolic pathway, and carbohydrate metabolic pathway were significantly reduced, while the number of SNPs in *E. coli* increased significantly (indicating an increased probability of nucleotide mutation) [130]. Additionally, studies have shown that flavonoids reduce microorganism total RNA and DNA synthesis, as well as protein synthesis [131], which may be related to the inhibition of enzymes involved in DNA synthesis (such as DNA gyrase and ATP synthase) [132].

Briefly, flavonoids inhibit microorganisms primarily by blocking population sensing, disrupting biofilm formation, impeding adhesion, reducing the release of virulence factors, enhancing cell membrane permeability, and inhibiting genetic material replication and protein synthesis and nutrient metabolism.

### 3.2.2 | Remodeling/restoring gut microbiota

Unfortunately, the balance of the gut microbiota can be readily disrupted by diets high sugar and fat, enteropathy, and stress [16, 18].+ Remodeling gut microbiota to promote health by regulating dietary flavonoids is a frontier of food nutrition research. Emerging evidence suggests that flavonoids possess the potential to reshape or restore the balance of the gut microbiota, thus contributing to the regulation of host immunity, metabolism, and inflammation [13, 45].

Long-term or short-term high-fat diets have been shown to alter microbiota structure and diversity, such as a higher F/B, a higher abundance of bile acid-resistant and pathogenic bacteria, and a lower abundance of probiotics (*Bifidobacterium*, *Lactobacillus*, *Akkermansia muciniphila*, etc.), resulting in gut microbiota dysbiosis. Altering gut permeability increases blood endotoxin levels, activates the inflammatory response, and further exacerbates complications resulting from high-fat diets [133, 134]. Sun et al. supplemented rats on a high-fat diet for 12 weeks with myricetin and found that myricetin significantly increased the Shannon index and decreased the ratio of Firmicutes to Bacteroidetes (F/B) and LPS levels, and principal coordinate analysis also showed that myricetin significantly corrected the changes in gut microbiota caused by the high-fat diet [135]. Similarly, supplementation with other flavonoids in other high-fat diet trials has been observed to reshape gut microbiota, increase probiotic abundance and reduce pathogenic bacterial abundance [136, 137]. Ulcerative colitis (UC) is a clinically common chronic nonspecific inflammatory bowel disease. Qu et al. observed that kaempferol reshaped the gut microbiota structure, decreased F/B and increased the level of beneficial bacteria such as *Prevotellaceae* and *Rhinococcus*. Additionally, the transplantation of fecal microbiota from kaempferol-treated mice into DSS-induced mice resulted in decreased levels of serum IL-1$\beta$, IL-6, TNF-$\alpha$, and LPS, increased colon length, decreased DAI score, and alleviation of pathological features. These findings provide confirmation that kaempferol attenuated inflammation through the regulation of gut microbiota [45]. Similar results were observed in UC mice supplemented with baicalin by Zhu et al., baicalin effectively reduced the abundance of the F/B and endotoxin-producing Proteobacteria, thereby reversing the dysbiosis in the gut microbiota induced by UC. Additionally, baicalin significantly increased the fecal butyrate content, which exhibited a strong positive correlation with the abundance of *Butyricimonas* spp., *Roseburia* spp., *Subdoligranulum* spp., and *Eubacteriu* spp. [46].

The remodeling/restoring of the gut microbiota by flavonoids may be attributed to an increase in intestinal probiotics [138]. Several studies have demonstrated that flavonoids serve as a source of nutrients for probiotics, providing both energy and nutrients to promote their growth and reproduction [11, 139]. For instance, Feng et al. conducted in vitro fermentation experiments and observed that lotus leaf brass stimulated the growth of Actinobacteria and Firmicutes in colonic contents, inhibited the growth of Proteobacteria, and triggered the production of fermentation gases and short-chain fatty acids (SCFAs) [140]. The intestinal environment plays a critical role in the proliferation of probiotics as well. Intestinal microor-

ganisms can metabolize flavonoids to produce short-chain fatty acids, such as propionic acid and butyric acid [139, 141]. These acids help maintain the acid-base balance in the intestines, regulate intestinal pH, inhibit the proliferation of harmful bacteria, and create an intestinal environment that is more conducive to the growth of probiotics [142]. Moreover, short-chain fatty acids not only act as a carbon source for probiotics like *Lactobacillus* and *Bifidobacterium*, but also provide energy and nutritional support to intestinal epithelial cells [143]. This, in turn, helps maintain the integrity and barrier function of the intestinal mucosa and further promotes the colonization of probiotics [11, 143]. Yan et al. found that flavonoids from green seaweed significantly increased the relative abundance of Lachnospiraceae, Odoribacter, and Alisties members in an animal model of type 2 diabetes [144]. Notably, Lachnospiraceae and Alisties belong to the core genus of the gut and are among the most abundant bacteria producing SCFAs [143]. In addition, mulberry leaf flavonoids increased Akkermansia levels and Bacteroidetes/Firmicutes ratio in animal models of obesity fed with high-fat diet [145]. In the animal model of high-fat diet induced obesity and insulin resistance, nobiletin increased the relative abundance ratio of Bacteroidetes to Firmicutes, and decreased the relative abundance of Oscillibacter [146]. Recent studies have shown that the increase in the relative abundance of Oscillibacter may lead to inflammatory response, obesity and insulin resistance, and the increase in the relative abundance of Oscillibacter is closely related to excessive intestinal permeability [138, 147]. Previous studies have demonstrated that flavonoids have the capability to alter the composition of the gut microbiota. However, the current literature on flavonoid remodeling of the gut microbiota has mainly focused on phenotypic changes, while the mechanisms of remodeling have rarely been reported and should be emphasized to better understand the gut microbiota remodeling process.

## 4 | INTERACTION BETWEEN FLAVONOIDS AND GUT MICROBIOTA TO MODULATE LIPID METABOLISM

The interaction between flavonoids and gut microbiota to modify lipid metabolism is complex, and the exact mechanism of interaction is still unclear (Figure 2). In general, on the one hand, flavonoids are metabolized by gut microbiota to produce secondary metabolites such as phenolic acids, which are absorbed through the gut, activating relevant pathways and directly participating in the modulation of lipid metabolism; on the other hand, some flavonoids, together with their secondary metabolites, act on the gut microbiota to indirectly improve lipid metabolism by modulating relevant pathways through the gut microbiota and its metabolites.

### 4.1 | Flavonoid secondary metabolites modulate lipid metabolism

The gut microbiota plays an important role in the metabolism of flavonoids, promoting not only flavonoid absorption but also some flavonoid metabolites, which exhibit enhanced effects [157]. Equol is a microbial metabolite of isoflavones that plays an important role in the modulation of lipid metabolism by isoflavones. Estramol activates Nrf2, alleviates endoplasmic reticulum stress, downregulates hepatic *FAS* expression, improves the plasma lipid profile and reduces fat accumulation, but there are sex differences [158, 159].

Hidalgo et al. fermented malvidin-3-glucoside, a mixture of anthocyanins, with human hindgut microorganisms and discovered that malvidin-3-glucoside was metabolized to syringic acid, and the anthocyanin mixture was metabolized to produce gallic acid, syringic acid, and *p*-coumaric acid, all of which could positively modulate lipid metabolism [109, 160, 161]. Gallic acid can improve glucose transport in adipose tissue by partially activating *PPARγ* and *PI3K*/*p-Akt* signaling while enhancing *β*-oxidation, glycolysis and ketogenesis to control adipogenesis [161–163]. *p*-coumaric acid increases nonshivering thermogenesis, upregulates *carnitine palmitoyltransferase 1* expression, decreases lipogenic enzyme activity, increases fecal lipid excretion and reduces fat deposition and adipocyte size [164, 165]. Ham et al. observed that syringic acid reduced lipogenesis (*CIDEA*, *PPARγ*, *SREBP-1C*, *SREBP-2*, *HMGCR*, *FASN*) and inflammation (*TLR4*, *MyD88*, *NF-κB*, *TNF-α*, *IL-6*)-related genes, upregulated fatty acid oxidation (*PPARα*, *ACSL*, *CPT1*, *CPT2*)-related genes, and increased fatty acid oxidase activity, thereby reducing fat deposition and weight gain due to high-fat diets [160].

This is an intriguing line of research to contribute to the understanding of flavonoid metabolism. Unfortunately, due to the complexity of flavonoid species and gut microbiota, studies on the metabolism of flavonoids by gut microbiota are mainly in vitro only, and few systematic and complete studies have been carried out. Therefore, there is a desire to combine multiomics approaches to investigate the microbial metabolites of flavonoids in animals to better understand the interactions between flavonoids and gut microbes, as well as to identify the active ingredients in which flavonoids function and suggest more clinical treatment strategies.

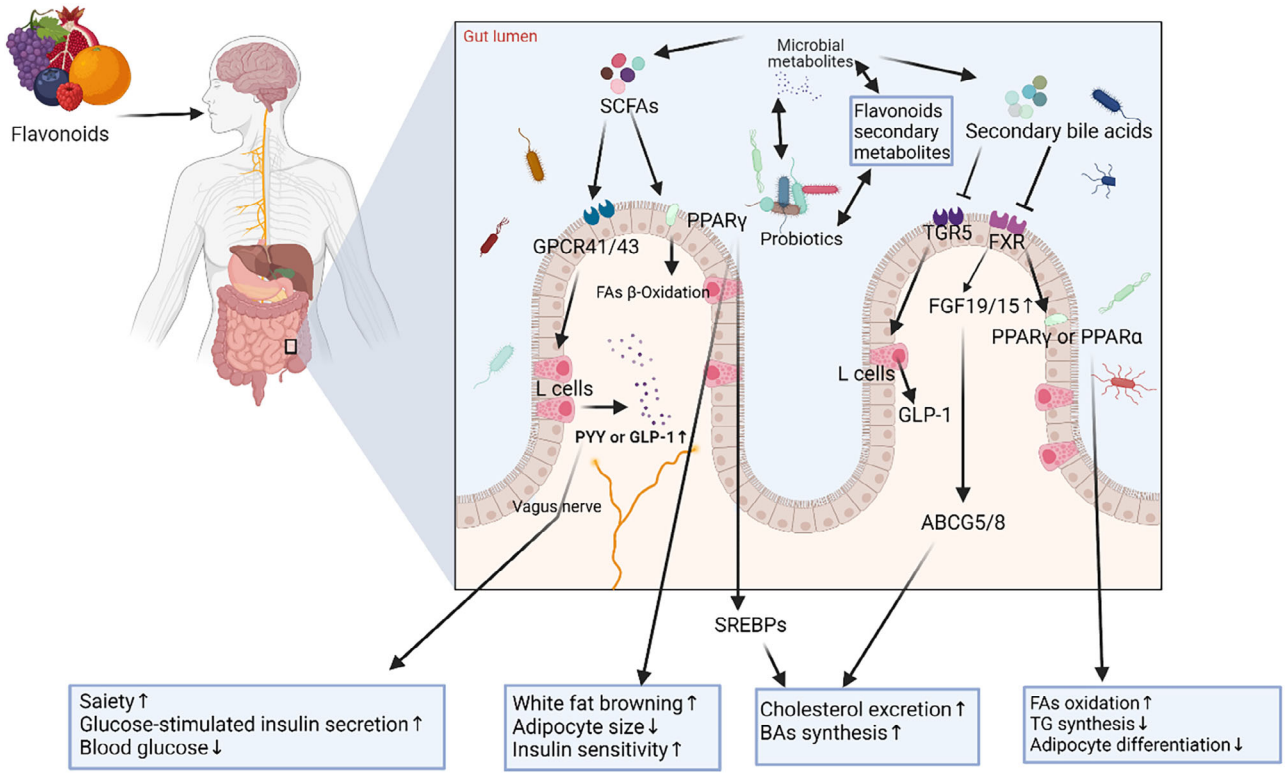



**FIGURE 2** The pathway of the interaction between flavonoids and gut microbiota on lipid metabolism. After flavonoids are ingested by the body, some of them enter the blood directly, and some of them are decomposed by microorganisms in the gut to produce secondary metabolites, while flavonoids and their secondary metabolites affect the gut microbiota and change the microbial metabolites, both of which are absorbed by the body into the blood and reach the liver, brain, fat, and other tissues to improve host lipid metabolism.

## 4.2 | Modulation of lipid metabolism by the gut microbiota and its metabolites

### 4.2.1 | Probiotics

Recently, the regulation of host lipid metabolism by probiotics has become an attractive emerging direction. Probiotics and their microbial metabolites serve as substrates for some gut microorganisms and promote their proliferation. Hidalgo et al. observed that anthocyanins enhanced the growth of *Bifidobacterium* spp. and *Lactobacillus–Enterococcus* spp. [109]. Other studies have observed that quercetin, proanthocyanidin and epicatechin promote the growth of *Akkermansia muciniphila* [166–168]. To date, a number of microorganisms have also been characterized as having a positive role in lipid metabolism, such as *Bifidobacterium*, *Lactobacillus*, and *Akkermansia muciniphila* [169–171].

These probiotics can regulate lipid metabolism through a variety of pathways. Similar to the next-generation probiotic *Akkermansia muciniphila*, which colonizes the gut mucus layer, which can improve the gut barrier, reduce food intake, increase fecal fat excretion, and improve blood lipid parameters, it induces the secretion of systemic GLP-1 and *UCP1* expression in BAT, inhibiting BAT whitening and the inflammatory response, reducing adipocyte size and infiltration, simultaneously activating PPAR-$\alpha$ and PPAR-$\gamma$ to promote fatty acid oxidation, downregulating the mRNA expression of lipid synthesis-related genes, and upregulating the mRNA expression of lipid transport-related genes, to improve host lipid metabolism [172–176]. Furthermore, Lukovac et al. observed that the *Akkermansia muciniphila* metabolite propionate regulated the expression of *FIAF*, *GPR43*, *HDACs*, and *PPAR-γ*, which are vital regulators of lipolysis and satiety [177]. Interestingly, several studies have shown that the extracellular vesicles, membrane proteins, and pasteurized forms of *Akkermansia muciniphila* exhibit better lipid metabolism modulating activity [173, 174, 178].

Imperfectly, numerous intestinal probiotics remain unidentified or isolated due to technical limitations and the unique growth requirements of certain microorganisms. Functional verification is predominantly confined to in vitro experiments or animal models, and limited clinical research findings have been acquired.

### 4.2.2 | Gut microbiota metabolites

The gut microbiota is thought to be a massive metabolic organ, and its metabolites, such as SCFAs, BAs, tryptophan and its derivatives, are vital signaling molecules for the host to sustain health. Acetic acid, propionic acid, butyric acid, valeric acid, and other short-chain fatty acids are metabolites of gut microorganisms such as *Rumenococcus*, *Bauerella*, *Faecoccus*, *Salmonella*, and insoluble carbohydrates such as dietary fiber in the gut [179]. The total SCFA content of the intestinal chyme was 30% lower in the rat UC model than in healthy mice, and the butyric acid amount was halved. However, after puerarin supplementation, the acetic acid, propionic acid, and butyric acid levels in the chyme were dramatically increased, as was the overall SCFA content. The content is 391.80 mol/g, which is approximately 80% greater than that of the UC model. SCFAs provide energy to epithelial cells and suppress associated pathogenic bacteria, thus promoting intestinal homeostasis and UC repair [150]. Additionally, Li et al. observed that puerarin increased fecal and serum levels of acetate, butyric acid, valeric acid and total SCFA in a rat model of osteoporosis [151]. SCFA levels vary as a result of flavonoids affecting the composition and abundance of bacteria involved in SCFA production [135, 152]. Primary BAs can also be metabolized into free BAs and secondary BAs in the gut by some bacteria involving BSH and 7$\alpha$- dehydroxylase, respectively [180]. According to Han et al., supplementation with catechins, quercetin, and rutin can decrease the amount of secondary BAs found in mouse feces, including neutral sterols, lithocholic acid, and hyodeoxycholic acid [153]. Theabrownin is an oxidized polymer of catechins that decreases the relative abundance and activity of bile salt hydrolase-producing microorganisms such as *Lactobacillus*, *Bacillus*, *Streptococcus*, and *Lactococcus*, as well as the hydrolysis of glycine- and taurine-bound BAs, thereby increasing ileum combined BA levels [154]. Additionally, the gut microbiota controls the synthesis, transportation, and metabolism of certain amino acids. Citrus polymethoxyflavonoid extracts have the potential to reshape the gut microbiota of metabolic syndrome model mice fed a high-fat diet. Thus, valine, leucine, iso leucine, and phenylalanine levels in serum and feces are increased [155]. Quercetin reduces atherosclerosis in mice produced by a high cholesterol diet by modulating tryptophan metabolism [156].

*SCFAs*

SCFAs, the fermentation products of nondigestible carbohydrates, which are a key class of metabolic signaling molecules, are also altered in individuals with disorders of lipid metabolism, usually with lower levels of acetic, propionic and butyric acids [16]. There is an inextricable relationship between SCFAs and lipid metabolism. Our previous study discovered that supplementation of acetic acid to mice on a high-fat diet upregulated *PPAR$\gamma$* and *LXR* expression in subcutaneous adipose tissue, promoted lipolysis, reduced adipocyte size and fat mass, and decreased weight gain [19].

For energy intake, acetic acid, propionic acid and butyric acid bind to *GPR41* and *GPR43* to promote the secretion of GLP-1 and PYY from intestinal L cells, modulate host insulin release and appetite, reduce food intake and increase glucose consumption [181, 182]. Regarding lipid synthesis and catabolism, SCFA-dependent activation of PPAR$\gamma$, especially butyrate, promotes fatty acid $\beta$-oxidation and white fat browning, reduces adipocyte size, increases the number of small adipocytes and enhances insulin sensitivity, while PPAR$\gamma$ activation increases *SREBP* expression and promotes cholesterol and lipid excretion [183, 184]. Notably, sometimes PPAR$\gamma$ also promotes adipocyte differentiation and increases lipid synthesis and lipid droplet aggregation [185, 186]. Other studies have also shown that acetic acid promotes leptin secretion from adipocytes, suppresses appetite, reduces energy intake, increases energy expenditure and inhibits fat synthesis. It also induces lipid oxidation in enterocytes by upregulating the *AMPK*/*PGC-1α*/*PPARα* pathway after acetate uptake by enterocytes [187–189]. In addition, SCFAs are also involved in the control of inflammation, like butyrate inhibit Gram-negative bacteria, reduce LPS production, activate NF-$\kappa$b, and inhibit TLR2/4 [190, 191].

Emerging research shows that flavonoids restore host SCFA levels by increasing the number of SCFA-producing microorganisms and by acting as metabolic substrates. Several studies have demonstrated that supplementation with baicalin can increase the levels of SCFA-producing microorganisms, such as *Aeromonas butyricus*, *Rhus* spp., *Alcaligenes subtilis*, *Eubacterium* spp., *Heterobacterium* spp., and *Bifidobacterium* spp., thereby restoring acetate, propionic acid, butyric acid, isobutyric acid, valeric acid, and isovaleric acid levels [46, 192]. *Akkermansia muciniphila* generates propionate, and flavonoids such as quercetin and proanthocyanidins can also promote its growth and increase its density [166–168, 177].

*Bile acids*

In addition to being involved in the digestion and absorption of lipids such as triglycerides, BAs are also important signaling molecules regulated in glucolipid and energy metabolism [16]. It was shown that BAs mainly regulate glucose and lipid metabolism through FXR and TGR5 to modulate glycolipid metabolism [193]. BAs are natural ligands for FXR and TGR5 in the gut, but different forms of BAs have different activating abilities, such as free BAs over bound BAs and secondary BAs over primary BAs.

Notably, the structural transformation of BAs in the gut is strongly based on the microbial enzyme system [194].

Secondary BAs activate FXR, which on the one hand induces FGF19 expression and secretion in the gut, downregulates BA synthesis, increases BA excretion and reduces fat digestion and absorption. On the other hand, it activates PPAR$\gamma$ and PPAR$\alpha$, which promote fatty acid oxidation, reduce TG synthesis and regulate adipocyte differentiation [195]. Additionally, FXR induces the production of FGF15, which excretes more than 60% of absorbed cholesterol into the intestinal lumen via ATP-binding cassette transporter protein G5 and ATP-binding cassette transporter protein G8. More interestingly, FXR inhibition also has a positive role in lipid metabolism [196]. Wang et al. found that 3 weeks of hesperidin supplementation reduced the abundance of BSH-producing and 7$\alpha$-dehydroxylase microorganisms such as *Bacteroides*, *Bifidobacterium*, and *Clostridium* in ApoE$^{-/-}$ female mice on high-fat diets, which subsequently reduced the hydrolysis of bound BAs and inhibited the FXR/FGF15 pathway to upregulate *CYP7A1* to promote the conversion of cholesterol to bile acids, thereby reducing body TG levels and improving atherosclerosis [197]. As the only known endogenous ligand for TGR5, BAs activate TGR5 and initiate cAMP and its downstream related signaling pathways to induce glucagonogenic gene expression and promote GLP-1 secretion in intestinal L cells, which improves insulin resistance and appetite for food [198]. He et al. supplemented mice on a high-fat diet with pure total flavonoids for 12 weeks and showed that pure total flavonoids significantly increased the abundance of *Bacteroidaceae* and *Christensenellaceae*, increased the content of secondary BAs, activated FXR and TGR5, reduced serum TG levels, and improved nonalcoholic steatohepatitis in mice [199].

Growing evidence shows that flavonoids are linked to lipid metabolism not only by modulating the synthesis and excretion of BAs but also by improving secondary BA production through the modulation of microorganisms [197, 200]. However, few studies have been conducted to compare the ability of different flavonoids to interact with gut microbiota to modulate bile acids to the extent that we do not know which flavonoids are more appropriate and more promising for clinical studies.

## 5 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Increasing evidence indicates that flavonoids play a part in lipid metabolism regulation by decreasing appetite and energy intake, decreasing fat absorption, inhibiting fat cell differentiation, promoting fat cell apoptosis, increasing lipolysis, promoting WAT browning and nonshivering thermogenesis, and restructuring the microbiota imbalance caused by metabolic disorders. Although the interaction between gut microbiota and flavonoids provides a novel dimension to understand the mechanisms of flavonoids regulating host lipid metabolism, flavonoids are complex in structure, and animal and clinical experiments mostly focus on plant polyphenols. Nevertheless, numerous questions and research directions for future research persist. These include: determining which flavonoid composition is more promising for clinical applications and exploring the interactions among different flavonoid components; identifying the configuration with greater biological potency, the most effective modification of the radical group, and whether modifications in the modified radical group undergo metabolic changes affecting potency; investigating if the biological potency of flavonoids is influenced by diet and lifestyle, and developing strategies to mitigate these lifestyle differences. The clinical application of flavonoids still has some way to go, and there is a need for increased clinical research and the application of modern technology to explore the mechanisms by which flavonoids interact with the body organs to better understand the regulatory targets.

## 6 | LITERATURE COLLECTION METHODS

A comprehensive search was conducted across the PubMed and Google Scholar databases to retrieve relevant literature. The primary search criteria encompassed various keywords such as “flavonoids,” “flavonoid metabolism,” “quercetin,” “baicalin,” “gut microbiota,” “microbial metabolites,” “lipid metabolism,” “obesity,” “antioxidant,” “antibacterial,” and “anti-obesity.” The retrieved search results underwent evaluation to ascertain their compliance with the predefined inclusion criteria.

### AUTHOR CONTRIBUTIONS

Miao Zhou: Writing-Original draft preparation, revision, and investigation. Jie Ma and Jie Yin: Revision. Wenjie Tang: Conceptualization. Siting Xia and Meng Kang: Investigation. Yulong Yin: Validation. All authors contributed to the article and approved the submitted version.

### ACKNOWLEDGMENTS

The present study was financially supported by the Sichuan Science and Technology Programmes (2021JDYZ0001, 2021ZDZX0009), the Scientific Research Project of Hunan Provincial Education Department (20C0950) and the Postgraduate Scientific Research Innovation Project of Hunan Province (CX20210656).

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated during the current study.

## REFERENCES

1. Schlesinger S, Neuenschwander M, Schwedhelm C, et al. Food groups and risk of overweight, obesity, and weight gain: a systematic review and dose-response meta-analysis of prospective studies. *Advances Nutr (Bethesda, Md)*. 2019;10:205-218.
2. San-Cristobal R, Navas-Carretero S, Martínez-González MÁ, et al. Contribution of macronutrients to obesity: implications for precision nutrition. *Nat Rev Endocrinol*. 2020;16:305-320.
3. Miller V, Webb P, Cudhea F, et al. Global dietary quality in 185 countries from 1990 to 2018 show wide differences by nation, age, education, and urbanicity. *Nat Food*. 2022;3:694-702.
4. Yoon H, Shaw JL, Haigis MC, Greka A. Lipid metabolism in sickness and in health: emerging regulators of lipotoxicity. *Mol Cell*. 2021;81:3708-3730.
5. Michos ED, McEvoy JW, Blumenthal RS. Lipid management for the prevention of atherosclerotic cardiovascular disease. *N Engl J Med*. 2019;381:1557-1567.
6. Piché M-E, Tchernof A, Després J-P. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res*. 2020;126:1477-1500.
7. González-Muniesa P, Mártinez-González M-A, Hu FB, et al. Obesity. *Nat Rev Dis Primers*. 2017;3:1-18.
8. Schachter J, Martel J, Lin C-S, et al. Effects of obesity on depression: a role for inflammation and the gut microbiota. *Brain Behav Immun*. 2018;69:1-8.
9. Shin S-K, Cho H-W, Song S-E, et al. Oxidative stress resulting from the removal of endogenous catalase induces obesity by promoting hyperplasia and hypertrophy of white adipocytes. *Redox Biol*. 2020;37:101749.
10. Peluso I, Miglio C, Morabito G, et al. Flavonoids and immune function in human: a systematic review. *Crit Rev Food Sci Nutr*. 2015;55:383-395.
11. Pei R, Liu X, Bolling B. Flavonoids and gut health. *Curr Opin Biotechnol*. 2020;61:153-159.
12. Cassidy A, Minihane A-M. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. *Am J Clin Nutr*. 2017;105:10-22.
13. Song H, Shen X, Zhou Y, Zheng X. Black rice anthocyanins alleviate hyperlipidemia, liver steatosis and insulin resistance by regulating lipid metabolism and gut microbiota in obese mice. *Food Funct*. 2021;12:10160-10170.
14. Yang C, Deng Q, Xu J, et al. Sinapic acid and resveratrol alleviate oxidative stress with modulation of gut microbiota in high-fat diet-fed rats. *Food Res Int (Ottawa, Ont)*. 2019;116:1202-1211.
15. Han X, Zhao W, Zhou Q, et al. Procyanidins from hawthorn (Crataegus pinnatifida) alleviate lipid metabolism disorder via inhibiting insulin resistance and oxidative stress, normalizing the gut microbiota structure and intestinal barrier, and further suppressing hepatic inflammation and lipid accumulation. *Food Funct*. 2022;13:7901-7917.
16. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19:55-71.
17. Ma J, Duan Y, Li R, et al. Gut microbial profiles and the role in lipid metabolism in Shaziling pigs. *Anim Nutr*. 2022;9:345-356.
18. Crovesy L, Masterson D, Rosado EL. Profile of the gut microbiota of adults with obesity: a systematic review. *Eur J Clin Nutr*. 2020;74:1251-1262.
19. Yin J, Li Y, Han H, et al. Melatonin reprogramming of gut microbiota improves lipid dysmetabolism in high-fat diet-fed mice. *J Pineal Res*. 2018;65:e12524.
20. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Nat Acad Sci USA*. 2007;104:979-984.
21. Xie Y, Yang W, Tang F, et al. Antibacterial activities of flavonoids: structure-activity relationship and mechanism. *Curr Med Chem*. 2015;22:132-149.
22. Pietta PG. Flavonoids as antioxidants. *J Nat Prod*. 2000;63:1035-1042.
23. Wang C-M, Hsu Y-M, Jhan Y-L, et al. Structure elucidation of procyanidins isolated from rhododendron formosanum and their anti-oxidative and anti-bacterial activities. *Molecules*. 2015;20:12787-12803.
24. Ku Y-S, Ng M-S, Cheng S-S, et al. Understanding the composition, biosynthesis, accumulation and transport of flavonoids in crops for the promotion of crops as healthy sources of flavonoids for human consumption. *Nutrients*. 2020;12:1717.
25. Sies H. Oxidative stress: a concept in redox biology and medicine. *Redox Biol*. 2015;4:180-183.
26. Rice-Evans C. Flavonoid antioxidants. *Curr Med Chem*. 2001;8:797-807.
27. Peng X, Zhang Z, Zhang N, et al. In vitro catabolism of quercetin by human fecal bacteria and the antioxidant capacity of its catabolites. *Food Nut Res*. 2014;58(1):23406.
28. Zheng Y-Z, Deng G, Liang Q, et al. Antioxidant activity of quercetin and its glucosides from propolis: a theoretical study. *Sci Rep*. 2017;7:7543.
29. Chang W-T, Shao Z-H, Yin J-J, et al. Comparative effects of flavonoids on oxidant scavenging and ischemia-reperfusion injury in cardiomyocytes. *Eur J Pharmacol*. 2007;566:58-66.
30. Huang Z-Q, Chen P, Su W-W, et al. Antioxidant activity and hepatoprotective potential of quercetin 7-rhamnoside in vitro and in vivo. *Molecules*. 2018;23:1188.
31. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology*. 2011;283:65-87.
32. Kejík Z, Kaplánek R, Masařík M, et al. Iron complexes of flavonoids-antioxidant capacity and beyond. *Int J Mol Sci*. 2021;22:646.
33. Bhuiyan MNI, Mitsuhashi S, Sigetomi K, Ubukata M. Quercetin inhibits advanced glycation end product formation via chelating metal ions, trapping methylglyoxal, and trapping reactive oxygen species. *Biosci Biotechnol Biochem*. 2017;81:882-890.
34. Liu Y, Guo M. Studies on transition metal-quercetin complexes using electrospray ionization tandem mass spectrometry. *Molecules*. 2015;20:8583-8594.
35. Dong Y, Lei J, Zhang B. Effects of dietary quercetin on the antioxidative status and cecal microbiota in broiler chickens fed with oxidized oil. *Poult Sci*. 2020;99:4892-4903.

36. Dong D, Zhang Y, He H, et al. Alpinetin inhibits macrophage infiltration and atherosclerosis by improving the thiol redox state: requirement of GSk3$\beta$/Fyn-dependent Nrf2 activation. *FASEB J*. 2022;36:e22261.
37. Cao D, Li H, Yi J, et al. Antioxidant properties of the mung bean flavonoids on alleviating heat stress. *PLoS One*. 2011;6:e21071.
38. Zhang C, Wang K, Yang L, et al. Lipid metabolism in inflammation-related diseases. *Analyst*. 2018;143:4526-4536.
39. Chen X-M, Tait AR, Kitts DD. Flavonoid composition of orange peel and its association with antioxidant and anti-inflammatory activities. *Food Chem*. 2017;218:15-21.
40. Zhang L, Sun Y, Xu W, et al. Baicalin inhibits Salmonella typhimurium-induced inflammation and mediates autophagy through TLR4/MAPK/NF-$\kappa$B signalling pathway. *Basic Clin Pharmacol Toxicol*. 2021;128:241-255.
41. Zou M, Yang L, Niu L, et al. Baicalin ameliorates Mycoplasma gallisepticum-induced lung inflammation in chicken by inhibiting TLR6-mediated NF-$\kappa$B signalling. *Br Poult Sci*. 2021;62:199-210.
42. Lv Q, Shi C, Qiao S, et al. Alpinetin exerts anti-colitis efficacy by activating AhR, regulating miR-302/DNMT-1/CREB signals, and therefore promoting Treg differentiation. *Cell Death Dis*. 2018;9:890.
43. Biasizzo M, Kopitar-Jerala N. Interplay between NLRP3 inflammasome and autophagy. *Front Immunol*. 2020;11:591803.
44. Liu Z, Gao S, Bu Y, Zheng X. Luteolin protects cardiomyocytes cells against lipopolysaccharide-induced apoptosis and inflammatory damage by modulating Nlrp3. *Yonsei Med J*. 2022;63:220-228.
45. Qu Y, Li X, Xu F, et al. Kaempferol alleviates murine experimental colitis by restoring gut microbiota and inhibiting the LPS-TLR4-NF-$\kappa$B axis. *Front Immunol*. 2021;12:679897.
46. Zhu L, Xu L-Z, Zhao S, et al. Protective effect of baicalin on the regulation of Treg/Th17 balance, gut microbiota and short-chain fatty acids in rats with ulcerative colitis. *Appl Microbiol Biotechnol*. 2020;104:5449-5460.
47. Shon JC, Kim WC, Ryu R, et al. Plasma lipidomics reveals insights into anti-obesity effect of chrysanthemum morifolium ramat leaves and its constituent luteolin in high-fat diet-induced dyslipidemic mice. *Nutrients*. 2020;12:2973.
48. Song D, Cheng L, Zhang X, et al. The modulatory effect and the mechanism of flavonoids on obesity. *J Food Biochem*. 2019;43:e12954.
49. Dinda B, Dinda M, Roy A, Dinda S. Dietary plant flavonoids in prevention of obesity and diabetes. *Adv Protein Chem Struct Biol*. 2020;120:159-235.
50. Jia Y, Ma Y, Cheng G, et al. Comparative study of dietary flavonoids with different structures as $\alpha$-glucosidase inhibitors and insulin sensitizers. *J Agric Food Chem*. 2019;67:10521-10533.
51. Mokashi P, Khanna A, Pandita N. Flavonoids from Enicostema littorale blume enhances glucose uptake of cells in insulin resistant human liver cancer (HepG2) cell line via IRS-1/PI3K/Akt pathway. *Biomed Pharmacother*. 2017;90:268-277.
52. Panickar KS. Effects of dietary polyphenols on neuroregulatory factors and pathways that mediate food intake and energy regulation in obesity. *Mol Nutr Food Res*. 2013;57:34-47.
53. Grau-Bové C, González-Quilen C, Terra X, et al. Effects of flavanols on enteroendocrine secretion. *Biomolecules*. 2020;10:844.
54. Jung CH, Cho I, Ahn J, et al. Quercetin reduces high-fat diet-induced fat accumulation in the liver by regulating lipid metabolism genes. *Phytother Res*. 2013;27:139-143.
55. Yang J, Lee J, Kim Y. Effect of deglycosylated rutin by acid hydrolysis on obesity and hyperlipidemia in high-fat diet-induced obese mice. *Nutrients*. 2020;12:1539.
56. Rahman HA, Sahib NG, Saari N, et al. Anti-obesity effect of ethanolic extract from Cosmos caudatus Kunth leaf in lean rats fed a high fat diet. *BMC Complement Altern Med*. 2017;17:122.
57. Zhou X, Chen S, Ye X. The anti-obesity properties of the proanthocyanidin extract from the leaves of Chinese bayberry (Myrica rubra Sieb.et Zucc.). *Food Funct*. 2017;8:3259-3270.
58. Zang Y, Zhang L, Igarashi K, Yu C. The anti-obesity and anti-diabetic effects of kaempferol glycosides from unripe soybean leaves in high-fat-diet mice. *Food Funct*. 2015;6:834-841.
59. Lee CW, Seo JY, Lee J, et al. 3-O-Glucosylation of quercetin enhances inhibitory effects on the adipocyte differentiation and lipogenesis. *Biomed Pharmacother*. 2017;95:589-598.
60. Ahn J, Lee H, Kim S, et al. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochem Biophys Res Commun*. 2008;373:545-549.
61. Li Y, Huang X, Yang G, et al. CD36 favours fat sensing and transport to govern lipid metabolism. *Prog Lipid Res*. 2022;88:101193.
62. Lim SH, Yu JS, Lee HS, et al. Antidiabetic flavonoids from fruits of morus alba promoting insulin-stimulated glucose uptake via Akt and AMP-activated protein kinase activation in 3T3-L1 adipocytes. *Pharmaceutics*. 2021;13:526.
63. Akindehin S, Jung Y-S, Kim S-N, et al. Myricetin exerts anti-obesity effects through upregulation of SIRT3 in adipose tissue. *Nutrients*. 2018;10:1962.
64. Han Y, Wu J-Z, Shen J-Z, et al. Pentamethylquercetin induces adipose browning and exerts beneficial effects in 3T3-L1 adipocytes and high-fat diet-fed mice. *Sci Rep*. 2017;7:1123.
65. Moon J, Do H-J, Kim OY, Shin M-J. Antiobesity effects of quercetin-rich onion peel extract on the differentiation of 3T3-L1 preadipocytes and the adipogenesis in high fat-fed rats. *Food Chem Toxicol*. 2013;58:347-354.
66. Bae C-R, Park Y-K, Cha Y-S. Quercetin-rich onion peel extract suppresses adipogenesis by down-regulating adipogenic transcription factors and gene expression in 3T3-L1 adipocytes. *J Sci Food Agric*. 2014;94:2655-2660.
67. Torres-Villarreal D, Camacho A, Castro H, et al. Anti-obesity effects of kaempferol by inhibiting adipogenesis and increasing lipolysis in 3T3-L1 cells. *J Physiol Biochem*. 2019;75:83-88.
68. Shimizu M, Li J, Inoue J, Sato R. Quercetin represses apolipoprotein B expression by inhibiting the transcriptional activity of C/EBP$\beta$. *PLoS One*. 2015;10:e0121784.
69. Li H, Qi J, Li L. Phytochemicals as potential candidates to combat obesity via adipose non-shivering thermogenesis. *Pharmacol Res*. 2019;147:104393.
70. Chen C-C, Kuo C-H, Leu Y-L, Wang S-H. Corylin reduces obesity and insulin resistance and promotes adipose tissue browning through SIRT-1 and $\beta$3-AR activation. *Pharmacol Res*. 2021;164:105291.
71. Lee HE, Yang G, Han S-H, et al. Anti-obesity potential of Glycyrrhiza uralensis and licochalcone A through induction of adipocyte browning. *Biochem Biophys Res Commun*. 2018;503:2117-2123.

72. Hu T, Yuan X, Wei G, et al. Myricetin-induced brown adipose tissue activation prevents obesity and insulin resistance in db/db mice. *Eur J Nutr*. 2018;57:391-403.
73. Pei Y, Otieno D, Gu I, et al. Effect of quercetin on nonshivering thermogenesis of brown adipose tissue in high-fat diet-induced obese mice. *J Nutr Biochem*. 2021;88:108532.
74. Nakagawa Y, Ishimura K, Oya S, et al. Comparison of the sympathetic stimulatory abilities of B-type procyanidins based on induction of uncoupling protein-1 in brown adipose tissue (BAT) and increased plasma catecholamine (CA) in mice. *PLoS One*. 2018;13:e0201203.
75. You Y, Yuan X, Liu X, et al. Cyanidin-3-glucoside increases whole body energy metabolism by upregulating brown adipose tissue mitochondrial function. *Mol Nutr Food Res*. 2017;61(11):1700261.
76. Varela CE, Rodriguez A, Romero-Valdovinos M, et al. Browning effects of (-)-epicatechin on adipocytes and white adipose tissue. *Eur J Pharmacol*. 2017;811:48-59.
77. Gao X, Guo M, Zhang Z, et al. Baicalin promotes the bacteriostatic activity of lysozyme on *S. aureus* in mammary glands and neutrophilic granulocytes in mice. *Oncotarget*. 2017;8:19894-19901.
78. Song Y, Liu J, Zhang F, et al. Antioxidant effect of quercetin against acute spinal cord injury in rats and its correlation with the p38MAPK/iNOS signaling pathway. *Life Sci*. 2013;92:1215-1221.
79. Oh D-R, Kim JR, Kim YR. Genistein inhibits Vibrio vulnificus adhesion and cytotoxicity to HeLa cells. *Arch Pharmacal Res*. 2010;33:787-792.
80. Wang S, Yao J, Zhou B, et al. Bacteriostatic effect of quercetin as an antibiotic alternative in vivo and its antibacterial mechanism in vitro. *J Food Prot*. 2018;81:68-78.
81. Hou D-D, Zhang W, Gao Y-L, et al. Anti-inflammatory effects of quercetin in a mouse model of MC903-induced atopic dermatitis. *Int Immunopharmacol*. 2019;74:105676.
82. Kuo P-C, Hung H-Y, Hwang T-L, et al. Anti-inflammatory Flavan-3-ol-dihydroretrochalcones from Daemonorops draco. *J Nat Prod*. 2017;80:783-789.
83. Khayyal MT, El-Hazek RM, El-Sabbagh WA, et al. Micellar solubilization enhances the anti-inflammatory effect of xanthohumol. *Phytomedicine*. 2020;71:153233.
84. Koteswari LL, Kumari S, Kumar AB, Malla RR. A comparative anticancer study on procyanidin C1 against receptor positive and receptor negative breast cancer. *Nat Prod Res*. 2020;34:3267-3274.
85. Hashemzaei M, Delarami Far A, Yari A, et al. Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo. *Oncol Rep*. 2017;38:819-828.
86. Hu P, Ma L, Wang Y-G, et al. Genistein, a dietary soy isoflavone, exerts antidepressant-like effects in mice: involvement of serotonergic system. *Neurochem Int*. 2017;108:426-435.
87. Song X, Wang W, Ding S, et al. Puerarin ameliorates depression-like behaviors of with chronic unpredictable mild stress mice by remodeling their gut microbiota. *J Affect Disord*. 2021;290:353-363.
88. Li G, Yang J, Wang X, et al. Effects of EGCG on depression-related behavior and serotonin concentration in a rat model of chronic unpredictable mild stress. *Food Funct*. 2020;11:8780-8787.
89. Nettore IC, Rocca C, Mancino G, et al. Quercetin and its derivative Q2 modulate chromatin dynamics in adipogenesis and Q2 prevents obesity and metabolic disorders in rats. *J Nutr Biochem*. 2019;69:151-162.
90. Wan Y, Yu Y, Pan X, et al. Inhibition on acid-sensing ion channels and analgesic activities of flavonoids isolated from dragon's blood resin. *Phytother Res*. 2019;33:718-727.
91. Giannini I, Amato A, Basso L, et al. Flavonoids mixture (diosmin, troxerutin, hesperidin) in the treatment of acute hemorrhoidal disease: a prospective, randomized, triple-blind, controlled trial. *Tech Coloproctol*. 2015;19:339-345.
92. Dai W, Bi J, Li F, et al. Antiviral efficacy of flavonoids against enterovirus 71 infection in vitro and in newborn mice. *Viruses*. 2019;11:625.
93. Tian X, Jiang H, Chen Y, et al. Baicalein accelerates tendon-bone healing via activation of Wnt/$\beta$-catenin signaling pathway in rats. *Biomed Res Int*. 2018;2018:3849760.
94. Choudhary A, Kant V, Jangir BL, Joshi VG. Quercetin loaded chitosan tripolyphosphate nanoparticles accelerated cutaneous wound healing in Wistar rats. *Eur J Pharmacol*. 2020;880:173172.
95. Süntar I, Küpeli Akkol E, Keles H, et al. Exploration of the wound healing potential of Helichrysum graveolens (Bieb.) Sweet: isolation of apigenin as an active component. *J Ethnopharmacol*. 2013;149:103-110.
96. Kim MH, Choi YY, Lee JE, et al. Topical treatment of hair loss with formononetin by modulating apoptosis. *Planta Med*. 2016;82:65-69.
97. Taguchi N, Yuriguchi M, Ando T, et al. Flavonoids with two OH groups in the B-ring promote pigmented hair regeneration. *Biol Pharm Bull*. 2019;42:1446-1449.
98. Kwon OS, Han JH, Yoo HG, et al. Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine*. 2007;14:551-555.
99. Abdou HM, Hamaad FA, Ali EY, Ghoneum MH. Antidiabetic efficacy of Trifolium alexandrinum extracts hesperetin and quercetin in ameliorating carbohydrate metabolism and activating IR and AMPK signaling in the pancreatic tissues of diabetic rats. *Biomed Pharmacother*. 2022;149:112838.
100. Ge X, He X, Lin Z, et al. 6,8-(1,3-Diaminoguanidine) luteolin and its Cr complex show hypoglycemic activities and alter intestinal microbiota composition in type 2 diabetes mice. *Food Funct*. 2022;13:3572-3589.
101. Feng Z, Wang C, Yue Jin, et al. Kaempferol-induced GPER upregulation attenuates atherosclerosis via the PI3K/AKT/Nrf2 pathway. *Pharm Biol*. 2021;59:1106-1116.
102. Chen G, Xu H, Wu Y, et al. Myricetin suppresses the proliferation and migration of vascular smooth muscle cells and inhibits neointimal hyperplasia via suppressing TGFBR1 signaling pathways. *Phytomedicine*. 2021;92:153719.
103. Wang Z, Zhang M, Wang Z, et al. Cyanidin-3-O-glucoside attenuates endothelial cell dysfunction by modulating miR-204-5p/SIRT1-mediated inflammation and apoptosis. *Biofactors*. 2020;46:803-812.
104. Tian L, Tan Y, Chen G, et al. Metabolism of anthocyanins and consequent effects on the gut microbiota. *Crit Rev Food Sci Nutr*. 2019;59:982-991.

105. Cheng J-R, Liu X-M, Chen Z-Y, et al. Mulberry anthocyanin biotransformation by intestinal probiotics. *Food Chem*. 2016;213:721-727.
106. Ozdal T, Sela DA, Xiao J, et al. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients*. 2016;8:78.
107. Lin W, Wang W, Yang H, et al. Influence of intestinal microbiota on the catabolism of flavonoids in mice. *J Food Sci*. 2016;81:H3026-H3034.
108. González-Paramás AM, Ayuda-Durán B, Martínez S, et al. The mechanisms behind the biological activity of flavonoids. *Curr Med Chem*. 2019;26:6976-6990.
109. Hidalgo M, Oruna-Concha MJ, Kolida S, et al. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *J Agric Food Chem*. 2012;60:3882-3890.
110. Labib S, Erb A, Kraus M, et al. The pig caecum model: a suitable tool to study the intestinal metabolism of flavonoids. *Mol Nutr Food Res*. 2004;48:326-332.
111. Zhang M, Zhu S, Yang W, et al. The biological fate and bioefficacy of citrus flavonoids: bioavailability, biotransformation, and delivery systems. *Food Funct*. 2021;12:3307-3323.
112. Soukup ST, Stoll DA, Danylec N, et al. Metabolism of daidzein and genistein by gut bacteria of the class coriobacteriia. *Foods (Basel, Switzerland)*. 2021;10:2741.
113. Wang Q, Spenkelink B, Boonpawa R, et al. Use of physiologically based kinetic modeling to predict rat gut microbial metabolism of the isoflavone daidzein to S-equol and its consequences for ER$\alpha$ activation. *Mol Nutr Food Res*. 2020;64:e1900912.
114. Braune A, Blaut M. Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut Microbes*. 2016;7:216-234.
115. Bitner BF, Ray JD, Kener KB, et al. Common gut microbial metabolites of dietary flavonoids exert potent protective activities in $\beta$-cells and skeletal muscle cells. *J Nutr Biochem*. 2018;62:95-107.
116. Yu J, Yan F, Lu Q, Liu R. Interaction between sorghum procyanidin tetramers and the catalytic region of glucosyltransferases-I from Streptococcus mutans UA159. *Food Res Int (Ottawa, Ont)*. 2018;112:152-159.
117. Vasudevan S, Thamil Selvan G, Bhaskaran S, et al. Reciprocal cooperation of type A procyanidin and nitrofurantoin against multi-drug resistant (MDR) UPEC: a pH-dependent study. *Front Cell Infect Microbiol*. 2020;10:421.
118. Raut J, Rathod V, Karuppayil SM. Cell surface hydrophobicity and adhesion: a study on fifty clinical isolates of Candida albicans. *Nippon Ishinkin Gakkai Zasshi*. 2010;51:131-136.
119. Rodríguez-Pérez C, Quirantes-Piné R, Uberos J, et al. Antibacterial activity of isolated phenolic compounds from cranberry (Vaccinium macrocarpon) against *Escherichia coli*. *Food Funct*. 2016;7:1564-1573.
120. Alejo-Armijo A, Glibota N, Frías MP, et al. Synthesis and evaluation of antimicrobial and antibiofilm properties of A-type procyanidin analogues against resistant bacteria in food. *J Agric Food Chem*. 2018;66:2151-2158.
121. Nobakht M, Trueman SJ, Wallace HM, et al. Antibacterial properties of flavonoids from kino of the eucalypt tree, corymbia torelliana. *Plants (Basel, Switzerland)*. 2017;6:39.
122. Alam K, Farraj DAA, Mah-E-Fatima S, et al. Anti-biofilm activity of plant derived extracts against infectious pathogen-Pseudomonas aeruginosa PAO1. *J Infect Public Health*. 2020;13:1734-1741.
123. Luo J, Kong J-L, Dong B-Y, et al. Baicalein attenuates the quorum sensing-controlled virulence factors of Pseudomonas aeruginosa and relieves the inflammatory response in *P. aeruginosa*-infected macrophages by downregulating the MAPK and NF$\kappa$B signal-transduction pathways. *Drug Des Dev Ther*. 2016;10:183-203.
124. Chen Y, Liu T, Wang K, et al. Baicalein inhibits staphylococcus aureus biofilm formation and the quorum sensing system in vitro. *PLoS One*. 2016;11:e0153468.
125. Gopu V, Meena CK, Shetty PH. Quercetin influences quorum sensing in food borne bacteria: in-vitro and in-silico evidence. *PLoS One*. 2015;10:e0134684.
126. Mostafa I, Abbas HA, Ashour ML, et al. Polyphenols from salix tetrasperma impair virulence and inhibit quorum sensing of pseudomonas aeruginosa. *Molecules*. 2020;25:1341.
127. Luo J, Dong B, Wang K, et al. Baicalin inhibits biofilm formation, attenuates the quorum sensing-controlled virulence and enhances Pseudomonas aeruginosa clearance in a mouse peritoneal implant infection model. *PLoS One*. 2017;12:e0176883.
128. Kusuda M, Inada K, Ogawa T-O, et al. Polyphenolic constituent structures of Zanthoxylum piperitum fruit and the antibacterial effects of its polymeric procyanidin on methicillin-resistant *Staphylococcus aureus*. *Biosci Biotechnol Biochem*. 2006;70:1423-1431.
129. Li X, He C, Song L, et al. Antimicrobial activity and mechanism of Larch bark procyanidins against Staphylococcus aureus. *Acta Biochim Biophy Sin*. 2017;49:1058-1066.
130. Lin Z, Lin Y, Zhang Z, et al. Systematic analysis of bacteriostatic mechanism of flavonoids using transcriptome and its therapeutic effect on vaginitis. *Aging*. 2020;12:6292-6305.
131. Ulanowska K, Tkaczyk A, Konopa G, Wegrzyn G. Differential antibacterial activity of genistein arising from global inhibition of DNA, RNA and protein synthesis in some bacterial strains. *Arch Microbiol*. 2006;184:271-278.
132. Wu T, Zang X, He M, et al. Structure-activity relationship of flavonoids on their anti-Escherichia coli activity and inhibition of DNA gyrase. *J Agric Food Chem*. 2013;61:8185-8190.
133. Tong Y, Gao H, Qi Q, et al. High fat diet, gut microbiome and gastrointestinal cancer. *Theranostics*. 2021;11:5889-5910.
134. Jamar G, Ribeiro DA, Pisani LP. High-fat or high-sugar diets as trigger inflammation in the microbiota-gut-brain axis. *Crit Rev Food Sci Nutr*. 2021;61:836-854.
135. Sun W-L, Li X-Y, Dou H-Y, et al. Myricetin supplementation decreases hepatic lipid synthesis and inflammation by modulating gut microbiota. *Cell Rep*. 2021;36:109641.
136. Duan R, Guan X, Huang K, et al. Flavonoids from whole-grain oat alleviated high-fat diet-induced hyperlipidemia via regulating bile acid metabolism and gut microbiota in mice. *J Agric Food Chem*. 2021;69:7629-7640.
137. Shen C-Y, Hao Y-F, Hao Z-X, et al. Flavonoids from *Rosa davurica* Pall. fruits prevent high-fat diet-induced obesity and liver injury *via* modulation of the gut microbiota in mice. *Food Funct*. 2021;12:10097-10106.
138. Li Z, Ren Z, Zhao L, et al. Unique roles in health promotion of dietary flavonoids through gut microbiota regulation:

current understanding and future perspectives. *Food Chem*. 2023;399:133959.

139. Filannino P, Bai Y, Di Cagno R, et al. Metabolism of phenolic compounds by Lactobacillus spp. during fermentation of cherry juice and broccoli puree. *Food Microbiol*. 2015;46:272-279.
140. Feng J, Wang J, Bu T, et al. Structural, in vitro digestion, and fermentation characteristics of lotus leaf flavonoids. *Food Chem*. 2023;406:135007.
141. Cheng Y, Liu J, Ling Z. Short-chain fatty acids-producing probiotics: a novel source of psychobiotics. *Crit Rev Food Sci Nutr*. 2022;62:7929-7959.
142. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*. 2016;7:189-200.
143. de Vos WM, Tilg H, van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. *Gut*. 2022;71:1020-1032.
144. Yan X, Yang C, Lin G, et al. Antidiabetic potential of green seaweed enteromorpha prolifera flavonoids regulating insulin signaling pathway and gut microbiota in type 2 diabetic mice. *J Food Sci*. 2019;84:165-173.
145. Sheng Y, Liu J, Zheng S, et al. Mulberry leaves ameliorate obesity through enhancing brown adipose tissue activity and modulating gut microbiota. *Food Funct*. 2019;10:4771-4781.
146. Zhao C, Guo J, Du C, Xu Y. Modulation of fat deposition-gut interactions in obese mice by administrating with nobiletin. *Genes*. 2023;14:1062.
147. Li Z, Gurung M, Rodrigues RR, et al. Microbiota and adipocyte mitochondrial damage in type 2 diabetes are linked by Mmp12+ macrophages. *J Exp Med*. 2022;219:e20220017.
148. Jang S, Sun J, Chen P, et al. Flavanol-enriched cocoa powder alters the intestinal microbiota, tissue and fluid metabolite profiles, and intestinal gene expression in pigs. *J Nutr*. 2016;146:673-680.
149. Zhao T, Shen X, Dai C, Cui L. Benefits of procyanidins on gut microbiota in Bama minipigs and implications in replacing antibiotics. *J Vet Sci*. 2018;19:798-807.
150. Wu Y, Li Y, Ruan Z, et al. Puerarin rebuilding the mucus layer and regulating mucin-utilizing bacteria to relieve ulcerative colitis. *J Agric Food Chem*. 2020;68:11402-11411.
151. Li B, Liu M, Wang Y, et al. Puerarin improves the bone micro-environment to inhibit OVX-induced osteoporosis via modulating SCFAs released by the gut microbiota and repairing intestinal mucosal integrity. *Biomed Pharmacother*. 2020;132:110923.
152. Guadamuro L, Azcárate-Peril MA, Tojo R, et al. Impact of dietary isoflavone supplementation on the fecal microbiota and its metabolites in postmenopausal women. *Int J Environ Res Public Health*. 2021;18:7939.
153. Han Y, Haraguchi T, Iwanaga S, et al. Consumption of some polyphenols reduces fecal deoxycholic acid and lithocholic acid, the secondary bile acids of risk factors of colon cancer. *J Agric Food Chem*. 2009;57:8587-8590.
154. Huang F, Zheng X, Ma X, et al. Theabrownin from Pu-erh tea attenuates hypercholesterolemia via modulation of gut microbiota and bile acid metabolism. *Nat Commun*. 2019;10:4971.
155. Zeng S-L, Li S-Z, Xiao P-T, et al. Citrus polymethoxyflavones attenuate metabolic syndrome by regulating gut microbiome and amino acid metabolism. *Sci Adv*. 2020;6:eaax6208.
156. Wu D-N, Guan L, Jiang Y-X, et al. Microbiome and metabonomics study of quercetin for the treatment of atherosclerosis. *Cardiovasc Diagn Ther*. 2019;9:545-560.
157. Osborn LJ, Claesen J, Brown JM. Microbial flavonoid metabolism: a cardiometabolic disease perspective. *Annu Rev Nutr*. 2021;41:433-454.
158. Zhang T, Hu Q, Shi L, et al. Equol attenuates atherosclerosis in apolipoprotein E-deficient mice by inhibiting endoplasmic reticulum stress via activation of Nrf2 in endothelial cells. *PLoS One*. 2016;11:e0167020.
159. Ni YD, Wei XJ, Zhang CX, et al. The effect of equol injection in ovo on lipid metabolism and hepatic lipogenic gene expression in broilers. *Animal*. 2012;6:1444-1450.
160. Ham JR, Lee H-I, Choi R-Y, et al. Anti-steatotic and anti-inflammatory roles of syringic acid in high-fat diet-induced obese mice. *Food Funct*. 2016;7:689-697.
161. Chao J, Cheng H-Y, Chang M-L, et al. Gallic acid ameliorated impaired lipid homeostasis in a mouse model of high-fat diet-and streptozotocin-induced NAFLD and diabetes through improvement of $\beta$-oxidation and ketogenesis. *Front Pharmacol*. 2020;11:606759.
162. Gandhi GR, Jothi G, Antony PJ, et al. Gallic acid attenuates high-fat diet fed-streptozotocin-induced insulin resistance via partial agonism of PPAR$\gamma$ in experimental type 2 diabetic rats and enhances glucose uptake through translocation and activation of GLUT4 in PI3K/p-Akt signaling pathway. *Eur J Pharmacol*. 2014;745:201-216.
163. Huang D-W, Chang W-C, Yang H-J, et al. Gallic acid alleviates hypertriglyceridemia and fat accumulation via modulating glycolysis and lipolysis pathways in perirenal adipose tissues of rats fed a high-fructose diet. *Int J Mol Sci*. 2018;19(1):254.
164. Seo SH, Jo S-M, Truong TTM, et al. Peanut sprout rich in p-coumaric acid ameliorates obesity and lipopolysaccharide-induced inflammation and the inhibition of browning in adipocytes via mitochondrial activation. *Food Funct*. 2021;12:5361-5374.
165. Yoon DS, Cho SY, Yoon HJ, et al. Protective effects of p-coumaric acid against high-fat diet-induced metabolic dysregulation in mice. *Biomed Pharmacother*. 2021;142:111969.
166. Sheng L, Jena PK, Liu H-X, et al. Obesity treatment by epigallocatechin-3-gallate-regulated bile acid signaling and its enriched Akkermansia muciniphila. *FASEB J*. 2018;32:fj201800370R.
167. Xu B, Qin W, Xu Y, et al. Dietary quercetin supplementation attenuates diarrhea and intestinal damage by regulating gut microbiota in weanling piglets. *Oxid Med Cell Long*. 2021;2021:6221012.
168. Zhang L, Carmody RN, Kalariya HM, et al. Grape proanthocyanidin-induced intestinal bloom of Akkermansia muciniphila is dependent on its baseline abundance and precedes activation of host genes related to metabolic health. *J Nutr Biochem*. 2018;56:142-151.
169. Falcinelli S, Rodiles A, Hatef A, et al. Influence of probiotics administration on gut microbiota core: a review on the effects on appetite control, glucose, and lipid metabolism. *J Clin Gastroenterol*. 2018;52(Suppl 1):S50-S56.
170. Abuqwider JN, Mauriello G, Altamimi M. Akkermansia muciniphila, a new generation of beneficial microbiota in

modulating obesity: a systematic review. *Microorganisms*. 2021;9:1098.
171. Han Q, Huang X, Yan F, et al. The role of gut microbiota in the skeletal muscle development and fat deposition in pigs. *Antibiotics (Basel, Switzerland)*. 2022;11:793.
172. Ashrafian F, Shahriary A, Behrouzi A, et al. Akkermansia muciniphila-derived extracellular vesicles as a mucosal delivery vector for amelioration of obesity in mice. *Front Microbiol*. 2019;10:2155.
173. Depommier C, van Hul M, Everard A, et al. Pasteurized Akkermansia muciniphila increases whole-body energy expenditure and fecal energy excretion in diet-induced obese mice. *Gut Microbes*. 2020;11:1231-1245.
174. Ashrafian F, Keshavarz Azizi Raftar S, Lari A, et al. Extracellular vesicles and pasteurized cells derived from Akkermansia muciniphila protect against high-fat induced obesity in mice. *Microb Cell Fact*. 2021;20:219.
175. Deng L, Ou Z, Huang D, et al. Diverse effects of different Akkermansia muciniphila genotypes on brown adipose tissue inflammation and whitening in a high-fat-diet murine model. *Microb Pathog*. 2020;147:104353.
176. Yoon HS, Cho CH, Yun MS, et al. Akkermansia muciniphila secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. *Nat Microbiol*. 2021;6:563-573.
177. Lukovac S, Belzer C, Pellis L, et al. Differential modulation by Akkermansia muciniphila and Faecalibacterium prausnitzii of host peripheral lipid metabolism and histone acetylation in mouse gut organoids. *mBio*. 2014;5(4):10-1128.
178. Plovier H, Everard A, Druart C, et al. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat Med*. 2017;23:107-113.
179. Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. *Nat Rev Microbiol*. 2021;19:77-94.
180. Odermatt A, Da Cunha T, Penno CA, et al. Hepatic reduction of the secondary bile acid 7-oxolithocholic acid is mediated by 11$\beta$-hydroxysteroid dehydrogenase 1. *Biochem J*. 2011;436:621-629.
181. Tolhurst G, Heffron H, Lam YS, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes*. 2012;61:364-371.
182. Christiansen CB, Gabe MBN, Svendsen B, et al. The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. *Am J Physiol Gastrointest Liver Physiol*. 2018;315:G53-G65.
183. Legchenko E, Chouvarine P, Borchert P, et al. PPAR$\gamma$ agonist pioglitazone reverses pulmonary hypertension and prevents right heart failure via fatty acid oxidation. *Sci Transl Med*. 2018;10:eaao0303.
184. den Besten G, Bleeker A, Gerding A, et al. Short-chain fatty acids protect against high-fat diet-induced obesity via a PPAR$\gamma$-dependent switch from lipogenesis to fat oxidation. *Diabetes*. 2015;64:2398-2408.
185. Jester JV, Potma E, Brown DJ. PPAR$\gamma$ regulates mouse meibocyte differentiation and lipid synthesis. *Ocul Surf*. 2016;14:484-494.
186. Semple RK, Chatterjee VKK, O'Rahilly S. PPAR gamma and human metabolic disease. *J Clin Invest*. 2006;116:581-589.
187. Zaibi MS, Stocker CJ, O'Dowd J, et al. Roles of GPR41 and GPR43 in leptin secretory responses of murine adipocytes to short chain fatty acids. *FEBS Lett*. 2010;584:2381-2386.
188. Soliman M, Kimura K, Ahmed M, et al. Inverse regulation of leptin mRNA expression by short- and long-chain fatty acids in cultured bovine adipocytes. *Domest Anim Endocrinol*. 2007;33:400-409.
189. Araújo JR, Tazi A, Burlen-Defranoux O, et al. Fermentation products of commensal bacteria alter enterocyte lipid metabolism. *Cell Host Microbe*. 2020;27:358-375. e7.
190. Dou X, Ma Z, Yan Di, et al. Sodium butyrate alleviates intestinal injury and microbial flora disturbance induced by lipopolysaccharides in rats. *Food Funct*. 2022;13:1360-1369.
191. Dou X, Yan Di, Ma Z, et al. Sodium butyrate alleviates LPS-induced kidney injury via inhibiting TLR2/4 to regulate rBD2 expression. *J Food Biochem*. 2022;46:e14126.
192. Wu D, Ding L, Tang X, et al. Baicalin protects against hypertension-associated intestinal barrier impairment in part through enhanced microbial production of short-chain fatty acids. *Front Pharmacol*. 2019;10:1271.
193. Thomas C, Pellicciari R, Pruzanski M, et al. Targeting bile-acid signalling for metabolic diseases. *Nat Rev Drug Discov*. 2008;7:678-693.
194. Funabashi M, Grove TL, Wang M, et al. A metabolic pathway for bile acid dehydroxylation by the gut microbiome. *Nature*. 2020;582:566-570.
195. Gonzalez FJ, Jiang C, Patterson AD. An intestinal microbiota-farnesoid X receptor axis modulates metabolic disease. *Gastroenterology*. 2016;151:845-859.
196. de Boer JF, Schonewille M, Boesjes M, et al. Intestinal farnesoid X receptor controls transintestinal cholesterol excretion in mice. *Gastroenterology*. 2017;152:1126-1138. e6.
197. Wang F, Zhao C, Tian G, et al. Naringin alleviates atherosclerosis in ApoE-/- mice by regulating cholesterol metabolism involved in gut microbiota remodeling. *J Agric Food Chem*. 2020;68:12651-12660.
198. Castellanos-Jankiewicz A, Guzmán-Quevedo O, Fénelon VS, et al. Hypothalamic bile acid-TGR5 signaling protects from obesity. *Cell Metab*. 2021;33:1483-1492. e10.
199. He B, Jiang J, Shi Z, et al. Pure total flavonoids from citrus attenuate non-alcoholic steatohepatitis via regulating the gut microbiota and bile acid metabolism in mice. *Biomed Pharmacother*. 2021;135:111183.
200. Yan X, Zhang Y, Peng Y, Li X. The water extract of Radix scutellariae, its total flavonoids and baicalin inhibited CYP7A1 expression, improved bile acid, and glycolipid metabolism in T2DM mice. *J Ethnopharmacol*. 2022;293:115238.

**How to cite this article:** Zhou M, Ma J, Kang M, et al. Flavonoids, gut microbiota, and host lipid metabolism. *Eng Life Sci*. 2024;24:e2300065. https://doi.org/10.1002/elsc.202300065