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REVIEW

Bioavailability Based on the Gut Microbiota: a New Perspective

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SUMMARY The substantial discrepancy between the strong effects of functional foods and various drugs, especially traditional Chinese medicines (TCMs), and the poor bioavailability of these substances remains a perplexing problem. Understanding the gut microbiota, which acts as an effective bioreactor in the human intestinal tract, provides an opportunity for the redefinition of bioavailability. Here, we discuss four different pathways associated with the role of the gut microbiota in the transformation of parent compounds to beneficial or detrimental small molecules, which can enter the body's circulatory system and be available to target cells, tissues, and organs. We further describe and propose effective strategies for improving bioavailability and alleviating side effects with the help of the gut microbiota. This review also broadens our perspectives for the discovery of new medicinal components.

KEYWORDS bioavailability, gut microbiota, host metabolism, nutrient and drug outcomes, short-chain fatty acid

INTRODUCTION

Considerable attention has been paid to the substantial discrepancy between the strong biological effects of some drugs and functional foods and the poor bioavailability of these substances. Recent studies by Zimmermann et al. have opened the door to a revolution in understanding the important roles of the gut microbiota in the metabolism of many pharmaceuticals, which could lead to a possible redefinition of bioavailability (1, 2).

For orally administered drugs and functional foods, bioavailability generally sum-

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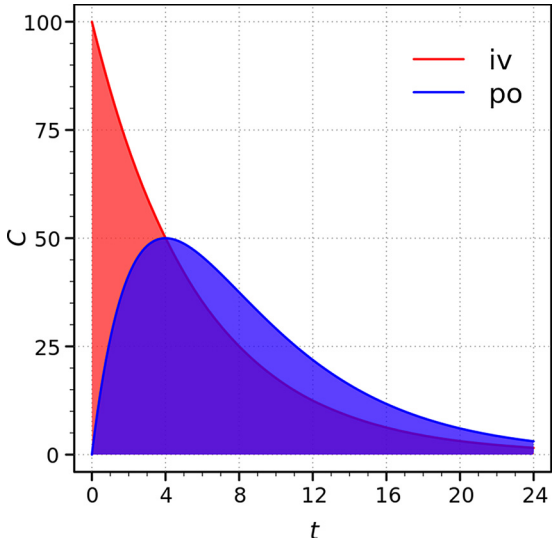


FIG 1 General understanding of bioavailability: the ratio of the areas under the curves. iv, intravenous administration; po, oral route; *C*, plasma concentration (in arbitrary units) (3, 4).

marizes the quantity or proportion of the ingested dose that is directly absorbed in the small intestine to enter the living system (into circulation) (Fig. 1) (3, 4). However, the parent ingredients of compounds, especially many Chinese herbs and medicinal foods, are difficult to detect in the circulatory system after oral administration, while many Chinese herbs and medicinal foods have been proven to be efficient for thousands of years. Troubleshooting and other strategies, such as modification of structures and delivery systems, have been carried out to improve bioavailability in the small intestine, but most of these attempts have been in vain. Recent great progress in studies on the gut microbiota has shed light on understanding the discrepancy between the explicit effects of parent compounds and low plasma concentrations. It has been reported that the influence of intestinal commensal bacteria on the utilization of these compounds might explain such a discrepancy (5–7).

Zimmermann et al. utilized a combination of germfree animals and *Bacteroides thetaiotaomicron* transposon mutants deficient in enzymes that could convert brivudine (BRV) to bromovinyluracil (BVU) as a pharmacokinetic paradigm to quantitatively predict host and microbiome contributions to drug metabolic transformation. Astonishingly, the contributions of the microbiome to the metabolism of some drugs are much more than 50% (1). Chemical modifications of 271 oral drugs under microbiome-encoded enzymes of 76 diverse gut bacteria were further identified as being the results of oxidation, reduction, deacetylation, hydrogenation, hydroxylation, acetylation, and propionylation, which changed the masses of metabolites with respect to the corresponding parent drugs. This revealed causal links between the microbiota gene content and interpersonal differences in drug metabolism and drug responses (2). In addition, another model of a special population can demonstrate the roles of the intestinal microbiota in the human body in the regulation of bioavailability. Ileostomists, first reported by Hollman et al. in 1995 (6), are patients who have their colons surgically isolated from their bodies. Ileostomists are ideal model systems for examination of the absorption ratios of dietary substances in the human small and large intestines. During the 24 h after ingestion of coffee, the ratio of the metabolites presented in the urine of ileostomy patients to chlorogenic acid intake was 8% $\pm$ 1%, while this ratio was 29% $\pm$ 4% for the group consisting of healthy subjects (8). With the help of such a model for humans, Stalmach et al. indicated that the absorption of chlorogenic acid in instant coffee occurred in both the small and large intestines and that absorption occurred primarily in the large intestine (9). Thus, the microbiota in both the small intestine and colon should be considered to influence the bioavailability of foods or

drugs. Therefore, the classic conceptual framework of bioavailability needs to be reexamined. The important roles of the gut microbiota in the metabolism of many pharmaceuticals and foods have led to a possible redefinition of bioavailability. Here, we summarize four pathways in the regulation of bioavailability by the gut microbiota and present constructive proposals for the improvement of bioavailability based on modulation of the gut microbiota.

THE GUT MICROBIOTA: A BIOREACTOR OF VARIOUS BIOACTIVE METABOLITES FROM PARENT COMPOUNDS

A vast number of gut bacteria have colonized the human intestinal tract throughout human history. These microbes are referred to as our second genome due to their high abundance and vital role. The gut microbiota was found to be a strong regulator of energy harvesting in 2004 (10); accordingly, these microbes have shown strong correlations with processes such as lipometabolism (11–14), glycometabolism (15–18), intestinal infection (19–21), brain function (22–26), immunity (27–29), and tumorigenesis (30–32). The gut microbiota is influenced by both genetic (33) and environmental (34, 35) factors, although the latter are more important than the former.

The gut microbiota can help hosts to digest ingested foods or drugs via enzymes that are secreted only by bacteria and via the excretion of fecal energy. The main metabolic reactions have been reported to be conducted by intestinal microbial enzymes, including β-glucosidase, β-glucuronidase, azoreductase, sulfatase, nitroreductase, and nitrate reductase (36, 37). Important biotransformations, including reductive metabolism, hydrolytic reactions, demethylation, deamination, dehydroxylation, deacylation, decarboxylation, and oxidation, are considered to be conducted by specific gut microbes (36, 38–40). Although the metabolites and related enzymes that participate in these biotransformations have been described for some reactions, an understanding of the roles of the enteric community of bacteria in these biochemical reactions remains largely uncharacterized (41).

The intestinal microbiota has significant effects on the digestion of foods and the synthesis of beneficial bioactive substances, such as short-chain fatty acids (SCFAs) (18, 42–44) and vitamins (45, 46), and detrimental molecules, such as lipopolysaccharides (LPSs) (47, 48), branched-chain amino acids (BCAAs) (49), bile acids (50, 51), and trimethylamine (TMA), the precursor of TMA *N*-oxide (TMAO) (52, 53). Therefore, despite the direct effects of some substances on human health, many biological functions are performed by small bioactive molecules transformed from either foods or drugs by the gut microbiota. We propose that the intestinal microbiota has significant effects on the formation of bioactive small molecules via four pathways (Fig. 2): the gut microbiota biotransforms the parent functional foods and drugs directly into bioactive compounds (pathway 1), nonparent components trigger the metabolism of the parent nutrients by beneficial gut bacteria to produce additional beneficial molecules (pathway 2), the gut microbiota is modulated by nonparent molecules to decrease the entry of detrimental metabolites from the parent drugs or foods into the bloodstream (pathway 3), and specific gut bacteria that can transform the parent drugs into inactive compounds are inhibited by nonparent molecules to increase the entry of drugs into the circulatory system (pathway 4). Notably, in pathway 1, the investigated components are the parent molecules, the metabolites of which are the bioactive molecules, and in pathway 4, the investigated compounds are the bioactive components themselves. In contrast, in pathways 2 and 3, the investigated compounds are the nonparent compounds that affect the bioavailability of the parent compounds (frequently from the daily diet) via modulation of the gut microbiota. Therefore, when discussing bioavailability, we should distinguish parent compounds from nonparent compounds. Furthermore, the four pathways (especially pathways 1 and 2) are seldom mutually exclusive and occur separately.

Most of the interactions between parent foods or drugs and the intestinal microbiota can potentially be classified into one of the above-described four pathways. Therefore, it is crucial to reasonably improve the bioavailability of parent foods or drugs effectively based on one of these four pathways to improve the therapeutic effects of

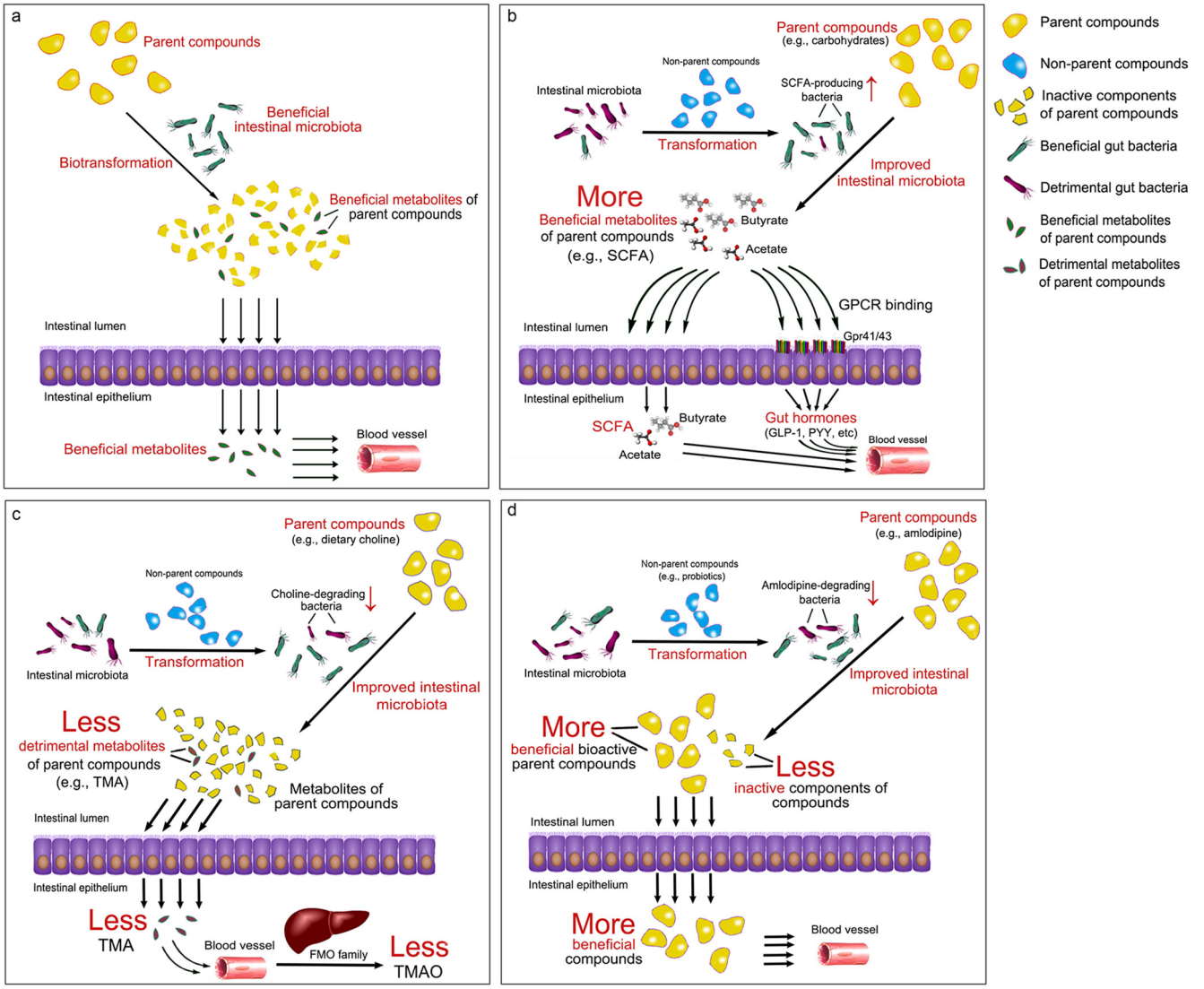


FIG 2 Four pathways by which the gut microbiota alters the bioavailability of food and medicine. (a) Pathway 1: direct biotransformation of parent compounds to beneficial metabolites by the gut microbiota. (b) Pathway 2: increase of beneficial metabolites from parent compounds by specific gut bacteria enriched by nonparent compounds. (c) Pathway 3: decrease of detrimental metabolites from parent compounds via modulation of the gut microbiota by nonparent compounds. (d) Pathway 4: inhibition of specific gut bacteria transforming parent compounds into inactive forms by nonparent compounds.

these substances. Unquestionably, such a development would rapidly expand the market for researchers and producers of functional foods and pharmaceuticals.

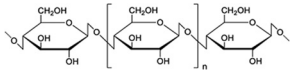
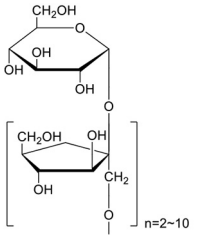
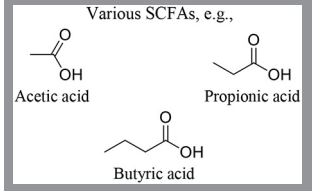
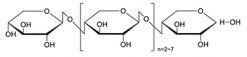
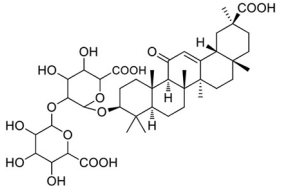
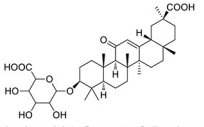
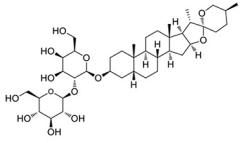
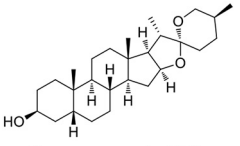
THE FOUR PATHWAYS: A BREAKTHROUGH IN THE SEARCH FOR THE EXACT BIOACTIVE MOLECULES

The gut microbiota improves the bioavailability of the parent ingested substances via four pathways to promote the therapeutic effects of these substances. These four pathways also lay the foundation for subsequent breakthroughs in the search for functional foods and new drugs. All the parent compounds, metabolites, and key gut bacteria involved in the improvement of bioavailability mentioned in this review are summarized in Table 1.

Pathway 1: Direct Biotransformation of Parent Compounds into Beneficial Metabolites by the Gut Microbiota

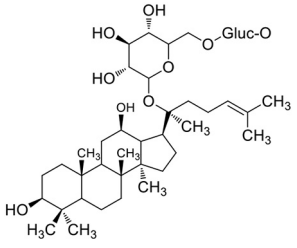
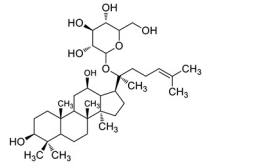
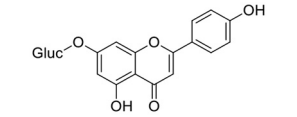
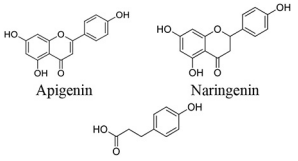
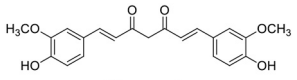
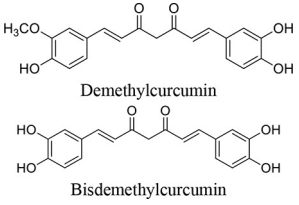
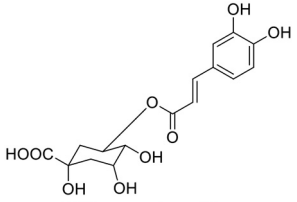
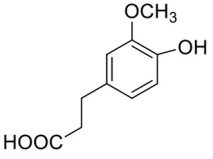
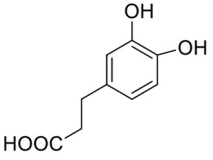
An abundance of evidence has demonstrated that the gut microbiota can interact with indigestible dietary compounds and herbal medicines, such as polysaccharides,

TABLE 1 Participants involved in the four pathways to improve bioavailability

Parent compound	Metabolite(s) of parent compound	Gut bacterium(a)	Function(s)	Reference(s)
Pathway 1: direct biotransformation of parent compounds to beneficial metabolites by the gut microbiota				
 Dietary fiber		*Faecalibacterium prausnitzii*, *Bifidobacterium* spp., *Lactobacillus* spp.	Alleviation of T2DM	18
Ganoderma atrum polysaccharides		S24-7, SMB53, Rc4-4, *Rikenellaceae*, *Allobaculum*, *Ruminococcaceae*	Promotion of secretory immunoglobulin A in the intestine	62, 64
Polygonatum odoratum polysaccharides		*Ruminococcus* spp., *Prevotella* spp.	Alleviation of hyperglycemia, hyperlipidemia, and obesity	60
Cordyceps sinensis polysaccharides		Unidentified gut bacteria	Enhancement of immune function of mesenteric lymph node lymphocytes and promotion of proliferation and inhibition of apoptosis of intestinal epithelial cells	62
 Fructo-oligosaccharide (FOS)	 Various SCFAs, e.g., Acetic acid, Propionic acid, Butyric acid	*Lactobacillus* spp., *Bifidobacterium* spp.	Decrease of ghrelin, glucose, and insulin levels; enhancement of peptide YY levels	65, 69
 Xylooligosaccharide (XOS)		*Bifidobacterium* spp.	Alleviation of chronic kidney disease and ulcerative colitis	70–72
 Glycyrrhizin (GL)	 Glycyrrhetic acid 3-O-mono-β-D-glucuronide (GAMG)	*Eubacterium* sp. GLH, *Ruminococcus* sp. PO1-3, *Clostridium innocuum* ES24-06	Improvement of anti-inflammatory, antiviral, antioxidative, and anticancer effects	95–97
 Timosaponin AIII (TA)	 Sarsasapogenin (SG)	Unidentified gut bacteria	Anti-inflammatory effect	84

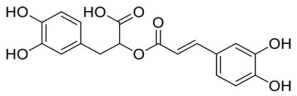
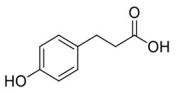
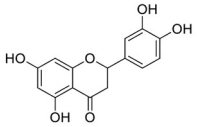
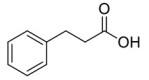
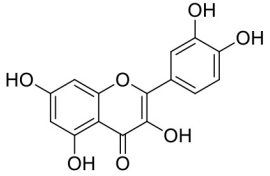
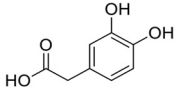
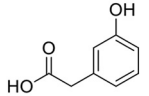
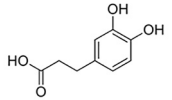
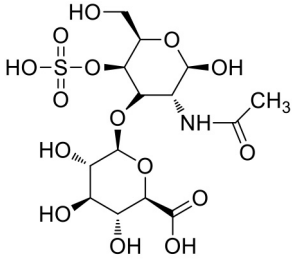
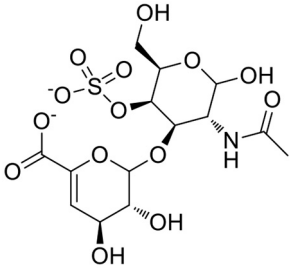
(Continued on next page)

TABLE 1 (Continued)

Pathway 1: direct biotransformation of parent compounds to beneficial metabolites by the gut microbiota				
Parent compound	**Metabolite(s) of parent compound**	**Gut bacterium(a)**	**Function(s)**	**Reference(s)**
 Protopanaxadiol ginsenoside (ginsenoside Rb1)	 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol	Unidentified gut bacteria	Antimetastatic effects	100
 Flavone apigenin-7-glucoside (A7G)	 Apigenin Naringenin 3-(4-Hydroxyphenyl) propionic acid	*Enterococcus avium*, *Clostridium orbiscindens*, *Eubacterium ramulus*, *Bacteroides distasonis*	Antimutagenic, antiproliferative, and antiallergic effects	102
 Curcumin	 Demethylcurcumin Bisdemethylcurcumin	*Blautia* spp.	Anti-inflammatory, antioxidant, antimutagenic, and anticancer effects	7, 113
 Chlorogenic acids	 Dihydroferulic acid  Dihydrocaffeic acid	Unidentified gut bacteria	Prevention of oxidation of human LDL	114, 115

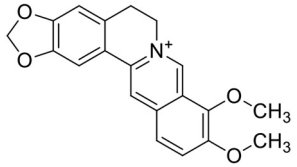
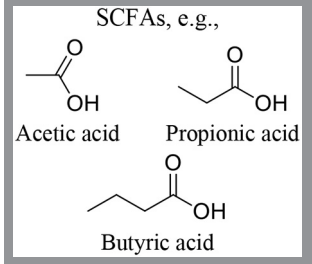
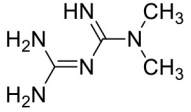
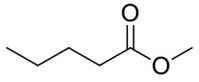
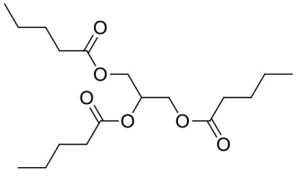
(Continued on next page)

TABLE 1 (Continued)

Pathway 1: direct biotransformation of parent compounds to beneficial metabolites by the gut microbiota				
Parent compound	**Metabolite(s) of parent compound**	**Gut bacterium(a)**	**Function(s)**	**Reference(s)**
 Rosmarinic acid	 Hydroxyphenylpropionic acids	*Lactobacillus johnsonii*, *Eubacterium ramulus*, *Clostridium orbiscindens*	Antioxidative effect	54, 116
 Eriodictyol	 Phenylpropionic acids			
 Quercetin	 3,4-Dihydroxyphenylacetic acid  3-Hydroxyphenylacetic acid  3,4-Dihydroxyphenylpropionic acid	*Enterococcus casseliflavus*, *Clostridium orbiscindens*	Antioxidative effect	158
 Chondroitin sulfate	 Delta-UA-GalNAc4S	*Bacteroides thetaiotaomicron* J1, *Bacteroides thetaiotaomicron* 82, *Bacteroides ovatus* E3, *Clostridium hathewayi* R4	Treatment of osteoarthritis	122

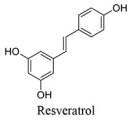
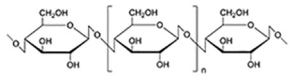
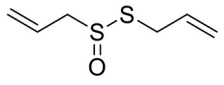
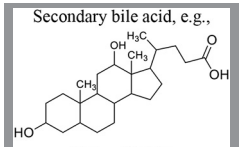
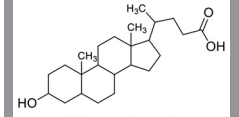
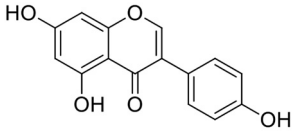
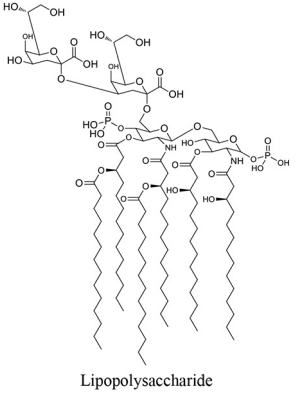
(Continued on next page)

TABLE 1 (Continued)

Pathway 2: increase of beneficial metabolites from parent compounds (mainly foods) by specific gut bacteria enriched by nonparent compounds				
Nonparent compound	**Beneficial metabolite(s) of the parent compound (mainly foods)**	**Gut bacteria**	**Function(s)**	**Reference**
 Berberine	 SCFAs, e.g., Acetic acid, Propionic acid, Butyric acid	*Allobaculum*, *Bacteroides*, *Blautia*, *Butyricicoccus*, *Phascolarctobacterium*	Improvement of glucose tolerance in treatment of T2DM; antibiotic effect on diarrhea	123
 Metformin			Inhibition of hepatic gluconeogenesis via activation of AMPK	123
 Monovalerin (MV)	SCFAs, e.g., Acetic acid, Propionic acid, Butyric acid	*Bacteroidetes*, *Tenericutes*, *Anaeroplasma*	Increase of acetic acids in liver and brain	124
 Trivalerin (TV)				

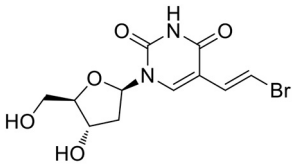
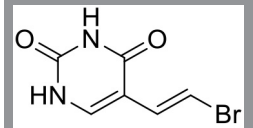
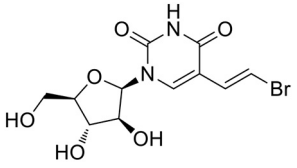
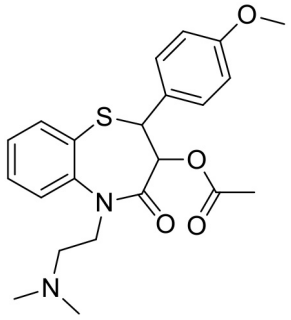
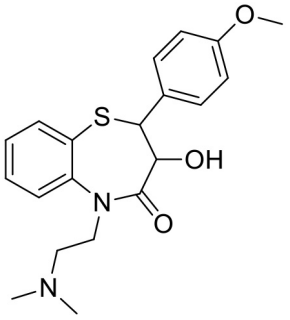
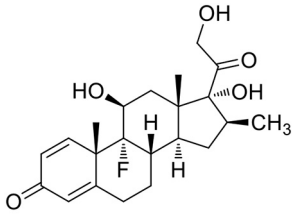
(Continued on next page)

TABLE 1 (Continued)

Pathway 3: decrease of detrimental metabolites from parent compounds (mainly foods) via modulation of the gut microbiota by nonparent compounds				
Nonparent compound	**Detrimental metabolite(s) of the parent compound (mainly foods)**	**Gut bacterium(a)**	**Function(s)**	**Reference**
 Resveratrol		*Bacteroides* spp., *Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia* spp.	Reduction of synthesis of TMA and TMAO	126
 Dietary fiber	 TMA TMAO	*Akkermansia* spp., *Bifidobacterium* spp.	Reductions of TMA, TMAO, and LPS levels	18
 Allicin		*Robinsoniella* spp.	Antimicrobial effect	128
Scutellaria baicalensis extract + metformin	Secondary bile acid, e.g.,  Deoxycholate  Lithocholic acid	*Lactobacillus*, *Bacteroides*	Synergetic cholesterol-lowering effect	130
Rhizoma coptidis		*Sporobacter termitidis*, *Alcaligenes faecalis*, *Akkermansia muciniphila*	Reduction of plasma cholesterol levels; increase of SCFAs from dietary carbohydrates	131
Lignin-rich fraction of brewer's spent grain		*Clostridium* spp., *Bacteroides* spp.	Promotion of deconjugation of bile acids	132
 Genistein	 Lipopolysaccharide	*Prevotella*, *Akkermansia*	Decreases of LPS levels and endotoxemia	133

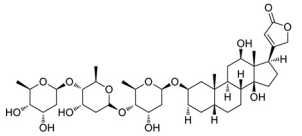
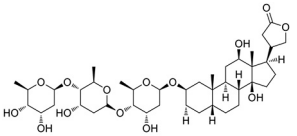
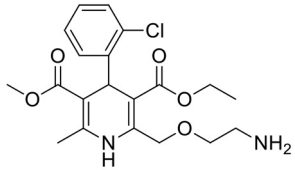
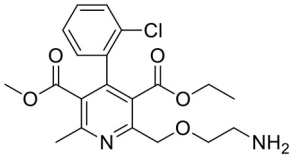
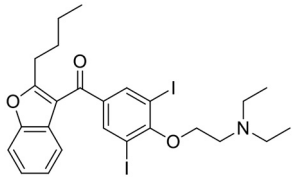
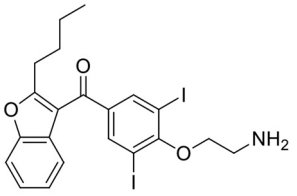
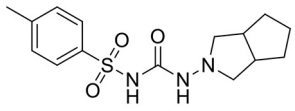
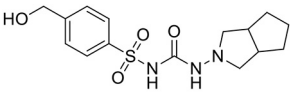
(Continued on next page)

TABLE 1 (Continued)

Pathway 4: inhibition of specific gut bacteria transforming parent compounds into inactive forms				
Parent compound	**Metabolite of the parent compound**	**Gut bacterium(a)**	**Function(s)**	**Reference(s)**
 Brivudine	 Bromovinyluracil	*Bacteroides thetaiotaomicron*, *Bacteroides ovatus*	Treatment of zoster	1
 Sorivudine		*Bacteroides thetaiotaomicron*	Antiviral effect	1
 Diltiazem	 Desacetyldiltiazem	*Bacteroides thetaiotaomicron*	Treatment of hypertension, arrhythmia, and angina pectoris	2
 Dexamethasone	Unidentified metabolite (mol wt, 332.179 Da)	*Clostridium scindens*	Anti-inflammatory, antitoxic, and antiallergic effects	2

(Continued on next page)

TABLE 1 (Continued)

Pathway 4: inhibition of specific gut bacteria transforming parent compounds into inactive forms				
Parent compound	**Metabolite of the parent compound**	**Gut bacterium(a)**	**Function(s)**	**Reference(s)**
 Digoxin	 Dihydrodigoxin	*Eggerthella lenta*	Decrease of cardiac activity	137
 Amlodipine	 Dehydroamlodipine	Unidentified gut bacteria	Increase of antihypertension effects by combination therapy with *Lactobacillus plantarum* IS-10506 and antibiotics	144, 147
 Amiodarone	 N-desethylamiodarone	Unidentified gut bacteria	Increase of antiarrhythmic effects by combination therapy with *Escherichia coli* Nissle 1917	148
 Gliclazide	 Pyridine metabolite (M1)	Unidentified gut bacteria	Increase of antidiabetic effects by combination therapy with *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Lactobacillus rhamnosus*	149

oligosaccharides, saponins, and phenolic compounds, directly transforming these molecules into more active compounds and improving their oral bioavailability (54–58).

Indigestible carbohydrates. Indigestible carbohydrates, including dietary fiber, polysaccharides, and oligosaccharides, have been proven to be the active components of a large number of pharmaceuticals and functional foods. However, these compounds cannot be easily digested in the small intestine. Many studies have shown that the important metabolites, SCFAs, are the primary final products of the fermentation of polysaccharides or oligosaccharides by potential beneficial bacteria (59).

Dietary fiber has been reported to greatly enrich acetic acid- and butyric acid-producing bacteria in a randomized controlled clinical study. Accordingly, the concentrations of these two SCFAs also increased during the intervention period. Alleviation of type 2 diabetes mellitus (T2DM) was correlated with an improvement in the gut microbiota, an upregulation of SCFA production, and increased serum glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) levels. Notably, an elevation of an index based on mathematical modeling of the 15 SCFA producers could predict a reduction in glycosylated hemoglobin (HbA1c, an important glycometabolism parameter), indicating significant roles of the SCFAs derived from beneficial gut bacteria during the alleviation of T2DM (18).

Polysaccharides in medicinal and edible plants and in marine organisms not only are metabolized to produce high levels of SCFAs but also reduce metabolic syndrome or play immunoregulatory functions; in addition, these compounds exhibit improved therapeutic effects in clinical applications via the enrichment of SCFA-producing gut bacteria (60–63). For instance, polysaccharides from *Ganoderma atrum* might regulate the gut microbiota, play a core role in the bioactive effects, and enhance the concentrations of SCFAs and secretory immunoglobulin A in the intestinal tracts of rats (62, 64). *Polygonatum odoratum* polysaccharides can restore the composition of the impaired intestinal microbiota of high-fat diet (HFD)-fed rats to that of the control group by increasing the abundance of SCFA-producing bacteria, which is correlated with an improvement in obesity parameters (60). *Cordyceps sinensis* polysaccharides significantly enhanced butyrate levels produced by the gut microbiota and not only improved histone H3 acetylation, mediating modulatory T (Treg) cell-specific Foxp3, but also markedly reversed the increases in interleukin-17 (IL-17) and IL-21 levels induced by cyclophosphamide in mice (62).

Oligosaccharides exhibit considerable modulatory effects on the gut microbiota, leading to the production of various SCFAs and a favorable influence on metabolic disorders and colonic motility. For example, fructo-oligosaccharide (FOS), galactose-oligosaccharide (GOS), and isomaltose-oligosaccharide (IMO) treatments increased the levels of SCFA-producing bacteria, including *Lactobacillus* and *Bifidobacterium* (65). SCFAs such as butyric acid could rectify motility in germfree mice (66), possibly by increasing histone H3 acetylation in enteric neurons (67), leading to the alleviation of constipation by the enhancement of vagal activity (68).

Furthermore, FOS intake facilitated decreases in the levels of ghrelin, glucose, and insulin and an increase in the level of PYY (69). Xylo-oligosaccharide (XOS) and inulin-type fructans can also increase the abundance of *Bifidobacterium* and the levels of butyric acid and acetic acid for significant alleviation of chronic kidney disease and ulcerative colitis (70–72). Therefore, although the bioavailability of herbs and functional foods containing polysaccharides or oligosaccharides is low, SCFAs metabolized from these two complex-carbohydrate components by beneficial bacteria might be key bioactive molecules. Detecting SCFA levels might be much more important than focusing on the bioavailability of herbs and functional foods containing these two complex carbohydrates.

SCFAs such as propionic acid are biotransformed from carbohydrates by the gut microbiota primarily via the succinate pathway, the acrylate pathway, and the propanediol pathway. The succinate pathway is the primary pathway adopted by a number of *Bacteroidetes* species to synthesize propionate (73). The succinate pathway also exists in *Ruminococcus flavefaciens*, which generates succinate, but not propionate,

and succinate is a precursor of propionate (74). The conversion of lactate to propionate involves the succinate pathway and the acrylate pathway, as observed in *Veillonella* spp. (via the succinate pathway) and *Megasphaera* spp. (via the acrylate pathway) (75). *Escherichia coli*, *Anaerostipes rhamnosivorans*, and *Bacteroides* species can all degrade deoxy sugars via the propanediol pathway (76, 77).

SCFAs can bind to G-protein-coupled receptors (GPCRs), mainly GPR41 (referred to as FFAR3) and GPR43 (referred to as FFAR2), on intestinal epithelial cells; regulate inflammatory responses (78, 79); and trigger the secretion of gut hormones, mainly GLP-1 and PYY (80, 81). GPR41 and GPR43 have been discovered on several cells other than intestinal cells, such as adipocytes, endocrine cells, and immune cells. SCFAs in the bloodstream could reach these cells and bind to these SCFA-sensing receptors.

Saponins. Many poor-circulatory bioavailable herbs have been found to exert pharmacological effects without SCFA production. Recently, increasing numbers of bioactive molecules have been gradually discovered to be metabolized from these functional herbs by the gut microbiota. Saponins are valuable bioactive components that exhibit anti-inflammatory and anticancer activities. However, these molecules are poorly absorbed into human blood, resulting in very low efficacy in human tissues (82, 83).

The gut microbiota provides new opportunities to overcome the poor bioavailability of saponins by transforming these compounds into beneficial metabolites (84, 85). Among these saponin compounds, glycyrrhizin (GL), a typical and well-known triterpenoid saponin extracted from licorice, has many valuable pharmacological effects, such as antiviral (86), antioxidative (87), anticancer (88), and anti-inflammatory (89) effects, and has been attracting our attention. It is also one of the few ingredients whose fate is relatively clear after metabolism by specific gut microbiota. Based on this discovery, glycyrrhetic acid 3-*O*-mono-β-D-glucuronide (GAMG), a metabolite with higher bioavailability than the parent compound GL, has been commercially developed through direct biotransformation in the food and pharmaceutical industries in Japan (90–93). GL is not easily absorbed from the intestine into the blood when administered orally to humans, as the structure, consisting of two glucuronide molecules, is strongly polar (94). However, one distal glucuronic acid of GL can be hydrolyzed by β-D-glucuronidase (β-GUS) derived from intestinal bacteria and then converted to GAMG, which exhibits moderate membrane permeability with suitable molecular polarity, possibly because of the sugar conjugation in this molecule, leading to an elevation in bioavailability (95, 96). Gut bacteria, including *Eubacterium* sp. strain GLH, *Ruminococcus* sp. strain PO1-3, and *Clostridium innocuum* ES24-06, play significant roles in the modification of the chemical structure of GL to produce other relevant intestinally absorbed metabolites (such as GAMG, 3α-hydroxyglycyrrhetic acid [3α-hydroxyGA], and 3-oxo-glycyrrhetic acid [3-oxoGA]) with relatively strong pharmacological activities (97) (Fig. 3). Timosaponin AIII (TA), another saponin compound, is metabolized to its active metabolite sarsasapogenin (SG) in the intestine via cleavage of the glycosyl moieties of TA by the gut microbiota to exert diverse pharmacological effects. Interestingly, SG exhibits a higher anti-inflammatory effect than the parent compound (TA), mainly via inhibition of NF-κB activation and proinflammatory cytokine (tumor necrosis factor alpha [TNF-α], IL-1β, and IL-6) expression in LPS-stimulated macrophages (84). Ginseng, whose pharmacological activities are primarily ascribed to ginseng saponins (98), generally exhibits restorative effects, tonicity, and revitalization effects (99). An unexpected phenomenon occurred in which ginseng and a ginseng-derived triterpenoid saponin, ginsenoside Rb1 (Rb1), exhibited different efficacies among individual patients based on the different Rb1 hydrolysis potentials of the intestinal bacteria. The results also indicated that Rb1 cannot be highly absorbed in its native forms to exert health benefits after oral administration as a natural prodrug. Rb1 can be hydrolyzed to its active form, 20-*O*-β-D-glucopyranosyl-20(*S*)-protopanaxadiol, by Rb1-hydrolyzing intestinal bacteria via cleavage of the glycosyl moieties, allowing Rb1 to reach the plasma and thereby exert its strong antimetastatic activity (100). These studies reveal that parent saponins are deglycosylated into their relevant metabolites to exert bio-

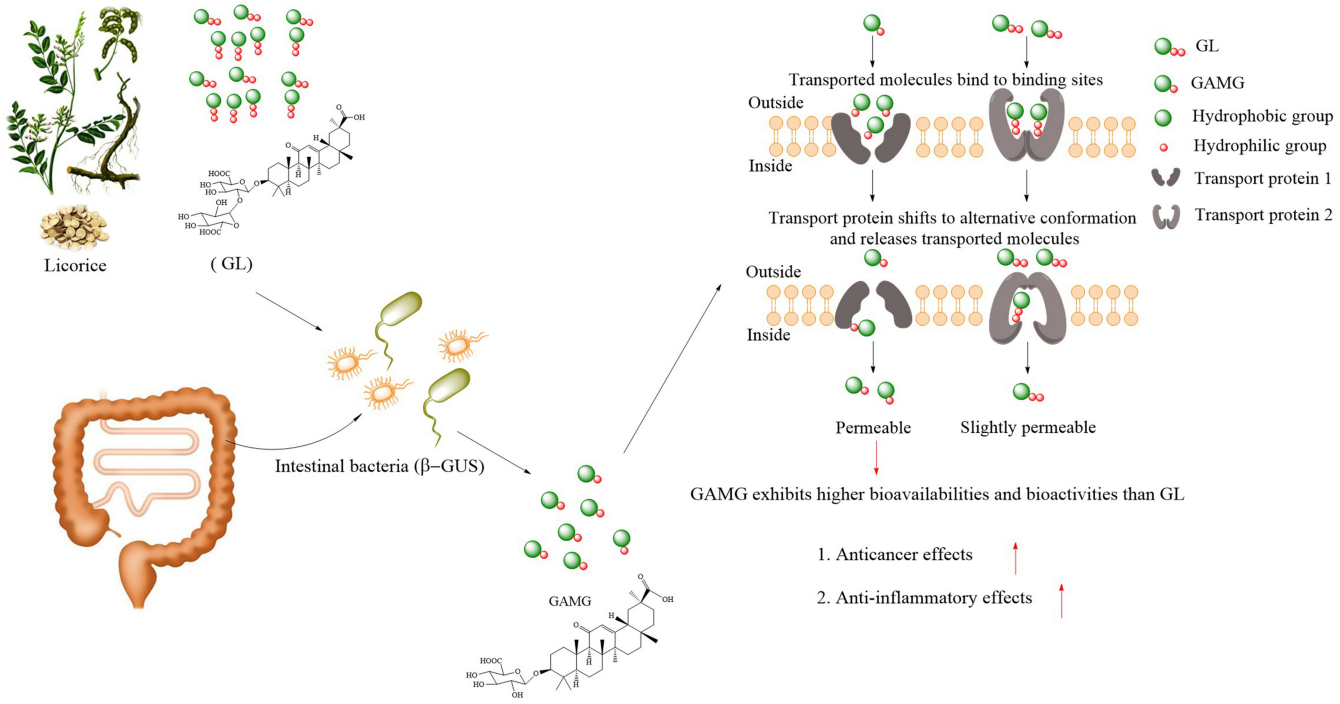


FIG 3 Representative example with a promising application of pathway 1: metabolism of a parent compound (glycyrrhizin, for example) into value-added compounds by regulation of the gut microbiota.

logical activities, which are mediated mainly by digestive enzyme secretion by the gut microbiota (55).

Phenolic compounds. Phenolic compounds, classified as flavonoids and nonflavonoids, are commonly detected in food plants. These compounds exhibit potent antioxidative effects and affect human health. However, the bioavailability of these compounds varies due to their vast structural diversity. A portion of phenolic compounds is transformed by host-derived enzymes into bioactive metabolites, while the others are not absorbed in the small intestine and may be fermented and transformed by the gut microbiota (101).

Flavones are the major flavonoids, and apigenin is a flavone aglycone. Apigenin-7-glucoside (A7G), which is the parent compound of apigenin, exhibits antimutagenic, antiproliferative, and antiallergic effects (102). By applying A7G to germfree and human-microbiota-associated rats, Hanske et al. (102) showed that relatively few A7G metabolites were present in the urine and feces of germfree rats; the main A7G metabolites in germfree and human-microbiota-associated rats were apigenin and 3-(4-hydroxyphenyl)propionic acid, respectively, and the compounds detected in the blood samples of germfree rats were apigenin conjugates, while the compound detected in blood samples of human-microbiota-associated rats was phloretin. These results indicate that the human intestinal microbiota influenced A7G metabolism and impacted the bioavailability of flavones. Anthocyanins, another type of flavonoid, have been mistaken to be considerably less bioavailable than other flavonoid subclasses in previous studies. Recent studies have suggested that anthocyanins are extremely potent and that the bioavailability of these compounds has been underestimated (103). Most of the ingested anthocyanins possibly arrive at the colon and are metabolized by the colonic microbiota (104). By feeding ileostomy patients raspberries, blueberries, and grapes, approximately 40% of the ingested anthocyanins were found to remain in the ileal effluent (105–107). In healthy humans with intact colons, anthocyanins can enter the colon and be deglycosylated. The dissociation of the C ring leads to the decomposition of aglycones and the conversion of these molecules into several phenolic constituents with additional effects (108).

As another example of a flavonoid compound, curcumin, which exhibits antioxidant, anti-inflammatory, antiviral, antibacterial, and beneficial effects in the treatment of some diseases, including cancers, cardiovascular diseases, diabetes, liver diseases, and neurodegenerative diseases, has been receiving considerable attention (109–111). Due to the β-diketones present in the structure of curcumin, this compound exhibits high hydrophobicity and poor solubility and "bioavailability." Therefore, a high daily intake of curcumin is necessary to observe strong health-promoting effects. Unfortunately, a high intake of curcumin may have harmful effects and reduce effectiveness, which has limited the utilization of curcumin for illness prevention (112). The metabolites of curcumin generated by gut bacteria, rather than the original forms of curcumin, exhibit the biological effects. Curcumin is reported to be converted to demethylcurcumin and bisdemethylcurcumin via methyl aryl ether cleavage caused by the human intestinal bacterium *Blautia* sp. strain MRG-PMF1 (7). The evidence indicates that unabsorbed curcumin can modulate the colonic microbiota indirectly, with beneficial effects on multifarious diseases by producing additional bioavailable and bioactive molecules (such as di-*O*-demethylcurcumin and dimethoxycurcumin) (113).

As a familiar example of nonflavonoid compounds, chlorogenic acids, which are richly contained in coffee beans, can prevent the oxidation of human low-density lipoprotein (LDL), which plays a pivotal role in the formation of atherosclerotic plaques (101). Stalmach et al. indicated that chlorogenic acid absorption occurred in both the small and large intestines but primarily in the large intestine (9). Most chlorogenic acids arrived in the colon intact, and several bacteria produce a number of esterases for the hydrolysis of phenol-quinic acid linkages (114). Released chlorogenic acids are easily transformed by bacteria to their dihydro forms, such as dihydroferulic acid and dihydrocaffeic acid, and are then absorbed by the colonic epithelium. Next, dihydroferulic acid, dihydroferulic acid-4′-*O*-sulfate, and dihydrocaffeic acid-3′-*O*-sulfate can enter the circulation at high concentrations (115). Moreover, some other phenolic compounds with low bioavailability, such as rosmarinic acid, eriodictyol, and some quercetin derivatives, are fermented into absorbable and bioactive phenolic acids by the colon microbiota, e.g., hydroxyphenylpropionic acids, phenylpropionic acids, and 3,4-dihydroxyphenylacetic acid (54, 116). These bioactive microbial metabolites may be absorbed and transported by the circulatory system to organs and tissues or exert their effects in the intestinal lumen (54, 102, 116, 117).

All of the above-mentioned examples indicate that improvement of the gut microbiota is potentially a good strategy for the evaluation of the bioavailability of parent substances. However, the metabolites of a large number of functional foods and drugs with low bioavailability remain unknown. Furthermore, the characteristics of individual gut microbes should be considered to identify methods to increase the bioavailability of foods and drugs.

Specifically, oral formulations of chondroitin sulfate (CS) (a high-molecular-weight glycosaminoglycan) have been used as drugs for a long time to treat osteoarthritis (118). Regrettably, 1,200 mg/day has been required to observe the expected curative properties in clinical trials (119). The absorption of CS in the small intestine is low, with the bioavailability of CS estimated to be only 0 to 13% after oral administration (118–120). CS is nondegradable in the stomach and small intestine and is mostly removed or degraded by the colonic microbiota after oral administration (121). By analyzing the degradation of CS by the intestinal microbiota in the distal gastrointestinal (GI) tracts of six healthy subjects, Shang et al. found that each individual's CS-degrading bacteria (*Bacteroides thetaiotaomicron* J1, *Bacteroides thetaiotaomicron* 82, *Bacteroides ovatus* E3, and *Clostridium hathewayi* R4) had different degradation effects, but 2-acetamido-2-deoxy-3-*O*-(β-D-gluco-4-Δ enepyranosyluronic acid)-4-*O*-sulpho-D-galactose (Δ-UA-GalNAc4S) was the product in all cases (122). This study indicated that although different individuals carried bacteria with the same function, the species might determine the degradation rates of the drugs, leading to differences in bioavailability. Therefore, we believe that the bioavailability of a food or drug is

determined not simply by the substance itself but also by an individual's functional gut bacteria.

Pathway 2: Increase of Beneficial Metabolites from Parent Compounds by Specific Gut Bacteria Enriched by Nonparent Compounds

Some medicinal components, such as alkaloids (berberine, etc.) and metformin, cannot be transformed by the gut microbiota into SCFAs, but these compounds can trigger an increase in the production of SCFAs from dietary carbohydrates by the gut microbiota. Berberine, an extract from traditional Chinese herbal drugs such as *Coptis chinensis*, previously regarded as an antibiotic drug for diarrhea in China, was recently found to improve glucose tolerance in the treatment of T2DM. However, the clinical efficacy of berberine could not be easily explained because of the low oral bioavailability of this compound. Compared to berberine, metformin has high oral bioavailability, and the mechanisms of action of metformin in the treatment of metabolic diseases are well understood, i.e., the inhibition of hepatic gluconeogenesis via the activation of AMP-activated protein kinase (AMPK). Recent studies have indicated that the intestinal microbiota has an important effect on the efficacy of metformin. Metformin and berberine exhibit contrasting effects on HFD-induced alterations of the composition of the intestinal microbiota. Putative SCFA-producing bacteria, including *Allobaculum*, *Bacteroides*, *Blautia*, *Butyricicoccus*, and *Phascolarctobacterium* species, were enriched by berberine and metformin (123). Interestingly, some types of SCFAs could even trigger the production of other types of SCFAs or organic acids by the gut microbiota. The addition of monovalerin (MV) and trivalerin (TV) to an HFD improved not only valeric acid levels but also acetic acid levels in the brain. Although the increment of valeric acid was considered to have been released from the delivered esters, increased amounts of acetic acid, which did not originate from MV or TV, were also observed in the serum and liver in both the MV and TV groups. However, MV and TV tended to decrease the concentrations of acetic acid in the cecum, which indicated that cecal acetate could be transferred to the brain. Furthermore, acetic acid levels in the brain were notably negatively correlated with the abundances of TM7, the S24-7 family, and rc4-4 and positively correlated with the abundances of *Anaeroplasma* and *Tenericutes* in the cecal microbiota. These results implied that the promotion of acetate levels in the brain might be traced back to the microbial alteration in the cecum induced by MV and TV (124).

In summary, several studies have shown that the extracts of some drugs and functional foods exhibit poor bioavailability but strong effects on host health. Nonparent compounds can enhance biological effects by regulating the gut microbiota to metabolize parent compounds rather than having a direct impact on the host. Furthermore, the functions of some bioactive molecules have sometimes originated from the metabolites of the parent compounds produced by beneficial bacteria, such as polysaccharides and oligosaccharides, rather than from the parent compounds themselves. However, bioactive effects can frequently be detected only after the intake of beneficial foods or drugs. To date, we have seldom been able to determine whether beneficial molecules exert their effects directly or indirectly via metabolism by the gut microbiota. Therefore, it is not easy to distinguish between pathways 1 and 2. In our opinion, it is necessary to identify therapeutic molecules via metabolomics studies and correlation analysis of each separate metabolite with the host's phenotype and try to increase the distribution of these molecules in the bloodstream.

Pathway 3: Decrease of Detrimental Metabolites from Parent Compounds via Modulation of the Gut Microbiota by Nonparent Compounds

In addition to the upregulation of beneficial molecules by modulating the gut microbiota, downregulation of the absorption of detrimental molecules by the microbiota could also be beneficial for human health. Detrimental microbes also interact with the host via a number of predictable pathways.

Some foods, such as a red-meat-rich diet, can induce the generation of harmful molecules by the gut microbiota, such as TMA/TMAO and bile acid/cholesterol. Increasing evidence indicates that phenolic phytochemicals with low bioavailability may reduce the levels of harmful compounds, primarily via remodeling of the gut microbiota. TMA, derived from the degradation of choline and L-carnitine by the gut microbiota, is absorbed into the bloodstream and then rapidly oxidized to TMAO by flavin-containing monooxygenase 3 (FMO3), which is a hepatic enzyme (52, 125). Resveratrol (a natural phenolic compound) reduces the synthesis of TMA and TMAO by reshaping the gut microbiota. A genus-level analysis indicated that resveratrol increased the relative abundances of *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* in mice. Simultaneously, resveratrol administration caused declines in the relative abundances of *Prevotella* and *Ruminococcaceae* and in the synthesis of TMA and TMAO (126). In addition to natural drugs, dietary fiber also reduces TMAO levels by altering the gut microbiome. A study demonstrated that dietary fiber feeding reshaped the intestinal microbial ecology; enhanced the growth of *Akkermansia* and *Bifidobacterium*, etc.; and restrained the growth of harmful species to reduce TMA and TMAO metabolism via remodeling of the gut microbiota structure in mice (127). Furthermore, some bioactive molecules from foods, such as allicin, also influence TMA and TMAO production (128).

Some intestinal bacteria metabolize primary bile acids and produce secondary bile acids, which can lead to dysbiosis of glycometabolism and lipid metabolism after excessive accumulation in human serum (129). K. Han et al. discovered that the coadministration of a *Scutellaria baicalensis* extract and metformin has a synergetic cholesterol-lowering effect in rats by the excretion of bile acids through feces (130). Excess cholesterol is discharged into the intestinal lumen by primary bile acid secretion. The abundances of some beneficial bacteria in the intestinal tract were increased due to this combination treatment, including *Lactobacillus* and *Bacteroides*, which may promote the deconjugation of bile acids that eventually failed to be reabsorbed in the blood. In contrast, *Clostridium* and *Enterobacter* showed the opposite effect (130). *Rhizoma coptidis* alkaloids, which contain berberine, coptisine, palmatine, and epiberberine, clearly enhanced the abundances of *Sporobacter termitidis*, *Alcaligenes faecalis*, and *Akkermansia muciniphila* in the intestinal tracts of fed mice. However, the growth of *Escherichia coli*, *Desulfovibrio* sp. strain C21_c20, and *Parabacteroides distasonis* was inhibited, which promoted the deconjugation of bile acids to reduce cholesterol levels in the blood (131). Therefore, *R. coptidis* alkaloids and metformin can not only trigger an increase in the production of SCFAs by enriching a group of SCFA-producing gut bacteria but also reduce the absorption of harmful substances by the body via regulation of the gut microbiota. Furthermore, a lignin-rich fraction of brewer's spent grain (BSG), as a special dietary fiber containing β-glucan and arabinoxylan, could also promote the deconjugation of bile acids (132).

LPSs, which are membrane components of Gram-negative bacteria, are another class of detrimental substances that are not intestinal metabolites. In 2018, Zhao et al. revealed that dietary fiber intake inhibited the growth of potentially detrimental bacteria and reduced LPS levels but enriched SCFA-producing bacteria in T2DM patients (18). Lopez et al. indicated that genistein, as a dietary bioactive compound in soy, can regulate the intestinal microbiota in HFD-fed mice by increasing the abundances of the genera *Prevotella* and *Akkermansia*. These increases resulted in decreases in circulating levels of LPS and reduced metabolic endotoxemia (133). In addition, many other harmful metabolites in the bloodstream, such as microbiome-generated indoxyl sulfate and *p*-cresol sulfate, can be reduced by remodeling the gut microbiota in patients with chronic renal disease (134, 135).

In summary, functional components can reduce the production of harmful intestinal metabolites by remodeling the intestinal microbiota. To fully understand bioavailability, it is essential to take into account the declining levels of harmful bioavailable molecules. Therefore, a reduction in the bioavailability of detrimental molecules can also alleviate metabolic diseases. In many cases, some functional foods or drugs can not

only increase the abundance of beneficial bacteria (frequently SCFA producers) but also decrease the abundance of detrimental bacteria to improve various diseases.

Pathway 4: Inhibition of Specific Gut Bacteria Transforming Parent Compounds into Inactive Forms by Nonparent Compounds

In pathway 1, we describe a group of intestinal bacteria that can transform the parent inactive components into highly beneficial bioactive and absorbable compounds. Conversely, the degradation of some functional components in drugs or foods by specific intestinal bacteria can decrease the bioavailability of these compounds. In contrast to the strategy for the enrichment of beneficial bacteria in pathway 1, effective methods to inhibit intestinal bacteria that degrade bioactive parent drugs might increase the bioavailability of these drugs.

After oral administration, drugs experience first-pass metabolism in the gut and liver, which mostly affects the outcomes and adverse effects of drugs. Many drugs enter the intestine and are metabolized by the gut microbiota, leading to reduced efficacy. For example, Zimmermann et al. found that among eight bacterial species representing five dominant phyla in the mammalian gut microbiota, *Bacteroides thetaiotaomicron* and *B. ovatus* show the highest metabolic activity to convert BRV to BVU (1), while the latter can interact with some other drugs and trigger fatal effects. Sorivudine (SRV), which is structurally similar to BRV, can be slowly converted to BVU by *B. thetaiotaomicron*. In addition, *B. thetaiotaomicron* can also participate in a diltiazem deacetylation reaction generating desacetyldiltiazem (2). Besides, sulindac is reduced by the intestinal microbiota to sulindac sulfide (136). Digoxin can be converted to dihydrodigoxin and dihydrodigoxigenin *in vitro*. These derivatives result in decreased cardiac activity (137). Some studies have illustrated that some bonds can be transformed by enzymes carried by specific gut bacteria. For example, the azo bond of sulfasalazine is reduced by colonic bacterial azoreductases to form mesalazine and sulfapyridine (138, 139). The absorption of sulfapyridine in the colon can result in some adverse effects, such as nausea, skin rash, headache, dizziness, and decreased appetite (140). Nitrazepam experiences a nitroreduction catalyzed by gut bacterial enzymes, but the products of this reaction have teratogenic effects (141). The intestinal microbiota is mainly involved in a modification in which zonisamide is primarily converted to 2-sulfamoylacetyl-phenol by the reduction of the benzisoxazole ring (142).

Another example tactfully demonstrated the effects of the gut microbiota on the degradation of active parent drugs into inactive components. Amlodipine, one of the most frequently prescribed drugs for the treatment of hypertension, is absorbed in the GI tract, with a bioavailability of approximately 60% after oral administration (143).

Some gut microbiota-targeted methods have been developed to improve bioavailability. It has been found that coadministration of amlodipine with antibiotics resulted in increased amlodipine absorption in the GI tract. Researchers found that amlodipine could be metabolized by intestinal microbial enzymes and yield the major pyridine metabolite, which suggested that the intestinal microbiota is associated with the metabolism of amlodipine. Furthermore, coadministration of amlodipine and antibiotics increased the human plasma concentration of amlodipine to almost twice that of the amlodipine monotherapy group (144). The use of antibiotics could change the intestinal microbiota, leading to metabolic changes in the coadministered antihypertension drugs. This finding strongly indicated that the gut microbiota might affect the pharmacokinetics of antihypertensive drugs. However, antibiotics have an associated risk of dysregulation of the gut microbiota (145, 146), which limits the use of these compounds to increase the bioavailability of amlodipine. Compared with amlodipine monotherapy, coadministration with *Lactobacillus plantarum* IS-10506 in rabbits significantly enhanced the amlodipine concentration. The authors speculated that *L. plantarum* IS-10506 could enhance red blood cells and hematocrit, leading to a lower sedimentation rate and increased levels of plasma proteins, which bind amlodipine (147). In addition, a live bacterial suspension of the probiotic *Escherichia coli* Nissle 1917 enhanced the bioavailability of amiodarone, which is an antiarrhythmic drug, in rats

(148), and mixed cultures of *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Lactobacillus rhamnosus* increased the bioavailability of gliclazide, an antidiabetic drug, in diabetic rats (149). Beneficial bacteria can limit the expansion of competing opportunistic pathogens (150, 151). Thus, in our opinion, this improvement in bioavailability might be associated with a decreased abundance of drug-degrading bacteria due to competition pressure from beneficial bacteria.

Prebiotics are also able to modulate the gut microbiota. The use of prebiotics has also been reported to enhance the absorption of some parent compounds. For example, the coadministration of genistin and FOS improved the absorption of genistin, leading to this compound reaching its target tissues, such as bone, with high effectiveness (152). However, the underlying mechanism has not been explained.

In addition, gut microbes can interact with receptors in the liver and other organs via the corresponding metabolites. Indoles, which are microbial tryptophan metabolites, have been shown to induce some cytochrome P450s, which are responsible for the metabolism of most therapeutic drugs and play vital roles in bioavailability and drug-drug interactions via an aryl hydrocarbon receptor-mediated mechanism in the liver. Furthermore, antibiotics decreased the hepatic expression and enzymatic activity of cytochrome P450 3a (153). Regardless of the direct (in the intestine) or indirect (in the liver) influence on first-pass metabolism, the gut microbiota might play significant roles in these processes.

Taken together, these results show that antibiotics, beneficial bacteria, and prebiotics are able to increase the absorption of some oral drugs by inhibiting the abundance of drug-degrading bacteria.

REDEFINITION AND IMPROVEMENT OF BIOAVAILABILITY

To address the perplexingly low bioavailability of pharmaceuticals and functional foods, various strategies have been carried out to promote bioavailability. However, high bioavailability frequently does not lead to health improvements. On the other hand, despite poor bioavailability, some drugs or functional foods continue to exhibit strong therapeutic effects. Thus, the mechanisms by which these substances function *in vivo* are puzzling to researchers. Recently, the correlation of gut microbiota dysbiosis and the occurrence and progression of a series of diseases was gradually verified. Poor bioavailability of drugs or foods might provide an opportunity for cross talk among these nonabsorbable components and bacteria in both the small and large intestines. Thus, determining whether such cross talk has a significant effect on the biotransformation of these substances with low bioavailability is of great interest. This review demonstrates that four pathways associated with these medicines or foods with low bioavailability determine the effects of these substances aided by the gut microbiota. First, the functional components derived from these drugs or foods by the gut microbiota exhibit key effects on the improvement of health. In other words, the high availability of these functional metabolites successfully overcomes the low availability of the parent substances. Second, many drugs or functional foods can modulate the structure and function of the gut microbiota and facilitate the production of beneficial metabolites from daily nutrient substances via the gut microbiota. Thus, highly bioavailable beneficial components (SCFAs, etc.) metabolized from healthy foods consumed daily (dietary fiber, etc.), which are different from the investigated drugs or functional foods, by the improved intestinal microbiota play key roles in health promotion. Third, the improved gut microbiota modulated by drugs or functional foods can downregulate the production of some harmful molecules metabolized from unhealthy foods (dietary choline, etc.) by the gut microbiota. We further propose that the understanding of bioavailability can be expanded to include the downregulation of the availability of detrimental metabolites. Thus, in addition to the enhancement of the bioavailability of beneficial components, inhibition of the bioavailability of detrimental components might be an effective method for the promotion of human health. Fourth, the "binding partner" approach for food or drugs and targeted inhibitors can be considered to improve bioavailability and therapeutic effects. Targeted inhibitory substances in the intestine specifically inhibit bacterial degra-

dation of functional components, allowing functional components to "escape" degradation by the gut microbiota and enter the circulatory system with higher absorption. This approach will facilitate developmental breakthroughs to improve the bioavailability of drugs and foods that could be degraded by the intestinal microbiota. Of course, we also need to consider the possible interactions between the two substances and the side effects on the organisms.

Regardless of the pathways mentioned above, gut microbes are effective modulators of the bioavailability of these pharmaceuticals or foods. For example, dietary fiber can be directly metabolized into biologically active substances, i.e., substances that have biological effects on the enhancement of the levels of SCFAs, which might be derived from dietary carbohydrates via the enrichment of SCFA producers. On the other hand, based on the functions of the gut microbiota, dietary fiber can also reduce TMA, TMAO, and LPS metabolism by remodeling the gut microbiota structure, which suggests that pathways 1 and 3 play important roles in the bioavailability-promoting effects of dietary fiber (18, 127). Metformin, the exact pharmacological mechanism of which is unknown, can also increase the abundance of SCFA producers. Additionally, metformin can reduce the levels of secondary bile acids, which implies that metformin can have beneficial effects via both pathways 2 and 3 (123, 130). Therefore, when discussing the bioavailability of components, we should pay attention to various bioavailability-promoting pathways based on the multidimensional effects of the gut microbiota. Importantly, even if we find that some water extracts or crude extracts of functional foods or drugs have biological effects, there is a strong possibility that these extracts themselves do not exhibit the effects. Instead, it is likely that small bioactive substances produced by the gut microbiota play roles in these biological processes. Simultaneously, these phenomena also remind us that we cannot be satisfied with the biological effects of crude extracts, and we should study the small-molecule bioactive substances that enter the bloodstream to improve the bioavailability and, ultimately, the therapeutic effects of these molecules. These substances can be extracted and used in the pharmaceutical industry.

In addition, almost all traditional Chinese medicines (TCMs) have poor bioavailability, so the medical effects of these medicines cannot be easily explained based on Western medicine. However, TCMs have helped Asian doctors cure patients for thousands of years. Some unknown mechanisms might play important roles in the therapeutic processes. The effects of the human commensal microbiota may explain the mechanisms underlying these processes and help us understand the effects of TCMs.

Notably, in pathway 4, some modulators of the gut microbiota may be used for the downregulation of drug-degrading bacteria to both elevate the bioavailability and reduce the side effects of parent drugs. Furthermore, some microbial metabolites might induce cytochrome P450s and decrease first-pass metabolism in the liver.

In addition to the *in vivo* (1), *in vitro* (2), and human (8) models mentioned above, some other models, such as a simulator of the human intestinal tract (154, 155), continuous-culture systems (156), a GI-targeted release model (extended or immediate release) (157), and an *in vitro* culture combination of key functional strains, might be potential tools to illustrate the roles of the gut microbiota in bioavailability. In this review, bioavailability can be improved by either increasing the abundance of beneficial gut bacteria or decreasing the concentration of detrimental bacteria. Some potential methods, in our opinion, may be launched. First, beneficial metabolites from parent or nonparent compounds by the gut bacteria in pathways 1 and 2 can be produced via *in vitro* fermentation or by chemical synthesis for direct administration. Second, targeted beneficial bacteria for directly improving bioavailability need to be identified according to studies on the cross talk of these bacteria and the parent compounds in pathways 1 and 2. The isolation, culture, and transplantation of these beneficial bacteria might be a promising method. On the other hand, although targeted inhibition of the detrimental bacteria in pathways 3 and 4 is difficult, the utilization of some competitive beneficial bacteria can be expected. Third, prebiotics can also be used to enrich beneficial bacteria in pathways 1 and 2 and thereafter inhibit detrimental bacteria in pathways 3 and 4. Last,

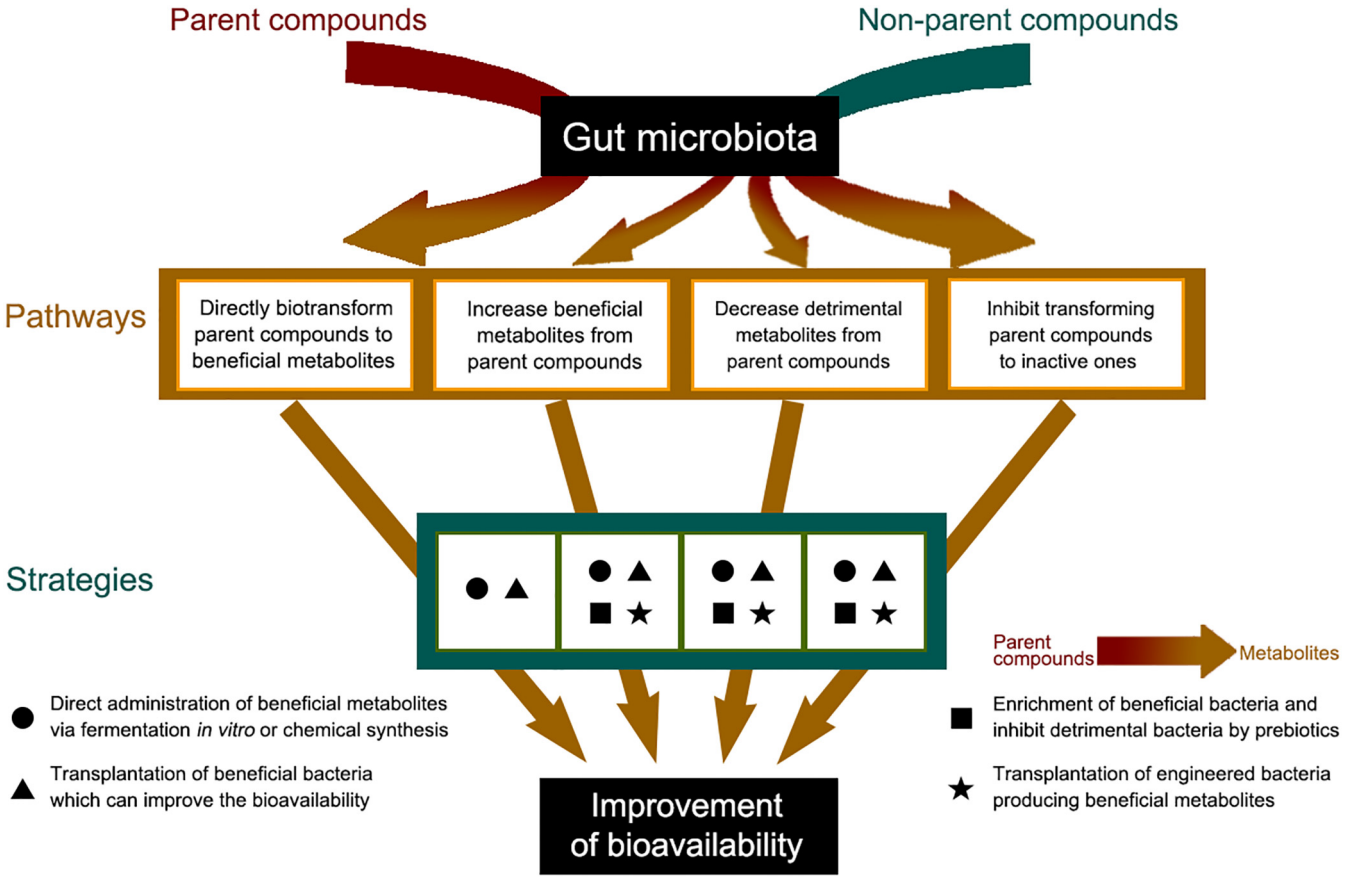


FIG 4 Strategies for improving the bioavailability of food and medicine via modulation of the gut microbiota toward each pathway.

there are broad prospects in using engineered bacteria harboring specific genes to produce beneficial metabolites to be used in pathways 1 and 2.

In summary, based on the interactions between drugs or functional foods and the gut microbiota, a redefinition of bioavailability will provide novel insights into the roles of many medicines or functional foods in human health. The modulation of the structure of the gut microbiota will be a novel strategy for the promotion of bioavailability, the alleviation of side effects, and the discovery and design of novel pharmaceuticals (Fig. 4).

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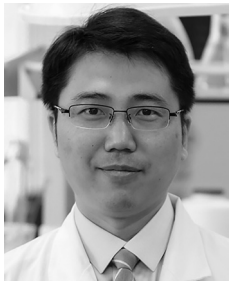
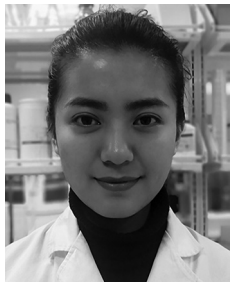
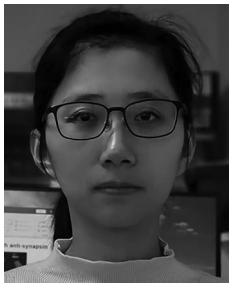


Feng Zhang studies the roles of gut microbiota in metabolic diseases, including obesity, type 2 diabetes, prediabetes, gestational diabetes mellitus, and polycystic ovarian syndrome. As the coauthor of research published in *Science* entitled "*Gut Bacteria Selectively Promoted by Dietary Fibers Alleviate Type 2 Diabetes*," he and his collaborators focused on the effects of dietary fiber on the enrichment of SCFA-producing bacteria, which could enhance GLP-1 levels and thereafter alleviate type 2 diabetes. Recently, he has been interested in the roles of the gut microbiota in the alleviation of metabolic diseases by functional foods.

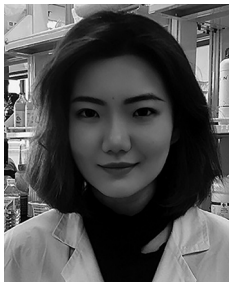


Fang He studies the roles of functional foods and nutrients in human health and wellness, especially the regulation of the gut microbiota by these compounds. She has been active in the interaction between the gut microbiota and the host for several years. Currently, she is mainly studying the effects and mechanisms of prebiotics such as xylo-oligosaccharides in the alleviation of type 2 diabetes by modulating the gut microbiota. She has screened several gut bacteria that have the potential to treat obesity and diabetes.

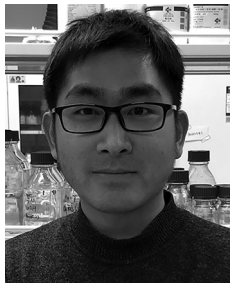


Li Li studies learning and memory, individual variations in learning ability, and their underlying mechanisms. She has a particular interest in the interactions among the gut microbiota, the brain, and cognitive performance. She obtained her Ph.D. in Biological Sciences in 2017 at the Queen Mary University in London, United Kingdom, with a Ph.D. dissertation entitled *The Neural Mechanisms Underlying Bumblebee Visual Learning and Memory*. After her Ph.D., she has worked as a postdoctoral researcher in the School of Food Science and Technology at Jiangnan University, China, focusing on the brain-gut-microbiome axis. Two research grants sponsor her current work, and she has accumulated abundant knowledge about the effects of the gut microbiota on brain function and the potential pathways.

Lichun Guo studies the roles of the gut microbiota and enzymatic modifications to overcome the poor bioavailability of saponins such as glycyrrhizin (GL). She focuses on research on the enzymes derived from microbes that display great potential to transform these compounds into beneficial metabolites, especially glycyrrhetic acid 3-*O*-mono-β-D-glucuronide (GAMG), which has higher bioactivity than the parent compound GL. Currently, she is studying the effects and mechanisms of hypoglycemic drugs in the treatment of obesity and diabetes, especially the regulation of the gut microbiota by these compounds. She has found a beneficial metabolite modified by the gut microbiota that has potential in the prevention and treatment of diabetes and related symptoms.



Bin Zhang studies the gut microbiota and their metabolites. She has been pursuing a Ph.D. in Food Science and Technology at Jiangnan University since 2018. Her research focuses on the regulatory mechanism of hydrogen sulfide (a kind of metabolite produced by the gut microbiota) with glycometabolism in type 2 diabetes.



Shuhuai Yu studies the structure, function, catalytic mechanism, and evolutionary relationship of enzymes involved in the metabolic process of carbohydrates. In this field, he revealed the mechanism and evolutionary relationship of difructose anhydride III hydrolase and inulin fructotransferase using crystallography, the result of which was published in *ACS Catalysis* (2018) entitled "*Structural and Functional Basis of Difructose Anhydride III Hydrolase, Which Sequentially Converts Inulin Using the Same Catalytic Residue*." At Harvard University, he studied molecular evolution with experimental and computational methodologies in the Department of Chemistry and Chemical Biology. After his Ph.D., he has worked as an associate professor in the School of Food Science and Technology at Jiangnan University, China, continuing his investigation of enzymes, including their exploitation and modification. Recently, he has been interested in the ecology of bacteriophage interactions with bacterial populations, finally applying this to phage therapy.

Wei Zhao studies the relationship between nutrition and health and the efficacy and mechanisms of bioactive compounds in the body. He has been active in these studies for almost 15 years and has published more than 150 peer-reviewed papers. Dr. Zhao is currently a full professor in Food Science at Jiangnan University. He has commercially developed several prebiotics and functional food ingredients in industry and has successfully applied them to alleviate metabolic diseases. Recently, he has become interested in the roles of the gut microbiota in metabolic diseases, including obesity and type 2 diabetes.