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Metabolic insights into gut microbiota in the pharmacology of natural medicines

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Review

Metabolic insights into gut microbiota in the pharmacology of natural medicines

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ABSTRACT

Natural medicines (NMs) demonstrate distinct advantages in the clinical management of chronic diseases. Recent years have seen growing recognition of the gut microbiota's role in the efficacy and synergy of NMs, providing new impetus for elucidating the material basis and mechanisms of NMs and their path toward modernization. A fundamental question that has emerged is how NM-microbiota interactions integrate into the multi-target holistic mechanisms of NMs, the answer to which may also illuminate new avenues for drug discovery. Metabolic regulation *via* small-molecule metabolites has been increasingly implicated in host-microbe interaction. This review presents an integral metabolic perspective on NMs-microbiota interaction in host health and disease. It highlights the emerging understanding of gut microbiota-related metabolic signals implicated in NM components' local and systemic actions. Additionally, it discusses key issues and prospects related to drug development and the translational study of NMs.

1. Introduction

Natural medicines (NMs), also known as natural products, have an extensive history of application and rich clinical experience. The discovery and development of NMs represent the primary sources of original drugs in China, playing a crucial role in preventing and treating chronic diseases. According to data from the Food and Drug Administration (FDA), among all drugs approved between 1981 and 2019, over 35% were natural products, derivatives of natural products, or natural product analogs. NMs have consistently maintained a significant role in pharmaceutical research, substantially influencing the treatment of human diseases [1, 2]. Furthermore, numerous clinical trials for NMs-based new drug development are currently underway globally [3-6]. Despite these advancements, the material basis and mechanism of action of NMs have not been fully elucidated, which remains a key obstacle to their modernization.

In recent years, advancements in bioinformatics, proteomics, transcriptomics, and metabolomics have significantly enhanced our understanding of life, health, and diseases, accelerating the elucidation of natural products and their mechanisms of action [7]. The human body is recognized as a superorganism comprised of the host and symbiotic microorganisms. Over the past decade, the crucial role of gut microbiota in health, disease, and therapeutic outcomes has gained increasing recognition [8-10]. Furthermore, the interaction between drugs and gut microbiota has attracted growing attention for its role in mediating individual variations in drug efficacy and adverse effects [11]. Correspondingly, evidence demonstrates that gut microbiota is involved in the pharmacology of NMs, particularly those with low oral bioavailability. For instance, a series of studies on the interplay between gut microbiota and berberine have provided novel mechanistic insights into its clinical efficacy in managing dyslipidemia and reducing blood glucose levels [12]. Additionally, investigations into gut microbiota and ginsenosides offer new perspectives for comprehending their antidepressant mechanisms and pave the way for identifying new therapeutic targets [13]. Consequently, gut microbiota modulation has emerged as a dynamic field in NM research, with implications for elucidating clinical efficacy, guiding rational drug use, and inspiring novel drug discovery.

As evidence accumulates supporting the role of gut microbiota in the efficacy of NMs, a critical question emerges: how does the interplay between NMs and microbiota integrate into the multi-target holistic mechanisms and clinical effectiveness of NMs? Recent years have witnessed a surge in studies demonstrating the crucial involvement of gut microorganisms in NM action, primarily *via* pharmacokinetic (PK) and pharmacological pathways [14-16] (Fig. 1). A comprehensive review of the PK mechanisms underlying microbiota-NM interactions has recently been published, offering insights into microbial regulation of NM biodisposition [17]. Another compelling aspect is the involvement of small-molecule metabolites from gut microbiota in the pharmacological effects of NM components. This review highlights recent research progress on NM mechanisms of action from the perspective of gut microbiota metabolic signals, aiming to inspire novel approaches to drug discovery. Additionally, we discuss key issues related to further elucidating the metabolic regulatory basis of NMs through gut microbiota modulation and its clinical translation into new therapeutics.

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2. Metabolic crosstalk between the gut microbiota and NMs

2.1. Gut microbiota affecting the PKs and metabolism of NM components

Due to extensive interactions in the gastrointestinal tract, gut microbiota can significantly influence the quality and quantity of active substances from NMs, thereby affecting their PK behavior and biological effects (Fig. 2). For instance, research has demonstrated that cyclic enol ether terpene glycosides can undergo hydrolysis by bacterial *β*-glucosidase, resulting in the formation of corresponding glycosidic ligands. Typically, these secondary glycosidic ligands are the active ingredients absorbed by the intestinal tract, exerting therapeutic effects. Furthermore, gut microbiota can directly or indirectly alter drug bioavailability by impacting mucosal barrier function and absorption. The prevalent types of drug metabolism mediated by gut microbiota include hydrolysis and reduction [18, 19]. Additionally, under the unique biochemical conditions of the gut, functional group transfer and cleavage reactions may occur [20, 21] (Table 1).

Gut microbiota hydrolysis refers to the process by which gut microorganisms metabolize complex molecules into smaller, more absorbable, and utilizable fragments (e.g., monosaccharides, amino acids, fatty acids) through specific hydrolase enzymes. Saponins constitute the primary active ingredients in numerous commonly used Chinese medicinal materials, such as *Panax ginseng* and *Panax notoginseng*. A growing body of research indicates that protopanaxadiol (PPD) saponin exhibits broad pharmacological effects [22, 23]. The majority of PPD is produced through bacterial hydrolysis of the glucose molecule at the C-20 position of ginsenoside compounds, facilitated by glycoside hydrolases from *Bacteroides*, *Clostridium*, and *Bifidobacterium* spp., emphasizing the significance of bacterial metabolism in ginsenoside pharmacology [24]. Studies have shown that ginsenoside Rb1, a representative of PPD, increases the abundance of intestinal *Lactobacillus*, while ginsenoside Rg1 enriches *Akkermansia muciniphila* and inhibits farnesoid X receptor (FXR)-fibroblast growth factor 15, thereby facilitating metabolic elimination of cholesterol [25]. Furthermore, research has demonstrated that bacterial biotransformation of NM components into small-molecule metabolites contributes to their efficacy. For instance, paeoniflorin and albiflorin, the main components of white peony root, are characterized by low oral bioavailability, which appears paradoxical to their antidepressant effects. Recent investigations have revealed that carboxylesterase catalyzes the hydrolysis of paeoniflorin and albiflorin, releasing benzoic acid, which contributes to fatty acid amide hydrolase inhibition in the brain and the antidepressant effect of traditional Chinese medicine (TCM) formulas such as Xiaoyao San [26].

Gut microbiota reduction describes the process by which intestinal microorganisms transform specific substances, such as nitrates and sulfates, into lower-valence compounds like nitrites and hydrogen sulfide through specialized enzyme systems. Research has demonstrated that nitroreductase from *Escherichia coli* can convert poorly absorbable berberine into dihydroberberine, a more readily absorbable form with a 5−10 times higher absorption rate in the gut [27]. This insight has significant implications for understanding the microbiota-regulated mechanisms of NM absorption and individual variations in berberine blood concentrations. Additionally, a notable discovery is that the reduction of digoxin by *Eggerthella lenta*, which possesses cardiac glycoside reductase 1 and cardiac glycoside reductase 2, can inactivate digoxin. This finding provides a crucial explanation for why

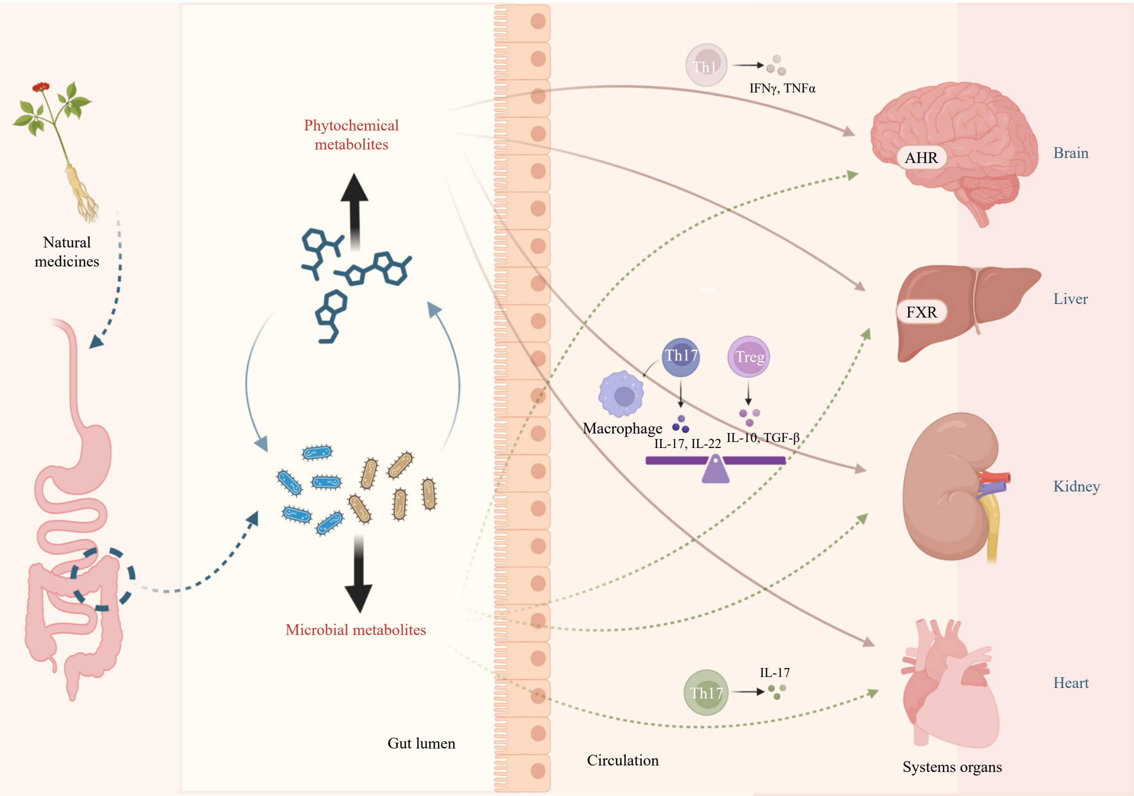

Fig. 1 Metabolic interactions of gut microbiota and natural medicines underlying local and systemic effects. Oral administration of natural medicines initiates a bidirectional metabolic interaction between gut microbiota and phytochemicals within the intestinal environment. Gut microbiota can transform phytochemicals *via* chemical processes such as hydrolysis, reduction, and demethylation, influencing the quality and quantity of active substances from NMs and their subsequent exposure and biological effects on system organs. Conversely, phytochemicals can reshape the gut microbial composition, thereby altering the production of various small-molecule metabolites, which function as signaling molecules between the gut and system organs. Consequently, these small-molecule metabolites derived from gut microbiota contribute to the pharmacological effects of NM components, particularly for those exhibiting poor absorption.

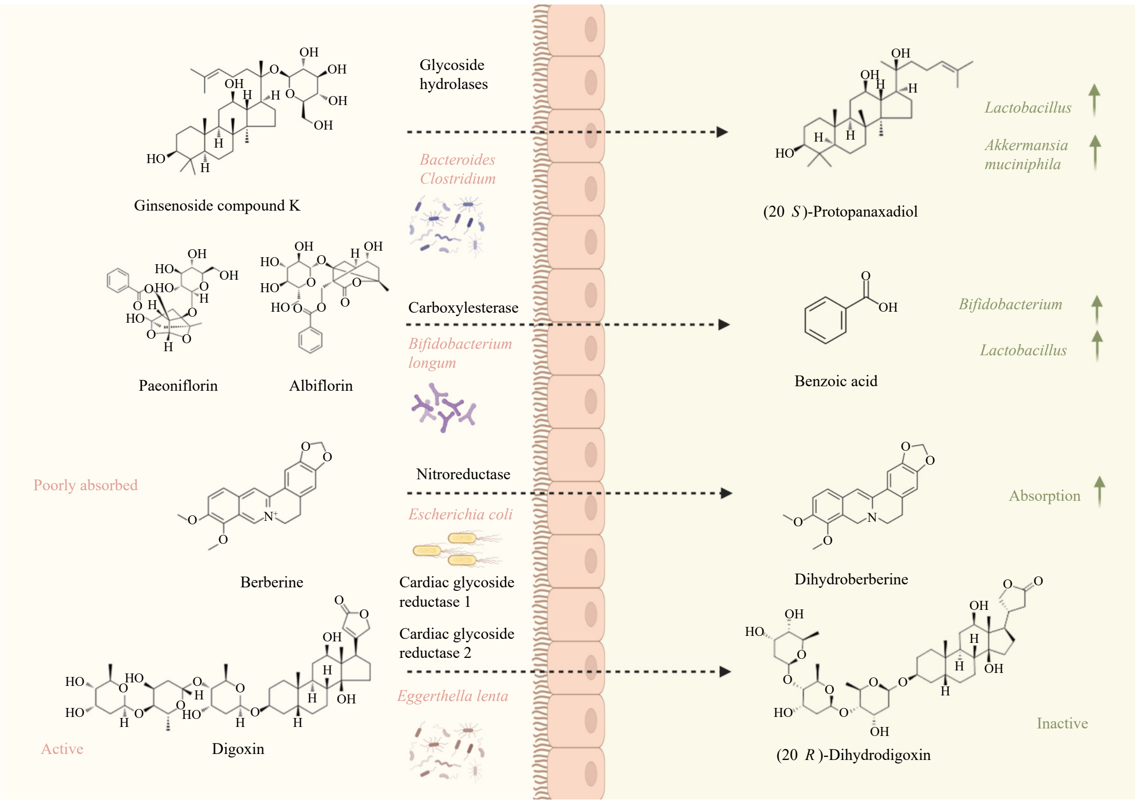

Fig. 2 Gut microbiota influencing the PK properties and metabolism of NM components. Specific bacterial species such as *Bacteroides*, *Clostridium*, and *Bifidobacterium longum* produce enzymes, including glycoside hydrolases, carboxylesterases, and nitroreductases that metabolize NM compounds, such as ginsenoside compound K, paeoniflorin, albiflorin, and berberine. These enzymatic reactions transform poorly absorbed or inactive compounds into more bioavailable and active metabolites, like (20*S*)-protopanaxadiol, benzoic acid, and dihydroberberine. Conversely, species such as *Escherichia coli* and *Eggerthella lenta* can diminish the activity of digoxin through reductase enzymes. Collectively, the gut microbiota-mediated metabolism of NM components affects their absorption, bioavailability, and pharmacological effects.

Table 1 Chemical transformation of phytochemicals by gut microbiota.

Natural medicines	Phytochemicals	Metabolic pathway	Metabolites	Pharmacological activity	Ref.
Ginseng and *Panax notoginseng*	Ginsenoside Rb1, Ginsenoside Rg1	Hydrolysis	Protopanaxadiol Protopanaxatriol	Anti-tumor; reduces the formation of atherosclerotic plaque	24, 25, 91, 92
White peony root	Paeoniflorin, albiflorin	Hydrolysis	Benzoic acid	Antidepressant	26
Digitalis lanata	Digoxin	Reduction	Dihydrodigoxin	Treatment of chronic heart failure	28
	Polymethoxyflavone	Demethylation	Demethylated metabolites	Anti-inflammatory, anti-allergic, and neuroprotective effect	29
	Nobiletin Polymethoxyflavone		Phenolic metabolites	Anti-obesity, anti-hyperglycemia, anti-hypercholesterolemia, and anti-inflammatory	93, 94
Paeonia lactiflora Pall	Paeoniflorin	Hydrolysis	Benzoic acid	Immunomodulatory and antidepressant effects	45, 95
Paeonia lactiflora Pall	Paeoniflorin	Hydrolysis	PM-I	Immunomodulatory and antidepressant effects	96
Scutellaria baicalensis	Baicalin	Hydrolysis	Baicalein	Anxiolytic and anticancer activities	97
	Chlorogenic acid	Hydrolysis	Caffeic acid	Anticancer effect	98
	Curcumin	Demethylation	Demethoxycurcumin	Anticancer, antioxidant, anti-inflammatory	99

certain patients do not respond effectively to cardiac glycoside analog therapy [28].

Gut microbiota facilitates the demethylation of NM components such as emodin, apigenin, kaempferol, luteolin, and quercetin through demethylase, generating a variety of demethylated products with diverse biological functions. Polymethoxyflavones (PMFs), a distinct class of flavonoids, exemplify this process. The demethylase encoded by *Blautia* spp. mediates the metabolism of PMFs, converting PMFs into various demethylated metabolites, which serve as the material basis for PMFs' anti-inflammatory, anti-allergic, and neuroprotective effects [29]. Consequently, the abundance and activity of microbial demethylase in the microbiome may significantly influence the individualized benefits of PMF intake. These findings underscore the importance of understanding gut microbiota-mediated drug metabolism for comprehending the substance basis, mechanisms of action, and clinical efficacy of NMs.

2.2. NMs remodel the configuration of gut microbiota

Recent studies have demonstrated that the gut microbial composition and its interaction with host pathophysiology underlie the local and systemic effects of NMs, complementing the pharmacokinetic approach. For instance, colorectal cancer (CRC), accounting for approximately 10% of all cancers, has been associated with gut microbiota in recent research [30]. The inhibitory effect of echinacoside (ECH), a phenylethanoid glycoside, on CRC metastasis is linked to abundance changes in indigenous bacteria, including *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus*. Specifically, ECH-reshaped *Faecalibacterium prausnitzii* downregulated tumoral epithelial to mesenchymal transition and phosphoinositide 3-kinase/AKT signaling by modulating immune cells and inflammatory responses [31]. Pien Tze Huang (PZH), a well-established traditional drug beneficial for cancer, demonstrated co-exclusion correlations between probiotics and pathogenic bacteria in treated mice, such as *Lactobacillus johnsonii–Aeromonas veronii* and *Pseudobutyrivibrio xylanivorans–Peptoniphilus harei*. Culture supernatants of probiotics *P. xylanivorans* and *Eubacterium limosum*, enriched after PZH treatment, significantly inhibited CRC cell viability and colony formation. These findings suggest that PZH-enriched probiotics may antagonize pathogenic bacteria to produce anti-CRC efficacy [32]. The pathogenesis of irritable bowel syndrome (IBS), a functional gastrointestinal disorder characterized by abnormal stool form and recurrent abdominal pain, is closely related to the loss of gut microbial diversity and richness [33]. A recent study elucidated the mechanism of Da-Jian-Zhong Decoction (DJZD), a traditional Chinese medicine decoction, in alleviating diarrhea-predominant irritable bowel syndrome (IBS-D) phenotypes in rats. DJZD altered the abundance of *Akkermansia*, *Alistipes*, and *Bacteroidaceae* bacteria in IBS-D rats, accompanied by improved intestinal immune responses, particularly the T helper (Th) 17/Treg balance and cytokines [34].

NMs can function as prebiotics to regulate gut dysbiosis, potentially influencing extraintestinal conditions such as metabolic syndrome and autoimmune diseases. This effect is traditionally associated with poorly absorbed polyphenols and polysaccharides in herbal medicines [35]. Research indicates that certain polyphenols from herbal medicines, such as PMFs, can effectively reduce body weight and increase the abundance of *Bacteroides* after supplementation to diet-induced obese mice [29]. Nobiletin, a representative PMF, has been demonstrated to ameliorate hepatic lipid storage, triglyceride accumulation, inflammation, and fibrosis by enriching gut symbionts like *Allobaculum stercoricanis* and *Lactobacillus casei*, contributing to the treatment of nonalcoholic fatty liver disease (NAFLD) [36]. Similarly, treating high-fat diet (HFD) mice with water extract of *Ganoderma lucidum* mycelium (WEGL) reversed HFD-induced gut dysbiosis, maintained intestinal barrier integrity, and reduced metabolic endotoxemia. Specifically, WEGL decreased the *Firmicutes*-to-*Bacteroidetes* ratio and levels of endotoxin-bearing *Proteobacteria*, underlying its effects on obesity-related metabolic disorders [36]. Studies on human populations and animal models have implicated gut dysbiosis in the pathogenesis of autoimmune diseases such as multiple sclerosis. An isoflavone-rich diet has been found to enrich bacteria belonging to *Parabacteroides* and *Adlercreutzia* genera, which metabolize isoflavones into the protective compound S-equol [37]. Collectively, these findings strongly suggest that gut microbiota remodeling is a common mechanism underlying the action of many NMs or their components. However, it remains unclear how the remodeled microbiota mechanistically contributes to the pharmacology of NMs and integrates with their multi-target regulatory mode, representing a frontier in this field of study.

2.3. NMs reshape the metabolites from gut microbiota

The gut microbiota and host coexist in a symbiotic relationship characterized by intricate molecular interactions. Recent years have witnessed an increasing understanding of the role of metabolic enzymes from gut bacteria in the disposition of xenobiotics [38] and endogenous components [39]. Small-molecule metabolites co-produced by gut microbiota and the host have been identified as chemical mediators facilitating microbiota-host communication, connecting environmental fluctuations with the host's internal homeostasis. These signaling metabolites, including short-chain fatty acids (SCFAs), amino acids, and bile acids (Table 2), play crucial roles. The following section highlights several representative studies demonstrating how these metabolic signals may underpin the holistic pharmacology of NMs [40].

Gut microbiota exemplify their functional diversity by decomposing dietary fibers like cellulose to generate SCFAs. Butyrate, for instance, provides energy for intestinal epithelial cells and influences mucosal immune cell fate *via* its action as a histone deacetylase inhibitor [41]. Additionally, acetate regulates the function of distant organs, such as adipose tissue and the brain, through blood circulation [18]. These multifaceted effects form the foundation for elucidating NM pharmacology. In a rat model of IBS, berberine exerts regulatory effects on microglia activation and visceral hypersensitivity through enrichment of SCFA-producing bacteria *Lachnoclostridium* and *Anaerostipes*, explaining its ameliorative effects on IBS severity without direct inhibition of spinal microglia [42]. Similarly, berberine alleviates rheumatoid arthritis (RA) by reducing the abundance of *Prevotella* and increasing butyrate-producing bacteria in collagen-induced arthritis (CIA) rats, supporting the potential of promoting butyrate generation from gut microbiota as a strategy for treating RA [43]. SCFAs also underlie the cerebral effects of NMs. For instance, *Cistanche tubulosa* extract influences SCFA production through gut microbiota, contributing to the restoration of serotonin and brain-derived neurotrophic factor in the brain of depressed rats and improving depressive-like behavior symptoms [44]. Moreover, SCFAs demonstrate the ability to attenuate osteoporosis progression in psoriatic arthritis (PsA) mice by inhibiting osteoclast differentiation. Compared to control mice, bone marrow osteoclast progenitor cells (OCPs) in PsA mice express higher levels of SCFA receptors, and the transcriptome of bone marrow OCPs is significantly altered in SCFA-treated mice, suggesting that SCFAs directly affect bone marrow OCPs in osteoporosis [24].

Amino acids and their metabolites from the gut microbiota have been established as signaling molecules in host-microbe interactions. Recent studies have linked microbial amino acid metabolites to the mechanisms of action of NMs. Total glucosides of peony (TGP), extracted from the root and rhizome of *Paeonia lactiflora* Pall, demonstrate clinically confirmed immunomodulatory efficacy. Paeoniflorin, a major component of TGP, has been shown to improve colonic injury and gut microbial dysbiosis in colitis mouse models [45]. Through fecal microbiota transfer and antibiotic treatment, the gut microbiota was causally implicated in the therapeutic effects. Indole-3-lactate (ILA), a microbial tryptophan metabolite, was identified as an inhibitor of epithelial autophagy, and its decrease contributed to the protective benefits of TGP. Metabolic signals from amino acid metabolism are also involved in the distal effects of poorly absorbed NM components. Sinomenine significantly increased the abundance of *Lactobacillus species*, *Lactobacillus paracasei*, and *Lactobacillus casei*, which regulate tryptophan metabolism in the gut microbiota, influencing microbial tryptophan metabolism and activating the aryl hydrocarbon receptor (AhR) through tryptophan metabolites to alleviate CIA symptoms in rats [46]. Notably, sodium oligomannate (GV-971), an Alzheimer's disease (AD) therapy approved by the National Medical Products Administration in China, is believed to improve cognition *via* a gut microbiome-related mechanism. Specifically, GV-971 suppresses gut dysbiosis-associated phenylalanine/isoleucine accumulation, which contributes to inhibiting pro-inflammatory Th1 cell-mediated neuroinflammation and cognitive impairment [47]. This finding highlights a novel strategy for AD therapy through the regulation of gut microbial metabolism.

Multiple metabolites from the bile acids pathway have been identified as mediators in the microbiota's influence on host physiology [40, 48]. FXR, a nuclear receptor expressed in the liver

Table 2 Representative studies of NMs based on gut microbial regulation.

Diseases		Natural medicine	Active components	Gut microbial changes	Metabolic/immune/neural mechanism	Ref.
Gastrointestinal disease	Inflammatory bowel disease	Baitouweng Decoction		*Firmicutes*, *Bacteroidetes*	Activates IL-6/STAT3 signaling pathway	100
		Astragalus membranaceus and *Codonopsis pilosula*	Polysaccharides	*Bacteroidetes*↑ *Firmicutes and Proteobacteria*↓	IL-6↓ IL-10, IL-22↑	101
		Qingchang Huashi Formula		*Firmicutes*↑ *Bacteroidetes*↓	Inhibits NLRP3/IL-1β pathway	102
	Irritable bowel syndrome	*Berberis heteropoda* Schrenk		*S. aureus*, *E. coli*, *P. aeruginosa*, and *S. faecalis*↓	Reduces the expression of CHAT, 5-HT, C-FOS, and CGRP	103
	Colorectal cancer	*Panax notoginseng* saponins	Ginsenoside compound K	*Akkermansia* spp.↑	Inhibit the proliferation of human CRC cells	104
		Pien Tze Huang	Ginsenoside-F2 and ginsenoside-Re	*Pseudobutyrivibrio xylanivorans*↑ *Eubacterium limosum*↑ *Campylobacter jejuni*, *Collinsella aerofaciens*↓	Taurine, bile acids↑ PI3K–Akt, IL-17↓	32
Metabolic disease	Alcoholic liver disease	*Cornus officinalis*	Iridoid glycosides	*Lactobacillus*↑	Enhances antioxidant activity; reduces inflammation	105
	NAFLD	*Terminalia bellirica*	Gallic acid and ellagic acid	*Intestinimonas*, *Lachnoclostridium*, *Akkermansia*↑	Restores the glycerolipid metabolism, taurine, and hypotaurine metabolism	77
		Ilex hainanensis	Triterpenoid saponins	*Firmicutes*↓ *Bacteroidetes Akkermansia*↑		78
		Ganoderma meroterpene derivative	Arjunolic acid	*Bacteroides xylanisolvens*, *Bacteroides thetaiotaomicron*, *Bacteroides dorei*↑	Inhibits the *α*-glucosidase	54
	Obesity	*Ganoderma lucidum* mycelium	Polysaccharides	*Eubacterium* spp.↑	Reduces macrophages; decreases MCP-1 expression; increases IL-10 expression and Treg cells	106
		Auricularia auricula	Polysaccharides	*P. cinnamivorans*↑	Reduces metabolic endotoxemia; alleviates cytokine production; inhibits the activation of JAK-STAT signaling	107
	Diabetes	Simiao Wan	Berberine	*Allobaculum*, *Akkermansia*, *Lactobacillus*↑ *Halomonas*, *Coprococcus*↓	The classical pathway by CYP7A1 and CYP8B1 The alternative pathway by CYP27A1 and CYP7B1	79
		Platycodon grandiflorus root extract	*Platycodon* saponins	*Akkermansia muciniphila*↑	Activates hepatic PI3K/PIP3/Akt insulin signaling pathway	80
Neuropsychiatric disease	Depression	*Ginkgo biloba* extract (GBE)		*P.excrementihominis*↓	UDCA↓	14
	AD	GV-971		*Bacteroides*, *Firmicutes*, *Verrucomicrobia*↑	Suppresses phenylalanine/isoleucine accumulation	47
		Seamin		*Helicobacter hepaticus*, *Clostridium*, *Bacillaceae*↓	Increases SCFAs	108
	Neurological damage	*Panax notoginseng*	Ginsenoside Rb1	*Lactobacillus helveticus*↑	Attenuates decreases in protein and mRNA levels of GABAA (α2, β2, and γ2) and GABAB (1b and 2) receptor subunits	109
	Anxiety behaviors	*Schisandra chinensis*	Lignans	*Lachnospiraceae*↑ *Bacteroides*↓	The expression of liver GPR81 was decreased, and the molecules in the cAMP pathway were increased	110
Cardiovascular disease	Atherosclerosis	*Ginkgo biloba* leaf extract		*Akkermansia*, *Alloprevotella*, *Alistipes*, *Parabacteroides*↑		111
Autoimm-une disease	Arthritis	Flavonol	Kaempferol	Regulates the abundance of *Lachnospiraceae*, *Erysipelotrichaceae*, *Staphylococcaceae*	Deoxycholic acid↓	63
		Clematis mandshurica Rupr.	Total Clematis triterpenoid saponins	Bacteroidetes↓	SCFAs↓	112
	Multiple sclerosis	Phytoestrogen	Isoflavone	*P. distasonis*, *A. equolifaciens*↑	Decreases the infiltration of immune cells; decreases activation and proliferation of MOG-specific CD4 T cells	37

and intestine, plays a crucial role in the dynamic interaction between gut microbiota and bile acids [49]. Additionally, the FXR axis is involved in various biological functions of bile acids, including lipid metabolism, liver fibrosis, and inflammatory bowel disease [50]. Consequently, this axis has been implicated in the therapeutic effects of TCM. Studies have shown that total *Astragalus* saponins, the primary components of Astragali Radix, potentially alleviate cholestatic liver fibrosis by restoring taurine-conjugated bile acids [51]. Recent research has focused on the role of bile acids in regulating neuropsychiatric diseases, offering new perspectives on the antidepressant mechanisms of NMs. *Ginkgo biloba* extract (GBE), a widely used TCM for brain disorders, demonstrates an antidepressant effect in depressive mice by restoring gut microbial composition. Specifically, GBE reduces the abundance of *Parasutterella excrementihominis*, thereby decreasing the pro-depressive bile acid metabolite ursodeoxycholic acid (UDCA), which elucidates GBE's antidepressant effect [14]. Bacterial bile salt hydrolases (BSH), crucial enzymes linking gastrointestinal microbial communities with host physiology, play a significant role in determining bile acid composition [52]. For instance, Astragaloside IV (AS-IV) has been reported to alleviate hepatic steatosis by reducing bacterial BSH activity. Specifically, AS-IV ameliorated NAFLD by decreasing BSH activity and increasing tauro-*β*-muricholic acid levels, which inhibited intestinal FXR signaling [53].

Recent research has illuminated the role of additional metabolites as signaling molecules connecting gut microbiota and NMs. A study demonstrated that oral administration of *Ganoderma* meroterpene derivative enriches *Bacteroides xylanisolvens*, which produces folic acid and mitigates NAFLD by activating the intestine-liver signaling pathway mediated by folic acid. This effect is dependent on the folic acid synthesis gene *folp* in *Bacteroides xylanisolvens* [54]. Another investigation revealed that theabrownin increases the abundance of 5-hydroxytryptamine-related species, including *Akkermansia*, *Bacteroides*, and *Parabacteroides*, thereby regulating 5-hydroxytryptamine-related signaling pathways in the liver and impeding NAFLD progression [55]. In an atherosclerosis rat model, oral berberine was found to reduce plasma and fecal concentrations of trimethylamine (TMA) and trimethylamine N-oxide (TMAO) in a gut microbiota-dependent manner, contributing to improved lipid profiles and alleviated arterial lesions. Notably, dihydroberberine, a gut microbial metabolite of berberine, inhibits the enzyme activities of choline-TMA lyase and flavin monooxygenase in gut microbiota, thereby reducing the conversion of choline to TMA to TMAO and improving arterial plaque scores [13]. Inulin-type fructo-oligosaccharide (FOS), approved by the China National Medical Products Administration in 2012 for treating mild to moderate depression, has demonstrated antidepressant effects. Chi et al. observed that FOS treatment mitigated depression-like behavior and restored gut microbiota balance in rats subjected to chronic unpredictable mild stress, including an increase in the abundance of *Cyanobacteria*, which can secrete H_2S and other antidepressant metabolites [56]. Furthermore, a study on ginseng extract revealed that the improvement of metabolic syndrome in *db/db* mice was attributed to the enrichment of *Enterococcus faecalis* in the gut, which produced myristoleic acid to activate brown adipose activity [57].

The identification of chemical inhibitors of bacterial enzymes from NMs holds significant implications for novel drug discovery. A notable example is the discovery of phytochemical inhibitors of bacterial β-glucuronidase (β-GUS), which is considered a crucial source for therapies aimed at mitigating irinotecan-induced diarrhea [58]. Recent research has revealed that bacterial β-GUS plays a key role in regulating endobiotic homeostasis by reactivating hormones and neurotransmitters [59]. Consequently, it is plausible to suggest that the modulation of bacterial β-GUS activity could be an underlying mechanism explaining the pharmacological effects of NMs. Another intriguing case is the recent identification of Dau-d4, a daurisoline derivative, as an inhibitor of the gut microbial isozyme of dipeptidyl peptidase 4. This compound has demonstrated the ability to suppress bacterial degradation of active glucagon-like peptide-1, thereby restoring glucose homeostasis in HFD-fed mice [60, 61].

3. Open questions on gut microbiota-based metabolic regulation

As demonstrated, gut microbiota can mediate the pharmacological effects of NMs through direct chemical modification of NM components or by producing diverse signaling metabolites due to the remodeling of microbial configuration (Fig. 3). In this way, the gut microbiota provides a crucial interface where NM components may influence host health and disease processes through a gut-to-systems organ signaling network. Indeed, the field of gut microbiota-based NM research has experienced significant growth in the past decade, offering new insights into the identification of the material basis and pharmacological mechanisms of NMs. This is particularly relevant for understanding the mechanism of action of bioactive NM ingredients, such as curcumin, ginsenosides, and berberine, which exhibit a paradox between poor absorption and well-confirmed systemic effects. However, a central question for future studies is how the interaction between NMs and microbiota integrates into the multi-target holistic mechanisms and clinical efficacy of NMs. In this section, we highlight several major open questions and discuss potential solutions and strategies.

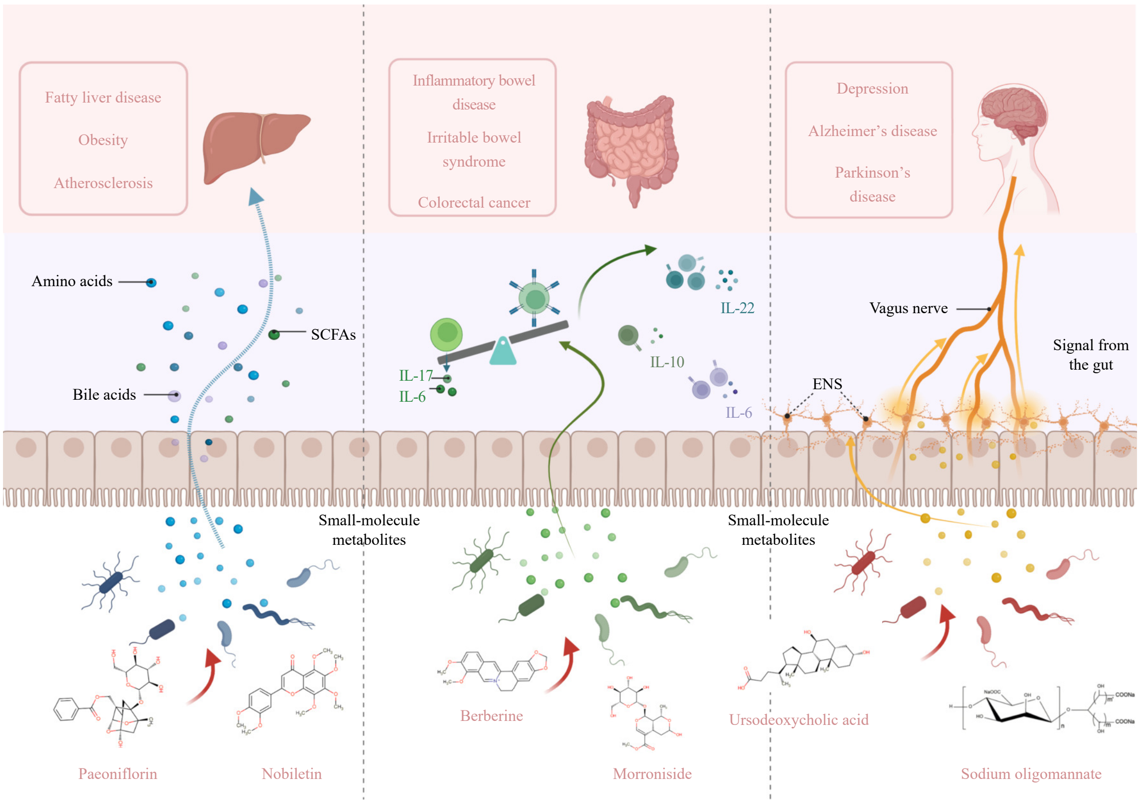

Fig. 3 Gut microbial metabolites mediate the local and systemic effects of natural medicines. Natural medicine components influence gut microbiota metabolism and host-microbe metabolic interactions, resulting in altered profiles of bioactive metabolites, including bile acids, SCFAs, and amino acids. These small-molecule microbial metabolites act as crucial mediators for microbial-host communication, either directly or indirectly, *via* modulation of immune and neuronal signals. For instance, bacterial metabolites such as butyrate and deoxycholic acid affect immune cell responses and the release of inflammatory factors like IL-6, IL-10, and IL-22, thereby influencing the progression of immune-related diseases. Recent years have witnessed the emergence of the brain-gut axis concept, emphasizing its role as a bidirectional neural pathway connecting the brain, central nervous system, enteric nervous system (ENS), and autonomic nervous system. This involves the interaction of bacterial metabolites with the ENS and afferent neural pathway, which is closely associated with various neurological disorders.

3.1. Identifying targets and signaling mechanisms for bacterial metabolites

Emerging evidence demonstrates that microbial metabolites regulate host physiological and pathological processes through interactions with the immune, endocrine, and nervous systems, collectively constituting critical mechanisms by which microbiota influence host health and disease [62-64]. A growing body of research indicates that microbial metabolites modulate the maturation and functional tuning of the host immune system, exerting extensive effects on both gut and extraintestinal organs. Gut microbial metabolites play a crucial role in shaping the balance of mucosal immunity, affecting the homeostasis of the gut epithelial system and resistance to external pathogens. Additionally, these metabolites can influence the function of immune cell trafficking to other organs, such as the lung and brain, critically determining systemic immune responses. Consequently, bacterial metabolic signals may serve as mediators underlying the immunomodulatory effects of NM components both locally and in systemic organs [65].

A compelling and emerging field is the neurometabolic interactions underlying host-microbiota communication. At the local gut level, gut microbiota closely regulate the development and restructuring of the enteric nervous system *via* metabolic and immune factors [66]. Furthermore, gut microbiota establish bidirectional communication with the brain through the autonomous nervous system, influencing emotional and cognitive processes. Notably, dysbiosis of gut microbiota may induce pathological changes such as neurotransmitter imbalance and altered neuroplasticity, potentially triggering neuropsychiatric disorders like anxiety and depression. Recent research by our group reveals that gut G-protein-coupled receptor (Gpr35) mediates a microbe-to-brain metabolic pathway, modulating neuronal plasticity and depressive behavior in mice. Specifically, *Gpr35* knockout mice and mice colonized with *Parabacteroides distasonis* exhibited a reduction in indole-3-carboxaldehyde and an increase in ILA, which differentially influence neuroplasticity in the nucleus accumbens, a brain region associated with depression. These findings emphasize the crucial role of gut-brain interactions in psychiatric conditions and highlight the potential of targeting such pathways in pharmaceutical research to develop novel treatments for human diseases [48, 67]. The interactions between gut microbiota metabolites and the central nervous system offer valuable insights for understanding the neuroprotective effects of NMs, particularly the mechanisms of their poorly absorbed components [68].

The signaling of microbial metabolites has been extensively reviewed [69-72], and we have previously summarized the putative receptors and targets of these signaling metabolites. Notably, metabolites such as acetate, propionate, butyrate, indole-3-acetate, indole-3-aldehyde, tryptamine, and histamine demonstrate pharmacological effects when interacting with host targets like AhR and serotonin receptor 4 [68]. The integration of chemoproteomics, clustered regularly interspaced short palindromic repeat gene screening, and machine learning approaches is anticipated to rapidly expand our understanding of the targetome landscape of microbial metabolites. An intriguing yet complex characteristic of bacterial metabolites is their potential to interact with multiple receptors/targets across different cells in a promiscuous manner. Furthermore, metabolite analogs may exert varying effects on the same target, leading to the concurrent presence of agonists and antagonists from a single metabolic pathway. This phenomenon may elucidate the well-balanced regulation of host phenotypes by the gut microbiota, reminiscent of NMs. However, as current research predominantly focuses on individual metabolites, there is a need to investigate how NMs may broadly regulate multiple metabolites to collectively produce a well-defined pharmacological effect. Addressing these open questions may provide profound insights into NM pharmacology and inspire novel therapeutic approaches.

3.2. Understanding the mechanisms of gut microbiota-NM interaction

Advancements in multi-omics and sequencing technologies have facilitated significant progress in analyzing alterations in gut microbiota structure and metabolites influenced by NMs [16, 73, 74]. Notably, high-throughput detection methods and enhanced analytical databases have diminished the “dark matter” component of gut microbes and metabolites [75], establishing a robust foundation for elucidating the interaction between NMs and microbiota. Nevertheless, the majority of studies examining the interaction between NM components and microbiota remain at the level of describing taxonomic and metabolite differences. These studies often do not delve deeper into how NMs affect the bacterial community and their ecological niche in the gut, how gut bacteria interact with NM components to generate key metabolites, or the bacterial origins and pathways of these metabolites.

The signaling network underlying the interaction between NM components and gut microbiota provides insights into a multi-target approach for chronic diseases. It is crucial to recognize that this interaction is not confined to a single bacterial species or metabolite but is determined by the intricate complexity of gut microbiota and the diverse array of NM components [76-81]. A key objective for future research is to elucidate the regulation of gut microbiota from the perspective of microbial interactions. For instance, previous studies have demonstrated the role of gut dysbiosis in Parkinson’s disease (PD), and variations in gut bacteria have been associated with the individualized metabolism of levodopa (L-DOPA), which influences brain dopamine availability during drug treatment [82]. Interestingly, a recent study suggests that oral berberine may potentially supply $H^{\bullet}$ through the provision of dihydroberberine (a reduced form of berberine produced by bacterial nitroreductase) and promote the production of tetrahydrobiopterin (BH4), leading to increased BH4 levels. This elevation in BH4 enhances tyrosine hydroxylase activity, accelerating the production of L-DOPA by intestinal bacteria such as *Enterococcus faecalis* and *Enterococcus faecium*, thereby potentially ameliorating PD [83]. Thus, despite the poor absorption of berberine, the promotion of L-DOPA by gut microbiota could contribute to increased brain dopamine, addressing dopamine deficiency in PD. Indeed, the study demonstrated that berberine combined with fecal microbiota transplantation conferred enhanced therapeutic effects in the PD mouse model. This research reinforces the concept that NMs can modulate bacterial interactions and communities to influence metabolic signals for host interaction.

It is commonly accepted that NMs reshape the gut microbiota *via* direct interaction with the microbial community. However, our understanding of how NMs influence the intestinal microenvironment to affect the microbial community remains limited. This aspect warrants consideration, given that the microbial community is highly responsive to the host’s physiochemical and pathophysiological factors [84]. Consequently, future research is expected to expand our knowledge of how NMs remodel the gut microbiota *via* modulation of host factors in the gut. Furthermore, the role of NM interactions with the fungal community in the gut microbiome, recently implicated in various common diseases, in mediating pharmacological effects remains largely unexplored [85].

3.3. Decoding the synergistic effects of NM components based on metabolic regulation

The unique feature of NMs in managing chronic diseases is believed to be their multiple-component, multiple-target approach. The role of gut microbiota in NM actions suggests the need to incorporate this mechanism into a comprehensive understanding of NM working mechanisms. It is plausible to propose that gut microbial remodeling is co-regulated by several NM components; alternatively, gut microbe regulation may serve as one of the complementary pathways through which NMs exert therapeutic effects. *Panax ginseng* is commonly used in treating cardiometabolic diseases, but the synergistic action of its components remains largely unclear. Our recent study indicates that ginsenoside Rb1, a PPD-type saponin, has the potential to increase intestinal *Lactobacillus* abundance, contributing to intestinal conjugated bile acid hydrolysis and excretion, as well as metabolic elimination of cholesterol. Additionally, ginsenoside Rg1, representing protopanaxatriol-type saponins, protects against atherogenesis-triggered gut leakage and metabolic endotoxemia, producing a synergistic anti-atherosclerosis effect. This study provides compelling evidence that ginsenoside Rb1/Rg1 combinations could serve as a novel therapeutic strategy against atherosclerosis *via* gut microbiome regulation [25].

The current understanding of gut microbiota's role in host health and disease remains incomplete. The complex interactions within these biological networks involve direct or indirect signal transduction through chemical mediators, neuronal pathways, and the immune system [86]. The advancement and integration of multi-omics technologies, along with the refinement of research theories such as the gut-brain axis, gut-liver axis, and gut-lung axis, offer new avenues for exploring the downstream mechanisms of NM-microbiota interactions. Furthermore, it is crucial to elucidate how various mechanisms and pathways of microbial regulation may synergistically contribute to the holistic efficacy of NMs.

3.4. Prospects for clinical translation

The interaction between gut microbiota and NMs has significant implications for clinical translation. Individual variations in gut microbiota composition may result in considerable differences in NM metabolism, influencing the absorption, toxicity, and efficacy of active ingredients [87, 88]. Moreover, the collective metabolic response to the NM may underlie the individual response to the clinical therapy. Therefore, in theory, the active metabolites from NM and gut microbiota could serve as combinatorial biomarkers to guide individualized therapy with NMs. In this regard, it would be necessary to perform longitudinal sampling in patients receiving NM therapy, focusing on serum and fecal metabolites that showed a close temporal relationship with disease index and NM regimen. Ideal clinical biomarkers should be objective and reproducible, and whether gut microbial characteristics could be employed as useful prognostic markers remains to be determined [89].

The impact of diet and genetics, crucial determinants of microbiome and microbiota profiles, on gut microbiota responses to NM requires comprehensive investigation. Future microbiome research may elucidate the relationship between gut microbiota and NM treatment, potentially identifying key microbial species and metabolites as robust clinical biomarkers for pharmacological effects. To mitigate observed microbiome feature heterogeneity and individual variations, verification in large, human-centered cohorts is essential. This process should exclude microbiota-specific and disease-specific factors to confirm their utility as biomarkers for NM treatment effects and risk assessment. Furthermore, given that data reliability, reproducibility, and statistical rigor significantly influence the validity of conclusions, researchers should exercise caution in data interpretation and explanation of controversial findings.

The intricate composition and biological attributes of the gut microbiota present significant challenges in simulating authentic human interactions within simplified experimental models. The substantial disparities between rodent and human gut microbiomes continue to impede the translation of mechanistic observations to the human gut microbiota. To enhance the reproducibility and comparability of microbiome research findings, it is crucial to prioritize clinical samples and conduct extensive, multicenter regional studies to obtain compelling results. However, at present, there remains a paucity of high-quality clinical studies investigating gut microbiota-based therapeutic mechanisms for NMs in human subjects.

Recent advancements in microbiome research have revealed the potential of probiotics, engineered bacteria, and prebiotics as novel avenues for drug discovery. As our understanding of the interactions between microbiota and NMs grows, particularly in relation to their effects on drug absorption, efficacy, and toxicity, it becomes imperative to explore the translation of this frontier into future therapeutics. Studies have demonstrated that NMs can exert prebiotic-like effects on gut dysbiosis, necessitating the identification of active components (e.g., polysaccharides) and investigation of their combination with other well-absorbed components to better replicate the holistic effects of NMs. Another crucial consideration is the identification of key signaling metabolites for new drug development. As proposed by our research group [48], bacterial metabolites serve as valuable templates for the design of novel drugs, potentially offering a bionic approach to restore inner homeostasis and balance. Utilizing NMs and active components as probes, it is essential to identify causal metabolites and underlying mechanisms, which could subsequently guide the optimization process in the development of new therapeutic agents.

4. Conclusion

NMs have demonstrated significant advantages in managing chronic diseases clinically. Their characteristics of multiple components, targets, and pathways offer therapeutic benefits while presenting challenges for mechanistic research. The past decade has witnessed rapid expansion in the study of gut microbiota and its role in health and disease. This accumulating knowledge has greatly facilitated NM research, given the extensive interaction between NMs and gut microbiota. As discussed in this review, metabolic interaction provides a crucial perspective for unraveling the key questions surrounding NM, gut microbiota, and host interactions. Gut microbiota can specifically metabolize NMs to produce active ingredients, while NM components may directly or indirectly influence the output of multiple microbial metabolites. Given that gut microbiota can affect both local and remote organs, poorly bioavailable components in NMs may interact with the gut microbiota to exert pharmacological effects [90]. This necessitates an integrative approach to understanding the active components with both good and poor systemic distributions, as previously proposed [68]. Future research is expected to elucidate the dose-response relationship between NMs and microbiota, explore mechanisms for manipulating host microbiota and, consequently, disease through NMs, and fully leverage the interaction effects between gut microbiota and NMs for precision medicine and new drug development. As clinical validation studies increase, more information will become available for understanding the gut microbiome-based therapeutic mechanism of NMs and developing microbial feature-guided therapy with NMs.

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Declaration of competing interest

These authors have no conflict of interest to declare.

References

1 Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod*. 2020;83(3):770-803. https://doi.org/10.1021/acs.jnatprod.9b01285.

2 Luo Z, Yin F, Wang X, et al. Progress in approved drugs from natural product resources. *Chin J Nat Med*. 2024;22(3):195-211. https://doi.org/10.1016/s1875-5364(24)60582-0.

3 Chi X, Zhang H, Zhang S, et al. Chinese herbal medicine for gout: a review of the clinical evidence and pharmacological mechanisms. *Chin Med*. 2020;15:17. https://doi.org/10.1186/s13020-020-0297-y.

4 Zhang S, Luo H, Tan D, et al. Holism of Chinese herbal medicine prescriptions for inflammatory bowel disease: a review based on clinical evidence and experimental research. *Phytomedicine*. 2022;102:154202. https://doi.org/10.1016/j.phymed.2022.154202.

5 Chen J, Ding Z. Natural products as potential drug treatments for acute promyelocytic leukemia. *Chin Med*. 2024;19(1):57. https://doi.org/10.1186/s13020-024-00928-8.

6 Chen J, Ding Z. Advances in natural product anti-coronavirus research (2002-2022). *Chin Med*. 2023;18(1):13. https://doi.org/10.1186/s13020-023-00715-x.

7 Katz L, Baltz RH. Natural product discovery: past, present, and future. *J Ind Microbiol Biotechnol*. 2016;43(2-3):155-76. https://doi.org/10.1007/s10295-015-1723-5.

8 Zhang Y, Chen T, Hao X, et al. Mapping the regulatory effects of herbal organic compounds on gut bacteria. *Pharmacol Res*. 2023;193:106804. https://doi.org/10.1016/j.phrs.2023.106804.

9 Shen J, Guo H, Jin W, et al. Aberrant branched-chain amino acid accumulation along the microbiota-gut-brain axis: crucial targets affecting the occurrence and treatment of ischaemic stroke. *Br J Pharmacol*. 2023;180(3):347-368. https://doi.org/10.1111/bph.15965.

10 Cheng P, Wu J, Zong G, et al. Capsaicin shapes gut microbiota and pre-metastatic niche to facilitate cancer metastasis to liver. *Pharmacol Res*. 2023;188:106643. https://doi.org/10.1016/j.phrs.2022.106643.

11 Alexander JL, Wilson ID, Teare J, et al. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat Rev Gastroenterol Hepatol*. 2017;14(6):356-365. https://doi.org/10.1038/nrgastro.2017.20.

12 Wang S, Ren H, Zhong H, et al. Combined berberine and probiotic treatment as an effective regimen for improving postprandial hyperlipidemia in type 2 diabetes patients: a double blinded placebo controlled randomized study. *Gut Microbes*. 2022;14(1):2003176. https://doi.org/10.1080/19490976.2021.2003176.

13 Ma SR, Tong Q, Lin Y, et al. Berberine treats atherosclerosis *via* a vitamine-like effect down-regulating choline-TMA-TMAO production pathway in gut microbiota. *Signal Transduct Target Ther*. 2022;7(1):207. https://doi.org/10.1038/s41392-022-01027-6.

14 Zhou J, Fan Q, Cai X, et al. *Ginkgo biloba* extract protects against depression-like behavior in mice through regulating gut microbial bile acid metabolism. *Chin J Nat Med*. 2023;21(10):745-758. https://doi.org/10.1016/s1875-5364(23)60496-0.

15 Wang T, Wu L, Wang S, et al. Chang Wei Qing Decoction enhances the antitumor effect of PD-1 inhibitor therapy by regulating the immune microenvironment and gut microbiota in colorectal cancer. *Chin J Nat Med*. 2023;21(5):333-345. https://doi.org/10.1016/s1875-5364(23)60451-0.

16 Hu J, Ni J, Zheng J, et al. *Tripterygium hypoglaucum* extract ameliorates adjuvant-induced arthritis in mice through the gut microbiota. *Chin J Nat Med*. 2023;21(10):730-744. https://doi.org/10.1016/s1875-5364(23)60466-2.

17 Li M, Wang Y, Chen Y, et al. A comprehensive review on pharmacokinetic mechanism of herb-herb/drug interactions in Chinese herbal formula. *Pharmacol Ther*. 2024;264:108728. https://doi.org/10.1016/j.pharmthera.2024.108728.

18 Perry RJ, Peng L, Barry NA, et al. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. *Nature*. 2016;534(7606):213-7. https://doi.org/10.1038/nature18309.

19 Board PG, Anders MW. Moonlighting in drug metabolism. *Drug Metab Rev*. 2021;53(1):76-99. https://doi.org/10.1080/03602532.2020.1858857.

20 Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, et al. Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature*. 2019;570(7762):462-467. https://doi.org/10.1038/s41586-019-1291-3.

21 Javdan B, Lopez JG, Chankhamjon P, et al. Personalized mapping of drug metabolism by the human gut microbiome. *Cell*. 2020;181(7):1661-1679.e22. https://doi.org/10.1016/j.cell.2020.05.001.

22 Zhang H, Xu HL, et al. 20(*S*)-Protopanaxadiol-induced apoptosis in MCF-7 breast cancer cell line through the inhibition of PI3K/AKT/mTOR signaling pathway. *Int J Mol Sci*. 2018;19(4):1053. https://doi.org/10.3390/ijms19041053.

23 Zhang Z, Zhang Y, Li J, et al. The neuroprotective effect of tea polyphenols on the regulation of intestinal flora. *Molecules*. 2021;26(12):3692. https://doi.org/10.3390/molecules26123692.

24 Chen Z, Zhang Z, Liu J, et al. Gut microbiota: therapeutic targets of ginseng against multiple disorders and ginsenoside transformation. *Front Cell Infect Microbiol*. 2022;12:853981. https://doi.org/10.3389/fcimb.2022.853981.

25 Wang Y, Wu J, Yu H, et al. Ginsenosides retard atherogenesis *via* remodelling host-microbiome metabolic homeostasis. *Br J Pharmacol*. 2024;181(12):1768-1792. https://doi.org/10.1111/bph.16320.

26 Zhang ZW, Han P, Fu J, et al. Gut microbiota-based metabolites of Xiaoyao Pills (a typical traditional Chinese medicine) ameliorate depression by inhibiting fatty acid amide hydrolase levels in brain. *J Ethnopharmacol*. 2023;313:116555. https://doi.org/10.1016/j.jep.2023.116555.

27 Wen HY, Pan LB, Ma SR, et al. Structural basis for the transformation of the traditional medicine berberine by bacterial nitroreductase. *Acta Crystallogr D Struct Biol*. 2022;78(Pt 10):1273-1282. https://doi.org/10.1107/s2059798322008373.

28 Koppel N, Bisanz JE, Pandelia ME, et al. Discovery and characterization of a prevalent human gut bacterial enzyme sufficient for the inactivation of a family of plant toxins. *Elife*. 2018;7:e33953. https://doi.org/10.7554/eLife.33953.

29 Zeng SL, Li SZ, Xiao PT, et al. Citrus polymethoxyflavones attenuate metabolic syndrome by regulating gut microbiome and amino acid metabolism. *Sci Adv*. 2020;6(1):eaax6208. https://doi.org/10.1126/sciadv.aax6208.

30 Irrazábal T, Belcheva A, Girardin SE, et al. The multifaceted role of the intestinal microbiota in colon cancer. *Mol Cell*. 2014;54(2):309-320. https://doi.org/10.1016/j.molcel.2014.03.039.

31 Wei J, Zheng Z, Hou X, et al. Echinacoside inhibits colorectal cancer metastasis *via* modulating the gut microbiota and suppressing the PI3K/AKT signaling pathway. *J Ethnopharmacol*. 2024;318(Pt A):116866. https://doi.org/10.1016/j.jep.2023.116866.

32 Gou H, Su H, Liu D, et al. Traditional medicine Pien Tze Huang suppresses colorectal tumorigenesis through restoring gut microbiota and metabolites. *Gastroenterology*. 2023;165(6):1404-1419. https://doi.org/10.1053/j.gastro.2023.08.052.

33 Ford AC, Sperber AD, Corsetti M, et al. Irritable bowel syndrome. *Lancet*. 2020;396(10263):1675-1688. https://doi.org/10.1016/s0140-6736(20)31548-8.

34 Zhang MM, Dang M, Wu X, et al. Da-Jian-Zhong Decoction alleviates diarrhea-predominant irritable bowel syndrome *via* modulation of gut microbiota and Th17/Treg balance. *J Ethnopharmacol*. 2024;331:118275. https://doi.org/10.1016/j.jep.2024.118275.

35 Dai H, Han J, Wang T, et al. Recent advances in gut microbiota-associated natural products: structures, bioactivities, and mechanisms. *Nat Prod Rep*. 2023;40(6):1078-1093. https://doi.org/10.1039/d2np00075j.

36 Li SZ, Zhang NN, Yang X, et al. Nobiletin ameliorates nonalcoholic fatty liver disease by regulating gut microbiota and myristoleic acid metabolism. *J Agric Food Chem*. 2023;71(19):7312-7323. https://doi.org/10.1021/acs.jafc.2c08637.

37 Jensen SN, Cady NM, Shahi SK, et al. Isoflavone diet ameliorates experimental autoimmune encephalomyelitis through modulation of gut bacteria depleted in patients with multiple sclerosis. *Sci Adv*. 2021;7(28):eabd4595. https://doi.org/10.1126/sciadv.abd4595.

38 Han ND, Cheng J, Delannoy-Bruno O, et al. Microbial liberation of *N*-methylserotonin from orange fiber in gnotobiotic mice and humans. *Cell*. 2022;185(14):2495-2509.e11. https://doi.org/10.1016/j.cell.2022.06.004.

39 Jia B, Han X, Kim KH, et al. Discovery and mining of enzymes from the human gut microbiome. *Trends Biotechnol*. 2022;40(2):240-254. https://doi.org/10.1016/j.tibtech.2021.06.008.

40 Zheng X, Cai X, Hao HP. Emerging targetome and signalome landscape of gut microbial metabolites. *Cell Metab*. 2022;34(1):35-58. https://doi.org/10.1016/j.cmet.2021.12.011.

41 Schoeler M, Caesar R. Dietary lipids, gut microbiota and lipid metabolism. *Rev Endocr Metab Disord*. 2019;20(4):461-472. https://doi.org/10.1007/s11154-019-09512-0.

42 Zhang JD, Liu J, Zhu SW, et al. Berberine alleviates visceral hypersensitivity in rats by altering gut microbiome and suppressing spinal microglial activation. *Acta Pharmacol Sin*. 2021;42(11):1821-1833. https://doi.org/10.1038/s41401-020-00601-4.

43 Yue M, Tao Y, Fang Y, et al. The gut microbiota modulator berberine ameliorates collagen-induced arthritis in rats by facilitating the generation of butyrate and adjusting the intestinal hypoxia and nitrate supply. *FASEB J*. 2019;33(11):12311-12323 https://doi.org/10.1096/fj.201900425RR.

44 Li Y, Peng Y, Yang H, et al. Antidepressant-like effects of *Cistanche tubulosa* extract on chronic unpredictable stress rats through restoration of gut microbiota homeostasis. *Front Pharmacol*. 2018;9:967. https://doi.org/10.3389/fphar.2018.00967.

45 Schlegel N, Boerner K, Waschke J. Targeting desmosomal adhesion and signalling for intestinal barrier stabilization in inflammatory bowel diseases-lessons from experimental models and patients. *Acta Physiol (Oxf)*. 2021;231(1):e13492. https://doi.org/10.1111/apha.13492.

46 Jiang ZM, Zeng SL, Huang TQ, et al. Sinomenine ameliorates rheumatoid arthritis by modulating tryptophan metabolism and activating aryl hydrocarbon receptor *via* gut microbiota regulation. *Sci Bull*. 2023;68(14):1540-1555. https://doi.org/10.1016/j.scib.2023.06.027.

47 Wang X, Sun G, Feng T, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res*. 2019;29(10):787-803. https://doi.org/10.1038/s41422-019-0216-x.

48 Cheng L, Wu H, Cai X, et al. A Gpr35-tuned gut microbe-brain metabolic axis

regulates depressive-like behavior. *Cell Host Microbe*. 2024;32(2):227-243. e6. https://doi.org/10.1016/j.chom.2023.12.009.

49 Liu H, Hu C, Zhang X, et al. Role of gut microbiota, bile acids and their cross-talk in the effects of bariatric surgery on obesity and type 2 diabetes. *J Diabetes Investig*. 2018;9(1):13-20. https://doi.org/10.1111/jdi.12687.

50 Zhang YL, Li ZJ, Gou HZ, et al. The gut microbiota-bile acid axis: a potential therapeutic target for liver fibrosis. *Front Cell Infect Microbiol*. 2022;12: 945368. https://doi.org/10.3389/fcimb.2022.945368.

51 Zhang L, Shi J, Shen Q, et al. Astragalus saponins protect against extrahepatic and intrahepatic cholestatic liver fibrosis models by activation of farnesoid X receptor. *J Ethnopharmacol*. 2024;318(Pt A): 116833. https://doi.org/10.1016/j.jep.2023.116833.

52 Bourgin M, Kriaa A, Mkaouar H, et al. Bile salt hydrolases: at the crossroads of microbiota and human health. *Microorganisms*. 2021;9(6):1122. https://doi.org/10.3390/microorganisms9061122.

53 Zhai Y, Zhou W, Yan X, et al. Astragaloside IV ameliorates diet-induced hepatic steatosis in obese mice by inhibiting intestinal FXR *via* intestinal flora remodeling. *Phytomedicine*. 2022;107:154444. https://doi.org/10.1016/j.phymed.2022.154444.

54 Qiao S, Bao L, Wang K, et al. Activation of a specific gut bacteroides-folate-liver axis benefits for the alleviation of nonalcoholic hepatic steatosis. *Cell Rep*. 2020;32(6):108005. https://doi.org/10.1016/j.celrep.2020.108005.

55 Li HY, Huang SY, Zhou DD, et al. Theabrownin inhibits obesity and non-alcoholic fatty liver disease in mice *via* serotonin-related signaling pathways and gut-liver axis. *J Adv Res*. 2023;52:59-72. https://doi.org/10.1016/j.jare.2023.01.008.

56 Chi L, Khan I, Lin Z, et al. Fructo-oligosaccharides from *Morinda officinalis* remodeled gut microbiota and alleviated depression features in a stress rat model. *Phytomedicine*. 2020;67:153157. https://doi.org/10.1016/j.phymed.2019.153157.

57 Quan LH, Zhang C, Dong M, et al. Myristoleic acid produced by enterococci reduces obesity through brown adipose tissue activation. *Gut*. 2020;69(7): 1239-1247. https://doi.org/10.1136/gutjnl-2019-319114.

58 Yang F, Zhu W, Sun S, et al. Isolation and structural characterization of specific bacterial β-glucuronidase inhibitors from Noni (*Morinda citrifolia*) fruits. *J Nat Prod*. 2020;83(4):825-833. https://doi.org/10.1021/acs.jnatprod.9b00279.

59 Ning L, Hong J. Gut microbial β-glucuronidase: a key regulator of endobiotic homeostasis. *Cell Host Microbe*. 2024;32(6):783-785. https://doi.org/10.1016/j.chom.2024.05.007.

60 Wang K, Zhang Z, Hang J, et al. Microbial-host-isozyme analyses reveal microbial DPP4 as a potential antidiabetic target. *Science*. 2023;381(6657): eadd5787. https://doi.org/10.1126/science.add5787.

61 Li M, Li H. Microbial-host-isozyme: a new territory for understanding personalized responses towards drug therapy. *Chin J Nat Med*. 2023;21(8): 561-562. https://doi.org/10.1016/S1875-5364(23)60493-5.

62 Liu L, Wu Q, Chen Y, et al. Gut microbiota in chronic pain: novel insights into mechanisms and promising therapeutic strategies. *Int Immunopharmacol*. 2023;115:109685. https://doi.org/10.1016/j.intimp.2023.109685.

63 Aa LX, Fei F, Qi Q, et al. Rebalancing of the gut flora and microbial metabolism is responsible for the anti-arthritis effect of kaempferol. *Acta Pharmacol Sin*. 2020;41(1):73-81. https://doi.org/10.1038/s41401-019-0279-8.

64 Zhang Y, Geng J, Hong Y, et al. Orally administered crocin protects against cerebral ischemia/reperfusion injury through the metabolic transformation of crocetin by gut microbiota. *Front Pharmacol*. 2019;10:440. https://doi.org/10.3389/fphar.2019.00440.

65 Fan L, Xia Y, Wang Y, et al. Gut microbiota bridges dietary nutrients and host immunity. *Sci China Life Sci*. 2023;66(11):2466-2514. https://doi.org/10.1007/s11427-023-2346-1.

66 Fadlallah J, Sterlin D, Fieschi C, et al. Synergistic convergence of microbiota-specific systemic IgG and secretory IgA. *J Allergy Clin Immunol*. 2019;143(4): 1575-1585.e4. https://doi.org/10.1016/j.jaci.2018.09.036.

67 Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease. *Ageing Res Rev*. 2018;45:53-61. https://doi.org/10.1016/j.arr.2018.04.004.

68 Hao H, Zheng X, Wang G, et al. Insights into drug discovery from natural medicines using reverse pharmacokinetics. *Trends Pharmacol Sci*. 2014;35 (4):168-177. https://doi.org/10.1016/j.tips.2014.02.001.

69 Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. *Immunity*. 2017;46(4):562-576. https://doi.org/10.1016/j.immuni.2017.04.008.

70 Gao J, Xu K, Liu H, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. *Front Cell Infect Microbiol*. 2018;8:13. https://doi.org/10.3389/fcimb.2018.00013.

71 Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19(1):55-71. https://doi.org/10.1038/s41579-020-0433-9.

72 Shandilya S, Kumar S, Jha NK, et al. Interplay of gut microbiota and oxidative stress: perspective on neurodegeneration and neuroprotection. *J Adv Res*. 2022;38:223-244. https://doi.org/10.1016/j.jare.2021.09.005.

73 Liu Y, Li H, Wang X, et al. Anti-Alzheimers molecular mechanism of icariin: insights from gut microbiota, metabolomics, and network pharmacology. *J Transl Med*. 2023;21(1):277. https://doi.org/10.1186/s12967-023-04137-z.

74 Hu H, Yao Y, Liu F, et al. Integrated microbiome and metabolomics revealed the protective effect of baicalin on alveolar bone inflammatory resorption in aging. *Phytomedicine*. 2024;124:155233. https://doi.org/10.1016/j.phymed.2023.155233.

75 Han S, Treuren WV, Fischer CR, et al. A metabolomics pipeline for the mechanistic interrogation of the gut microbiome. *Nature*. 2021;595(7867): 415-420. https://doi.org/10.1038/s41586-021-03707-9.

76 Zhang X, Wang H, Xie C, et al. Shenqi compound ameliorates type-2 diabetes mellitus by modulating the gut microbiota and metabolites. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2022;1194:123189. https://doi.org/10.1016/j.jchromb.2022.123189.

77 Zhang B, Luo X, Han C, et al. *Terminalia bellirica* ethanol extract ameliorates nonalcoholic fatty liver disease in mice by amending the intestinal microbiota and faecal metabolites. *J Ethnopharmacol*. 2023;305:116082. https://doi.org/10.1016/j.jep.2022.116082.

78 Zhao W, Xiao M, Yang J, et al. The combination of ilexhainanoside D and ilexsaponin A1 reduces liver inflammation and improves intestinal barrier function in mice with high-fat diet-induced non-alcoholic fatty liver disease. *Phytomedicine*. 2019;63:153039. https://doi.org/10.1016/j.phymed.2019.153039.

79 Chen Y, Zhu L, Hu W, et al. Simiao Wan modulates the gut microbiota and bile acid metabolism during improving type 2 diabetes mellitus in mice. *Phytomedicine*. 2022;104:154264. https://doi.org/10.1016/j.phymed.2022.154264.

80 Luo Z, Xu W, Yuan T, et al. Platycodon grandiflorus root extract activates hepatic PI3K/PIP3/Akt insulin signaling by enriching gut *Akkermansia muciniphila* in high fat diet fed mice. *Phytomedicine*. 2023;109:154595. https://doi.org/10.1016/j.phymed.2022.154595.

81 Meng Q, Guo J, Lv K, et al. 5*S*-Heudelotinone alleviates experimental colitis by shaping the immune system and enhancing the intestinal barrier in a gut microbiota-dependent manner. *Acta Pharm Sin B*. 2024;14(5):2153-2176. https://doi.org/10.1016/j.apsb.2024.02.020.

82 Rekdal VM, Bess EN, Bisanz JE, et al. Discovery and inhibition of an interspecies gut bacterial pathway for levodopa metabolism. *Science*. 2019;364(6445):eaau6323. https://doi.org/10.1126/science.aau6323.

83 Wang Y, Tong Q, Ma SR, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. *Signal Transduct Target Ther*. 2021;6(1):77. https://doi.org/10.1038/s41392-020-00456-5.

84 Cheng L, Wu H, Chen Z, et al. Gut microbiome at the crossroad of genetic variants and behavior disorders. *Gut Microbes*. 2023;15(1):2201156. https://doi.org/10.1080/19490976.2023.2201156.

85 Yan Q, Li S, Yan Q, et al. A genomic compendium of cultivated human gut fungi characterizes the gut mycobiome and its relevance to common diseases. *Cell*. 2024;187(12):2969-2989.e24. https://doi.org/10.1016/j.cell.2024.04.043.

86 Soehnlein O, Libby P. Targeting inflammation in atherosclerosis-from experimental insights to the clinic. *Nat Rev Drug Discov*. 2021;20(8):589-610. https://doi.org/10.1038/s41573-021-00198-1.

87 Zhang Z, Geng J, Tang X, et al. Spatial heterogeneity and co-occurrence patterns of human mucosal-associated intestinal microbiota. *ISME J*. 2014;8 (4):881-893. https://doi.org/10.1038/ismej.2013.185.

88 Su Q, Tun HM, Liu Q, et al. Gut microbiome signatures reflect different subtypes of irritable bowel syndrome. *Gut Microbes*. 2023;15(1):2157697. https://doi.org/10.1080/19490976.2022.2157697.

89 Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89-95. https://doi.org/10.1067/mcp.2001.113989.

90 Lin TL, Lu CC, Lai WF, et al. Role of gut microbiota in identification of novel TCM-derived active metabolites. *Protein Cell*. 2021;12(5):394-410. https://doi.org/10.1007/s13238-020-00784-w.

91 Jin X, Zhou J, Zhang Z, et al. The combined administration of parthenolide and ginsenoside CK in long circulation liposomes with targeted tLyp-1 ligand induce mitochondria-mediated lung cancer apoptosis. *Artif Cells Nanomed Biotechnol*. 2018;46(sup3):931-942. https://doi.org/10.1080/21691401.2018.1518913.

92 Zhou L, Zheng Y, Li Z, et al. Compound K attenuates the development of atherosclerosis in $\text{ApoE}^{-/-}$ mice *via* LXRα activation. *Int J Mol Sci*. 2016;17(7): 1054. https://doi.org/10.3390/ijms17071054.

93 Lee YS, Cha BY, Saito K, et al. Nobiletin improves hyperglycemia and insulin resistance in obese diabetic *ob/ob* mice. *Biochem Pharmacol*. 2010;79(11): 1674-1683. https://doi.org/10.1016/j.bcp.2010.01.034.

94 Li S, Li X, Chen F, et al. Nobiletin mitigates hepatocytes death, liver inflammation, and fibrosis in a murine model of NASH through modulating hepatic oxidative stress and mitochondrial dysfunction. *J Nutr Biochem*. 2022;100:108888. https://doi.org/10.1016/j.jnutbio.2021.108888.

95 Zhao ZX, Fu J, Ma SR, et al. Gut-brain axis metabolic pathway regulates antidepressant efficacy of albiflorin. *Theranostics*. 2018;8(21):5945. https://doi.org/10.7150/thno.28068.

96 He JX, Goto E, Akao T, et al. Interaction between Shaoyao-Gancao-Tang and a laxative with respect to alteration of paeoniflorin metabolism by intestinal bacteria in rats. *Phytomedicine*. 2007;14(7-8):452-459. https://doi.org/10.1016/j.phymed.2006.09.014.

97 Han DH, Lee Y, Ahn JH. Biological synthesis of baicalein derivatives using *Escherichia coli*. *J Microbiol Biotechnol*. 2016;26(11):1918-1923. https://doi.org/10.4014/jmb.1605.05050.

98 Agunloye OM, Oboh G, Ademiluyi AO, et al. Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. *Biomed Pharmacother*. 2019;109: 450-458. https://doi.org/10.1016/j.biopha.2018.10.044.

99 Burapan S, Kim M, Han J. Curcuminoid demethylation as an alternative metabolism by human intestinal microbiota. *J Agric Food Chem*. 2017;65(16): 3305-3310. https://doi.org/10.1021/acs.jafc.7b00943.

100 Chen XQ, Lv XY, Liu SJ. Baitouweng Decoction alleviates dextran sulfate sodium-induced ulcerative colitis by regulating intestinal microbiota and the IL-6/STAT3 signaling pathway. *J Ethnopharmacol*. 2021;265:113357. https://doi.org/10.1016/j.jep.2020.113357.

101 Tang S, Liu W, Zhao Q, et al. Combination of polysaccharides from

Astragalus membranaceus and *Codonopsis pilosula* ameliorated mice colitis and underlying mechanisms. *J Ethnopharmacol*. 2021;264:113280. https://doi.org/10.1016/j.jep.2020.113280.

102 Hu J, Huang H, Chen Y, et al. Qingchang Huashi Formula attenuates DSS-induced colitis in mice by restoring gut microbiota-metabolism homeostasis and goblet cell function. *J Ethnopharmacol*. 2021;266:113394. https://doi.org/10.1016/j.jep.2020.113394.

103 Li L, Zhu HM, Yan Q, et al. The antibacterial activity of *Berberis heteropoda* Schrenk and its effect on irritable bowel syndrome in rats. *Chin J Nat Med*. 2020;18(5):356-368. https://doi.org/10.1016/S1875-5364(20)30042-X.

104 Li XM, Yuan DY, Liu YH, et al. *Panax notoginseng* saponins prevent colitis-associated colorectal cancer *via* inhibition IDO1 mediated immune regulation. *Chin J Nat Med* . 2022;20(4):258-269. https://doi.org/10.1016/S1875-5364(22)60179-1.

105 Han X, Liu J, Hang A, et al. An iridoid glycoside from *Cornus officinalis* balances intestinal microbiome disorder and alleviates alcohol-induced liver injury. *J Funct Foods*. 2021;82:104488. https://doi.org/10.1016/j.jff.2021.104488.

106 Chang CJ, Lin CS, Lu CC, et al. *Ganoderma lucidum* reduces obesity in mice by modulating the composition of the gut microbiota. *Nat Commun*. 2015;6:7489. https://doi.org/10.1038/ncomms8489.

107 Zong X, Zhang H, Zhu L, et al. *Auricularia auricula* polysaccharides attenuate obesity in mice through gut commensal *Papillibacter cinnamivorans*. *J Adv Res*. 2023;52:203-218. https://doi.org/10.1016/j.jare.2023.08.003.

108 Liu Q, Xie T, Xi Y, et al. Sesamol attenuates amyloid peptide accumulation and cognitive deficits in APP/PS1 mice: the mediating role of the gut–brain axis. *J Agric Food Chem*. 2021;69(43):12717-12729. https://doi.org/10.1021/acs.jafc.1c04687.

109 Chen H, Shen J, Li H, et al. Ginsenoside Rb1 exerts neuroprotective effects through regulation of *Lactobacillus helveticus* abundance and GABAA receptor expression. *J Ginseng Res*. 2020;44(1):86-95. https://doi.org/10.1016/j.jgr.2018.09.002.

110 Song Y, Shan B, Zeng S, et al. Raw and wine processed *Schisandra chinensis* attenuate anxiety like behavior *via* modulating gut microbiota and lipid metabolism pathway. *J Ethnopharmacol*. 2021;266:113426. https://doi.org/10.1016/j.jep.2020.113426.

111 Wang Y, Xu Y, Xu X, et al. *Ginkgo biloba* extract ameliorates atherosclerosis *via* rebalancing gut flora and microbial metabolism. *Phytother Res*. 2022;36(6):2463-2480. https://doi.org/10.1002/ptr.7439.

112 Guo LX, Wang HY, Liu XD, et al. Saponins from *Clematis mandshurica* Rupr. regulates gut microbiota and its metabolites during alleviation of collagen-induced arthritis in rats. *Pharmacolo Res*. 2019;149:104459. https://doi.org/10.1016/j.phrs.2019.104459.