Acupuncture and Herbal Medicine

Efficacy and toxicity in Gardeniae Fructus application: dual role effects mediated by gut microbiota–derived biotransformation

Zixin Zhao[1,2], Shilin Gong[1,2], Chunyue Liu[1,2], Jun Wen[1,2,*], Tingting Zhou[1,2,*]

[1]School of Pharmacy, Naval Medical University, Shanghai 200433, China; [2]Shanghai Key Laboratory for Pharmaceutical Metabolite Research, School of Pharmacy, Naval Medical University, Shanghai 200433, China

Abstract

Gardeniae Fructus (GF) is a well-known traditional Chinese medicine widely used in clinical prescriptions for its antidepressant, hepatoprotective, and other therapeutic effects. It contains multiple bioactive compounds, including iridoid glycosides, crocins, flavonoids, and organic acids. However, prolonged use or excessive doses of GF may lead to chronic or acute hepatotoxicity. This double-edged pharmacological profile has become a major obstacle to its clinical application. Accumulating evidence indicates that the gut microbiota plays a non-negligible role in the metabolism of traditional Chinese medicines. Notably, the dual effects of GF, both therapeutic and toxic, are closely associated with the microbial biotransformation of its active components, positioning the gut microbiota as a critical determinant of GF's efficacy and safety. Microbial enzymes may enhance the bioavailability and bioactivities of GF-derived ingredients, as well as generate novel metabolites with potential pharmacological activities. Concurrently, GF-induced alterations in bacterial composition may lead to changes in metabolic output, which further influence host physiological responses, thereby modulating the overall effects of GF. In this case, it is essential to incorporate gut microbiota–mediated bioactivities into the comprehensive evaluation of GF pharmacology. This review provides a comprehensive summary of the main bioactive compounds of GF and their biotransformation by the gut microbiota, and examines the dual effects of GF in the presence or absence of gut microbiota influences. Moreover, we discuss the potential of intestinal bacterial modulation as a strategy for balancing the efficacy and safety of GF. This review offers a thorough synthesis of the dual pharmacological actions of GF, while placing particular emphasis on the gut microbiota as a critical mediator of its divergent effects. We also offer new perspectives on the clinical potential of gut microbiota–targeted interventions to balance the dual effects of GF. The bidirectional crosstalk between gut microbiota and GF significantly influences the efficacy and toxicity of GF-derived compounds. Ecological management strategies may benefit the personalized treatment paradigm of GF, by accounting for interindividual variability in the gut microbiota.

Keywords: Efficacy and toxicity, Gardeniae Fructus, Genipin, Gut microbiota, Gut-X axis, Microbial biotransformation

Graphical Abstract: https://links.lww.com/AHM/A240

Introduction

Gardeniae Fructus (Zhizi in Chinese, abbreviated as GF), the dried ripe fruit of *Gardenia jasminoides Ellis*, represents one of the most important traditional Chinese medicines with a documented history spanning over two millennia[1–2]. The traditional Chinese clinical prescriptions containing GF, such as Zhi-Zi-Chi Decoction (ZZCD), are usually associated with antidepressant, anti-inflammatory, hepatoprotective, and cardiovascular protective effects[3–5]. GF is also permitted to be used in the food industry and is considered a dietary supplement with health benefits, which is widely utilized in our daily life[6–8]. A large number of recent investigations have been conducted to explore the constituents of GF, revealing various bioactive components including iridoids, flavonoids, terpenoids, and polysaccharides[9–10]. Among these ingredients, geniposide and crocetin glycosides (crocins) are the major bioactive constituents selected as control markers[9,11]. Notably, the metabolites generated following oral administration are also responsible for the pharmacological effects of these compounds[12]. Therefore, the *in vivo* metabolism of GF should also be taken into consideration when evaluating its pharmacological activities.

Gut microbiota in the gastrointestinal tract is a huge ecosystem, which contains over 400 bacterial species[13–14]. Previous studies have uncovered that gut microbiota constitutes the intestinal micro-ecosystem and participates in physiological processes including nutritional absorption, biological barriers, immune regulation, fat metabolism, and anti-tumor activities[12].

Zixin Zhao and Shilin Gong contributed equally to this work.

**Corresponding author. Jun Wen, E-mail: wenjunapple@163.com; Tingting Zhou, E-mail: tingting_zoo@163.com.*

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HM9_V6N3.indb 387 26-Sep-26 15:38:25

For GF, which is usually administered orally, it is certain to contact the gut microbiota when transported into the intestine. The ingredients of GF are transformed by these bacteria and their metabolic enzymes, which may generate new active metabolites. The secondary metabolites produced by intestinal bacteria can further conjugate with bioactive compounds in GF to build new metabolites with different biological effects. Therefore, the bioavailability, bioactivity, and toxicity of components in GF are closely related to the composition of gut microbiota[12,15–16]. Notably, there is a bidirectional influence between bioactive compounds and intestinal bacteria; the composition of the intestinal micro-ecosystem could be modulated by those metabolites in GF[17–19]. In this case, the influences between gut microbiota and GF components are non-negligible when investigating GF bioactivities.

On the other hand, prolonged usage or excessive doses of GF in clinical use may induce adverse effects[20]. Hepatotoxicity and nephrotoxicity are the most commonly reported adverse effects of GF. These adverse effects are closely related to geniposide, which is also the primary active compound in GF[21]. However, the direct cause of GF's toxicity is genipin, the reactive metabolite of geniposide transformed by intestinal bacteria[22–23]. It can be noted that the biotransformation mediated by intestinal bacteria is essential for GF-induced adverse effects. Considering the critical role of gut microbiota in both activities and toxicities of GF, it is worth discussing the modulation of intestinal bacteria intervening in GF's biofunctions.

Comprehensive literature search was performed in multiple electronic databases, including PubMed, Web of Science, and google scholar, covering publications from database inception up to March 2026. The search strategy utilized keywords such as "Gardeniae Fructus" "Zhizi" "Gardenia jasminoides" "geniposide" "genipin" "gut microbiota" "microbial biotransformation" "gut–liver axis" "gut–brain axis" "gut–X axis" "efficacy" "toxicity" "hepatotoxicity" and their combinations. Here we summarize the biotransformation of bioactive compounds in GF and its related physiological effects, as well as those pharmacological effects involving gut microbiota metabolites modulated by GF. Moreover, the dual role of gut microbiota in both the toxic mechanisms of GF and the corresponding detoxification approaches is also focused on.

Main components of GF

Ingredients contained in GF and their *in vivo* transformation are critical for GF's efficacy and toxicity. In this case, the GF chemical components and their metabolism are discussed as follows.

Chemical components in GF

There are many activity-related metabolites in GF; over 200 small-molecule compounds are reported, including iridoid, crocins, triterpenoids, flavonoids, and phenolic acids[9,11]. Besides, the macromolecular components of GF can also contribute to its biological activities, with polysaccharides being recognized as key functional components[24]. Here, the main components in GF are summarized according to their structural characteristics.

Iridoid glycosides

Iridoid glycosides are characteristic compounds of GF, which consist of a parent nucleus of hemiacetal and cyclopentane[25]. Various iridoid glycosides have been identified in GF, including geniposide, gardenoside, geniposidic acid, and shanzhiside, etc, which typically account for 5% to 8% of the dried fruit weight depending on geographic origin, harvest time, and processing methods[11,26]. These iridoid glycosides were regarded as major contributors to the total biological activities of GF, such as anti-inflammatory, central nervous system protective activities, liver protective effects, and antidepressant activities[10,15,27]. Among them, geniposide is the predominant iridoid glycoside, constituting approximately 3% to 6% of the dried fruit, and is selected as a critical marker for GF quality control in the Chinese Pharmacopoeia Commission. Moreover, geniposide, as one of the primary anti-inflammatory and hepatoprotective compounds of GF, has been found to be distributed differently in raw seed and raw pericarp of GF, and its content could be influenced by processing conditions[9]. These investigations showed the importance of iridoid glycosides in GF.

Crocins

Crocins are major water-soluble carotenoids in GF, which are responsible for the yellow color of GF[26]. As reported, crocins account for 14.09% of the dry fruit weight and 9.56% of the fresh fruit weight[28–29]. The main differences between crocins are the diverse sugar moieties esterified to cis- and trans-formed crocetin[26]. Crocins have been found to generate various biological activities; for example, the anti-inflammatory and hepatoprotective effects of GF are primarily attributed to *trans-crocin I* and *geniposides*[9]. Besides, crocetin can break through the blood-brain barrier (BBB) and reach the central nervous system (CNS) through a slow process, which also contributes to the nervous system protective activities of GF[30–31]. Therefore, crocins are considered additional major active constituents in GF besides iridoid glycosides[16].

Flavonoids and organic acids

The flavonoid content is lower than that of iridoid glycosides and crocins in GF, but these compounds are usually regarded as functional components, such as antioxidant compounds[11,15,32], in natural products. The content of total flavonoids accounts for 3.23% of GF[25–26]. Quercetin, rutin, kaempferol, and their glycosylated derivatives are representative flavonoids in GF[9]. Some flavonoids are also chosen as chemical markers for GF quality control and improvement of processing techniques, such as rutin and taxifolin[10,32–33].

Organic acids

Organic acids are rich in GF; 33 organic acids were identified in GF[9], among which chlorogenic acid has a high content in GF. Besides, other organic acids such as quinic acids, caffeic acids, and caffeoylquinic acid derivatives have also been discovered in GF[25]. Due to their potential bioactivities and differential distributions in GF with diverse processing techniques, organic acids are usually present in candidates for chemical markers of GF[10,32–33].

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Polysaccharides

When small-molecule components in GF showed prospective functions, GF polysaccharides were also found to exhibit satisfactory pharmacological activities and have attracted increasing attention[6]. The polysaccharides in GF are quite abundant, accounting for 4% to 11% of the content in fruit[34]. The complex structures and high specificity of polysaccharides also make them suitable for drug development and potentially a comprehensive candidate for complex disease treatment[6]. Many polysaccharides isolated and purified from GF showed diverse activities. For example, crude extracts of GF polysaccharides could alleviate α-naphthyl isothiocyanate (ANIT)–induced liver damage and protect intestinal barrier function in cholestatic mice[35]. A new type of branched galacturonic acid, GJE0.2-2, was purified from GF and generated CCl4-induced liver fibrosis prospective effects through toll-like receptor 4/nuclear factor kappa-B (TLR4/NF-κB) signaling[36]. Moreover, two low-methoxyl pectin components, GJP50-3 and GJP50-4, were proven to have immunomodulatory activity[37]. Additionally, the potent antioxidant effect and modulation of gut microbiota composition property of GF polysaccharides distinguished them from other polysaccharides derived from other plants such as coffee cherry peel and *Astragalus* polysaccharides[6,38–40].

Pectin is an acidic polysaccharide, which has multiple biological activities and is widely applied in the food industry as a gelling agent, stabilizer, emulsifier, and thickener[41]. In recent years, due to pectin's safety and potential activities, pectin derived from GF has attracted increasing research interest. Wang et al.[8] have established a rapid and eco-friendly extraction technique for preparing a pectin gel from GF. Using this technique, extracts with pectin, crocin, and other high-value components were further obtained from GF, which could form a gel with antioxidant effects in acidic environments[7]. Moreover, Ao et al.[42] successfully obtained a self-assembled Gardenia Pectin Gel (GPG) based on GF pectin extracts with co-extracted geniposide that spontaneously encapsulated. GPG showed significant hepatoprotective effects in cholestatic liver disease (CLD) mice, which is more effective than geniposide[42].

Metabolism of GF in vivo

Metabolism of GF components with microbiota

Microbiota-derived biotransformation of bioactive compounds in GF is associated with the bioavailability and bioactivity of these ingredients, as well as producing novel bioactive metabolites. Therefore, we summarize the metabolism of GF ingredients in the presence of gut microbiota.

Microbiota metabolism of iridoid glycosides

It should be noted that the poor intestinal absorption induced by the glycosidic linkage differentiates the pharmacokinetic properties of iridoid glycosides. The intestinal absorption of iridoid glycosides is reduced by their hydrophilic properties, which emphasizes the crucial role of intestinal microbiota for their *in vivo* metabolism[16,43]. The primary metabolism pathway of iridoid glycosides involves the hydrolysis of the β-glucosidic bond by β-D-glucosidases (β-GC) produced by gut microbiota, and then diverse reactions follow, including methoxylation, reduction, and conjugation with ammonia produced by intestinal bacterial nitrogen metabolism[1,12]. Take geniposide as an example (Figure 1A); it is first hydrolyzed to generate genipin by β-GC, which is produced by diverse microbiota such as *Eubacterium* sp. A-44 and *Lactobacillus* antri[12,44–45]. Then, some genipin will be transformed into the liver for further metabolism catalyzed by hepatic microsomal enzymes, while some of it continues with microbiota-induced metabolism. Genipin is sulfonated and glucuronidated in the presence of sulfotransferase (SULT) and β-glucuronidase (β-Glu), and further hydroxylation, reduction, and other biotransformations occur to generate a series of metabolites (Figure 1A). Table 1 summarizes the microbiota-induced transformation of geniposide and other iridoid glycosides.

As mentioned, geniposide is poorly absorbed in its prototype; however, with the following microbial conversion to genipin, the bioavailability increases substantially to approximately 80%[16]. Therefore, microbiota can improve the biological effects of iridoid glycosides by enhancing their bioavailability. Moreover, genipin can be transformed into a reactive form to covalently conjugate with cysteines, GSH, and proteins to induce liver injury, which leads to geniposide hepatotoxicity[72]. Regulation of gut microbiota can attenuate hepatotoxicity induced by geniposide by mediating specific enzymes to promote genipin to generate non-toxic metabolites[1]. These findings underscore the critical role of the gut microbiota in determining the systemic bioavailability of active metabolites derived from iridoid glycosides.

Microbiota metabolism of crocins

Similar to iridoid glycosides, crocins are hard to penetrate the intestinal lumen even in high concentrations; deglycosylation mediated by gut microbiota is vital for them to cross over the intestinal barrier[30]. Crocins are first deglycosylated by β-glucosidase (β-GC) produced by gut bacteria, and a gradual deglycosylation continues until all glycosidic bonds are hydrolyzed to produce crocetin, which is the aglycone form containing an apocarotenoid dicarboxylic acid (Figure 1B)[51]. Another study found that the plasma concentration of crocetins in normal rats is significantly higher than those in germ-free rats, indicating intestinal bacteria are essential to produce crocetin from crocins[52,73]. Some crocetins can be further metabolized by gut microbiota to produce dihydrocrocetins and tetrahydrocrocetins by reduction and demethylation reactions (Figure 1B)[51]. Moreover, with decarboxylation of crocetins, fatty acids with different chain lengths are also found (Figure 1B)[51]. Given the direct dependence of crocin absorption on the gut microbiota, microbial transformation constitutes a prerequisite for its pharmacological activity.

Microbiota metabolism of flavonoids

As reported, flavonoids in plants are mainly formed as glycosides, resulting in poor absorption in the small intestine, while those absorbed flavonoids may return to the

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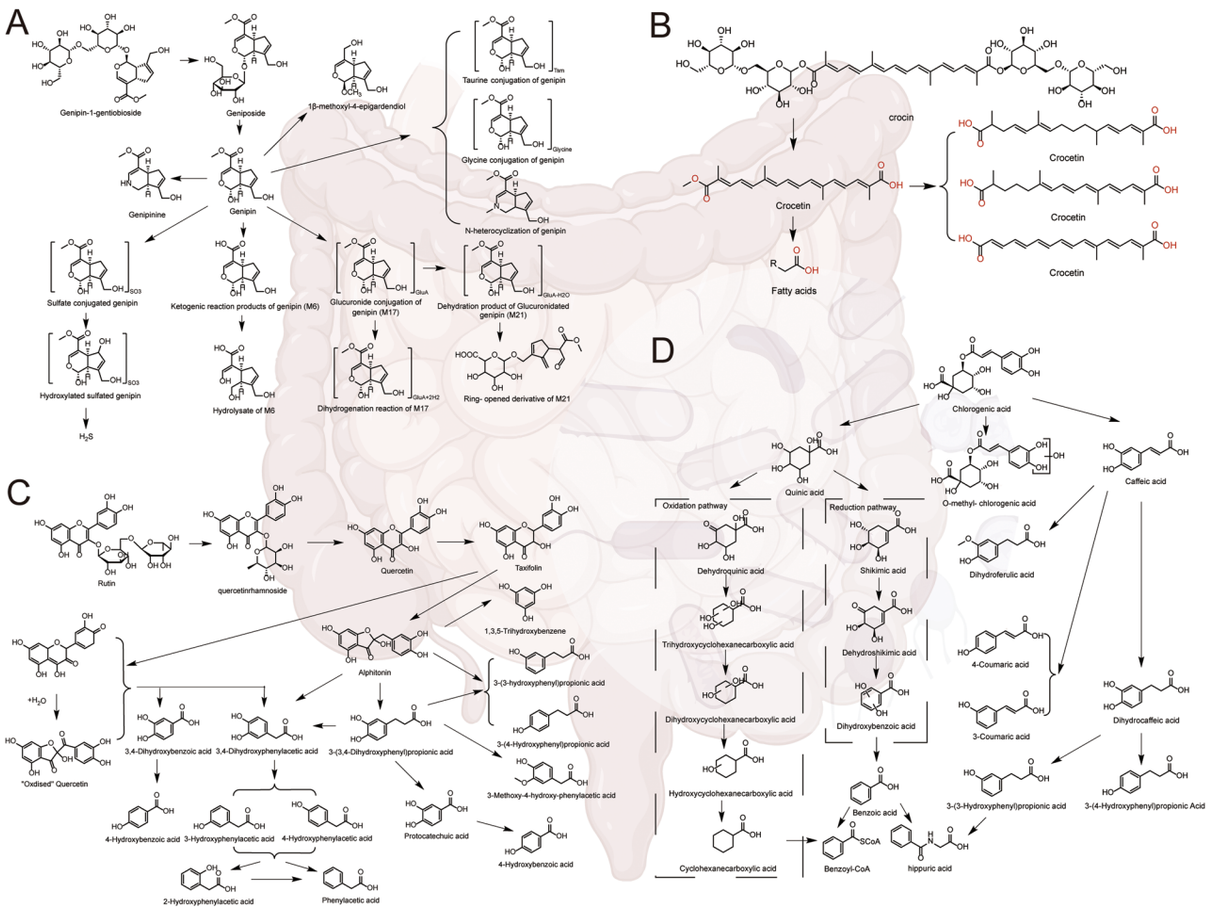


Figure 1. Metabolism of representative GF components with microbiota. (A) Metabolism of representative iridoid glycosides (genipin-1-gentiobioside). (B) Metabolism of representative crocins (crocin). (C) Metabolism of representative flavonoids (rutin). (D) Metabolism of representative organic acid (chlorogenic acid). GF: Gardeniae Fructus. Created in BioRender. Zhao Z. (2026). https://BioRender.com/oa272co.

intestine in conjugated form through enterohepatic circulation[63]. In this case, the microbiota metabolism pathway seems to be critical for flavonoids, which may improve their bioavailability and generate bioactive products[59]. Flavonoids are usually transformed through multiple reactions catalyzed by intestinal bacteria to produce simple phenolic acids, including O- and C-deglycosylation, demethylation, dehydroxylation, ester cleavage, reduction of carbon–carbon double bonds, isomerization, ring fission, extension and truncation of the aliphatic carbon chain, and decarboxylation[12,59].

Flavonoids in GF are also found in glucoside form, such as rutin and quercetin-rhamnoside[74–75]. They are primarily deglycosylated by β-GCs generated by bacteria including *Blautia* sp. MRGPMF1, Lactiplantibacillus *plantarum* HAC03, and *Enterococcus casseliflavus* M1 (Table 1), to yield quercetin, about 65% to 81% of which will be transported into the liver through the epithelium[76]. The remaining quercetin continues to degrade, and the main metabolic pathway is B-ring cleavage, which finally generates phenolic acids such as 3-hydroxyphenylacetic acid, 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid, 3-(3-hydroxyphenyl)propionic acid, and 3,4-dihydroxyphenylacetic acid (Figure 1C)[60]. Among them, 3-methoxy-4-hydroxyphenylacetic acid has been selected as a biomarker for microbial metabolism of quercetin[68,77]. It has been found that the antioxidant activity of quercetin and 3,4-dihydroxyphenylacetic acid is higher than that of rutin, followed by 3,4-dihydroxybenzoic acid and taxifolin[60]. This highlights that gut microbiota–mediated metabolism not only enhances the bioavailability of such flavonoids but also potentiates their biological activities.

Microbiota metabolism of organic acids

The absorption rates of different organic acids in the intestine vary over a wide range. Free phenolic acids are easily absorbed in the small intestines, while organic acids with ester groups can cross the intestinal barrier[57]. For instance, only 30% of chlorogenic acid, which is the caffeic ester of quinic acid, can be assimilated in intestine[78–79]. Most chlorogenic acid is transformed into quinic acid and caffeic acid by hydrolysis induced by intestinal bacteria such as *Bifidobacterium animalis* (Table 1, Figure 1D)[57]. Caffeic acid and quinic acid will be subsequently transformed into other metabolites such as m-coumaric acid and hydroxylated derivatives of phenylpropionic, benzoic, and hippuric acids[58,80]. For caffeic acid, dehydroxylation generates m-coumaric acid, and hydrogenation results in dihydrocaffeic acid, while 3-hydroxyphenylpropionic acid and benzoic acids seem to be the major products catalyzed by gut microbiota

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Table 1

Metabolism of GF components with microbiota

Substrate	Product	Formula	Biotransformation	Microbiota	Ref.
Genipin-1-β-d-gentiobioside	Geniposide	$C_{17}H_{24}O_{10}$	Deglycosylation	Rat intestinal bacteria	[46]
	Genipin	$C_{11}H_{14}O_5$	Deglycosylation	Rat intestinal bacteria	[46]
Geniposide	Genipinine	$C_{11}H_{15}NO_3$	Deglycosylation and *N*-heterocyclization	*Peptostreptococcus anaerobius*, *Klebsiella pneumoniae*, *Fusobacterium nucleatum*, *Bacteroides fragilis* ssp. thetaotus	[47]
	Genipin	$C_{11}H_{14}O_5$	Hydrolysis	Mice intestinal bacteria, *Eubacterium* sp. A-44, *Lactobacillus* antri β-D-glucosidases	[1, 22, 43–45]
	1β-methoxyl-4-epigardendiol	$C_{11}H_{16}O_5$	Hydrolysis, methoxylation, and rearrangement	*Aspergillus niger* DQWM-G11	[48]
	Unknown			Rat and human intestinal bacteria	[16, 49–50].
	Taurine conjugated genipin	$C_{13}H_{19}NO_7S$	Hydrolysis and taurine conjugation	Rat intestinal bacteria	[1]
	Sulfate-conjugated genipin	$C_{11}H_{14}O_8S$	Hydrolysis and sulfate conjugation	Rat intestinal bacteria	[1]
	Hydroxylated sulfated genipin	$C_{11}H_{14}O_9S$	Hydrolysis, sulfate conjugation, and hydroxylation	Rat intestinal bacteria	[1, 46]
	Glucuronide conjugated genipin (M17)	$C_{17}H_{22}O_{11}$	Hydrolysis and glucuronide conjugation	Rat intestinal bacteria	[1]
	Dihydrogenated M18 (M19)	$C_{17}H_{26}O_{11}$	Hydrolysis, glucuronide conjugation, dehydrogenation	Rat intestinal bacteria	[1]
	Glucuronidated and hydrogenated genipin	$C_{17}H_{24}O_{11}$	Glucuronidation and hydrogenation of genipin	Rat intestinal bacteria	[46]
Gardenoside	Gardenine	$C_{11}H_{13}NO_4$	Deglycosylation	Human intestinal bacteria	[47]
Gardoside	Cystenin-conjugated genipin	$C_{13}H_{17}NO_4S$	Deglycosylation and cystenin conjugation	Mice intestinal bacteria	[44]
Geniposidic acid	Deglycosylated geniposidic acid	$C_{10}H_{12}O_4$	Deglycosylation	Mice intestinal bacteria	[44]
Mussaenosidic acid	Hydrogenated mussaenosidic acid	$C_{16}H_{26}O_9$	Deoxidation and hydrogenation	Mice intestinal bacteria	[44]
Jasminoside B	Deglycosylated jasminoside B	$C_{10}H_{16}O_3$	Deglycosylation	Mice intestinal bacteria	[44]
6α or 6β-hydroxygeniposide	Deglycosylated 6α or 6β-hydroxygeniposide	$C_{11}H_{14}O_6$	Deglycosylation	Mice intestinal bacteria	[44]
Crocin	Intermediate crocins with different degrees of glycosylation	$C_{44}H_{64}O_{24}$-$C_{6n}H_{10n}O_{5n}$	Deglycosylation	Human fecal microflora	[51]
	Crocetin	$C_{21}H_{26}O_4$	Deglycosylation	Mice intestinal bacteria, human fecal microflora, rat intestinal bacteria	[50–53]
	trans-crocetin	$C_{20}H_{24}O_4$	Deglycosylation	Mice intestinal bacteria	[30]
	Fatty acids		Degrade the apocarotenoid backbone to smaller alkyl units	Mice intestinal bacteria	[30]
Crocetin	Dihydro crocetins	$C_{20}H_{30}O_4$	Reduction	Human fecal microflora	[51]
	Tetrahydro crocetins	$C_{20}H_{28}O_4$	Demethylation	Human fecal microflora	[51]
	Di-demethyl crocetin	$C_{18}H_{20}O_4$	Decarboxylation	Human fecal microflora	[51]
Chlorogenic acid	Quinic acid	$C_7H_{12}O_6$	Ester hydrolysis	*Bifidobacterium animalis*, human fecal microflora, rat intestinal bacteria	[54–56]
	Caffeic acid	$C_9H_8O_4$	Ester hydrolysis	Bifidobacterium animalis, human fecal microflora, rat intestinal bacteria	[54–57]
	4-HPP	$C_9H_{10}O_3$	Reduction and dehydroxylation	Human fecal microbiota	[58]

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HM9_V6N3.indb 391 26-Sep-26 15:38:27

Table 1
(Continued)

Substrate	Product	Formula	Biotransformation	Microbiota	Ref.
	BA	$C_7H_6O_2$	Reduction and dehydroxylation	Human fecal microbiota	[58]
	O-methyl-chlorogenic acid	$C_{17}H_{20}O_9$	Methylation	Rat intestinal bacteria	[55]
	DHPPA	$C_9H_{10}O_4$	Ester hydrolysis and hydrogenation	*Bifidobacterium animalis*	[57]
	DHPPG	$C_{12}H_{16}O_6$	Hydrogenation	*Bifidobacterium animalis*	[57]
	DHPP-QA	$C_{16}H_{20}O_9$	Hydrogenation	*Bifidobacterium animalis*	[57]
	HCi-QA	$C_{16}H_{18}O_8$	Dehydroxylation	*Bifidobacterium animalis*	[57]
	HPPA	$C_9H_{10}O_3$	Ester hydrolysis, hydrogenation, and dehydroxylation	*Bifidobacterium animalis*	[57]
	HPE	$C_8H_{10}O_2$	Dehydroxylation, hydrogenation, and ester hydrolysis	*Bifidobacterium animalis*	[57]
	PAA	$C_8H_8O_2$	Dehydroxylation, hydrogenation, ester hydrolysis, decarboxylation, dehydroxylation, and chain shortening	*Bifidobacterium animalis*	[57]
Caftaric acids	4-HPPA	$C_9H_{10}O_3$	Reduction and dehydroxylation	Human fecal microbiota	[58]
	HPPA	$C_9H_{10}O_3$	Dehydroxylation	Rat intestinal bacteria	[55–56]
	BA	$C_7H_6O_2$	Reduction and dehydroxylation	Human fecal microbiota	[58]
	Dihydroferulic acid	$C_{10}H_{12}O_4$	Methylation and hydrogenation	Rat intestinal bacteria	[55]
	m-Coumaric acid	$C_9H_8O_3$	Dehydroxylation	Rat intestinal bacteria	[56]
	DHPPA	$C_9H_{10}O_4$	Hydrogenation	Human fecal microflora, rat intestinal bacteria	[55–57]
Quinic acid	PA	$C_7H_6O_4$	Aromatization	*Lactobacillus plantarum*, *Acinetobacter calcoaceticus*, and *Gluconobacter* Dehydroshikimate dehydratase	[54]
	DHBA	$C_7H_6O_4$	Aromatization and oxidation		[54]
	DQA	$C_7H_{10}O_6$	Oxidation	Quinate dehydrogenase	[54]
	THCCA	$C_7H_{12}O_5$	Reduction and stepwise dehydroxylation	*Lactobacillus* sp.	[54]
	DSA	$C_7H_8O_5$	Oxidation	*Gluconobacter oxydans*	[54]
	SA	$C_7H_{10}O_5$	Oxidation	*Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria* Quinate dehydratase	[54]
	BA	$C_7H_6O_2$	Aromatization	Rat intestinal bacteria	[56]
	DHCCA	$C_7H_{12}O_4$	Reduction and stepwise dehydroxylation	*Lactobacillus* sp.	[54]
	HCCA	$C_7H_{12}O_3$	Reduction and stepwise dehydroxylation	*Lactobacillus* sp.	[54]
	CCA	$C_7H_{12}O_2$	Reduction and stepwise dehydroxylation	*Lactobacillus* sp.	[54]
Quercetin	Acetate	$C_2H_4O_2$	C-Ring cleavage	*Eubacterium ramulus* DSM 16296	[59]
	Alphitonin	$C_{15}H_{14}O_6$	C-ring cleavage and hydration	Human microflora, *Eubacterium ramulus* DSM 16296	[59–61]
	Butyrate	$C_4H_8O_2$	C-Ring cleavage	*Eubacterium ramulus* DSM 16296	[59]
	Kaempferol	$C_{15}H_{10}O_6$	Dehydroxylation	*Akkermansia muciniphila* and *Bacteroides uniformis*	[61–62]
	Phenylacetic acid	$C_8H_8O_2$	C-Ring cleavage and dehydroxylation		[63]
	Phloroglucinol	$C_6H_6O_3$	C-Ring cleavage	*Eubacterium ramulus* DSM 16296	[59]

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HM9_V6N3.indb 392 26-Sep-26 15:38:27

Table 1
(Continued)

Substrate	Product	Formula	Biotransformation	Microbiota	Ref.
	Protocatechuic acid (3,4-dihydroxybenzoic acid)	$C_7H_6O_4$	C-Ring cleavage and dehydroxylation	Human microflora	[60, 63–64]
	Taxifolin	$C_{15}H_{12}O_7$	C-ring cleavage, hydration, and hydrogenation	*Bacteroides uniformis, Eubacterium ramulus* DSM 16296, human microflora	[59–60, 62]
	Unknown			*Escherichia coli, Streptococcus lutetiensis, Lactobacillus acidophilus, Weissella confusa, Enterococcus gilvus, Clostridium perfringens*, and *Bacteroides fragilis*	[65]
	α,2',3,4,4',6'-Hexahydroxydihydrochalcone	$C_{15}H_{14}O_7$	C-Ring cleavage	*Eggerthella (Eubacterium)* sp. SDG-2	[59]
	1, 3, 5-Trihydroxybenzene	$C_6H_6O_3$	C-ring cleavage and hydration and breakdown product	Human microflora	[60]
	2-Hydroxyphenylacetic acid	$C_8H_8O_3$	C-Ring cleavage and dehydroxylation		[63]
	3-(3,4-Dihydroxyphenyl)propionic acid	$C_9H_{10}O_4$	C-Ring cleavage		[63]
	3-(3-Hydroxyphenyl)propionic acid	$C_9H_{10}O_3$	C-Ring cleavage and dehydroxylation	Human microflora	[60, 63–64, 66]
	3-(4-Hydroxyphenyl)propionic acid	$C_9H_{10}O_3$	C-Ring cleavage and dehydroxylation		[63]
	Homoprocatechuic acid (3,4-dihydroxyphenylacetic acid)	$C_8H_8O_4$	C-Ring cleavage, dehydroxylation, and hydration	*Flavonifractor plautii (Clostridium orbiscindens)* strains ATCC 49531, 257, 258 and 264, *Flavonifractor plautii (Clostridium orbiscindens)* I2, *Eubacterium ramulus* DSM 16296, *Clostridium perfringens, Bacteroides fragilis*	[59–60, 63–64]
	3,4-Dihydroxyphenylglyoxylic acid	$C_8H_6O_5$	Hydrogenation, C-ring cleavage and hydration	*Bacteroides uniformis*	[62]
	3-Hydroxyphenylacetic acid	$C_8H_8O_3$	C-Ring cleavage and dehydroxylation	Human microflora	[63]
	3-Methoxy-4-hydroxy-phenylacetic acid	$C_9H_{10}O_4$	C-Ring cleavage and dehydroxylation	Human microflora	[63]
	4-Hydroxybenzonic acid	$C_7H_6O_3$	C-Ring cleavage, dihydroxylation, and dehydroxylation	Human microflora	[60, 63–64]
	4-Hydroxyphenylacetic acid	$C_8H_8O_3$	C-Ring cleavage, dihydroxylation, and dehydroxylation	Human microflora	[63]
Quercetin R	Deoxidated Quercetin	$C_{15}H_{10}O_5$	Deoxidation	Mice intestinal bacteria	[44]
Nicotiflorin	Hydrogenated Nicotiflorin	$C_{27}H_{32}O_{15}$	Hydrogenation	Mice intestinal bacteria	[44]
Rutin	Acetate	$C_2H_4O_2$	Deglycosylation, C-ring cleavage	*Eubacterium ramulus* DSM 16296	[59]
	Alphitonin	$C_{15}H_{14}O_6$	Deglycosylation, C-ring cleavage and hydration	Human microflora, *Eubacterium ramulus* DSM 16296, *Bacteroides uniformis*	[59–61]
	BA	$C_7H_6O_2$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	Butyrate	$C_4H_8O_2$	Deglycosylation and C-ring cleavage	*Eubacterium ramulus* DSM 16296	[59]
	Dihydroxybenzene	$C_6H_6O_2$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]

(Continued)

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Table 1
(Continued)

Substrate	Product	Formula	Biotransformation	Microbiota	Ref.
	Dihydroxybenzene sulfate	$C_6H_6O_5S$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	3,4-Dihydroxybenzoic acid	$C_7H_6O_4$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	3,4-Dihydroxyphenylacetic acid	$C_8H_8O_4$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	Hippuric acid	$C_9H_9NO_3$	Deglycosylation, C-ring cleavage, dihydroxylation, and dehydroxylation	Human microflora	[63]
	4-Hydroxybenzoic acid	$C_7H_6O_3$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67–68]
	Hydroxyhippuric acid	$C_9H_9NO_4$	Deglycosylation, C-ring cleavage, dihydroxylation, and dehydroxylation	Human fecal microflora	[67]
	3-Hydroxyphenylacetic acid	$C_8H_8O_3$	C-Ring cleavage and dehydroxylation	Human fecal microflora, rat intestinal bacteria	[63, 67]
	4-Hydroxyphenylacetic acid	$C_8H_8O_3$	C-Ring cleavage and dehydroxylation	Human fecal microflora, rat intestinal bacteria	[67–68]
	Hydroxyphenylpropionic acid	$C_9H_{10}O_3$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	Isoquercetin	$C_{21}H_{20}O_{12}$	Deglycosylation	*Lactiplantibacillus. plantarum* HAC03, *Enterococcus avium* EFEL009 α-L-rhamnosidase	[59, 69]
	Phenylacetic acid	$C_8H_8O_2$	Deglycosylation, C-ring cleavage, dihydroxylation, and dehydroxylation	Human microflora	[63]
	Phloroglucinol	$C_6H_6O_3$	Deglycosylation, C-ring cleavage	*Eubacterium ramulus* DSM 16296	[59]
	Protocatechuic acid	$C_7H_6O_4$	Deglycosylation, C-ring cleavage, and dehydroxylation	Human microflora	[63, 68]
	Quercetin	$C_{15}H_{10}O_7$	Deglycosylation	*Blautia* sp. MRGPMF1, *Lactiplantibacillus. plantarum* HAC03, *Enterococcus casseliflavus* M1, *Enterococcus avium* LY1, *Enterococcus avium* EFEL009, *Eubacterium ramulus* DSM 16296, Human fecal microflora, β-rhamnosidases and β-glucosidases	[59–60, 63, 67, 69]
	Quercetin-3,4'-O-glucoside	$C_{21}H_{20}O_{12}$	Deglycosylation		[63]
	Quercetin-3-O-glucoside	$C_{21}H_{20}O_{12}$	Deglycosylation	*Parabacteroides distasonis (Bacteroides distasonis)* strain	[59, 63]
	Quercetin-4'-O-glucoside	$C_{21}H_{20}O_{12}$	Deglycosylation		[63]
	Taxifolin	$C_{15}H_{12}O_7$	Deglycosylation, C-ring cleavage, and hydration	*Eubacterium ramulus* DSM 16296, human microflora	[59–60, 68]
	1,3,5-Trihydroxybenzene	$C_6H_6O_3$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	Trihydroxybenzoic acid	$C_7H_6O_5$	C-Ring cleavage and dehydroxylation	Human fecal microflora	[67]
	1, 3, 5-Trihydroxybenzene	$C_6H_6O_3$	Deglycosylation, C-ring cleavage, hydration, and breakdown product	Human microflora	[60]
	2-Hydroxyphenylacetic acid	$C_8H_8O_3$	Deglycosylation, C-ring cleavage, and dehydroxylation	Human microflora	[63]
	3-(3,4-Dihydroxyphenyl)propionic acid	$C_9H_{10}O_4$	Deglycosylation and C-ring cleavage	Human microflora	[63]

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HM9_V6N3.indb 394 26-Sep-26 15:38:27

Table 1
(Continued)

Substrate	Product	Formula	Biotransformation	Microbiota	Ref.
	3-HPPA	$C_9H_{10}O_3$	Deglycosylation, C-ring cleavage, hydration, and breakdown product	Human microflora	[60, 63]
	4-HPPA	$C_9H_{10}O_3$	Deglycosylation, C-ring cleavage, and dehydroxylation	Human microflora	[63]
	3,4-Dihydroxyphenylacetic acid	$C_8H_8O_4$	Deglycosylation and C-ring cleavage	*Flavonifractor plautii (Clostridium orbiscindens)* I2, *Eubacterium ramulus* DSM 16296	[59, 63]
	3-Methoxy-4-hydroxy-phenylacetic acid	$C_9H_{10}O_4$	Deglycosylation, C-ring cleavage, and dehydroxylation	Human microflora	[63, 68]
	4-Hydroxybenzonic acid	$C_7H_6O_3$	Deglycosylation, C-ring cleavage, dihydroxylation, and dehydroxylation	Human microflora	[63]
	4-Hydroxyphenylacetic acid	$C_8H_8O_3$	Deglycosylation, C-ring cleavage, dihydroxylation, and Dehydroxylation	Human microflora	[63]
Quercetin-3-rutinoside	3-Hydroxyphenylacetic acid	$C_8H_8O_3$	Hydrolysis, C-ring cleavage, and dehydroxylation	Human fecal microflora	[70]
	3,4-Dihydroxyphenylacetic acid	$C_8H_8O_4$	Hydrolysis, C-ring cleavage	*Eubacterium ramulus,* human fecal microflora	[70–71]
	Acetate	$C_2H_4O_2$	Hydrolysis, C-ring cleavage	*Eubacterium ramulus, Enterococcus casseliflavus*	[71]
	Butyrate	$C_4H_8O_2$	C-Ring cleavage	*Eubacterium ramulus*	[71]
	Formate	CH_2O_2	Degradation of sugar moiety	*Enterococcus casseliflavus*	[71]
	$_L$-lactate	$C_3H_6O_3$	Degradation of sugar moiety	*Enterococcus casseliflavus*	[71]
	Ethanol	C_2H_6O	Degradation of sugar moiety	*Enterococcus casseliflavus*	[71]
Quercitrin	Quercetin	$C_{15}H_{10}O_7$	Hydrolysis	Mice intestinal bacteria	[63]

3-HPPA: 3-(3-Hydroxyphenyl)propionic acid; 4-HPP: Hydroxyphenylpropionic; 4-HPPA: 3-(4-Hydroxyphenyl)propionic acid; BA: Benzoic acids; CCA: Cyclohexanecarboxylic acid; DHBA: Dihydroxybenzoic acid; DHCCA: Dihydroxycyclohexanecarboxylic acid; DHPP-QA: Dihydrochlorogenic acid; DHPPA: Dihydrocaffeic acid; DHPPG: Dihydrocaffeoylglycerol; DQA: Dehydroquinic acid; DSA: Dehydroshikimic acid; HCCA: Hydroxycyclohexanecarboxylic acid; HCi-QA: Dehydroxy-chlorogenic acid; HPPA: 3-(3-Hydroxyphenyl)propanoic acid; HPE: 2-(3-Hydroxyphenyl)-ethanol; PA: Protocatechuic acid; PAA: Phenylacetic acid; SA: Shikimic acid; THCCA: Trihydroxycyclohexanecarboxylic acid.

(Figure 1D)[58]. As for quinic acid, two degradation pathways are observed. Route 1 is an oxidation pathway, which results in the aromatization and accumulation of protocatechuic acid; Route 2 involves a reduction transformation, leading to cyclohexane carboxylic acid generation through dehydroxylation[54]. In this case, the biotransformation of organic acids induced by gut microbiota could significantly enhance their bioavailability and benefit their biological activities.

Metabolism of GF components without microbiota

Typically, metabolites in GF and their gut microbiota-transformed metabolites may undergo extensive hepatic biotransformation catalyzed by cytochrome P450 (CYP450) enzymes and phase II conjugation systems. For example, genipin-1-β-D-gentiobioside incubated with hepatocytes may generate geniposide, and further demethylation would be induced by P450 enzymes to produce geniposidic acid[27]. Geniposidic acid undergoes a series of metabolic reactions such as glucuronic acid reaction, demethylation, and hydroxylation to produce other secondary metabolites in the liver[1]. Especially, genipin can form a reactive intermediate catalyzed by CYP450 enzymes, which further covalently binds to carbamoyl phosphate synthetase 1 (CPS1) protein to disrupt the urea cycle and redox homeostasis, resulting in liver injury[23]. This emphasizes the dual role of GF in pharmaceutical effects and toxicities.

Crocetin undergoes phase II glucuronidation and sulfation following absorption[81–82]. Studies using human liver microsomes have identified crocetin glucuronides as the primary hepatic metabolites, with UGT1A1 and UGT1A3 being the principal isoforms involved[82]. Unlike genipin, crocetin is not significantly metabolized by CYP450 enzymes, reflecting its carotenoid structure that is less susceptible to oxidative biotransformation[82].

It is essential to the interplay between microbial and hepatic metabolism is essential, as it significantly affects the activity and toxicity of active ingredients in GF. As an example, fewer metabolites of Genipin-1-β-D-gentiobioside were determined in germ-free rats than in conventional rats due to the lower production of geniposide or genipin primarily transformed by intestinal bacteria[46]. This emphasized the effective functions of gut microbiota as a "pre-processing" system that converts poorly absorbed hydrophilic glycosides into bioavailable lipophilic aglycones, priming them for subsequent hepatic metabolism. Some conjugated metabolites catalyzed by hepatic enzymes may also be

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transported to the intestine for microbial metabolism. In this case, differences in both gut microbiota composition and hepatic enzyme activity can influence the ultimate systemic exposure to active metabolites and affect the biological effects of GF.

Pharmacological effects of GF

GF components are involved in various biofunctions, including anti-inflammatory, antioxidant, anti-tumor, and immunomodulatory effects. Some of these pharmacological actions are exerted through the gut microbiota, whereas others operate *via* microbiota-independent mechanisms. In this case, the bioactivities of GF are categorized into two classes, microbiota-dependent and microbiota-independent, for further mechanistic discussion.

Pharmacological effects of GF mediated by gut microbiota: gut-X axis perspective

The therapeutic efficacy of GF is closely associated with its bidirectional crosstalk with the gut microbiota. Specifically, GF constituents reshape microbial composition, promoting the proliferation of beneficial bacteria while suppressing pathogenic strains. This modulation leads to the production of multiple bioactive metabolites and subsequent regulation of downstream signaling cascades. Conversely, the gut microbiota converts GF glycosides into pharmacologically active aglycones. These microbiota-mediated actions propagate to peripheral organs through the gut–liver, gut–brain, and gut–metabolic axes, constituting a coordinated host–microbe interaction network[83]. In this section, we interpret the microbiota-mediated pharmacological activities of GF through the lens of the gut-X axis paradigm.

Gut–liver axis

The gut–liver axis constitutes a fundamental bidirectional communication pathway between the gut microbiota and the host liver. Metabolites derived from the gut microbiota, including bile acids (BAs) and short-chain fatty acids (SCFAs), are transported to the liver through the portal circulation and orchestrate hepatic metabolic and inflammatory responses. Moreover, hepatically synthesized BAs are secreted into the intestinal lumen, where they shape the composition and function of the gut microbial community[84–85]. GF and its bioactive constituents exert critical therapeutic effects in the management of hepatic disorders, such as cholestasis and nonalcoholic fatty liver disease (NAFLD), by restructuring the intestinal microbiota, modulating the BA pool, and reinforcing intestinal barrier function (Figure 2).

Cholestasis serves as a shared pathological feature in diverse hepatobiliary pathologies. Cholestasis severely impairs the gut microbiota's ability to metabolize BAs and the ensuing dysbiosis further worsens BA metabolic derangements, creating a vicious cycle. GF extract inhibits primary BA synthesis through upregulation of Cyp8b1 expression while enhancing farnesoid X receptor (FXR) and Oatp1 gene expression to facilitate BA elimination *via* the intestinal–fecal route, thereby restoring BA enterohepatic circulation[86]. Similarly, GF polysaccharide exerts modulatory effects on BA metabolism disorders and generates hepatoprotective effects, largely through the remodeling of gut microbiota and enhancement of butyrate production, which subsequently activates hepatic FXR signaling. In ANIT-induced cholestatic mice, GF polysaccharide dose-dependently alleviates hepatic function and histopathological damage, upregulating hepatic FXR, PXR, and BA efflux transporters, and decreasing multiple BA levels[35]. At the intestinal level, GF polysaccharide corrects microbial dysbiosis by promoting *Bacteroidetes* and *Lachnospiraceae* enrichment while suppressing *Proteobacteria* and *Enterobacteriaceae*[35]. Further fecal microbiota transplantation (FMT) experiments validate that GF polysaccharide–shaped bacteria exhibit similar hepatoprotection and intestinal barrier-preserving phenotypes with GF polysaccharide, indicating the gut microbiota as a key mediator of GPS action with butyrate and its related metabolites as candidate functional effectors[35]. Follow-up investigations figure out the impact of GF polysaccharide on gut microbial metabolites both *in vitro* and *in vivo*. Results showed that GF polysaccharide enriches butyrate-producing genera (*Lactobacillus* and *Dubosiella*), raises fecal and serum butyrate levels, and upregulates tight junction proteins (occludin, claudin-1, Zonula occludens-1 [ZO-1]) to strengthen intestinal barrier function[87]. This reduces circulating endotoxin, suppresses TLR4/NF-κB signaling, and lowers tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) expression, ultimately mitigating inflammatory infiltration and protecting against cholestatic liver injury[87]. In summary, GF polysaccharide acts as a prebiotic by promoting butyrate-producing bacteria, increasing butyrate output, and activating hepatic FXR to upregulate BA efflux transporters, thereby reducing BA accumulation and hepatic inflammation, and ultimately restoring liver function. In addition, intestinal bacteria transform geniposide into genipin, which generates reactive dialdehyde intermediates that covalently modify intestinal proteins, thereby restoring microbial compositional balance and potentiating bile salt hydrolase (BSH) and 7α-dehydroxylase activities[88]. Consequently, the intestinal FXR–FGF15–hepatic CYP7A1 axis is activated, culminating in the reestablishment of BA homeostasis[88].

The development and progression of metabolic dysfunction–associated steatotic liver disease (MASLD) are closely related to gut microbial dysbiosis[89–90]. Geniposide has been demonstrated to alleviate hepatic steatosis and inflammation through modulation of the gut microbiota alone or in various combination regimens, including co-administration with chlorogenic acid[91–92], with rhein and 6,7-dimethoxycoumarin (DGR)[93], or with isoquercitrin and peanut skin extract (MPGI)[94]. Collectively, these combination therapies profoundly restructure the gut microbial community in MASLD models, consistently enriching beneficial genera such as *Bacteroides* and *Akkermansia* while inhibiting pathogens including *Desulfovibrio*. Chlorogenic acid remodels the microbiota-derived BA pool to reduce FXR-antagonistic BAs (eg, TβMCA), upregulate hepatic FXR, SHP, and BSEP, and activate the intestinal FXR–FGF15–CYP7A1 axis[91]. The

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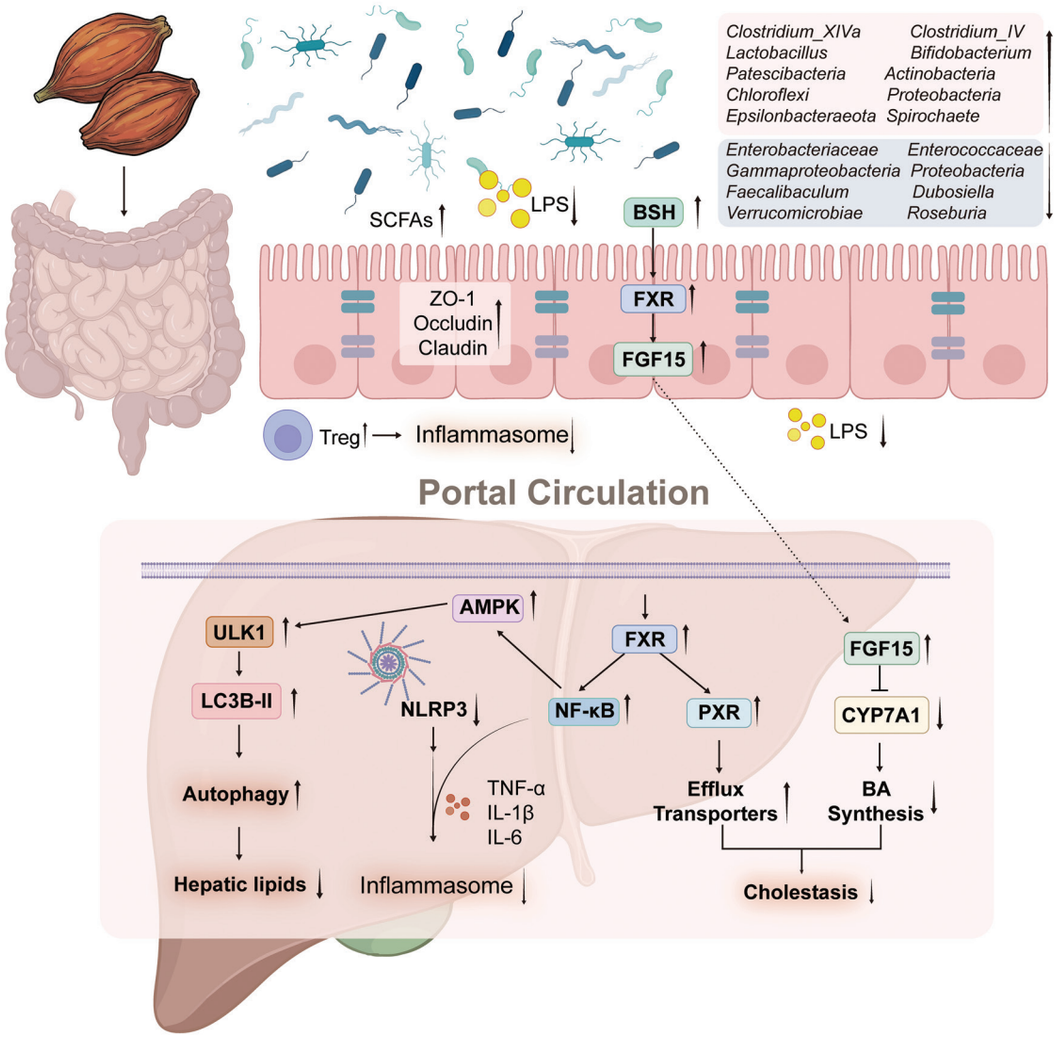


Figure 2. Microbiota–gut–liver axis regulations derived from GF components in hepatic diseases. In the gut, GF modulates microbial composition by enriching beneficial taxa and suppressing pathogens, thereby affecting SCFA, LPS, and BSH production, and reinforcing intestinal barrier integrity. In the liver, microbial metabolites and endotoxins enter *via* the portal circulation, activating inflammasome signaling, which regulates bile acid synthesis, efflux transport, lipid homeostasis, and inflammatory responses. The integrated gut–liver axis underlies GF's protective effects against cholestasis, hepatic steatosis, and inflammation. AMPK: AMP-activated protein kinase; BA: Bile acid; BSH: Bile salt hydrolase; FXR: Farnesoid X receptor; GF: Gardeniae Fructus; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; LC3B-II: Microtubule-associated protein 1 light chain 3 beta II; LPS: Lipopolysaccharide; NF-κB: Nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; SCFA: Short-chain fatty acid; TNF-α: Tumor necrosis factor alpha; ULK1: Unc-51-like autophagy activating kinase 1. Created in BioRender. Zhao Z. (2026). https://BioRender.com/ksusooy.

indispensability of the "microbiota–BA–FXR" axis in chlorogenic acid–derived therapeutic efficacy has been supported by antibiotic-mediated microbiota depletion and FXR knockout experiments[91]. Moreover, there is evidence that shows chlorogenic acid protects the liver from exposure to microbial products through increasing the abundance of SCFA-producing and Treg-inducing bacteria[92]. These bacteria can potentiate Treg activity, dampening inflammatory signaling, reinforcing intestinal barrier integrity, and consequently mitigating hepatic exposure to microbial products[92]. In NAFLD rats, treatment with DGR resulted in significant suppression of hepatic NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome components, including ASC, caspase-1, and the downstream pro-inflammatory cytokine IL-1β[93]. These effects are intimately linked to DGR-induced modulation of the gut microbiota and the consequent reduction in systemic endotoxin levels[93]. MPGI exerts its beneficial effects *via* concurrent anti-inflammatory actions, gut microbiota regulation, and modulation of the TLR4/NF-κB, AMP-activated protein kinase/acetyl-CoA carboxylase / Carnitine palmitoyltransferase 1 (AMPK/ACC/CPT1), and AMP-activated protein kinase / Unc-51-like autophagy activating kinase 1 / microtubule-associated protein 1 light chain 3 beta (AMPK/UKL1/LC3B) signaling axes[94]. In summary, geniposide-centered combination therapies exert pleiotropic hepatoprotective effects *via* synergistic modulation of the "microbiota–BA–FXR" axis and the "microbiota–barrier–lipopolysaccharide (LPS)–inflammation" axis, leading to concurrent improvements in hepatic steatosis, inflammatory responses, and oxidative stress. Notably, these combination regimens consistently exhibit greater efficacy than geniposide monotherapy, indicating that other natural constituents contribute complementary or synergistic actions in regulating the gut microbial community. This mode of action is highly analogous to that

HM9_V6N3.indb 397 26-Sep-26 15:38:29

observed with GF polysaccharide in cholestasis, where FXR activation is mediated by butyrate-producing bacteria and intestinal barrier integrity is preserved. These findings collectively support the concept that the regulation of gut microbiota by GF-derived constituents constitutes a shared and effective therapeutic approach for multiple hepatobiliary disorders.

Deacetyl asperulosidic acid methyl ester (DAM), an iridoid-type natural compound, has been shown to alleviate CCl_4-induced hepatic fibrosis *via* gut microbiota-dependent mechanisms[95]. DAM effectively restores microbial equilibrium in fibrotic models by remodeling the dysbiotic gut ecosystem, which reduces the prevalence of inflammation-associated bacterial taxa while increasing the relative abundance of the *Bacteroidetes* phylum[95]. In parallel, DAM reinforces intestinal barrier integrity, mitigates colonic mucosal damage, upregulates tight junction proteins (claudin-1, ZO-1, and occludin), and lowers circulating LPS levels, thereby curtailing endotoxin translocation[95]. Moreover, DAM markedly increases fecal concentrations of diverse SCFAs, which subsequently engage their cognate receptors GPR41 and GPR43, suppress histone deacetylase HDAC1 activity, and promote H3K9 hyperacetylation. This epigenetic reprogramming subsequently suppresses the aberrant activation of the Wnt/β-catenin pathway, ultimately preventing the progression of liver fibrosis[96].

Gut–brain axis

The bidirectional crosstalk between the gut microbiota and the CNS, commonly referred to as the microbiota–gut–brain axis (MGBA), has been increasingly recognized as a pivotal hinge involved in the pathogenesis of diverse neuropsychiatric conditions. The essence of MGBA is the gut microbiota's capacity to modulate host affective states, cognitive processes, and behavioral patterns. This modulation is accomplished through the generation of neuroactive compounds (eg, SCFAs and neurotransmitter precursors), regulation of inflammatory signaling along the periphery–brain axis, and maintenance of gut epithelial barrier homeostasis[97–99] (Figure 3). Notably, multiple bioactive constituents derived from GF have been validated to produce therapeutic efficacy in neurological diseases through MGBA[100].

In a sleep deprivation–induced anxiety rat model established using para-chlorophenylalanine (PCPA), a 7-day GF intervention markedly attenuated anxiety-like behavioral phenotypes and concurrently reduced hippocampal pro-inflammatory cytokine levels (TNF-α and IL-1β)[101]. Metabolomic profiling revealed that GF treatment modulated a variety of hippocampal metabolic pathways, including carbon metabolism, glycolysis/gluconeogenesis, the pentose phosphate pathway, and glycerophospholipid metabolism[101]. Besides, 16S rRNA amplicon sequencing demonstrated that GF effectively reversed gut microbial dysbiosis in anxious animals, with a notable enrichment of beneficial bacterial taxa[101]. Collectively, these data suggest that the anxiolytic effects of Gardenia may be mediated through coordinated regulation of hippocampal metabolic signatures and gut microbial composition. GF oil (OGF) exerted significant antidepressant effects in a chronic unpredictable mild stress (CUMS) mouse model, as evidenced by amelioration of depressive-like behaviors, alleviation of hippocampal and colonic histopathological lesions, and

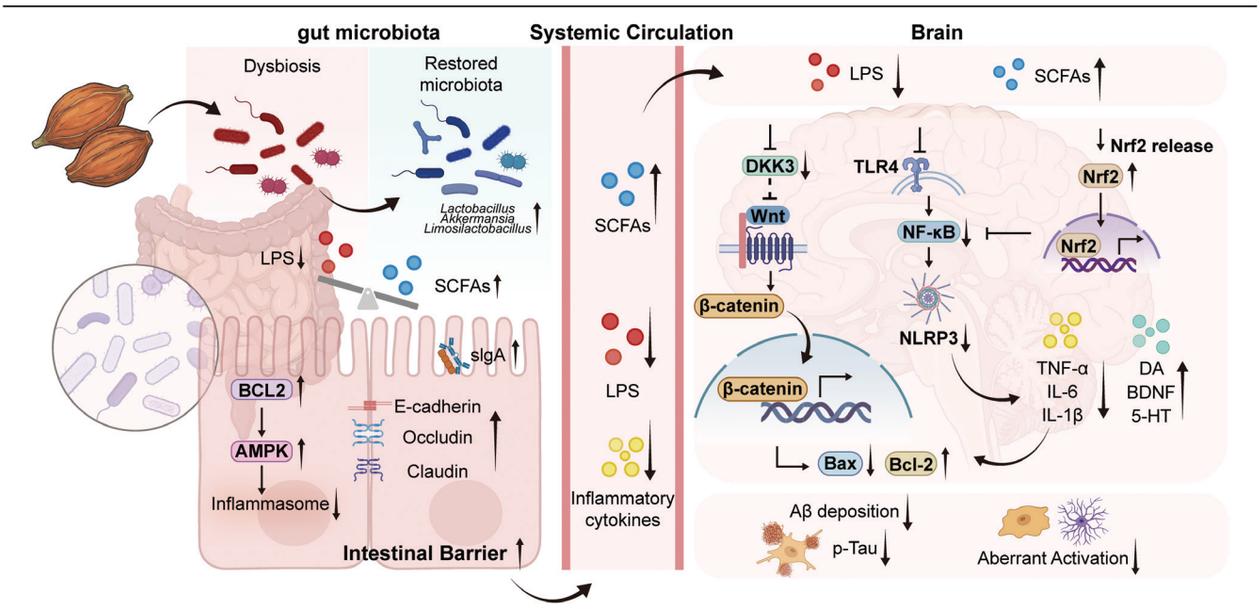


Figure 3. Microbiota–gut–brain axis regulatory effects mediated by GF components in neurological diseases. LPS, SCFAs, and inflammatory cytokines are key neuroactive compounds that can transport along the periphery–brain axis into the brain as well as maintain gut epithelial barrier homeostasis. AMPK: AMP-activated protein kinase; Aβ: β-Amyloid; BCL2: B-cell lymphoma 2; BDNF: Brain-derived neurotrophic factor; DA: Dopamine; DKK3: Dickkopf-related protein 3; GF: Gardeniae Fructus; 5-HT: Hippocampal serotonin; IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; LPS: Lipopolysaccharide; NF-κB: Nuclear factor kappa B; NLRP3: NOD-like receptor thermal protein domain associated protein 3; Nrf2: Nuclear factor erythroid-2–related factor 2; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor alpha; SCFA: Short-chain fatty acid; sIgA: Secretory immunoglobulin A; Wnt: Wingless-related integration site; ZO-1: Zonula occludens-1. Created in BioRender. Zhao Z. (2026). https://BioRender.com/56yldf1.

HM9_V6N3.indb 398 26-Sep-26 15:38:30

restoration of hippocampal serotonin (5-HT), dopamine (DA), and brain-derived neurotrophic factor (BDNF) levels[102]. OGF also reduced circulating IL-1β, IL-6, TNF-α, and LPS levels, upregulated colonic tight junction protein expression, and suppressed the hippocampal TLR4/NF-κB/NLRP3 signaling[102]. Antibiotic pretreatment (ABX) and FMT experiments proved the essential role of the gut microbiota in mediating the antidepressant actions of OGF[102]. Network pharmacology-based screening selected geniposide as the principal bioactive constituent of GF responsible for its antidepressant efficacy[103]. Both *in vitro* and *in vivo* investigations found that geniposide alleviated CUMS-induced depressive-like behaviors through multiple strategies, including upregulation of colonic BCL2 expression, activation of the AMPK signaling pathway, suppression of colonic inflammatory responses, enhancement of intestinal epithelial barrier integrity *via* E-cadherin upregulation, and restoration of balanced gut microbial ecology[103]. FMT experiments further supported the vital role of the gut microbiota in geniposide's antidepressant effects[103]. The antidepressant potential of geniposide was further validated in a human flora–associated depressive rat (HFADR) model, wherein geniposide specifically recovered the intestinal abundance of *Limosilactobacillus reuteri* and elevated its metabolic product butyrate level[104]. Butyrate accumulation ameliorates depressive-like behaviors *via* CNS Nrf2 pathway activation, which subsequently suppresses astrocytic activation, attenuates neuroinflammation, restores BDNF expression, and normalizes tryptophan metabolism[104]. Moreover, the antidepressant efficacy of crocetin-class constituents also relies on gut microbiota regulation. In the chronic social defeat stress (CSDS) model, oral crocin (300 mg/kg) produces significant antidepressant-like effects; however, its systemic exposure is extremely low (Cmax = 43.5 μg/L), while its gut microbial metabolite crocetin exhibited approximately 100-fold higher systemic concentrations (Cmax = 4662.5 μg/L)[53]. In pseudo-germ–free mice, crocin biotransformation was virtually abolished, and its rapid antidepressant effects were concomitantly lost, indicating that the neuroprotective activity of crocin is predominantly mediated by gut microbiota–dependent conversion to crocetin[53]. In a chronic restraint stress-induced mouse model, crocin-I rebalanced the disturbed gut microbiota, elevated SCFA levels, and improved compromised intestinal barrier function *via* upregulation of occludin and claudin-1[105]. The recovery of the intestinal barrier consequently diminishes serum LPS, IL-6, and TNF-α levels along with hippocampal TNF-α expression, while concurrently increasing hippocampal BDNF content, thereby producing robust antidepressant effects[105].

In addition to its antidepressant actions, crocin also shows neuroprotective effects in other pathological conditions with the biotransformation of gut microbiota to crocetin[106]. In a rat model of transient middle cerebral artery occlusion (MCAO), the efficacy of crocin was also demonstrated to be related to the gut microbiota-mediated biotransformation to crocetin, with the functional target identified as peripheral rather than within the central nervous system[52]. Crocin has also been reported to change gut microbial composition by inhibiting the intestinal colonization of pathogenic *Escherichia coli*, consequently attenuating the neurotoxic aggregation of mutant huntingtin protein in a Drosophila model of Huntington disease[107]. Crocin enhanced cognitive performance in 5xFAD transgenic mouse model of Alzheimer disease (AD) by reducing cerebral β-amyloid (Aβ) plaque burden and mitigating neuroinflammation. Furthermore, crocin increased gut microbial α-diversity, selectively enriched the beneficial genus Akkermansia, and upregulated tight junction proteins alongside secretory immunoglobulin A (sIgA) expression, collectively reinforcing intestinal barrier integrity[108]. In an Aβ1-42-induced rat model of AD, crocin efficiently recovered learning and memory deficits. It suppressed cerebral Aβ1-42 and phosphorylated tau (p-tau) accumulation, reduced circulating pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), resulting in alleviation of hippocampal histopathological injury[109]. 16S rRNA sequencing revealed that crocin modulated both α- and β-diversity of microbiota and restructured its composition. Markedly, overexpression of DKK3 reversed all of crocin's protective effects, suggesting that crocin acts by downregulating DKK3 to relieve Wnt/β-catenin signaling inhibition. This in turn facilitated intestinal epithelial turnover and barrier restoration, modulated gut microbiota, limited systemic endotoxin translocation, suppressed neuroinflammation, and ultimately safeguarded cognitive performance[109]. Above all, these observations confirm the gut–brain axis as a key mediator of GF's neuroprotective actions.

Gut microbiota–derived metabolic reprogramming

Metabolic diseases have emerged as a formidable global public health challenge; the fundamental mechanism of their pathophysiology involves metabolic reprogramming, a process of adaptive or pathological rewiring of metabolic circuits. Critically, metabolic reprogramming of the gut microbiota occurs as an early pathological event, preceding the emergence of clinically apparent host disease. Through remodeling lipids, glucose, amino acid, and uric acid metabolic networks, the gut microbiota generates a series of bioactive metabolites that disturb systemic metabolic and immune homeostasis, ultimately driving the progression of metabolic disorders. This positions the gut microbiota as a promising therapeutic target for metabolic diseases[110–111].

Accumulating evidence indicates that GF extract modulates digestive enzyme activities and alleviates glucolipid metabolic disturbances *via* the intestinal Akkermansia-TLR4/MyD88/NF-κB signaling axis[112]. In a chronic corticosterone (CORT)–induced mouse model of lipid metabolic dysregulation, crocin-I was found to restructure intestinal bacterial composition and effectively regulate the disordered levels of long-chain fatty acids[113]. In high-fat diet (HFD)–induced obese mice, crocin-I modulated gut microbial and restored SCFA levels. These microbiota-driven metabolic shifts potentiated intestinal barrier integrity, which upregulated expression of tight junction proteins (occludin, ZO-1) and mucins (Muc1, Muc2), alongside suppression of colonic pro-inflammatory cytokines[114]. Consequently, crocin-I downregulated hepatic lipogenic genes (ACC, Fasn, Srebp1c) and upregulated peroxisome proliferator-activated receptor α (PPARα)

HM9_V6N3.indb 399 26-Sep-26 15:38:30

expression, thereby repairing lipid dysmetabolism and alleviating obesity-associated metabolic complications[114]. GF polysaccharide showed similar efficacy in regulating metabolic disturbances. In a type 2 diabetes mouse model induced by HFD combined with streptozotocin (HFD/STZ), GF polysaccharide significantly reduced fasting blood glucose, improved oral glucose tolerance and insulin sensitivity, as well as attenuated pancreatic histopathological injury[115]. Mechanistically, GF polysaccharide restructured the gut microbial ecosystem, enriching SCFA-producing genera and elevating serum butyrate levels in diabetic animals. *In vitro* experiments evidenced that sodium butyrate administration upregulated PPARγ expression in HepG2 cells. At the hepatic level, GF polysaccharide upregulated PPARγ and its downstream effectors, enhanced glycogen synthesis, reinforced intestinal barrier function, and mitigated both hepatic and intestinal inflammation, resulting in improved insulin resistance and restored glycemic homeostasis[115].

Gut microbiota and intestinal disease

Gut microbial dysbiosis is intimately linked to the etiology and progression of diverse intestinal disorders, making the restoration of microbial equilibrium and metabolic homeostasis a promising therapeutic strategy[116–118]. Rectal delivery of geniposide exerted protective effects against experimental colitis in mice through a dual-pronged mechanism[119]. On one hand, it remodeled the gut microbiota by enriching beneficial taxa and depleting inflammation-associated populations, while suppressing the S100A8/S100A9–TLR4–NF-κB inflammatory cascade[119]. On the other hand, it restored BA metabolic homeostasis, and the resultant BA metabolites activated TGR5 signaling, which in turn inhibited NLRP3 inflammasome assembly and activation[119]. Geniposidic acid alleviated dextran sulfate sodium (DSS)–induced colitis by modulating gut microbial diversity. The recovery of gut microbiota composition further restored intestinal barrier integrity by inhibiting NF-κB–driven inflammatory signaling and reducing circulating pro-inflammatory cytokine levels[120]. Chlorogenic acid markedly elevated the abundance of beneficial bacteria and glycine content in the fecal samples of rats with post-infectious irritable bowel syndrome (PI-IBS)[121]. Notably, bacterial extracellular vesicles induced by glycine harbor a cargo of functional proteins that can mitigate inflammatory responses, reduce visceral hypersensitivity, and preserve mucosal barrier function[121]. Moreover, the gut microbial metabolite 4-hydroxyphenylacetic acid (4-HPA) can activate the JAK2/STAT3 signaling axis, upregulate CXCL3 transcription, and facilitate the accumulation of polymorphonuclear myeloid–derived suppressor cells (PMN-MDSCs) within the colorectal tumor microenvironment, finally impairing the anti-tumor cytotoxicity of $CD8^+$ T cells. Chlorogenic acid could convert this immunosuppressive state by diminishing 4-HPA production[121]. Moreover, cell-free supernatants from *Lactococcus lactis* pretreated with crocin exhibited superior antiproliferative activity against colorectal cancer HCT-116 cells compared to those from untreated bacteria. Crocin-treated *L. lactis* also displayed potent antimicrobial activity against various pathogenic bacteria and retained viability under acidic conditions, indicating that crocin may modulate gut microbial function to exert anti-tumor effects[122].

Interactions between gut microbiota and other organisms

In recent years, accumulated evidence has revealed that gut microbial dysbiosis exerts systemic effects that reach far beyond the intestinal tract, profoundly influencing the function of distal organs, including the heart, skin, and lungs. A growing number of investigations have discovered a series of novel pathophysiological axes, such as the gut–heart axis, gut–skin axis, and gut–lung axis. In a STZ-induced rat model of diabetic cardiomyopathy, crocin, administered either as a monotherapy or in combination with other agents, exerted pronounced cardioprotective effects[123]. These included attenuation of cardiac injury biomarkers, oxidative stress, inflammatory responses, and apoptotic cell death, accompanied by significant remodeling of the gut microbial community[123]. GF extract further showed capability in impairing 2,4-dinitrochlorobenzene (DNCB)-induced cutaneous inflammation through the gut–skin axis[124]. Antibiotic-induced gut dysbiosis aggravated DNCB-evoked skin inflammation, with GF extract significantly restoring gut microbial composition to reduce serum immunoglobulin E (IgE) and Th2-type cytokine levels, as well as reinforce intestinal barrier integrity[124]. Moreover, in an ovalbumin (OVA)-induced murine asthma model, geniposidic acid administration potently suppressed airway inflammatory infiltration, mucus overproduction, and NF-κB activation, while concomitantly upregulating the Nrf2/heme oxygenase-1 (HO-1) antioxidant pathway and effectively rectifying asthma-associated gut microbial dysbiosis[125]. Moreover, Genipin, the microbiota-mediated active metabolite of geniposide, is observed to decrease the content of pro-inflammatory cytokines to suppress endoplasmic reticulum stress in a sepsis-induced splenocyte apoptosis model[126]. Additionally, the anti-tumor effect of genipin involves G0/G1 phase cell cycle arrest and mitochondria-mediated apoptosis induced by the suppression of the phosphatidylinositol 3-kinase/protein kinase B signaling pathway (PI3K/Akt)[127]. Moreover, the HIF-1α/HSPG2 signaling axis can also be downregulated by genipin, which further inhibits the proliferation, migration, and angiogenesis of triple-negative breast cancer cells and the motility of endothelial cells[128]. Recent evidence shows that genipin generates its chondroprotective effect on osteoarthritis *via* covalent binding to PGK1 to increase methylglyoxal production, which in turn triggers antioxidant defense mechanisms, attenuates inflammation, downregulates matrix metalloproteinase expression, and limits extracellular matrix breakdown[129]. Despite these findings, the mechanistic basis of GF's pharmacological activities remains largely obscure. The majority of existing investigations are deficient in comprehensive mechanistic characterization. Critical gaps include the definitive identification of enzymes responsible for GF metabolism or targeted by its active components, alongside the elucidation of the downstream signaling networks through which these effects are mediated and the molecular targets involved. Resolving these questions is critical not

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only for a comprehensive understanding of GF physiology but also for its rational clinical use.

In summary, the gut-X axis perspective reveals a convergent core framework integrating SCFAs, intestinal barrier, and TLR4/NF-κB–driven inflammation. GF-derived compounds consistently restore SCFA production, reinforce epithelial barrier function, suppress endotoxin translocation, and dampen TLR4/NF-κB cascades, underpinning the broad-spectrum therapeutic potential of GF. Meanwhile, organ-specific signaling pathways confer functional specialization. These axis-specific responses, together with common gut-derived pathways, are unified within the gut-X axis framework, providing a mechanistic blueprint for GF's multi-organ actions.

Pharmacological effects of GF independent of gut microbiota interventions

Although microbiota-mediated effects of GF have attracted considerable attention, the overall pharmacological profile of GF remains of substantial importance. Numerous investigations have focused on physiological changes induced by GF and its bioactive constituents without addressing the role of gut bacteria. These pharmacological actions include anti-inflammatory, antioxidant, anti-tumor, and immunomodulatory effects (Figure 4). *In vitro* studies have demonstrated direct pharmacological actions of GF constituents by engaging specific signaling cascades and molecular targets, whereas *in vivo* findings often reflect microbiota-influenced effects. In this section, we summarize the representative compounds reported to elicit these bioactivities and delineate their underlying mechanisms.

Anti-inflammatory effect

Anti-inflammatory activity is one of the major pharmacological effects of GF, involving integrated regulation of key inflammatory enzymes, pro-inflammatory cytokines, and upstream signaling pathways of the inflammatory response (Figure 4). GF extracts and its bioactive ingredients may significantly reduce various pro-inflammatory mediators. Studies have shown that the extracts of GF and its crocetin derivatives, such as

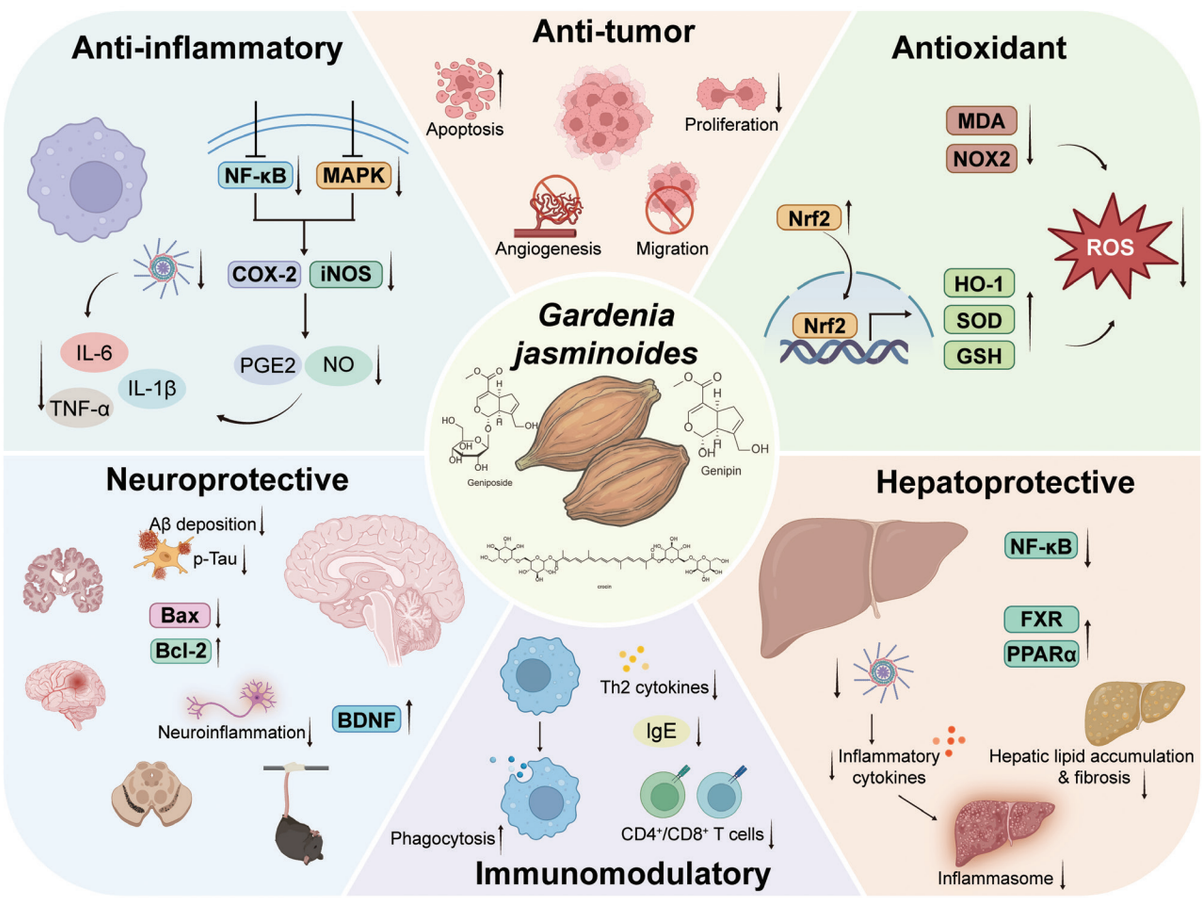


Figure 4. Overview of the multi-target pharmacological actions of GF. Anti-inflammatory, antioxidant, hepatoprotective, neuroprotective, anti-tumor, and immunomodulatory activities were summarized as the main therapeutic activities of GF. The major pathways and mediators involved in different physiological processes are also shown. Aβ: β-Amyloid; Bax: BCL2-associated X protein; Bcl-2: B-cell lymphoma 2; BDNF: Brain-derived neurotrophic factor; COX-2: Cyclooxygenase-2; FXR: Farnesoid X receptor; GF: Gardeniae Fructus; GSH: Glutathione; HO-1: Heme oxygenase-1; IgE: Immunoglobulin E; IL-6: Interleukin-6; IL-1β: Interleukin-1 beta; MAPK: Mitogen-activated protein kinase; MDA: Malondialdehyde; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; NOX: NADPH oxidase (Nicotinamide adenine dinucleotide phosphate oxidase); Nrf2: Nuclear factor erythroid-2–related factor 2; iNOS: Inducible nitric oxide synthase; PGE2: Prostaglandin E2; PPARα: Peroxisome proliferator-activated receptor alpha; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor alpha. Created in BioRender. Zhao Z. (2026). https://BioRender.com/wfhfx1d.

HM9_V6N3.indb 401 26-Sep-26 15:38:31

crocin and crocetin, could inhibit nitric oxide (NO) production in LPS-stimulated macrophages. These derivatives exert anti-inflammatory effects by downregulating the protein and mRNA expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), with crocetin demonstrating the strongest activity among them[130]. Besides, gardenoside alleviates osteoarthritis by reducing the expression of COX-2, iNOS, and inflammation-related genes[131]. Geniposide exerts its anti-inflammatory effects through the inhibition of iNOS and COX-2 overexpression, as well as the reduction of NO and prostaglandin E_2 (PGE_2) release[132]. Furthermore, GF broadly suppresses the production of pro-inflammatory cytokines. Extracts of GF[133–135] and its active components geniposide[132,136] have been proved to significantly reduce the expression of various pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, in both serum and tissues across multiple inflammation-related models. Previous studies indicate that the main mechanisms underlying the anti-inflammatory effects of GF and its active components involve the regulation of NF-κB, mitogen-activated protein kinase (MAPK), and other inflammatory signaling pathways, as well as inhibition of the NLRP3 inflammasome[132,137–139].

Antioxidant effect

The antioxidant activity of GF is mediated through multiple mechanisms, including radical scavenging, regulation of endogenous antioxidant enzyme systems, and modulation of oxidative stress signaling pathways (Figure 4). A variety of components present in GF extracts have been confirmed to directly scavenge free radicals[140]. For example, geniposide has been shown to reduce reactive oxygen species (ROS) generation and malondialdehyde (MDA) content in oxidatively stressed cells, while also decreasing the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2, thereby mitigating oxidative injury[141]. In addition, geniposide could benefit antioxidative defense ability through activation of nuclear factor erythroid-2–related factor 2 (Nrf2), which results in upregulation of HO-1 and superoxide dismutase (SOD), as well as reduced ROS and myeloperoxidase (MPO) levels[142]. Furthermore, geniposide exerts cardioprotective effects in a heart failure mouse model by regulating the MMP2/SIRT1/GSK3β pathway to facilitate Nrf2 transcriptional activation and attenuate cardiac oxidative stress[143]. Moreover, carbon dots derived from GF have demonstrated efficacy in reducing excessive oxidative stress in the MCAO model, showing elevated GSH and SOD levels and reduced MDA content[144].

Anti-tumor effect

The anti-tumor effects of GF are mediated *via* diverse mechanisms, including the suppression of proliferation, induction of apoptosis and autophagy, as well as inhibition of migration, invasion, and angiogenesis (Figure 4). GF extracts have been found to impair tumor cell migration, invasion, and colonization through the inhibition of NF-κB p65 nuclear translocation[145]. Geniposide can alter the state of tumor cells through AMPK pathway activation and JNK pathway inhibition[146]. Data show that geniposide treatment significantly triggers G2/M phase arrest, mitochondria-dependent apoptosis, and autophagy, while concurrently suppressing cell migration[146]. Furthermore, geniposide depresses the proliferation, migration, invasion, and epithelial–mesenchymal transition (EMT), as well as promotes apoptosis of non–small-cell lung cancer cells[147]. These effects are achieved by blocking the activation of the Wnt/β-catenin signaling pathway, thereby restraining tumor progression both *in vitro* and *in vivo*[147].

Immunomodulatory effects

Polysaccharides of GF have shown prospective immunomodulatory effects in previous studies. A pectin polysaccharide of GF with a predominant homogalacturonan (HG) structure has been demonstrated to activate NF-κB, JAK/STAT, and MAPK signaling pathways[24]. The modulation of these pathways induces M1 polarization of macrophages, enhancing cell proliferation and phagocytic activity, which contribute to the potent immunomodulatory activities of this GF pectin[24]. Besides, Shao et al.[37] have obtained two homogeneous acidic polysaccharides from GF containing HG domains and rhamnogalacturonan I (RG-I) domains with arabinan and arabinogalactan (AG) side chains, designated GJP50-3 (91.5 kDa) and GJP50-4 (140.3 kDa). GJP50-3 and GJP50-4 exhibit immunomodulatory effects by promoting the release of various interleukins and chemokines, as well as increasing NO levels and neutrophil counts in a zebrafish model[37]. Moreover, GF polysaccharides can enhance macrophage phagocytic activity and reverse LPS-induced immunosuppression and oxidative stress in mice through activation of the TLR4/NF-κB signaling pathway[148]. In addition to polysaccharides, other bioactive compounds in GF also contribute to the immunomodulatory effects of GF. Geniposide has been shown to generate anti-inflammatory and immunomodulatory properties in multiple studies on rheumatoid arthritis (RA)[149–150]. Furthermore, GF extracts removing crocin have been shown to modulate immune responses by regulating Th2-type cytokine release and IgE levels by inhibiting STAT1 activation, which significantly reduced the numbers of $CD4^+$ and $CD8^+$ T cells in the spleen and lymph nodes[151].

Neuroprotective effect

GF extracts and their bioactive components, particularly geniposide and crocetin, have been increasingly recognized for their neuroprotective effects in multiple preclinical models of CNS diseases owing to their anti-inflammatory and antioxidant activities (Figure 4)[100,152–154]. Geniposide and genipin-1-β-D-gentiobioside can ameliorate depressive-like behaviors in animal models *via* anti-inflammatory effects and upregulation of BDNF expression[155–157]. In AD models, GF and geniposide improve learning and memory capacities by suppressing amyloid-β (Aβ) deposition, reducing Tau hyperphosphorylation, as well as alleviating neuroinflammation and oxidative stress[158–161]. Crocin,

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another active component in GF, blocks Aβ-induced apoptosis and diminishes ROS levels by inhibiting the stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) signaling pathway and enhancing PI3K p85 phosphorylation[162]. Besides, geniposide exerts protective effects in Parkinson disease (PD) models *via* reducing the Bax/Bcl-2 ratio by downregulating the expression of the pro-apoptotic protein Bax and upregulating the expression of the anti-apoptotic protein Bcl-2, thereby inhibiting the activation of caspase-3[163]. This effect contributes to restoring tyrosine hydroxylase-positive dopaminergic neurons in the substantia nigra pars compacta and significantly improves locomotor function in model animals[163]. Crocin, in turn, confers neuroprotection *via* PI3K/Akt/mammalian target of rapamycin (mTOR) pathway activation, leading to reduced α-synuclein levels and restoration of tyrosine hydroxylase and DA content[164]. Furthermore, extracellular vesicles derived from GF have been reported to mitigate PD progression through increasing dopaminergic neuron populations[165]. In ischemic stroke models, geniposide and crocin reduce cerebral infarct volume and promote functional recovery by suppressing ERK1/2 and NF-κB signaling cascades and reducing neuroinflammation[166–168]. In a refractory status epilepticus model, GF extracts exert both anticonvulsant and neuroprotective actions *via* inhibition of HMGB1-mediated neuroinflammation and suppression of aberrant excitatory synaptic transmission[169]. Shanzhiside methyl ester targets HSP90AA1 to restrain HIF1A/STAT1 pathway-derived inflammation and glycolysis process, consequently ameliorating cognitive impairment in diabetic mice[170]. Taken together, GF and its major bioactive ingredients exhibit universal neuroprotective potential in diverse CNS disease models.

Hepatoprotective effect

Accumulating evidence has demonstrated that GF and its major iridoid glycosides could exert preventive and therapeutic effects against various liver diseases[171–174]. The protective effect of GF extract against high-fat, high-fructose diet–induced nonalcoholic steatohepatitis and liver fibrosis in rats is proved and attributed to the suppression of NF-κB p65-mediated inflammatory signaling, which further downregulates key fibrotic factors including matrix metalloproteinase-12 (MMP-12), alpha-smooth muscle actin (α-SMA), IL-13, and transforming growth factor-beta 1 (TGF-β1), and ameliorates hepatocellular injury as indicated by decreased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[175]. Geniposide alleviates bile duct ligation–induced liver fibrosis by activating SIRT1 to deacetylate FXR, restore BA homeostasis, and suppress NLRP3 inflammasome activation[176]. Differing from geniposides, geniposidic acid directly reacts with NLRP3 to inhibit NLRP3 inflammasome activation in hepatocytes and macrophages, resulting in a reduction of BA-induced pro-inflammatory cytokine release and ANIT-induced cholestatic liver inflammation[177]. Geniposidic acid may also directly activate SIRT6 to initiate PPARα signaling, reducing lipid accumulation, oxidative stress, inflammation, and fibrosis in MASLD models[178]. Additionally, geniposidic acid alleviates drug-induced liver injury (DILI) by promoting FXR nuclear translocation and CYP450-mediated BA metabolism, as well as inhibiting LXR-mediated cholesterol synthesis[179].

Other pharmaceutical effects

A variety of other bioactive properties induced by GF and its active components have also been revealed. Geniposide confers protection against myocardial ischemia-reperfusion injury by activating the AMPK signaling cascade[180]. This activation facilitates TXNIP translocation and reduces TXNIP–NLRP3 association, ultimately leading to the suppression of NLRP3 inflammasome activation and the inhibition of cardiomyocyte pyroptosis[180]. Geniposide can also mitigate dexamethasone-induced muscle atrophy and retard physical function decline in senescence-accelerated mice *via* AKT pathway-mediated inhibition of FoxO1 activity[181]. Besides, in rats with an acute myocardial ischemia model, GF extract not only improves cardiac function, alleviates myocardial pathological injury and apoptosis by reducing inflammatory mediators and oxidative stress, but also modulates coagulation function[182]. Moreover, geniposide directly conjugates with STAT3 to impede its phosphorylation and nuclear translocation, resulting in a reduction of hexokinase 2 (HK2)-derived glycolysis[183]. This consequently suppresses EMT in renal tubular epithelial cells and ameliorates unilateral ureteral obstruction–induced renal interstitial fibrosis[183]. In addition, evidence showed that geniposide could alleviate oxidative stress and pancreatic acinar cell injury in acute pancreatitis through inhibiting trypsinogen activation and diminishing trypsin-mediated cleavage of cystathionine β-synthase (CBS), thereby restoring transsulfuration pathway homeostasis[184]. SphK1 is demonstrated to be the direct target of geniposide, the conjugation between which restrains S1P/PI3K-Akt signaling, leading to reduced HDAC3/6 activity and enhanced HIF-1α acetylation and degradation[185]. Through this cascade, geniposide inhibits vascular endothelial growth factor (VEGF)-driven synovial angiogenesis and ameliorates articular pathology in a collagen-induced arthritis rat model[185]. In addition, HFD-induced atherosclerosis in mice can be alleviated by geniposide treatment[186]. This is attributed to the suppression of PI3K/AKT signaling, which restores lipophagy activity otherwise inhibited by PARP1, which markedly reduces vascular smooth muscle cell–derived foam cell formation, lipid accumulation, inflammation, and apoptosis[186].

While the studies cited in this section emphasize a direct causal relationship between GF/its active components and therapeutic efficacy, the concurrent influence of the gut microbiota must also be taken into account. Given that GF has been shown to induce functionally relevant structural changes in the gut microbial community, the gut microbiota and its metabolic products are considered important determinants of GF's overall bioactivity in most physiological contexts.

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Toxicological concerns of GF and strategies for balancing efficacy and safety

Although GF has been applied clinically for centuries as both a medicinal and edible material, multiple investigations have uncovered its high-dose–induced acute toxicity and prolonged-administration–induced chronic toxicity[187–188], which have also been found in the application of other traditional Chinese medicines (TCMs)[189]. This raises risk concerns for the clinical usage of GF. Therefore, a thorough illustration of GF-induced toxicity mechanisms and the discovery of promising toxicity attenuation strategies are essential for the safe and effective utilization of GF in clinical settings.

Previous analysis uncovered the "DEIT crosslink" between disease/diet (D) and drug metabolism, indicating that enzymes (E) in intestinal microbiota (I) altered by diet could modulate the trails of metabolism (T)[190]. This relationship also influences the toxic effects of GF and is crucial for adverse effects alleviation (Figure 5).

Gut microbiota plays a critical role in GF-induced adverse effects

Hepatotoxicity is the most commonly reported adverse effect induced by GF, which is also a main cause of drug withdrawal or the assignment of warning labels in the market. Research revealed that geniposide is the major hepatotoxicity-inducing compound in GF; meanwhile, it is the primary contributor to the pharmaceutical effects of GF[191]. Metabolome analysis indicates that geniposide treatment leads to liver injury in rats, along with disordered pyrimidine, purine, and amino acid metabolism, and pantothenate and CoA biosynthesis[192]. Geniposide also disturbs the metabolism of BA when it activates the NLRP3 inflammasome by inhibiting the FXR receptor[193]. Besides hepatotoxicity, long-term administration of geniposide may cause noticeable pathological abnormalities in the kidney as well. The constituent treatment of high-dose geniposide (100 mg/kg) for 26 weeks significantly enhances inflammatory indicators in serum and leads to liver and kidney damage[187]. Similar to the mechanism involved in geniposide-related hepatotoxicity, inhibition of the FXR receptor is the key step that further regulates FXR/PERK/TXNIP pathways to activate the NLRP3 inflammasome[194].

Notably, intestinal bacteria play an essential role in geniposide-induced toxicity[195]. The transformation of geniposide into genipin, mediated by bacteria such as *Bifidobacterium longum* and *Bacteroides fragilis*, is vital for toxicity generation[196]. In this case, enzymes in different bacteria are key points for geniposide toxicity generation; for example, *Eubacterium sp*. A-44 can transform geniposide into genipin, while *Ruminococcus sp*. PO1-3 cannot[43]. This is due to the specific β-D-glucosidases generated in *Eubacterium sp*. A-44. According to the comparison of toxic effects between geniposide and genipin at the same concentration, genipin is recognized as the primary metabolite mediating geniposide-induced toxicity[196]. An *in vitro* liver injury prediction system based on HepG2 cells also shows that genipin induces similar physiological disorders to those induced by GF administration and geniposides, which involve amino acid metabolism and CoA biosynthesis[21,192]. Previous studies also found that genipin could cause genotoxicity[197]. The mechanism of genipin-induced toxicity is quite special, as it is associated with its reactive dialdehyde intermediate. This reactive intermediate may covalently conjugate with amino acids that have electrophilic groups, such as lysines; these conjugates further induce cellular oxidative stress and result in liver injury[72]. Moreover, the reactive intermediate of genipin can also covalently bind to amino acid residues with electrophilic side chains in proteins, disturbing the biological effects of these proteins. Evidence indicates that genipin can generate liver protein adducts *via* lysine residues, and the levels of adducts show a relationship with genipin-induced liver damage[22]. A recent study integrating proteomics and metabolomics techniques revealed that genipin covalently modifies CPS1, depleting citrulline and significantly suppressing the production of its downstream metabolite fumarate[23]. Further validation confirmed that genipin induces hepatotoxicity by disrupting the urea cycle, which reduces fumarate production and impairs Nrf2-mediated antioxidant defense, thereby triggering oxidative stress.

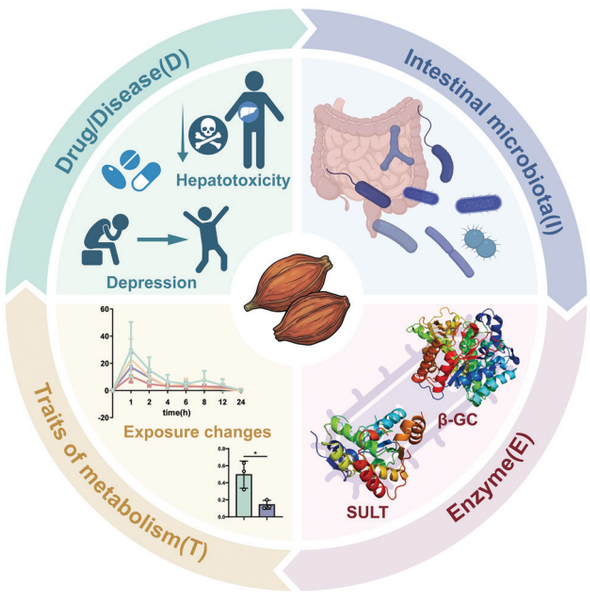


Figure 5. DEIT framework illustrating diet/disease–microbiota–enzyme–metabolism interactions in GF-induced adverse effects and alleviation interventions. The diagram depicts how diet and disease states (D) shape gut microbial ecology (I) and enzyme activities (E), which in turn determine the metabolic traits (T) governing drug bioavailability, efficacy, and toxicity. β-GC: β-D-Glucosidases; GF: Gardeniae Fructus; SULT: Sulfotransferase. Created in BioRender. Zhao Z. (2026). https://BioRender.com/f69l5fk.

Gut microbiota–targeting strategies to attenuate toxicity and amplify efficacy

Given the therapeutic efficacy of GF and the safety concerns associated with geniposide, it is imperative to develop effective strategies to mitigate its toxicity, thereby ensuring safe and efficacious clinical application. It should be noted that dosage and administration time are key factors in geniposide-induced toxicities. With the assistance of a

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comprehensive dosage-duration-efficacy/toxicity model, Qiu et al.[198] uncovered that genipin-induced adverse effects usually happen at higher doses and longer treatment durations. Besides, with the three-dimensional (3D) dose/time–effect analysis of over 400 animals included in 25 studies, a dose of 20 to 150 mg/kg/day for 5 to 28 days seems to be a safe administration strategy for genipin to generate a hepatoprotective effect and avoid toxicity[188]. However, this range is derived from animal studies, which could not be interpreted as a safe human clinical dose. Therefore, strictly controlling the dosage and administration time may partly benefit the clinical use of GF.

Moreover, the clinical application of GF, which is usually used with other herbal medicines, such as Semen *sojae preparatum* (SSP), suggests that the components in SSP may change the metabolism of GF *in vivo*. For example, isoflavones can change the pharmacokinetic profiles of four main iridoids of GF, including geniposide[27]. This supports the hypothesis that compatibility may alleviate GF-induced hepatotoxicity by influencing the biotransformation of geniposide (Figure 6). Metabolomic analysis further proves that the combined use of GF and SSP in ZZCD confers toxicity-attenuating effects[199]. This is achieved through the suppression of hepatotoxic species of genipin, alongside the improvement of protective metabolites including jasminoside A induced by isoflavones in SSP[199]. A recent study further emphasizes the essential role of gut microbiota in alleviating the hepatotoxicity of geniposide with SSP. The presence of isoflavones redirects geniposide metabolism *via* modulation of key metabolic enzymes, including β-GC and SULT, thereby shaping its pharmacokinetic and toxicological profile[1]. These enzymes are regulated through the alteration of gut microbiota structures, with *Lactobacillus* spp. as promising microbial targets[1]. In this case, gut microbiota play an important role in alleviating GF-related toxicities, which can inspire the development of prospective strategies for GF-induced liver injury prevention. For instance, probiotic and prebiotic supporting β-GC and SULT-enrichment bacteria, as well as engineered bacterial consortia that overexpress β-GC and SULT enzymes, may become prospective intervention approaches to enrich the spectrum of efficacy-safety balancing strategies for GF.

Clinical transformation prospects

With the summary mentioned earlier, it could be noted that gut microbiota is essential for GF in generating both efficacy and toxicity. The changes in gut microbiota composition and function induced by drugs and the chemical transformation of drugs by gut bacteria significantly influence the efficiency and toxicity of drugs[200]. The variability of personal gut microbiota is a primary reason for the differences in drug efficacy between patients[201]. In recent years, the gut microbiota shows potential for clinical applications in precision medicine[202–207]. Ecological management has been considered a promising strategy for improving therapeutic effects in many diseases[208]. Components of the gut microbiota—including enzymes, bacterial strains, species, and metabolites—can serve as biomarkers to guide personalized drug administration. Among them, the enzymatic activity of bacteria is the most probable biomarker due to its strong relationship with drug activity and transport or drug metabolism and disposition[201,209]. For example, cardiac glycoside reductase (cgr) in *Eggerthella lenta* was reported to be a predictable microbiota biomarker for digoxin deactivation[210]. For GF, detection of its effect-related enzymes such as β-GCs, and those enzymes involved in alleviating toxicity including SULT and β-Glu may benefit the dosage adjustment of GF during the treatment process. However, the clinical translation of such enzymatic biomarkers faces substantial limitations. A considerable gap exists between biomarker discovery and clinical validation; taking cgr as an example, not all *E. lenta* strains harbor the cgr operon, and among those that do, single amino acid variations in the Cgr2 enzyme can produce three distinct phenotypes of drug-metabolizing activity[211]. Moreover, inter-individual differences in baseline gut microbial composition, dietary patterns, and concomitant medications, as well as the technical limitation that fecal microbiota may not

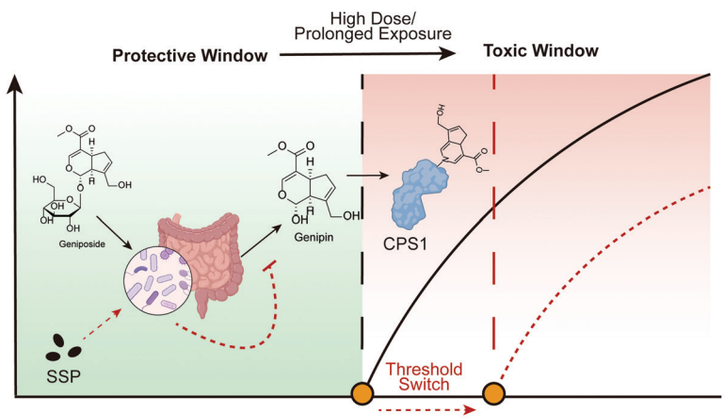


Figure 6. Mechanism of compatibility alleviation of GF-induced hepatotoxicity by influencing the biotransformation of geniposide. Isoflavones in SSP could redirect geniposide metabolism *via* modulation of gut microbiota, thereby shaping its pharmacokinetic and toxicological profile. CPS1: Carbamoyl phosphate synthetase 1; GF: Gardeniae Fructus; SSP: Semen *sojae preparatum*. Created in BioRender. Zhao Z. (2026). https://BioRender.com/crorquh.

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fully recapitulate the entire gut microbial ecosystem, further complicate clinical application. Despite these challenges, these investigations demonstrated the promising potential of microbial enzymatic biomarkers. With continued advances in multi-omics technologies and deeper mechanistic understanding, gut microbiota-derived enzymatic biomarkers hold promise as valuable tools for personalized pharmacotherapy.

Besides, disease phenotypes can also change the composition of intestinal microbiota, which further influences relevant enzyme bioactivities and traits of metabolism. It has been discovered that depression could induce dysbacteriosis, which increases the content of *Bacteroidota* while decreasing that of *Firmicutes*[17]. The activities of SULT and β-Glu are subsequently decreased, leading to an enhancement of the exposures of anti-depressive iridoid glycosides in the CUMS group compared to the control group[17]. Interestingly, with the administration of ZZCD, the dysbiosis of gut microbiota is recovered and the absorption of iridoid glycosides is also reduced[17]. This observation illustrates the personalized treatment paradigm of TCM formulas: the disease state creates a microbial dysbiosis that amplifies drug bioavailability, whereas TCM administration progressively reverses this phenotype, yielding a dynamic, disease-stage-tailored pharmacokinetic modulation that aligns with the principles of individualized therapy.

Moreover, rationally designed live bacterial consortia have emerged as a complementary approach that satisfies the requirements for safe and effective GF application[212–214]. Toxicity-alleviating strains, including *Lactobacillus* spp.[1], can be rationally engineered to optimize ecological stability and host–microbe interactions[215]. Moreover, efficacy-associated strains relevant to GF metabolism, such as *Limosilactobacillus reuteri*[104] and *Lactobacillus rhamnosus*[4], also present prospective potential to be rationally designed for co-utilization with GF. In addition, the development of synthetic biology and genetic engineering offers new insights into microbial management, which enables the engineering of bacteria to generate functional enzymes or metabolites[208,216]. Therefore, employing microbial strains with efficacy- and safety-associated enzyme activities may be suitable for further preclinical evaluation. Prebiotics offer another avenue for selectively enhancing the growth of particular bacterial strains[217]. For example, isoflavones present in fermented soybeans alleviate GF-associated liver injury through gut microbiota modulation. This observation raises the possibility of utilizing these isoflavones as prebiotic modulators.

Conclusion

In conclusion, gut microbiota emerges as a critical determinant in the pharmacological landscape of GF, functioning as a dual mediator of both therapeutic activity and toxic effects. This character underscores the critical importance of gut microbiota in herbal medicine research and clinical practice. Looking forward, the integration of gut microbiota management strategies with robust safety considerations will be key to unlocking the full therapeutic promise of GF and accelerating the development of microbiome-targeted therapeutics. Although combining gut microbiota management strategies with safety consideration may help realize the therapeutic potential of GF and support the development of microbiome-targeted therapeutics, the application of gut microbiota management strategies still requires further evidence and human validation.

Genipin epitomizes the "dual role" phenomenon in GF, being simultaneously a principal pharmacophore and a primary toxicophore. Accordingly, striking an optimal risk–benefit equilibrium constitutes a pivotal challenge for clinical translation. While rational herb compatibility has achieved appreciable success in toxicity–efficacy modulation, emerging mechanistic insights suggest that microbiota-targeted interventions may offer an additional dimension for refining this balance. The integration of TCM with cutting-edge microbiome strategies promises a new era of personalized, safe, and effective herbal therapeutics. There are still many challenges in clinical translation, including insufficient human clinical data, lack of engineered symbiotic bacteria research, and unclear processing-induced flora metabolic changes. However, with the development of determination techniques and further investigations into gut microbiota-mediated pharmacological effects of GF, these advances hold promise for refining GF-based therapeutics through microbiota-guided precision medicine.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Zixin Zhao and Shilin Gong drafted the original manuscript. Chunyue Liu contributed to figure preparation. Jun Wen and Tingting Zhou supervised and guided the review. All the authors have read and approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed in the current study.

HM9_V6N3.indb 406 26-Sep-26 15:38:33

Declaration of generative AI in scientific writing

During the preparation of this work, the authors did not use any generative artificial intelligence (AI) or AI-assisted technologies in the writing process or for the generation of any content. All citations in this manuscript were manually searched for and incorporated, and the authors take full responsibility for the integrity and accuracy of the manuscript.

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HM9_V6N3.indb 411 26-Sep-26 15:38:33