Potential roles of gut microbes in biotransformation of natural products: An overview

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Natural products have been extensively applied in clinical practice, characterized by multi-component and multi-target, many pharmacodynamic substances, complex action mechanisms, and various physiological activities. For the oral administration of natural products, the gut microbiota and clinical efficacy are closely related, but this relationship remains unclear. Gut microbes play an important role in the transformation and utilization of natural products caused by the diversity of enzyme systems. Effective components such as flavonoids, alkaloids, lignans, and phenols cannot be metabolized directly through human digestive enzymes but can be transformed by enzymes produced by gut microorganisms and then utilized. Therefore, the focus is paid to the metabolism of natural products through the gut microbiota. In the present study, we systematically reviewed the studies about gut microbiota and their effect on the biotransformation of various components of natural products and highlighted the involved common bacteria, reaction types, pharmacological actions, and research methods. This study aims to provide theoretical support for the clinical application in the prevention and treatment of diseases and provide new ideas for studying natural products based on gut biotransformation.

KEYWORDS
natural products, gut microbes, enzyme system, biotransformation, bioavailability

Introduction

The gut microbiota is composed of 1,000–1,250 kinds of bacteria that interact with humans in various forms, such as symbiosis and parasitism, and this interaction greatly affects human health via microbial metabolites as signal molecules (Liu et al., 2017; de Vos et al., 2022). The gut microbes constitute a dynamic and diversified micro-ecosystem, which is a natural barrier to resisting pathogenic bacteria (Chopyk and Grakoui, 2020; Zhao and Maynard, 2022). Gut microbes have abundant enzyme systems, including glucosidase, reductase, lyase, transferase, etc., and greatly expand the metabolic response pool in the human body (Wilson and Nicholson, 2017; Fushinobu and Abou Hachem, 2021).
Natural products are small molecules produced naturally by any organism including primary and secondary metabolites. This article mainly describes natural products of plant origin, including nutrients and drugs. They easily interact with gut microbiota because of their complex components and long residence time in the gut. Generally, the residence time for exogenous substances is 1–6 h in the small intestine and 1–3 days in the colon (Chu and Traverso, 2022). Specific gut microbes decompose and transform natural products to produce rich metabolites and functional compounds with physiological activities that cannot be synthesized by the host itself (Koppel et al., 2017; Xie et al., 2020). Microbial transformation in natural products usually refers to the chemical reactions that are used to modify the structure of natural products substrates, such as hydrolysis, methylation, demethylation, redox, and cyclization reaction (Morgan et al., 2022; Rocchetti et al., 2022). Gut microbiota remarkably affects the chemical modification, pharmacological activity, and metabolic mechanism of natural products. The potential utility of gut microbes for large-scale synthesis of active metabolites and production of compounds has not been investigated. Studying these gut microbes, metabolites, and the reactions involved in the interactions between natural products and gut microbiota is of great significance in the exploration of the pharmacological mechanisms and utilization of natural products. In this review, we introduce the resident gut microbes that contribute to the transformation of natural products and summarize the transformation pathways between natural products and specific microbes classified by the reactions. Moreover, the advantages, research methods, and future directions of gut microbial in the conversion of natural products are discussed to provide a theoretical basis for the modern application of natural products and the precise treatment through gut microbiota.

Key gut microbes in the biotransformation of natural products

Oral administration is the preferred route for drug delivery, and oral drugs account for 84% of the top 50 best-selling drugs in the US and European markets (Lennernäs and Abrahamsson, 2005; Vinarov et al., 2021). In recent years, the influence of gut microbiota on the stability of oral administration of natural products has received much attention. The intestinal tract has abundant bacteria that help with normal digestive function, in which about 98% of gut microbes in healthy subjects can be classified into four phyla, Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria (Manor et al., 2020; Ye et al., 2021; de Vos et al., 2022). Some gut microbes such as Escherichia coli, Bifidobacterium, Eubacterium, Lactobacillus, Bacteroides, and Streptococcus participate in the biotransformation of natural products, and part of their metabolites are conducive to intestinal absorption and play a notable pharmacological role (Al-Ishaq et al., 2021; Augusti et al., 2021; Figure 1).

Escherichia coli

Escherichia coli is a Gram-negative, spore-free, facultative anaerobic bacterium, which mainly inhabits the intestines of vertebrates (Foster-Nyarko and Fallon, 2022). Part of E. coli

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1 https://www.nature.com/subjects/natural-products

Abbreviations: DHC, dihydrocurcumin; THC, tetrahydrocurcumin; CurA, NADPH-dependent curcumin/dihydrocurcumin reductase; CHA, chlorogenic acid; CA, caffeic acid; GL, glycyrrhizin; 18β-GA, 18β-glycyrrhetinic acid; PM-I, paeonolmetabolin-I; GAMG, 18β-glycyrrhetinic acid-3-O-β-D-glucuronic acid; SGG, Streptococcus gallolyticus subsp. Galloyticus; DDAs, diester diterpenoid alkaloids; MDAs, monoester diterpene alkaloids; DHENL, (-)-dihydroxyenterolactone; 3′-DMAG, 3′-desmethylarctigenin; BBR, Berberine; dhBBR, dihydroberberine; DMC, demethoxycurcumin; bDMC, bis-demethoxycurcumin; CK, compound K; UA, Urolitin A.
can produce glycosidase to participate in the transformation of exogenous substances, resulting in its beneficial role (Rodríguez-Daza et al., 2021; Candeliere et al., 2022). For example, *E. coli* HGU-3 produces β-glucuronidase to hydrolyze the O-glycosidic bond in baicalin to yield baicalein (Han et al., 2016; Li D. et al., 2019). Feruloyl esterases from *B. animalis*, *L. reuteri*, *L. helveticus*, and *L. fermentum* catalyzes hydrolysis of chlorogenic acid into caffeic acid (Raimondi et al., 2015; Pang et al., 2016; Aguirre Santos et al., 2018). β-glucosidase of *Eubacterium* L-8 and Streptococcus L2-22 catalyzes hydrolysis of glycyrrhizin to 18β-glucorhyzic acid (Kim et al., 1999; Chen B. et al., 2021). α-L-rhamnosidase from Bacteroides sp. 45 catalyzes hydrolysis of rutin to quercetin 3-O-glucoside (Riva et al., 2020). O-Methyltransferase from Blautia sp. MRG-PMF1 catalyzes the demethylation of curcumin to demethoxycurcumin (Burapan et al., 2017a,b). Created with BioRender.com.

**Bifidobacterium**

*Bifidobacterium* is a widespread and abundant genus belonging to the phylum Actinobacteria and is among the first colonizers of gut microbiota for humans (Satti et al., 2021; He et al., 2022). The most common *Bifidobacterium* in the human gut include *B. adolescentis*, *B. longum*, *B. breve*, *B. catenulatum*, *B. dentium*, *B. longum*, *B. pseudocatenulatum*, and *B. pseudolongum* (Turroni et al., 2008; Hidalgo-Cantabrana et al., 2017), accounting for <10% of the adult human microbiome, but they are linked to host health (Turroni et al., 2008). Certain species of *Bifidobacterium* can generate phenolic acids by expressing feruloyl esterase. For example, the feruloyl esterase of *B. animalis* can hydrolyze chlorogenic acid (CHA) into caffeic acid (CAA);
CAAs (10–30 mg/kg) can prevent acetaminophen-induced acute liver injury in mice by increasing Nrf2 transcription (Raimondi et al., 2015; Pang et al., 2016). The participation of partial Bifidobacterium promotes the metabolism of flavanones, glycosides, and saponins in the gut. β-glucosidase and demethylase in B. longum R0175 promote 3-(3′-hydroxyphenyl) propionic acid and 3-(phenyl) propionic acid production from hesperidin through ring-cleavage and demethylation (Pereira-Caro et al., 2018). B. longum SBT2928 hydrolyzes six major human and two animal bile salts (Tánaka et al., 2000). Thus, Bifidobacterium may regulate bile acid metabolism and reduce cholesterol levels in vivo. In addition, B. breve ATCC 15700 produces β-glucosidase to cleave glycoside at the C-3 and C-20 positions of ginsenoside Rd. to generate deglycosylated ginsenoside compound K (Zhong et al., 2016; Zhang R. et al., 2019). These metabolic characteristics make Bifidobacterium a prime candidate for the development of symbiosis to make natural products potentially beneficial.

**Eubacterium**

The genus of Eubacterium strains is Gram-positive, which forms one of the core genera of the human gut microbiota and shows widespread colonization of the human gut (Mukherjee et al., 2020). Some Eubacterium species produce glycosidase, reductase, etc., and participate in the metabolism of exogenous substances (Zhang J. et al., 2019; Ellenbogen et al., 2021). E. ramulus is one of the most widely studied flavonoid-degrading gut bacteria, and it is prevalent in the human intestine. Chalcone isomerase and flavanone-/flavanolol-cleaving reductase from E. ramulus degrade certain flavonoids to produce chalcone, and dihydrochalcone (Gall et al., 2014). Dihydrochalcone and its metabolites have anti-inflammatory and antioxidant effects, which can down-regulate the secretion of pro-inflammatory cytokines in RAW 264.7 and rescue LPS-induced oxidative phosphorylation (Choi et al., 2021). Braune et al. investigated the degradation of flavonol quercetin and flavone luteolin by E. ramulus strain wK1 and found that resting cells and enzyme preparations convert these flavonoids into 3, 4-dihydroxyphenylacetic acid, and 3-(3, 4-dihydroxyphenyl) propionic acid via the reduction of 2, 3-position double bonds and subsequent ring fission (Braune et al., 2001). Phloretin hydrolase from E. ramulus strain wK1 hydrolytically cleaves the C-C bond, which is adjacent to the aromatic A-ring of phloretin to 3-(4-hydroxyphenyl)-propionic acid and chlorogluconol (Schoefer et al., 2004; Braune et al., 2019). E. cellulolytica ATCC 43171 may contribute to the deglycosylation of flavonoid O- and C-glycosides (luteolin 6-C-glucoside and apigenin 6-C-glucoside) through the fermentation of the liberated glucose portion. The deglycosylation of C-glycosides is exclusively catalyzed by bacterial enzymes (Braune and Blaut, 2012; Braune et al., 2016). Eubacterium L-8 hydrolyzed terpenoid glycyrrhizin (GL) to 18β-glycyrrhetinic acid (18β-GA; Kim et al., 2000). 18β-GA prevents OVA-induced airway allergic inflammation by inhibiting NF-κB phosphorylation and enhancing the Nrf2/HO-1 pathway (Liu et al., 2022). These metabolic transformations provide more information about the diverse array of benefits that humans derive from Eubacterium spp. However, further in vivo studies are necessary to maximize the potential benefits the Eubacterium genus has to offer.

**Lactobacillus**

The genus Lactobacillus belongs to the phylum Firmicutes, which can balance the micro-community and protect gastrointestinal mucosa (Dempsey and Corr, 2022). Some Lactobacillus species are rich in metabolic enzymes, such as α-rhamnosidas, tannase, galate decarboxylases, etc. and they transform exogenous substances (Reverón et al., 2017; Li B.C. et al., 2019; Ferreira-Lazarte et al., 2021). L. rhamnosus NCTC 10302, which has both β-glucosidase and α-rhamnosidase activities, converts hesperetin-7-O-rutinoside and naringenin-7-O-rutinoside to their respective aglycones and 3-(phenyl) propionic acid by hydrolysis, ring fission, and dehydroxylation (Pereira-Caro et al., 2018). L. plantarum expresses tannase to hydrolyze galate, protocatechuate esters with a short aliphatic alcohol substituent, and complex galactannins to produce gallic acid (Jiménez et al., 2014). Gallic acid (11.5–46 μg/ml) plays a protective role in LPS-induced inflammation and oxidative stress by inhibiting the MAPK/NF-κB pathway and activating the Akt/AMPK/Nrf2 pathway (Tánaka et al., 2018). Fang et al. observed that gallic acid and pyrogallol are produced by the degradation of galactannins by galactannin-metabolizing enzymes in L. plantarum WCFS1. This study implies the potential role of prebiotic-probiotic interactions in the prevention of diet-induced metabolic disorders (Reverón et al., 2015; Fang et al., 2019). Daidzein is reduced to dihydrodaidzein by Lactobacillus sp. Niu-O16 with daidzein reductase activity (Wang et al., 2007; Heng et al., 2019). Dihydrodaidzein (2.5–5 μM) inhibits NF-κB activation and MAPK phosphorylation, thereby improving osteoporosis (Kim et al., 2019). L. casei, L. plantarum, and L. acidophilus highly influence the deglycosylation of piceicid to resveratrol (Basholli-Salihu et al., 2016). This conversion is important for increasing the bioavailability and bioactivity of piceicid. Feruloyl esters from L. reuteri, L. helveticus, and L. fermentum hydrolyze chlorogenic acid to release caffeic acid (Aguirre Santos et al., 2018). These findings open a new perspective on the role of Lactobacillus in health-promoting pharmaceutical and food product applications. However, the underlying transformation mechanism deserves further study.

**Bacteroides**

Members of the genus Bacteroides are Gram-negative obligate anaerobes, which account for 25% of the total bacteria in the colon and play multiple roles in the human gut bacteriome (Zafar and...
Saier, 2021). Bacteroides species such as B. fragilis, B. distasonis, B. ovatus, and B. thetaiotaomicron are commonly detected in the clinic (Wexler, 2007). Bacteroidetes spp. possesses a series of hydrolases and participates in inter-species cross-feeding relationships with their microbial neighbors by converting foreign substances (Sonnenburg et al., 2004; Zafar and Saier, 2021). In vitro co-incubation experiments showed that certain Bacteroides species are involved in the biotransformation of flavonoids. Bacteroides sp. 45 expresses α-L-rhamnosidase and β-rutinosidase for the hydrolysis of rutin into quercetin 3-O-glucoside, quercetin, and leucocyanidin (Yang et al., 2012; Riva et al., 2020; Ferreira-Lazarte et al., 2021). Quercetin 3-O-glucoside is better absorbed than other forms of quercetin and can suppress the inflammatory response in mice with TNBS-induced colitis via the inhibition of the NF-κB and MAPK signaling pathways (Zhang D. et al., 2019). Bacteroides sp. 54 metabolizes quercitrin to hydroxyquercitrin and desmethylquercitrin. Quercitrin is also degraded to quercetin by α-L-rhamnosidase and undergoes further ring-cleavage to yield 3,4-dihydroxybenzoic acid by Bacteroides sp. 45 (Jiang et al., 2014). β-glucuronidase, which is expressed by Bacteroidetes J-37, metabolizes GL to 18β-GA (Kim et al., 1999; Guo et al., 2018). Based on the review of existing studies, natural products are biotransformed under the action of Bacteroidetes to produce metabolites with different functional activities. It is important to understand the whole process of natural products occurring in the body to assess the effect on human health.

**Streptococcus**

The Streptococcus species are Gram-positive, spherical, or ovoid cells, which are usually arranged in chains or pairs and widely exist in human feces and nasopharynx (Lannes-Costa et al., 2021). Meta-transcriptomic analysis indicates that the phosphotransferase system is majorly expressed by Streptococcus, suggesting that these bacteria are the main utilizers of the available carbohydrates in the small intestinal (Zoetendal et al., 2012). Streptococcus LJ-22 expresses β-glucuronidase to metabolize GL to 18β-glycyrrhetinic acid-3-O-β-D-glucuronic acid (GAMG; Kim et al., 2000; Park et al., 2004; Guo et al., 2018). GAMG has anti-inflammatory activity against LPS-induced RAW264.7 cells with IC50 value of 0.28 mM (Park et al., 2004). In addition, tannic acid is degraded by tannase of Streptococcus galolyticus subsp. Galloyticus (SGG) to produce pyrogallol. SGG may contribute to the development of colorectal cancer by eliminating the toxicity of tannic acid to tumor cells (Oehmcke-Hecht et al., 2020). Therefore, further in vivo studies are necessary to determine whether the elimination of these tannic acid-degrading microbes can support the effective treatment of colorectal cancer. S. thermophilus GIM 1.321 has a high production capacity of β-glucosidase for the degradation of fructus anthocyanins into CHA, CAA, and ferulic acid (Cheng J.R. et al., 2016). The administration of CAA and CHA (10/15 mg/kg/day) can lower blood pressure and exert an anti-oxidant effect (Agunloye et al., 2019). Streptococcus strains might be a commensal, pathogenic, and opportunistic pathogen in the gut, and more information is needed about its effect on human health. A better understanding of how Streptococcus metabolizes natural products may allow the regulation of the gut microbiome to improve therapeutic efficacy.

**Blautia**

Blautia species are strictly anaerobic, nonmotile, usually spherical or oval, and widely found in the gut and feces of mammals (Liu X. et al., 2021). There is increasing evidence for the probiotic properties of Blautia on the biotransformation of natural products (Tremaroli and Bäckhed, 2012). In the course of flavonoid biotransformation, the reactions catalyzed by Blautia include demethylation, O- and C- de glucosylation, and C-ring cleavage (Braune and Blaut, 2016), which may be catalyzed by the corresponding enzymes, such as O-glycosidase and β-glucosidases (Braune et al., 2016). Research indicates that the strain Blautia sp. MRG-PMF1 has a hydrolytic ability on aryl methyl ether functional groups by converting 5,7-dimethoxyflavone and 5,7,4-trimethoxyflavone into bioactive chrysin and apigenin, respectively. Blautia sp. MRG-PMF1 also possesses de glycosylation activity, and various isoflavones, flavones, and flavones were found to be metabolized into the corresponding aglycones (Kim et al., 2014). Besides, under anaerobic conditions, Blautia sp. MRG-PMF1 strain metabolizes icariin further to demethylcaritin with estrogenic effects (Wu et al., 2016). The strain can also catalyze curcumin to produce demethoxycurcumin with anti-inflammatory and anti-cancer properties (Burapan et al., 2017a; Hatamipour et al., 2019). In addition, Blautia sp. AUH-JLD56 is capable of solely biotransforming arctiin or arctigenin into demethylated products with better antioxidant capacity (Liu et al., 2013). Recently, a growing academic interest has been witnessed in the biotransformation and metabolism of herbal plants and functional foods by Blautia. Exploring the biotransformation of Blautia is of great significance for the development of new enzymes and bioactive metabolites (Meng et al., 2020).

**Key transformation types involved in natural products microbial metabolism**

Complex microbial enzymes catalyze the metabolism of natural products in the gut, resulting in lipophilic and low-molecule-weight metabolites conducive to host utilization/excretion (Weersma et al., 2020). Unlike human genetics, the gut microbiome is modifiable in terms of characteristics, making it a potential therapeutic target to optimize therapy. After oral natural products enter the digestive tract, they will first come into contact with a large number of gut microbes and the active enzymes produced by them. Therefore, natural products’ gut
bistaturation may occur before the first-pass effect through the liver (Xie et al., 2020). Natural products can be modified/deconjugated by the gut microbiome, and can also be transported to the liver to modify/bind and then excreted into the gut to react with gut microbes to form a series of metabolites (Koppel et al., 2017). The metabolites transformed by the host-microbial co-metabolic system may be functionally novel and not clearly defined. Therefore, the combination of specific strains, specific metabolic pathways, and specific enzymes associated with health/disease is important for the determination of the effect of gut microbes on the host.

Hydrolysis

Certain natural products have high molecular weight and low lipid solubility, and they are difficult to be absorbed by the body in the intestine and have low bioavailability (Hostetler et al., 2017). Through gut microbes-mediated hydrolysis, their physical properties are changed, and their biological activity and bioavailability are greatly improved (Wu and Tan, 2019). Slámová et al. indicated that most glycosides have low activity and are considered “natural prodrugs” (Slámová et al., 2018). After interacting with gut microbes, the sugar groups of glycosides are removed, and then, the aglycone portion is absorbed by intestinal cells to exert physiological effects (Wilson and Nicholson, 2017; Murota et al., 2018). The hydrolysis reaction is required for further transformation, and the products (e.g., sugars) participate in promoting the growth and survival of gut microorganisms (Theilmann et al., 2017). Figure 2 shows the hydrolysis reaction of partial natural products under the action of gut microbes.

Flavonoids

Flavonoids are natural phenolic compounds found abundantly in fruits and vegetables. Gut microbes may be partly responsible for the efficacy of flavonoids (glycoside forms), which have low bioavailability because of the presence of water-soluble sugar components (Murota et al., 2018; Al-Ishaq et al., 2021). Flavanoids with 3-hydroxyflavone base (3-hydroxy-2-phenylchromen-4-one) and planar ring system constitute a significant class of flavonoids. In the study of Du et al.,isorhamnetin-3-O-neohesperidoside was first deglycosylated to isorhamnetin-3-O-glucoside and subsequently to the aglycone isorhamnetin by Escherichia sp. 23 (Du et al., 2017). The gut microbes and derived enzymes (lactase phlorizin hydrolyase) jointly controlled the metabolism of epimedium koreanum nakai-prenylated flavonoids as determined by in vitro assays. In the present study, gut enzymes metabolized flavonoids faster than gut microbes (Zhou et al., 2013). Wu et al. found that α-L-rhamnosidase from Bacteroides thetaiotaomicron VPI-5482 could hydrolyze the α-1.2 glycosidic bond of epimedin C to produce icariside (Wu et al., 2018). β-xilosidase Dt-2,286, which is derived from Dictyoglomus turgidum, is highly active in hydrolyzing xylene and glucose groups in epimedium B to obtain baohuoside I and sagittatose B (Tong et al., 2021). Flavanones have a 2,3-dihydro-2-phenylchromen-4-one structure. Hesperidin is converted to its active form hesperetin by α-L-rhamnosidase, which is expressed by B. pseudocatenulatum (Mas-Capdevila et al., 2020). Isoflavones are mainly found in legumes. B. breve MCC1274 possesses the highest β-glucosidase activity for the conversion of daidzin to daidzein (Yao et al., 2019). The anthocyanin cyanidin 3-glucoside is converted to cyanidin by E. ramulus and Clostridium saccharogumia (Hanske et al., 2013). Human gut enzymes such as β-glucuronidase play a key role in the hydrolysis of wogonoside to its aglycone form wogonin (Xing et al., 2014). Theasinensin A, a bioactive catechin dimer found in black tea, is degalloylated to yield theasinensin C by human fecal microbiota (Liu Z. et al., 2021). In the present study, we observed the metabolic differences in flavane-3-ols, and the results suggest that steric hindrance may limit the degradation of partial flavane-3-ols C-ring by bacterial enzymes during gut microbial fermentation. Many other flavonoids can also undergo hydrolysis reactions under the action of gut microbes, as shown in Table 1. Notably, considering the structural differences of flavonoids, the degree of degradation of flavonoids by gut microbes varies greatly, thus affecting their bioaccessibility. Further efforts are required to investigate the role of gut metabolism in the bioavailability and absorption of flavonoids and the possible bacteria-flavonoid interaction activities.

Terpenoids

Terpenoids are the largest class of natural products with anticancer, anti-inflammatory, and neuroprotective effects (Agatonovic-Kustrin et al., 2020; El-Baba et al., 2021). Part of terpenoids can also be hydrolyzed by gut microbes. Geniposide produces genipin with the action of β-glucosidase expressed by Eubacterium sp. A-44 (Ako et al., 1994; Jiang et al., 2016). Paenoniflorin is transformed into PM-I under the action of β-glucosidase, which is expressed by L. brevis and B. fragilis (Abdel-Hafez et al., 1999; He et al., 2007). By incubating with rat anaerobic gut microbiota, paenoniflorin is also deglucosed and dephenyled into albiflorin and acyl albiflorin with a small molecular weight (Ke et al., 2016). Peng et al. demonstrated that several Bifidobacteria species with esterase can hydrolyze albiflorin to benzoic acid in vitro (Peng et al., 2022). In vitro study shows that asiasic acid is gradually deglycosylated by glycoside bond hydrolyase and produces corresponding aglycones (Weng et al., 2006). Saikosaponin B1 is gradually hydrolyzed to prosaikogenin and saikogenin A under the action of β-glucosidase and β-D-fucosidase, which are expressed by Eubacterium sp. A-44 (Kida et al., 1998). Except for the compounds mentioned above, terpenoids ginsenoside Rh2 (Guo et al., 2019), aridipusillosides I (Cao et al., 2015), mogroside III (Yang et al., 2007), and pedunculoside (Wu et al., 2019) can also undergo hydrolysis reactions under the action of gut microbes (Table 1). Therefore, gut microbes play an important role in terpenoid metabolism, and
the effects of their metabolites on gut microbiome and human health need to be further studied.

Other compounds

Ellagitannins, which have a very low bioavailability perform a pharmacological role only when it is hydrolyzed into derivatives such as ellagic acid and urolithis under the action of tannase from 
*Gordonibacter urolithinfaciens*, *Gordonibacter pamelaeae*, and *Ellagibacter isourolithinifaciens* (Beltrán et al., 2018; García-Villalba et al., 2020; Tang et al., 2021). The anthraquinone glycosides extracted from rhubarb are hydrolyzed into anthraquinone aglycones by gut microbes (Li Q. et al., 2020). Sennoside A, a major component of rhubarb extract, is metabolized into rhein anthrone by β-glucosidase of *Bifidobacterium* sp. strain SEN (Matsumoto et al., 2012; Kon et al., 2014). Under the action of carboxylesterase (CEs), which are expressed by gut microbes, diester diterpenoid alkaloids (DDAs, such as aconitine) hydrolyze the ester bonds of C-8 and C-14 to produce monoester diterpene alkaloids (MDAs, such as hypaconitine), which are less toxic (Zhang et al., 2015). *Pulsatilla Chinensis* is commonly used in Asia, and its major saponin anemoside B4 can be degraded by gut microbes to produce deglycosylation products (Wan et al., 2017). Table 1 shows that the alkaloids scopolamine (Wu et al., 2019), steroid compound pulsatilla saponin D (Yan et al., 2018), and cycasin (Goldin, 1990) undergo hydrolysis reactions under the action of gut microbes. The hydrolysis reaction is an important step in the metabolism of natural products by gut microbes and is required for the expression of biological activity and further biotransformation. The specific microorganisms and enzymes involved in this reaction should be focused on to fully understand the ultimate fate of natural products and their impact on human health and provide a basis for personalized treatment.

Methylation and demethylation

Gut microbes can express transferases and move functional groups between the two substrates through nucleophilic substitution reactions (Koppel et al., 2017). The addition of methyl...
| Classification | Gut microbiota | Enzyme | Substrate | End-product | Changes | Ref. |
|----------------|----------------|--------|-----------|-------------|---------|------|
| Flavonoid glycosides | *E. coli* HGU-3; *L. brevis* RO1 | β-glucuronidase | Baicalin; oroxylin A | Bioavailability↑ anti-inflammation↑ | Yim et al. (2004), Trinh et al. (2010) and Han et al. (2016) |
| | *E. coli* ATCC 43171 | β-glucosidase | Luteolin 7-O-glucoside; apigenin 7-O-glucoside | Bioavailability↑ | Braune and Blaut (2012) and Braune et al. (2016) |
| | *E. coli* ATCC 43171 | NA | Luteolin 6-C-glucoside; apigenin 6-C-glucoside | Bioavailability↑ | Braune and Blaut (2012) and Braune et al. (2016) |
| | Human gut microbes | β-glucuronidase | Wogonoside | Bioavailability↑ anti-inflammation↑ | Xing et al. (2014) |
| | Bacteroides JV-6; *Fusobacterium* | β-glucosidase | Rutin | Anti-oxidant↑ | Riva et al. (2020) and Ferreira-Lazarte et al. (2021) |
| | *E. coli* sp. 23 | β-glucosidase |isorhamnetin-3-O-neohesperidoside | Bioavailability↑ anti-inflammation↑ | Du et al. (2017) |
| | Rat gut microbes; *B. thetaiotaomicron* VPI-5482 | β-glucosidase | Epimedin A, B, C | Anti-osteoporosis↑ | Cui et al. (2013), Cui et al. (2014) and Wu et al. (2018) |
| | *Dictyoglomus turgidum* | β-xyllosidase Dt-2,286 | Epimedium B | Anti-osteoporosis↑ | Tong et al. (2021) |
| | *B. animalis* subsp. *lactis* AD011 | β-glucosidase | Kaempferol-3-O-sophoroside | Anti-aging↑ | Shimojo et al. (2018) |
| | *Lactobacillus paracasei* A221 | β-glucosidase | Astilbin | Cardiovascular protection↑ anti-tumor↑ anti-inflammatory↑ | Zhao et al. (2014) and Zhao et al. (2021) |
| | *Enterococcus* sp. 8B, 8-2,9-2 | β-glucosidase | Taxifolin | Anti-tumor↑ | Youn et al. (2012) |
| | Human gut microbes; *B. pseudocatenulatum* | α-L-rhamnosidase; β-glucosidase | Hesperidin | Anti-oxidant ↑ anti-inflammatory ↑ | Mas-Capdevila et al. (2020) |
| | Rat gut microbes | β-glucosidase | Calycosin-7-O-β-D-glucoside | Neuroprotection↑ anti-oxidant ↑ | Ruan et al. (2015) |
| | *E. ramulus*; *B. breve* MCC1274 | β-glucosidase | Daidzin | Neuroprotection↑ | Mace et al. (2019) and Yao et al. (2019) |
| | *Dorea species* PUE | C-deglycosylation enzymes (DgpB-C) |3″-oxo-puerarin | Bioavailability↑ | Nakamura et al. (2020) |
| | *E. ramulus*; *Clostridium saccharogumia* | β-glucosidase | Cyanidin 3-glucoside | Bioavailability↑ | Hanske et al. (2013) |
| | Human gut microbes | C-C glucosyl-cleaving enzyme | Thaseminens A | Bioavailability↑ | Liu Z. et al. (2021) |
| | *Bacillus* sp. KM7-1; *Bacteroides* sp. MANG | β-glucosidase | Mangiferin | Anti-cancer ↑ anti-diabetes↑ | Hasanah et al. (2021) |

(Continued)
| Classification | Gut microbiota | Enzyme | Substrate | End-product | Changes | Ref. |
|----------------|----------------|--------|-----------|-------------|---------|------|
| Terpenoids     | Eubacterium, sp. A-44 | β-glucosidase, carboxylesterases | Geniposide | Genipin; geniposidic acid | Bile secretion† anti-hepatitis† | Akao et al. (1994), Jang et al. (2016) and Tian et al. (2013) |
| B. fragilis, L. brevis, rat gut microbes | β-glucosidase | Paeoniflorin | PM-I; albiflorin and its aglycone; Deacetyl-paeonifloridin | Anti-convulsant† Bioavailability† | He et al. (2007) and Ke et al. (2016) |
| Rat gut microbes | Glycoside hydrolases | Asiaticoside | Corresponding aglycones | Bioavailability† | Weng et al. (2006) |
| Eubacterium sp. A-44 | β-glucosidase; β-D-fucosidase | Saikosaponin B1 | Prosaka genin; sakogenin A | Anti-inflammatory† Anti-oxidant† | Kida et al. (1998) |
| Eubacterium L-8; Bacteroidetes L-37; Streptococcus LJ-22 | β-glucuronidase | GL | 18β-GA; GAMG | Anti-platelet aggregation† anti-allergic† anti-tumor† anti-bacterial† | Kim et al. (1999), Kim et al. (2000), Park et al. (2004) and Guo et al. (2018) |
| Eubacterium sp. A-44; B. breve ATCC 15700 | β-glucosidase | Ginsenoside Rh2 | Ginsenoside F3 compound K | Bioavailability† | Zhong et al. (2016), Zhang R. et al. (2019) and Kim (2018) |
| B. breve; B. longum | Esterases | Albiflorin | Benzoic acid | Anti-depression† | Zhao et al. (2018) and Peng et al. (2022) |
| Human/rat gut microbes | β-glucosidase; α-L-rhamnosidase | Ardispasilloses I | Deglycosylated product | Bioavailability† | Cao et al. (2015) |
| Human gut microbes | NA | Mogroside III | Mogroside II mogrol | Bioavailability† | Yang et al. (2007) |
| B. adolescentis, B. breve | NA | Pedunculoside | Deglycosylated products | Bioavailability† | Wu et al. (2019) |
| Rat gut microbes | NA | Capilliposide C | Deglycosylated products esterolysis products | Bioavailability† | Cheng Z. et al. (2016) |
| Anthraquinones | Bifidobacterium sp. strain SEN | β-glucosidase | Sennoside A and B | Sennidin A/B-8-monoglucoside | Purgation† | Matsumoto et al. (2012) |
| Alkaloids Phenols | Human gut microbes | CEs | DDAAs | MDAAs | Toxicity† Anti-tumor† anti-inflammatory† | Zhang et al. (2015) and Dey (2019) |
| Rat gut microbes | NA | Scopolamine | Scopine | Anti-tumor† anti-inflammatory† | Jiménez et al. (2014) |
| L. plantarum | Tannase | Gallic tannins | Gallic acid | Anti-oxidant† anti-inflammatory† | Luca et al. (2020) |
| Akkermansia muciniphila | Tannase | Ellagittannins | Ellagic acid | Neuroprotection† | |
| Rat gut microbes | β-glucosidase | Amygdalin | Mandaedinitrile; prunasin; phenylacetonitrile; hydrogen cyanide | Toxicity† | Kim et al. (2008) and Qin et al. (2021) |
| B. animalis | Feruloyl esterase | CHA | CAA | Anti-oxidant† | Raimondi et al. (2015) |
| L. plantarum; L. johnsonii; L. acidophilus | Feruloyl esterases | CAA; p-coumaric acids | ferulic acid | Anti-oxidant† | Fritsch et al. (2017) |
| E. coli Nu; E. coli MC; E. coli WC-1 | Cinnamyl esterase | Conjugated hydroxycinnamates | Free hydroxycinnamates | Anti-oxidant† anti-cancer† | Couteau et al. (2001) |
to exogenous substances by gut microbes requires chemically activated co-substrates, such as acetyl coenzyme A, adenosine triphosphate, or S-adenosylmethionine, while demethylation requires cofactors that can undergo nucleophilic catalysis, such as COB (I) alamin, and tetrahydrofurfurato (Kumano et al., 2016). Methylation modification can optimize the physiological activity of natural products, and demethylation can release polar groups for further binding and excretion from the body, and provide a carbon source for the growth of gut microbes (Ticak et al., 2014). Figure 3 shows the methylation and demethylation of natural products under the action of gut microbes.

### Flavonoids

The flavonoid modification can be carried out at the C-2, C-3, C-4, C-5, C-6, C-7, and C-8 positions in the structure of flavonoids, and the bioavailability of methylated flavonoids is greatly improved (Wen and Walle, 2006). Bernini et al. found that O-methylated flavonoids have remarkable anti-inflammatory and resistance to hepatic metabolism (Bernini et al., 2011; Choi, 2019). After oral administration of rutin in rats, many methylated metabolites, such as methylrutin, methylisoorientin, and methylquercetin sulfate, are detected in fecal samples (Yang et al., 2012; Wu et al., 2017; Riva et al., 2020). Methoxylated isoflavonoids formononetin and biochanin A undergo demethylation to produce daidzein and genistein under the action of E. limosum ATCC 8486 (Hur and Rafii, 2000). Isoxanthohumol yields demethylation products 8-prenylnaringenin by E. limosum (Paraiso et al., 2019). Hesperidin, hesperetin (Pereira-Caro et al., 2018; Jiao et al., 2020), 5,7-dimethoxyflavone, xanthohumol (Paraiso et al., 2019), and 5,7,4′-trimethoxyflavone (Kim et al., 2014) can also undergo demethylation reactions under the action of gut microbes (Table 2).

### Alkaloids

Alkaloids are nitrogen-containing compounds, which are biosynthesized by both marine and terrestrial organisms, and they have anti-cancer (Tse et al., 2022) and anti-viral activity (Aboukleesh et al., 2022). Under the action of enzymes expressed by gut microbes, quassin ketone, the main alkaloid component in bitter wood, is methylated into quassic alkali butyl (Fan et al., 2013; Chen et al., 2021). Isoquinoline alkaloid palmatine yields demethylation products such as columbamine, jatrorrhizine, demethyleneberberine, and demethyleneberberine via in vitro anaerobic incubation (He et al., 2017; Liao et al., 2021). The demethylation of aconitine by gut microbes is demonstrated by ion trap electrospray ionization tandem mass spectrometry, and 16-O-demethyloaconitine is produced (Zhao et al., 2008; Zhang et al., 2017).

### Lignans

Dietary lignans are phytoestrogens that are mostly found in seeds, nuts, legumes, and vegetables. Arctiin can be demethylated to (−)-dihydroxyenterolactone (DHENL) and other products by Eubacterium sp. ARC-2 strain (Jin et al., 2007, 2013; Seyed Hameed et al., 2020). Liu et al. isolated a bacterium named Blautia sp. AUH-JLD56 from human fecal bacteria, and this species could efficiently transform arctiin or arctigenin into a demethylation metabolite 3′-desmethy lacorticigenin (3′-DMAg; Liu et al., 2013). Secoisolariciresinol, which is one of the most common lignans found in flaxseed, can be demethylated in the presence of Blautia producta, Gordonibacter and Lactonifactorlongoviformis to form enterolactone and enterodiol (Bess et al., 2020; Tse et al., 2022). Sesamin is metabolized into mammalian lignan enterolactone and enterodiol through methylation, demethylation, and other reactions by gut microbes (Peñañó et al., 2005). Matairesinol and phillygenin can also be demethylated to produce enterolactone (Clavel et al., 2006; Yamawaki et al., 2011; Michalak et al., 2018). Silybin A and B are demethylated into demethylsilybin A and demethylsilybin B by human fecal microbiota (Zheng et al., 2014; Valentová et al., 2020).

### Other compounds

Polyphenol compound curcumin is demethylated by Blautia sp. MRG-PMF1 to produce metabolites demethoxycurcumin (DMC) and bis-demethoxycurcumin (bDMC; Burapan et al., 2017a,b). The demethylated products of dihydro-isoforolic acid, such as dihydrocaffeic acid, are also obtained in fecal metabolites (Kay et al., 2017). Wang et al. found that the methylation reaction occurs at the internal and external glucuronic acid residues of the licorice saponin 22β-acetyl glycyrrhizin sugar chain, yielding 22β-acetoxy glycyrrhizin-6′-methyl ester (Wang et al., 2015). Compounds such as polyphenols danshensu (Gu et al., 2014), terpenoids genipin (Akao et al., 1994), stilbenoids thunbarene (Jarošova et al., 2019), and steroids pulsatilla saponin B3 (Liu et al., 2015) undergo methylation and demethylation under the action of gut microbes, as shown in Table 2. Methylation and demethylation reactions are important pathways of gut microbiol metabolism, and have been confirmed in many studies. However, the genes/enzymes that mediate this reaction have not been fully characterized.

### Redox reaction

Gut microbes can express many oxidoreductases and transform natural compounds by adjusting various functional

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**TABLE 1 (Continued)**

| Classification | Gut microbiota     | Enzyme         | Substrate                                      | End-product                          | Changes                           | Ref.          |
|---------------|--------------------|----------------|-----------------------------------------------|--------------------------------------|----------------------------------|--------------|
| Steroids      | Human gut microbes | NA             | Pulsatilla saponin D                          | Corresponding deglycosylation products | Bioavailability†                  | Yan et al. (2018) |
| Other         | Mouse gut microbes | β-glucosidase   | Cycasin                                       | Diazomethane                         | Toxicity†                         | Goldin (1990) |
groups, such as olefins, carboxylic acid derivatives, nitro, N-oxides, and a, b-unsaturated carboxylic acid derivatives, which influence the activity of natural products in vivo (Lavrijsen et al., 1995; Haiser et al., 2013; Abookleesh et al., 2022). Various cofactors such as NADH, NADPH, flavin, Fe/S cluster, heme, and molybdenum cofactor are involved in the mediation of the transfer of electron or hydride equivalent (H+, 2e−) to the substrate (Vanoni, 2021; Lubner et al., 2022). Figure 4 shows the oxidation and reduction reactions of natural products under the action of gut microbes.

**Flavonoids**

Daidzein is reduced to dihydrodaidzein and further tetrahydrodaidzein under the action of Clostridium sp. strain HGH6 and Lactobacillus sp. Niu-O16 (Zhao et al., 2011; Heng et al., 2019). The reduced product dihydrogenistein is produced by genistein under the action of human fecal bacteria (Mace et al., 2019). By using UPLC-ESI-Q-TOF-MS/MS analysis, compounds such as the deoxidized metabolites kaempferol and the C2-C3 double bond hydrogenation reduction product taxifolin were identified in the culture solution of rat gut fluid by incubation with quercetin under anaerobic conditions (Qin et al., 2017). Yang et al. discovered a flavone reductase from Flavonifractor plautii ATCC 49531, and this enzyme specifically catalyzes the hydrogenation of the C2-C3 double bond of flavones/flavanols C-ring and acts during the initial step of the entire biodegradation pathway of flavonoid (Goris et al., 2021; Yang et al., 2021). O-desmethylxanthohumol, a chalcone compound, is reduced to O-desmethyl-α, β-dihydroxanthohumol by E. ramulus (Paraiso et al., 2019).

**Alkaloids**

Nitroreductase, which is produced by gut microbes, catalyzes ether and coordination bond reactions in alkaloids.
| Classification | Gut microbiota | Enzyme | Substrate | End-product | Changes | Ref. |
|----------------|----------------|--------|-----------|-------------|---------|------|
| Flavonoids     | Rat gut microbes | Methyltransferase | Rutin | Methylrutin, Methyl-isoquercetin, methylquercetin sulfate | Bioavailability↑ | Wu et al. (2017) |
| Mice gut microbes | NA | Myricetin | Myricetin | Monol- and dimethylated myricetin | Toxicity↓ | Zhang et al. (2020) |
| Rat gut microbes | NA | Hesperidin; hesperetin | Demethylated products | Bioavailability↑ | Pereira-Caro et al. (2018) and Jiao et al. (2020) |
| E. limosum | O-demethylase | Formononetin; biochanin A | Daidzein; genistein | Estrogen effect↑ | Hur and Rafii (2000) |
| Blautia sp. MRG-PMF1 | Methyltransferase | 5,7-dimethoxyflavone; 5,7,4′-trimethoxyflavone | Chrysin; apigenin | Anti-oxidant↑ anti-inflammatory↑ anti-cancer↑ | Kim et al. (2014) |
| Blautia sp. MRG-PMF1 | Methyltransferase | Icariin | Desmethylicaritin | Estrogenic effects↑ | Wu et al. (2016) |
| E. limosum | O-demethylase | Isoxanthohumol | 8-prenylnaringenin | Anti-androgen↑ anti-osteoporosis↑ | Paraizo et al. (2019) |
| Alkaloids | Human gut microbes | Methyltransferase | Quassic ketone | Quassic alka butyl | Chen F.Z. et al. (2021) |
| Rat gut microbes | Methyltransferase | Palmatine | Columbinine; Jatrorrhizine; demethyleneberberine | Bioavailability↑ | He et al. (2017) and Liao et al. (2021) |
| Human gut microbes | O-demethylase | Aconitine | 16-O-demethylaconitine | Toxicity↓ | Zhao et al. (2008) and Zhang et al. (2017) |
| Lignans | Enterobacter sp. ARC-2; Blautia sp. AUH-ILD56 | O-demethylase | Arctin; arctigenin | DHENL; 3′-DMAG | Anti-oxidant↑ estrogen effect↑ | Jin et al. (2007), Jin et al. (2013), Liu et al. (2013) and Seyed Hameed et al. (2020) |
| Blautia producta DSM3507; Gordonibacter strains 3C and 28C; Lactonifactor longoforma DSM17459 | Guaiacol lignan methyltransferase; catechol lignan dehydroxylase; enterodiol lactonizing enzyme | Secoisolaricitresinol | Enterolactone; enterodiol | Estrogen effect↑ | Bess et al. (2020) and Tse et al. (2022) |
| Human gut microbes | O-demethylase | Sesamin | Enterolactone; enterodiol | Estrogen effect↑ | Peñalvo et al. (2005) |
| Rat gut microbes | O-demethylase | Mataresinol | 2,3-bis(3,4-dihydroxybenzyl) butyro lactone; enterolactone | Anti-inflammatory↑ estrogen effect↑ | Clavel et al. (2006), Yamawaki et al. (2011) and Michalak et al. (2018) |
| Human/rat gut microbes | O-demethylase | Phillygenin | Enterolactone | Anti-inflammatory↑ estrogen effect↑ | Michalak et al. (2018) |
| E. limosum ZL-II; human gut microbes | O-demethylase | Silybin A and B | Demethylsilybin A; demethylsilybin B | Anti-Alzheimer's disease↑ | Zhang et al. (2014) and Valentová et al. (2020) |
| Diketones | Blautia sp. MRG-PMF1 | Co O-Methyltransferase | Curcumin | DMC; bDMC | Anti-tumor↑ anti-inflammatory↑ | Burapan et al. (2017a,b) |
| Phenols | Rat gut microbes | NA | Danshensu | 3-(3-O-methyl-4-hydroxyphenyl)-2-hydroxypropanoic acid | Bioavailability↑ | Gu et al. (2014) |

(Continued)
Berberine (BBR), as the main component of *Coptis Chinensis*, can be reduced to dihydroberberine (dhBBR) by nitroreductase expressed by gut microbes, and this reduction product has high polarity. dhBBR could be absorbed in the intestine and then oxidized into the prototype BBR into the blood. The absorption rate of dhBBR in the intestine is five times that of BBR.
BBR (Feng et al., 2015). Li et al. found that the gut microbes could transform BBR into oxyberberine via oxidation (Li et al., 2020). Oxyberberine, a novel metabolite of BBR, may be a promising bioactive agent worthy to be explored. Coptisine is a natural protoberberine alkaloid with the same maternal structure as BBR. After oral administration of coptisine, the C-O bond is opened and cracked, followed by a reduction reaction to produce hydrogenated BBR (Cui et al., 2018). Avenanthramide-C is reduced by mice and the human gut microbiota into dihydroavenanthramide-C (Wang et al., 2015).

Phenylpropanoids

Caffeic acid (CAA), as the main dietary polyphenol in food and beverage, can easily enter the colon and react with gut microbiota after esterification. CAA is transformed to 3-hydroxyphenylpropionic acid through C4 double bond reduction and dehydroxylation, and then rapidly converted to 3-phenyl propionic acid via the β-oxidation of gut microbes in vitro (Gonthier et al., 2006). CAA can also be dehydroxylated to m-coumaric acid or hydrogenated to dihydrocaffeic acid (Garcia-Villalba et al., 2020). Danshensu, the major monomer phenolic acid of Salvia Miltiorrhiza, undergo dehydrogenation and deoxygenation by gut microbiota to produce 3-phenyl-2-hydroxy propionic acid, 3-(3,4-dihydroxy phenyl) 2-acrylic acid (caffeic acid), and 3-3-(3,4-dihydroxy phenyl)-propionate (Gu et al., 2014).

Other compounds

Glycyrrhizic acid generates 3-oxo-glycyrrhetinic acid by 3β-hydroxysteroid dehydrogenase of Ruminococcus sp. pol-3 in the cecum. Sennosides, a class of natural anthraquinone derivative and dimeric glycosides, are first hydrolyzed by β-glucosidase to produce sennoside-8-O-monoglycoside, and then reduced to rubaranthrone with purgative effect by Streptococcus in vivo (Hattori et al., 1988). Stilbenoids resveratrol is reduced to dihydroresveratrol by Slackia equalifaciens and Eggerthella lenta ATCC 4305 (Bode et al., 2013; Pallauf et al., 2019). Moreover, diketones curcumin (Hassaninasab et al., 2011; Tan et al., 2014), steroid compounds digoxin (Kumar et al., 2018) and other compounds aristolochic acid (Feng et al., 2019) can also be reduced in the presence of gut microbes (Table 3). Gut microbial flavone reductase and nitroreductase have special catalytic selectivity, filling key gaps in gut microbial transformation pathways. However, the specific genes and enzymes that mediate gut microbial reduction have not been fully determined.

Other reactions

As shown in Table 4, natural products are also transformed by gut microbes through ring fission, sulfuration, aromatization, and other reactions. Gentiopicroside, a natural iridoid glycoside, can be hydrolyzed to gentianaldehyde by gut microbial β-glucosidase, and then to nitrogen-containing compounds via N-heterocyclic reaction (el-Sedawy et al., 1989). The partial ring-opening of genipin acetone alcohol results in the formation of dialdehyde by gut microbes (Kang et al., 2012). Quinic acid can be aromatized to hippuric acid (Feng et al., 2015). Oxyberberine, a novel metabolite of BBR, may be the primary hydrolytic enzymes that mediate gut microbial reduction have not been fully determined.

This section summarizes the biotransformation of gut microbiota-mediated natural products from a single reaction. However, some limitations are observed. Firstly, considering the complexity of gut microbes and the diversity of gut microbial enzymes, natural products undergo complex transformations in the enormous metabolic potential of various gut microbiomes. The gut microbial metabolism of natural products and their role in host health should be the focus of future research.
the intestinal tract. A single reaction can only describe a certain process of metabolism. Therapy can be optimized by activating/inhibiting this process. In addition, considering that gut microbes contain various potentially multifunctional enzymes, more biotransformation reactions underplayed by natural products can be expected from gut microbes. To elucidate how gut microbial metabolism affects human health, researchers should link the functions of interest to genes and enzymes. A deep understanding

| Classification | Gut microbiota | Enterobacterial metabolic enzyme | Substrate | End-product | Changes | Ref. |
|----------------|----------------|----------------------------------|-----------|-------------|---------|------|
| Flavonoids     | Clotridium sp. strain HGH6; Lactobacillus sp. Niu-O16 | Dihydrodaidzein reductase; tetrahydrodaidzein reductase | Daidzein | Dihydrodaidzein; tetrahydrodaidzein | Anti-osteoporosis† | Wang et al. (2007) and Heng et al. (2019) |
|                | Aceoto Niu-O16 | NA | Genistein | Dihydrogenistein | Bioavailability† | Mace et al. (2019) |
|                | Rat gut microbes <i>E. ramalus</i> | Flavone reductase | Quercetin | Kaempferol, taxifolin | Bioavailability† | Qiu et al. (2017) |
|                | <i>E. ramalus</i> | Flavanone/-flavanonol-cleaving reductase | Xanthohumol; O- desmethylxanthohumol | α, β-dihydroxanthohumol; O-desmethyl-α, β-dihydroxanthohumol | Anti-bacterial† | Paraiso et al. (2019) |
| Alkaloids      | Mouse gut microbes | Nitroreductase | BBR, coptisine | dhBBR; hydrogenated berberine | Bioavailability† | Feng et al. (2015) and Cui et al. (2018) |
|                | Mouse gut microbes | NA | BBR | Onyberberine | Anti-fungal† | Li C. et al. (2020) |
|                | Mouse/human gut microbes | NA | Avenanthramide-C | Dihydroavenanthramide-C | Anti-inflammation† anti-atherogenesis† | Wang P. et al. (2015) |
| Phenolic acids | Human gut microbes | NA | CAA | Dihydrocaffeic acid | Bioavailability† | Gonthier et al. (2006) and Garcia-Villalba et al. (2020) |
|                | Rat gut microbes | NA | Isoferulic acid | Dihydrocaffeic acid | Anti-oxidant† anti-apoptosis† | Gu et al. (2014) |
|                | Rat gut microbes | NA | Dansensu | 3-phenyl-2-hydroxy propionic acid; 3-(3,4-dihydroxy phenyl)-2-acrylic acid; 3-(3,4-dihydroxy phenyl)-propionate | Bioavailability† | Gu et al. (2014) |
|                | Gordonibacter urolithinfaciens | Catechol-dehydroxylase | Chlorogenic acid; rosmarinic acid | Dihydro-chlorogenic acid; dihydro-rosmarinic acid | Bioavailability† | Garcia-Villalba et al. (2020) |
| Terpenoids     | <i>Ruminococcus sp. po1-3</i> | β-3-hydroxysteroid dehydrogenase | Glycyrretinic acid | 3-oxo-glycyrretinic acid | Anti-inflammatory† | |
| Anthraquinone  | Human gut microbes; <i>Streptococcus spp.</i> | NA | Senosside-8-O-monglycoside | Rhubaranthrone | Purgation† | Hattori et al. (1988) and Matsumoto et al. (2012) |
| Stilbenes      | <i>Slakia equilabilis, Eggerthella lenta</i> ATCC 4305 | NA | Resveratrol | Dihydroresveratro | Anti-oxidant† | Jung et al. (2009), Bode et al. (2013) and Pallaf et al. (2019) |
| Diketones      | <i>E. coli strain K-12, E. fergusonii ATCC 35469, E. coli strains ATCC 8739 and DH10B</i> | CurA | Curcumin | DHC, THC | Anti-oxidant† lipid-lowering† | Hassaninasab et al. (2011) and Tan et al. (2014) |
| Steroids       | Eubacterium lenta | Cardiac glycoside reductase | Digoxin | Dihydrodigoxin | Bioavailability† | Kumar et al. (2018) |
| Other classes  | Human gut microbes | NA | Aristolochic acid | Aristololactams | Anti-cancer† | Feng et al. (2019) |
TABLE 4 Other reactions of gut microbes to natural products.

| Classification | Gut microbiota | Biotransformation | Enterobacterial metabolic enzyme | Substrate | End-product | Changes | Ref. |
|----------------|----------------|-------------------|--------------------------------|-----------|------------|---------|------|
| Terpenoids     | Human gut microbes | Cyclization | β-glucosidase | Gentispicroside | Gentisaldehyde; nitrogen-containing compounds | Anti-inflammatory† | el-Sedawy et al. (1989) |
| Human gut microbes | Cyclization | NA | Geniposide | Nitrogen-containing compounds | Bioavailability† | Kawata et al. (1991) |
| Human gut microbes | Deglycosylation; deacetylation; dehydrogenation | NA | Astragaloside A | Cycloastragenol | Bioavailability† | He et al. (2019) |
| Phenolic acids | Rat gut microbes | Aromatization | NA | Quinic acid | Hippuric acid | Anti-cancer† anti-bacterial† | Pero and Lund (2011) |
| Egerthella lenta | Dehydroxylation | Catechol dehydroxylases | Dihydrocaffeic acid | 3-(3-hydroxyphenyl) propionic acid | Bioavailability† | Maini Rekdal et al. (2020) |
| Human gut microbes | Ring cleavage; sulfation methylation | NA | Tea polyphenols | Phenolic acids | Bioavailability† | Cheng et al. (2018) |
| L. plantarum WCFS1 | Ring fission; hydrolysis | Tannase; gallate decarboxylase | Gallotannins | Gallic acid; pyrogallol | Anti-oxidant† anti-inflammatory† | Reverón et al. (2015) and Fang et al. (2019) |
| SGG | Ring fission; hydrolysis | Tannase; gallate decarboxylase | Gallotannins | Gallic acid; pyrogallol | Anti-cancer† | Oehmike-Hecht et al. (2020) |
| Gordonibacter urolithinfaciens; Goronibacter pamelaeae; Ellagibacter isourolithinfaciens | Decarboxylation; lactone-ring cleavage; dehydroxylation | NA | Ellagic acid | Urolithins | Anti-cancer† anti-oxidant † anti-inflammatory† | Beltrán et al. (2018), García-Villalba et al. (2020) and Tang et al. (2021) |
| Flavonoids | Rat gut microbes | Sulfation | Aryl sulfotransferase | Luteolin | Luteolin-3′-O-sulfate; luteolin-4′-O-sulfate | | Li et al. (2017) and Káňová et al. (2020) |
| Clostridium sp. strain HGH136 | C-ring fission | 2-dehydro-O-demethylangolensin | Daidzein | O-desmethylangolensin | Anti-cancer† | Hur et al. (2002) |
| Egerthella sp. strain YY7918; B. breve ATCC 15700T; B. longum BBS36; L. paracasei CS2 | Ring-fission | Dihydroidaidzein racemase | Dihydroidaidzein | S-equol | Estrage effect† | Yokoyama and Suzuki (2008) and Mayo et al. (2019) |

(Continued)
| Classification | Gut microbiota | Biotransformation | Enterobacterial metabolic enzyme | Substrate | End-product | Changes | Ref. |
|---------------|---------------|-------------------|---------------------------------|-----------|-------------|---------|------|
| E. ramulus    | Ring-fission, reduction | Chalcone isomerase; flavanone-/flavanonol-cleaving reductase | Naringenin, eriodictyol | Naringenin chalcone; phloretin; 3-hydroxyphloretin | Bioavailability† | Gall et al. (2014) and Braune et al. (2019) |
| E. ramulus strain wK1 | Ring-fission | Phloretin hydrolase | Phloretin | 3-(4-hydroxyphenyl)-propionic acid; phloroglucinol | Bioavailability† | Schoefer et al. (2004) and Braune et al. (2019) |
| Bacteroides sp. 45; B. fragilis; E. ramulus | Ring-fission | Chalcone isomerase; phloretin hydrolase | Quercetin; luteolin | 4-hydroxybenzoic acid; 3,4-dihydroxyphenylacetic acid; 3,4-dihydroxybenzoic; 3-(3-hydroxyphenyl)propionic acid | Anti-platelet aggregation† anti-tumor† | Jiang et al. (2014) and Braune et al. (2001) |
| Rat gut microbes | Ring-fission; sulfation | Chalcone isomerase; phloretin hydrolase | Myricetin | 3,4,5-trihydroxyphenylacetic acid; myricetin-3-O-sulfate | Anti-inflammatory† | Zhang S. et al. (2019) and Káňová et al. (2020) |
| B. longum R0175 | Ring-cleavage; demethylation | Phloretin hydrolase; demethylase | Hesperidin | 3-(3′-hydroxyphenyl)propionic acid; 3-(phenyl)propionic acid | Bioavailability† | Pereira-Caro et al. (2018) |
| Eggerthella lenta; Flavonifractor plautii | C-ring cleavage | NA | (+)-epicatechin; (+)-catechin | 1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol; δ-(31,41-dihydroxyphenyl)-γ-valerolactone; δ-(31,41-dihydroxyphenyl)-γ-valeric acid | Bioavailability† | Ozdal et al. (2016) |
| Human gut microbes | C-ring cleavage | NA | Anthocyanidin | Protocatechuic acid; syringic acid; vanillic acid; phloroglucinol aldehyde | Bioavailability† | Aura et al. (2005) |
| Human gut microbes | C-ring cleavage | Tannase | Procyanidin B2 and A2 | 2- (3,4-dihydroxyphenyl)acetic acid; 5-(3,4-dihydroxyphenyl)-γ-valerolactone; benzoic acid | Anti-oxidant† | Stoupi et al. (2010), Ou et al. (2014) and Le Bourvellec et al. (2019) |

(Continued)
of the gene sequences of functional enzymes allows organisms with similar sequences to be assigned the same biological activity. Moreover, in addition to the regulation of gut microbes on the disposal of natural products, the regulation of natural products on gut microecology is important as a potential mechanism of efficacy.

**Biotransformation contributions to mining the active substance and mechanism**

The increasing research about gut microbiota gradually reveals the relationship between high pharmacological action and low oral availability of most natural products. Most glycosides have complex parent structures and are difficult to be absorbed by the intestine cells, thus limiting their tissue-specific bio-accessibility. These compounds are transformed into small molecule metabolites/unique metabolites through degradation reactions that are dependent on microbial/gut microbial enzymes and thus have a wide range of effects on the host (Wardman et al., 2022). Gut microbes also act on dietary phenolics to produce functional metabolites that contribute to host health (Loo et al., 2020).

Importantly, the biotransformation by gut microbes facilitates the therapeutic effects of natural products. The typical metabolization model of ginsenosides to compound K (CK) has been widely reported (Figure 5), with enhanced anti-tumor, anti-inflammatory, and lipid-lowering effects (Kim et al., 2013; Kim, 2018). At 50 μM, CK inhibits the growth of glioblastoma cells by upregulating caspase-3-, caspase-8-, caspase-9- and cAMP-dependent protein kinases (Lee et al., 2017); At 20 μM, CK reduces hepatic lipid accumulation in human hepatocellular carcinoma cells by activating AMPK (Zhang et al., 2022); CK attenuates macrophage inflammation and foam cell formation via autophagy induction and by modulating NF-κB, p38 and JNK/MAPK signaling (Lu et al., 2020). The chemical stability of DMC increases because of the absence of the methoxyl group in their prototype benzene ring structure, thus explaining the strong beneficial effects of curcumin (Burapan et al., 2017a). Notably, urolithin A (UA), a natural compound that is produced by gut microbes from ingested ellagitannins and ellagic acid, has significant anti-inflammatory and neuroprotective effects. At 1 μM, UA is sufficient for the decreased production of TNF-α and MCP-1 and the inactivation of TLR3/TRIF signaling in poly (I:C)-induced

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**TABLE 4 (Continued)**

| Substrate | Enterobacterial metabolic enzyme | Changes | End-product | Ref. |
|-----------|---------------------------------|---------|-------------|------|
| Alkaloids | [el-Makhsouy et al. (1993)] | Toxicity↓ | Strychnine; 16-hydroxystrychnine | NA |
| Alkoxy | [Bess et al. (2020); Xiao et al. (2021)] | Anti-apoptosis↑ | Lariceal; Lariciresinol; secoisolariciresinol | NA |
| Aldehydes | [el-Makhsouy et al. (1993)] | Anti-oxidant | Quercitin-3-O-rhamnoside; quercitin; aglycone myricetin | NA |

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**TABLE 4 (Continued)**

| Substrate | Enterobacterial metabolic enzyme | Changes | End-product | Ref. |
|-----------|---------------------------------|---------|-------------|------|
| Aliphatics | [Du et al. (2014)] | Anti-apoptosis↑ | Myristic acid | NA |
| Lignins | [Khan et al. (2022)] | Anti-oxidant↑ | Lariceal; lariciresinol; secoisolariciresinol | NA |
| Alkylamines | [Lee et al. (2013)] | Toxicity↓ | Strychnine | NA |
| Anthraquinones | [Wardman et al. (2022)] | Anti-apoptosis↑ | Strychnine; 16-hydroxystrychnine | NA |

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**TABLE 4 (Continued)**

| Substrate | Enterobacterial metabolic enzyme | Changes | End-product | Ref. |
|-----------|---------------------------------|---------|-------------|------|
| Alcohols | [Du et al. (2014)] | Anti-oxidant↑ | Lariceal; Lariciresinol; secoisolariciresinol | NA |
| Aldehydes | [Du et al. (2014)] | Anti-oxidant↑ | Myristic acid | NA |
| Aliphatics | [Du et al. (2014)] | Anti-oxidant↑ | Myristic acid | NA |

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**TABLE 4 (Continued)**

| Substrate | Enterobacterial metabolic enzyme | Changes | End-product | Ref. |
|-----------|---------------------------------|---------|-------------|------|
| Alcohols | [Khan et al. (2022)] | Anti-oxidant↑ | Myristic acid | NA |
| Aldehydes | [Khan et al. (2022)] | Anti-oxidant↑ | Myristic acid | NA |
| Aliphatics | [Khan et al. (2022)] | Anti-oxidant↑ | Myristic acid | NA |

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**TABLE 4 (Continued)**

| Substrate | Enterobacterial metabolic enzyme | Changes | End-product | Ref. |
|-----------|---------------------------------|---------|-------------|------|
| Alcohols | [Khan et al. (2022)] | Anti-oxidant↑ | Myristic acid | NA |
| Aldehydes | [Khan et al. (2022)] | Anti-oxidant↑ | Myristic acid | NA |
| Aliphatics | [Khan et al. (2022)] | Anti-oxidant↑ | Myristic acid | NA |
RAW264.7 cells (Huang et al., 2022). UA improves systemic insulin sensitivity and reduces liver IL-1β levels in high-fat diet mice (Toney et al., 2019). UA ameliorates cognitive impairment in APP/PS1 mice and inhibits neuroinflammation by decreasing the levels of IL-6, IL-1β, and TNF-α in the cortex and hippocampus (Gong et al., 2019). These studies highlight the importance of identifying natural products-microbial metabolism. Moreover, many in vitro pharmacological activity measurements should be performed in conjunction with microbial metabolites, which actually interact with biochemical receptors in vivo.

The composition, structure, function, and metabolites of gut microbes have become potential targets for natural products to exert beneficial effects and reduce toxicity as well. For instance, gut microbes can catalyze the ester bond hydrolysis of C-8 and C-14 of DDAs through CEs or catalyze the ester exchange of C-8 to produce less toxic MDAs (Zhang et al., 2015; Ding et al., 2019). The digoxin-reducing type strains of E. lenta contain cardiac glycoside reductase that can reduce the α and β-unsaturated lactone on the digoxin ring and metabolize it into dihydrodigoxin with less activity, thereby inhibiting its possible cardiotoxicity (Kumar et al., 2018). However, this ability is limited, and 50% of digoxin can be inactivated by gut microbial transformation (Lu et al., 2014). Cardiac glycoside reductase may be an effective biomarker for digoxin inactivation, and its expression can be inhibited by arginine (Haiser et al., 2013). Therefore, diet could explain the inter-individual variations in digoxin reduction and may modulate microbial metabolic activity in vivo. By contrast, toxic compounds can be produced by gut microbes. Cycasin is hydrolyzed into carcinogenicity diazomethane under the action of β-glucosidase from gut microbes (Goldin, 1990). Therefore, small molecule inhibitors of microbial gut enzymes should be developed to play a regulatory role in specific
transformation in this complex habitat. The toxicity difference between metabolites transformed by gut microbiota and precursor substances is worthy of further study. Moreover, excessive drugs may cause imbalance and adverse reactions in gut microbes (Lindell et al., 2022), and the effects of different doses of natural products on gut microbes and metabolism need further investigation.

**Multivariate technologies for studying biotransformation**

Considering that gut microbes can increase the host’s complex and variable response to drugs/natural products, this process is of great interest to researchers. Research on biotransformation is mainly conducted via in vitro approach (Sousa et al., 2008) as follows: (1) Intestinal fluid transformation. The large-scale preparation of transformed products can be realized by intestinal fluid biotransformation; (2) Incubation with a sample of the host microbiota. The type and quantity of prototype drugs and metabolites can be detected using the method. It has the advantage of accurate representation of the entire gut microbiome of the individual; (3) Incubation of representative strains. This method affords high-throughput potential, which is valuable for large-scale drug studies and contributes to the industrial production of beneficial metabolites. In addition, organ-on-a-chip microphysiological systems (Ashammakhil et al., 2020), gastrointestinal organoids (Singh et al., 2020), and various predictive/computational tools (Machado et al., 2018; Chowdhury and Fong, 2020) may help improve our understanding of microbial metabolism in the future.

In addition, the relationships between natural product metabolism and gut microbes have been studied in animal models, and the results can be used to investigate the distribution and form of metabolites (Yoshisue et al., 2000). Germ-free/antibiotic-treated animals with conventional animals have been compared to prove the key roles of gut microbes on natural product metabolism. The limitation of this method is that inherent gastrointestinal and microbiological differences exist between humans and rodents (Nguyen et al., 2015). Detailed microbiota and metabolite analysis of feces collected from subjects in clinical trials can comprehensively reflect the metabolic process of natural products in vivo and be used to explain individual differences. In addition, the application of sequencing technology needs to be increased to study the microbial transcriptional activity and metabolic profile. By using the single-cell method, the physiological structure of gut microbes can be characterized to determine their metabolic activity (Zheng et al., 2022). Metatranscriptomics (RNA-Seq) allows the direct analysis of gene expression profiles of microorganisms with strong metabolic activity in the human gut (Berlinberg et al., 2022). The combination of single-cell methods, metatranscriptomics, and metagenomics has been used to identify and characterize the active subsets of gut microbiota and determine their metabolic responses to natural products.

**Conclusions and future remarks**

The gut microbiota is a reservoir of genes that encode various metabolic enzymes (Flint et al., 2012). The activation of biological activities and potential health benefits of most natural products (e.g., flavonoids, alkaloids, and lignin) are extremely dependent on gut microbes as a substrate-machining factory (Braune and Blaut, 2016; Seyed Hameed et al., 2020; Plamada and Vodnar, 2021). Much research effort has been devoted to understanding how microbes uniquely modify natural products and the effects of these metabolites on host health (Luca et al., 2020; Shabbir et al., 2021). The following conclusions have been made: (1) gut microbes can transform natural products (Xie et al., 2020); (2) natural products can regulate the composition and abundance of gut microbes (Saccon et al., 2021); and (3) gut microbes can mediate the multi-component synergy of natural products (Feng et al., 2019). Although high-throughput methods are being developed to help people understand the importance of the gut microbiome in the metabolism of natural products, microbial metabolism-based screening has not been adopted as part of the drug development process, because its mechanism remains unclear (Zimmermann et al., 2019). Moreover, the great plasticity and interindividual differences of gut microbes are notable (Vujkovic-Cvijin et al., 2020). Therefore, researchers need to improve the understanding of the physiological, chemical, and microbial contributions of gut microbes to the metabolism of natural products to help in explaining the individual differences in natural product responses and provide support for personalized treatment (Klozdziejezyck et al., 2019; Javdan et al., 2020). Most of the data in the present study were obtained independently of the clinic, but clinical trials are already underway, and the results will influence clinical practice in the foreseeable future.

Increasing studies on the mechanism of how to exert the curative effect, the application of fecal transplantation, specific bacterial transplantation, and animal models will help in clarifying the role of gut microbes. Nevertheless, standardization of operation, reproducibility of experimental results, and variation between species and individuals greatly reduce the authenticity and stability of the research, and a standard and scientific operating procedure remain to be put forward. Thus, confirming the symbolic functional extremely involved in biotransformation and its material basis will help in exploring the mechanism of natural products in the treatment of diseases and explaining the treatment mode of indirect interaction between natural products with low bioavailability and gut microbiota.
**Author contributions**

YZ contributed to the data collection and preparation of the original draft. XZ, JY, and CS provided brief article ideas and language modifications. XZ and XW supervised and revised the manuscripts. All authors contributed to the article and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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