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Review

Mechanisms of gastrointestinal microflora on drug metabolism in clinical practice

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ABSTRACT

Considered as an essential "metabolic organ", intestinal microbiota plays a key role in human health and the predisposition to diseases. It is an aggregate genome of trillions of microorganisms residing in the human gastrointestinal tract. Since the 20th century, researches have showed that intestinal microbiome possesses a variety of metabolic activities that are able to modulate the fate of more than 30 approved drugs and immune checkpoint inhibitors. These drugs are transformed to bioactive, inactive, or toxic metabolites by microbial direct action or host-microbial co-metabolism. These metabolites are responsible for therapeutic effects exerted by these drugs or side effects induced by these drugs, even for death. In view of the significant effect on the drugs metabolism by the gut microbiota, it is pivotal for personalized medicine to explore additional drugs affected by gut microbiota and their involved strains for further making mechanism clear through suitable animal models. This review mainly focus on specific mechanisms involved, with reference to the current literature about drugs metabolism by related bacteria or its enzymes available.

Contents

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1. Introduction

Considered as an essential "metabolic organ", intestinal microbiome contains more than 1000 bacterial species whose total number is as high as 100 trillion, and has approximately 150 times the genetic capacity of the human genome (Ley et al., 2006; Qin et al., 2010; Tilg and Kaser, 2011; Lakshminarayanan et al., 2014). A large section of healthy intestinal microbiome comprises bacteria, with the phyla Firmicutes and Bacteroidetes being the most dominant, and a smaller section is composed of archea, protozoa, viruses and fungi (Eckburg et al., 2005; Ley et al., 2005; Sommer and Bäckhed, 2013). These microorganisms colonize the host body from birth, and their diversity then increases considerably at the strain level, to the point where adults have relatively stable gut microbiota (Arumugam et al., 2011). However, each individual has a specific microbial taxa (Costello et al., 2009; Wu et al., 2011), and even twins have <50% of the same bacterial species (Turnbaugh et al., 2010), which is influenced by lots of factors including host genotype (Benson et al., 2010), antibiotic usage (Jernberg et al., 2010; Dollive et al., 2013), concomitant diseases (Zhao, 2013), and the maternal environment (Behnsen et al., 2013). The unique community is indispensable for maintaining human health (Clemente et al., 2012). It can ferment proteins and carbohydrates that are not digested by host into absorbable energy and short chain fatty acids (SCFA) (Ramakrishna, 2013), maintain mucosal structure to shape the immune response (Artis, 2008), synthetize vitamins (B and K) (Ferreira et al., 2011), and metabolize many endogenous substances including cholesterol, bile acids, tryptophan, neurotransmitters (Kinross et al., 2011). These microorganisms and their metabolites are also considered important in metabolizing orally administered exogenous compounds, especially drugs (Jeong et al., 2013)). Therefore, inter-individual or intra-individual microbial diversity or dysbacteria is of potential clinical significance.

It is well known that the liver is a main organ responsible for pharmaceutical metabolism and biotransformation. However, the metabolism of drug may begin at the intestinal level earlier than that at liver. Great majority of intestinal microbes reside in colon where the quantity of microorganisms is as high as 10^{13}. Microbial distribution is characterized by a decrease in the quantity and species of microorganisms from the colon to the stomach (Sender et al., 2016). Oral delivery of medicines, especially those that are not completely absorbed from the small intestine or candidates for enterohepatic circulation, are in inevitable contact with microbiota of the distal gut (Moore, 2008). And the metabolic response performed by gut microbiota is completely different from that by the liver. Specifically, the microbiota mainly produces non-polar low-molecular weight metabolites through hydrolytic and reductive metabolism, while the liver primarily generates polar and high-molecular weight byproducts through oxidative and conjugative metabolism (Joh and Kim, 2010; Kim, 2015). Thus, the intestinal microbiota affects drug absorption, and changes pharmacological effects of drugs. The effect of gut microbiota on host-targeted drugs efficacy has long been recognised in the late 1930s (Mani et al., 2014), when the sulfa-based antibiotics are identified as substrates for microbial transformation. It is attributed to microbial estimated 3.3 million genes, particularly genes encoding heterogeneous biodegradation and metabolic pathways (Qin et al., 2010). In recent years, a large number of studies on drug metabolism mechanisms have proved that the intestinal microbiota possesses a variety of metabolic activities that are able to modulate the fate of more than 30 approved drugs and their bioavailability (Okuda et al., 1998; Clayton et al., 2009; Haiser et al., 2014). These medicines are transformed to bioactive, inactive, or toxic metabolite (s) (Jeong et al., 2013; Yoo et al., 2014). For instance, the enzymes from colonic bacteria catalyze the reduction of sulfasalazine into 5-aminosalicylic acid, which induces anti-inflammatory effects (Klotz, 1985; Hayllar and Bjarnason, 1991). And gut microbiota metabolizes levamisole into three activity-reduced metabolites (Shu et al., 1991). Other representative examples of pharmaceuticals metabolized by the gut microbiota include diclofenac, omeprazole, digoxin, irinotecan, glycyrrhizin and so on.

In addition, the metabolic association between the host and gut microbiota changes the pharmacokinetics and pharmacodynamics of drugs (Haiser and Turnbaugh, 2012; Carmody and Turnbaugh, 2014), such as acetaminophen. In view of the significant effects on drug metabolism by gut microbiota, this review mainly focus on specific mechanisms involved, with reference to current literature about drugs metabolism whose related bacteria or enzymes are available.

2. Diverse mechanisms of intestinal microflora affecting drug metabolism

In fact, all functional activities performed by humans beings, including drug metabolism, are determined by two sets of genomes – the genetically inherited human genome and the environmentally acquired microbiome (Lederberg, 2000). Among all environmentally-acquired microorganisms, intestinal microorganisms are most abundant. Accumulating evidences reveal that changes in the gut microbiome are linked to many diseases, including diabetes, obesity (Forslund et al., 2017), CDI (Ferreira et al., 2014), cardiovascular disease (Singh et al., 2016) and inflammatory skin disease (2018). And its diversification contributes to the interindividual differences of results with drugs therapy. Together, a wealth of information is emerging about the roles of the gut microbiota on pharmacokinetics and therapeutic outcomes, particularly on drugs metabolized by particular bacteria or known bacterial enzymes. There are also some medicines that are confirmed to be associated with the intestinal microbiota by animal models, but their associated microbiota and bacterial metabolites are unknown. Due to the differences in the quantity and diversity of intestinal microbiota in animal models and human, and various factors affecting pharmacokinetics *in vivo*, the specific correlation between these medicines and human intestinal microbiota needs further investigation. When we focus on drugs that are clearly related to the intestinal microbiota, we find out the bacteria participate in the biotransformations of administered drugs, even dietary compounds and environmental toxins, through a number of diverse direct or indirect mechanisms (Carmody and Turnbaugh, 2014; Klaassen and Cui, 2015). Several articles have reviewed the effects of gut microbiota on efficacy and toxicity of dietary components and environmental toxins (Spanogiannopoulos et al., 2016; Wilson and Nicholson, 2017). The list of drugs and phytochemicals that are metabolized by the specific gut microbiota or microbial enzyme through known mechanism is presented in Table 1.

Table 1
Drugs and phytochemicals that are metabolized by the specific gut microbiota or microbial enzyme.

Drug	Clinical application	Bacterial Species or enzymes involved	Mechanism	Ref.
Prontosil	Antibiotics	Azoreductases	Enzymatic cleavage of azo-bond to sulfanilamide	Hattori et al. (1980, 1983), Hayllar and Bjarnason (1991) and He et al. (2017)
Neoprontosil				Hattori et al. (1980, 1983) and Hayllar and Bjarnason (1991)
Sulfasalazine Balsalazide Olsalazine	Anti-inflammatory drugs		Enzymatic cleavage of azo-bond to sulfanilamide 5-aminosalicylic acid	He et al. (2017) Houston et al. (1982) Joh and Kim (2010)
Metronidazole	Antibacterial agent	*Clostridium perfringens*	Enzymatic cleavage of ring to N-(2-hydroxyethyl)-oxamic acid and acetamide	Kajinami et al. (2005)
Levamisole	Anthelmintic drug	*Bacteroidetes* and *Clostridium* spp.	Enzymatic cleavage of ring to levametabol-I, levametabol-II, and levametabol-III	Gingell and Bridges (1973)
Omeprazole	antiulcerotics	Anaerobic bacteria such as *Bacteroides* strains	Enzymatic reduction to corresponding sulfide metabolites	Kim (2015)
Zonisamide	Anticonvulsant	*Clostridium sporogenes*	Enzymatic reduction of benzisoxazole ring to 2-sulphamoylacetylphenol	Kim et al. (2000)
Lactulose	Laxative drug	*Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Clostridium perfringens*	Two enzymatic convertion to lactic and acetic acids	Kim et al. (1992, 1998)
Sodium picosulfate		Arylsulfate sulfotransferase of *Eubacterium rectale*	Enzymatic convertion to 4,49-(pyridin-2-ylmethanediyl) diphenol	Kim and Kobashi (1986) and Kim et al. (2013)
Glycyrrhizin	Antiviral drug	*Eubacterium*. sp. strain GLH	Enzymatic convertion to 18b-glycyrrhetic acid	Kinross et al. (2011) and Kitamura et al. (1997)
Buddleoside	Anticancer drug	α-l-rhamnosidase and β-d-glucosidase of *Escherichia* sp., *Escherichia* sp., *Enterococcus* sp. and *Bacillus* sp.	Two enzymatic convertion to acacetin	Klaassen and Cui (2015)
Ginsenoside Rb1	Health protection	Oscillibacter spp., Ruminococcus spp., Holdemania spp., and Sutterella spp.	Enzymatic convertion to 20-O-b-D-glucopyranosyl-20(S)-protopanaxadiol	Klotz (1985) and Koch and Goldman (1979)
Sennosides	Laxative drug	Reductase and 3-b-D-glucosidase	Two enzymatic convertion to rheinanthrone	Kourtesi et al. (2013)
Digoxin	Cardiotonics	*Eggerthella lenta* possessing a two-gene cytochrome-encoding operon	Enzymatic convertion to dihydrodigoxin and dihydrodigoxigenin	Lederberg (2000), Lee et al. (2015), and Ley et al. (2005, 2006)
Levodopa	Anti-psychotics	*Helicobacter pylori*	Enzymatic dehydroxylation to m-tyramine or m-hydroxyphenylacetic acid to sequestering it from brain	Li and Nikaido (2004), Liang et al. (2015) and Lindenbaum et al. (1981)
Acetaminophen	Analgesics	P-cresol-produce bacteria like*Clostridium difficile*	High baseline microbial metabolite p-cresol compete for clearance by hepatic sulfotransferase and diminish the host's metabolic capacity for Phase II sulfonation of acetaminophen	Niemi et al. (2011) and Okuda et al. (1998)
Sorivudine	Antiviral drug	*Bacteroidetes* sp. or enterobacteria (*Klebsiella pneumoniae*)	Enzymatic convertion to (e)-5-(2-bromovinyl) uracil binding to related enzymes irreversibly to inhibit the metabolism of 5-fluorouracil and incite drug toxicity	Fiddian-Green (2006), Putman et al. (2000) and Qin et al. (2010)
Irinotecan	Anticancer drug	β-glucuronidase	Hydrolysis of SN-38-G of irinotecan (pro-drug) release SN-38 in the intestines which leads to gastrointestinal toxicity	Ramakrishna (2013), Roberts et al. (2013, 2002), and Robertson et al. (1986)
Diclofenac	Anti-inflammatory drug		Microbial β-glucuronidase reactivate glucuronidated metabolite to cause gastrointestinal toxicity	Rooks and Garrett (2016)
Indomethacin	Anti-inflammatory drugs			Rooks and Garrett (2016) and Routy et al. (2018)
Ketoprofen	Anti-inflammatory drugs			Rooks and Garrett (2016)
Statins	Hypolipidemics	Bacteria like *Lactobacillus* sp. is involved in production of coprostanol	Microbially derived secondary bile acids may compete with simvastatin for hepatic uptake by SLCO1B1101 transporters	Robertson et al. (1986), Sepehr et al. (2009), Shu et al. (1991), and Singh et al. (2016)
Nitrazepam	Hypnotic, sedative, anticonvulsant and anxiolytic drug	Nitroreductase	Bactical enzymatic convertion to 7-aminonitrazepam, followed by acetylation to 7-acetylaminonitrazepam in the liver	Takeno et al. (1993), Takeno and Sakai (1991) and Tao et al. (2016)

2.1. Mechanisms of microbial direct action on drug metabolism

2.1.1. Secreting microbial enzymes to transform prodrug molecules

The earliest reported example about prodrug activation by enzymatic activity of intestinal microbiota is the conversion of oral **prontosil** and **neoprontosil** into sulfanilamide. Prontosil is the first commercially available antibacterial drug that is lower polar than neoprontosil. This pharmacologically active metabolite is the reason why the two prodrugs exhibit antibacterial activities *in vivo* (Gingell and Bridges, 1973), while minimal effect *in vitro*. Animal experiments using mouse models indicated that azoreductases produced by the colorectal microbiota are in charge of this modification (Gingell et al., 1971). It includes a two-step reaction, the formation of the hydrazo compound, followed by a reductive cleavage of the nitrogen bond (Ünsalan et al., 2011). Prontosil is converted to sulfanilamide also in the liver and kidney (Fouts et al., 1957). Moreover, prontosil injected intraperitoneally can experience gut bacterial metabolism by being excreted into the gastrointestinal tract via the bile. However, neoprontosil is excreted via the bile without reduction and absorption in the intestine due to its high polarity. Administration with antibiotics disturbing intestinal microbiota inhibits the activation of oral prontosil and neoprontosil into sulfanilamide in rats (Gingell et al., 1971).

Sulfasalazine is another sulfonamide drug that is metabolically activated by bacterial azoreductase enzymes (Peppercorn and Goldman, 1973). Structurally intact sulfasalazine is scarcely absorbed from the upper intestine, but it undergoes bacterial azo reduction, and releases sulfapyridine (SP) and 5-aminosalicylic acid (5-ASA, mesalazine) in the colon. 5-ASA (Houston et al., 1982), which is active in the colon, is used as an active anti-inflammatory moiety in treating inflammatory bowel disease (IBD), while systemically absorbed SP with its antibacterial and immunomodulatory effects, is considered to be useful in the treatment of rheumatoid arthritis (Mikov et al., 2006). Once sulfapyridine is absorbed in the colon, it may be the cause of side effects of sulfasalazine in some patients, such as rash, headache, and anorexia (Peppercorn and Goldman, 1973). To obviate these adverse effects, **balsalazide** was synthesized from salicylic acid and 4-aminobenzoyl-b-alanine. It can be converted potently into 5-ASA also by intestinal microbiota -secreting azoreductase (Chan et al., 1983). Another sulfasalazine analogue, **olsalazine**, is metabolized into two 5-ASAs by the same mechanism (Wadworth and Fitton, 1991). And as the active metabolites of three prodrugs, 5-ASA and SP further undergo acetylation performed by the gut microbiota in fecal suspensions from rats, guinea pigs, dogs and humans (Klotz, 1985). Notably, 5-ASA is acetylated into N-acetyl-5-aminosalicylic acid by individual bacteria under aerobic and anaerobic conditions in human faecal suspension (Hogezand et al., 1992; Deloménie et al., 2001).

Metronidazole, mainly used to treat trichomoniasis, amoebiasis, and giardiasis (Löfmark et al., 2010), is also a long-established antibacterial agent. In the liver, metronidazole is usually modified by side-chain oxidation and glucuronide formation to generate hydrophilic products. However, enzymes from *Clostridium perfringens* (an anaerobic gut bacterium) metabolize metronidazole into ring-cleavage products, N- (2-hydroxyethyl)-oxamic acid, and acetamide in the gut (Koch and Goldman, 1979). Another anthelmintic drug, **levamisole** is effective in both humans and animals, especially part active agent in colon cancer. It is metabolized into three thiazole ring-opened metabolites: levametabol-I, levametabol-II, and levametabol-III by human intestinal bacteria, mainly *Bacteroidetes and Clostridium* spp. under anaerobic conditions (Shu et al., 1991).

In addition, several other drugs metabolized directly by intestinal microbes have been reported. **Omeprazole** is used to treat gastric ulcer, and can be reduced into corresponding sulfide metabolites by anaerobic bacteria such as *Bacteroides* strains *in vitro* conditions. But in fact, this bacterial metabolism is unlikely to occur because oral omeprazole is absorbed well, and does not reach the colon *in vivo* (Watanabe et al., 1995). **Zonisamide,** an anticonvulsant clinically used to treat epilepsy, undergoes reduction of benzisoxazole ring performed by *Clostridium sporogenes* into 2-sulphamoylacetylphenol *in vivo* (Kitamura et al., 1997). Two laxative drugs, **lactulose** and **sodium picosulfate** (Laxoberon), exert their effects through gut microbial metabolism. The former is converted by enzymes of several kinds of intestinal bacteria (*Bifidobacterium bifidum, Lactobacillus acidophilus* and *Clostridium perfringens*) into fructose and galactose followed by transformation into lactic and acetic acids. These end products promote the excretion of ammonia and amines into the feces to relieve hepatic encephalopathy through lowering the pH within the intestine (Elkington et al., 1969; Grundmann, 2010). The latter is metabolized into 4,49-(pyridin-2-ylmethanediyl) diphenol by arylsulfate sulfotransferase of *Eubacterium rectale* in the colon (Kim and Kobashi, 1986; Kim et al., 1992). However, some anti-allergic drugs, such as diphenhydramine and chlorpheniramine, can cause or aggravate constipation by slowing intestinal peristalsis. This causes the feces to remain in the intestines for a long time and its moisture is excessively lower. Drinking 2500–3000 ml of water per day during medication or changing drugs with new antihistamines (loratadine and cetirizine) rather than taking laxatives, can improve this difficulty in defecation.

Some Chinese medicine ingredients are also metabolized by the intestinal microbial enzyme into the corresponding absorbable aglycones (Xu et al., 2017), and their prototypes are poorly absorbed in the intestines. **Glycyrrhizin** is a sweet-tasting compound of the root of Glycyrrhiza glabra and Glycyrrhiza uralensis, and is used to treat hepatitis C in Japan. *Eubacterium*. sp. strain GLH completely metabolizes glycyrrhizin into 18b-glycyrrhetic acid which is absorbed well (Hattori et al., 1983; Kim et al., 2000). α-L-rhamnosidase and β-d-glucosidase from some bacteria (*Escherichia* sp., *Escherichia* sp., *Enterococcus* sp. and *Bacillus* sp.) can convert **buddleoside** into cancer-combating acacetin via acacetin-7-glucoside (Tao et al., 2016). As the main ingredient of Panax ginseng, **ginsenoside Rb1** is metabolized into bioactive 20-O-b-D-glucopyranosyl-20 (S)-protopanaxadiol (compound K) by *Oscillibacter* spp., *Ruminococcus* spp., *Holdemania* spp., and *Sutterella* spp. (Akao et al., 1998; Kim et al., 2013) **Sennosides** is converted to be 8-glucosyl-rheinanthrone or sennidin monoglucosides by reductase and 3-b-D-glucosidase from the gut microbiota, and the latter is further metabolized into rheinanthrone with purgative property in the distal intestine (Hattori et al., 1980). Several **flavonoid glycosides** (Kim et al., 1998) (rutin, hesperidin, naringin, baicalin, wognoside, and poncirin) and **isoflavones** (daidzein, genistein (Sepehr et al., 2009) and baicalin (Trinh et al., 2010)are metabolized into their respective pharmacologically active metabolites by different intestinal microbiota and enzymes.

2.1.2. Expression of genetic element involved in drug inactivation

Orally administered cardiac glycoside drug **digoxin** is long known to be metabolized reductively and inactively into dihydrodigoxin and dihydrodigoxigenin by gut *Eggerthella lenta*. These two metabolites bind incompetently to the Na + -K + -ATPase of the myocardium in some patients (Lindenbaum et al., 1981; Saha et al., 1983; Robertson et al., 1986). These patients account for 10% of total population, and their gut microbiota convert over 40% of oral digoxin into inactive metabolites before its absorption (Li and Jia, 2013). Subsequent researches demonstrate that these people who can reduce digoxin, harbor some strains of *E. lenta* possessing a two-gene cytochrome-encoding operon, namely the cardiac glycoside reductase (cgr) operon (Haiser et al., 2014). This cgr

operon works by producing a protein-Cgr1-Cgr2 complex that binds to digoxin, and accounts for digoxin's consequent reduction. And arginine is found to inhibit the reduction of digoxin in this study, so high-protein diet can help improve the efficacy of digoxin in patients who carry cgr + E. lentas (Haiser et al., 2014).

2.1.3. Sequestering drugs from the site of action

Normally, orally administered **levodopa** (L-dopa), as a precursor of dopamine, passes through the blood-brain barrier, and undergoes decarboxylation within the central nervous system (CNS). It can increase the level of dopamine in the CNS to exert its therapeutic effect on Parkinson's disease. However, one study on incubation of levodopa with rat cecal contents showed that most of the L–dopa was converted to m-tyramine or m-hydroxyphenylacetic acid through gut microbial decarboxylation process, which makes operative L–dopa reduced in the CNS (Goldin et al., 1973). Moreover, people infected with *Helicobacter pylori* are more common in patients with Parkinson's disease than in healthy controls. Subsequent studies have revealed that Helicobacter pylori is the major strain involved the bacterial decarboxylation (Pierantozzi et al., 2001; Fiddian-Green, 2006; Hashim et al., 2014).

2.1.4. Developing bacterial transporters to change the efficacy of drugs

Bacteria have evolved multidrug transporters rather than highly selective drug-specific transporters to protect themselves from antibiotics and other antibacterials (Li and Nikaido, 2004). Great majority of these multidrug transporters belong to secondary transporters, using transmembrane electrochemical gradients, typically the proton motive force (Putman et al., 2000), to drive drug efflux. The secondary transporters include five subclass transporter families, namely resistance-nodulation-division (RND), the major facilitator superfamily (MFS), the multidrug and toxic compound efflux (MATE), and the small multidrug resistance (SMR) superfamily (Kourtesi et al., 2013). A few belong to another transporters, the ABC transporters, which utilizes the energy released from ATP hydrolysis (Davidson and Chen, 2004). *Bacillus subtilis* and *Lactococcus lactis* harbour two types of transporters. Genome of the former encodes for at least 78 ABC transporters, of which BmrA belongs to the ABC family, and Bmr and Blt are listed as the secondary transporter (Torres et al., 2009). Overexpression of any transporter in *B. subtilis* results in similar decreases in susceptibility to puromycin, chloramphenicol, doxorubicin, and fluoroquinolone antibiotics. However, *L. lactis* is found to express 40 putative drug transporters by *in silico* analysis of the genome (Li and Nikaido, 2004). Expression of the mdt (A) gene in *L. lactis* increased resistance to macrolides, streptogramins, lincosamides, and tetracyclines (Perreten et al., 2001). The presence of membrane protein BbmR in *Bifidobacterium breve* also increases its resistance to macrolides (Abelardo et al., 2006). These various transporters have an effect on the efficacy of antibacterials.

2.2. Mechanisms of gut microbes on affecting host's capacity of metabolizing therapeutic drugs

2.2.1. Producing microbial metabolites to compete enzymes with drugs

After exerting analgesic and antipyretic effects at the normal dose, **acetaminophen** is cleared in the form of conjugated metabolites, mainly through two phase II conjugation in the liver, namely glucuronidation and sulfation. However, a small part of excess acetaminophen can be transformed to N-acetyl-p-benzoquinone imine by CYP1A cytochrome (Wacher et al., 2001). N-acetyl-p-benzoquinone imine is further conjugated with hepatic glutathione (GSH) for detoxification. If GSH is absent, excess N-acetyl-p-benzoquinone imine is the cause of hepatotoxicity (Zhang et al., 2017). The pre-dose urinary concentration of a microbial metabolite, p-cresol, is related to the severity of acetaminophen hepatic toxicity (Clayton et al., 2009). As p-cresol and acetaminophen are both substrates for cytosolic sulfotransferases (Gamage et al., 2006), high baseline p-cresol produced by *Clostridium difficile* and others competes with acetaminophen for binding with the enzyme, leading to changes in the bioavailability of acetaminophen and its metabolites. This change induces the individual variation in acetaminophen metabolism and hepatic toxicity or failure (Larson et al., 2012). Concurrently, the liver damage resulted by acetaminophen administration at night is more severe than that in the morning (Kim and Lee, 1998). In a study with mice, Gong et al. reported that gut microbial metabolite, 1-phenyl-1,2-propanedione mediates diurnal variation of acetaminophen induced hepatotoxicity by exhausting hepatic GSH levels (Gong et al., 2018). However, given the complexity of acetaminophen metabolism and the opposite result of an animal experiment to the above findings (Possamai et al., 2015), the effects of intestinal microbial metabolism on acetaminophen-induced hepatotoxicity require further investigation. Other bacterial metabolites, pyruvic acid and lactic acid, induce dendrite protrusion via GPR31 in intestinal $CX3CR1^{+}$ mononuclear cells to enhance immune response, that may also influence drugs metabolism (Morita et al., 2019). **Sorivudine**, a Japanese antiviral drug, produces a lethal effect through a mechanism similar to acetaminophen (Okuda et al., 1998). There are 18 acute deaths of patients related to co-administration of sorivudine and 5-fluorouracil, since sorivudine metabolite (e)-5-(2-bromovinyl) uracil is produced by fermentation of the *Bacteroidetes* sp. (Nakayama et al., 1997)or enterobacteria (*Klebsiella pneumoniae*) (Ashida et al., 1993). When sorivudine is concomitantly administered with oral **5-fluorouracil** prodrug (an anticancer drug), the metabolite binds to related enzymes irreversibly to inhibit the metabolism of 5-fluorouracil and incite its toxicity.

2.2.2. Promoting enterohepatic recirculation of drugs to metabolize drugs again

In enterohepatic recirculation, drugs entering the gastrointestinal tract are absorbed intestinally by the enterocytes, and subsequently are taken up into the hepatocytes via the portal vein (Roberts et al., 2002). When the drug is secreted into the intestine with bile, the intestinal bacteria can restore the active drug by hydrolysis and reduction or allow it to be reabsorbed to its site of action (Martinez and Amidon, 2013). The metabolism of **Irinotecan** (CPT-11) is a good example of reactivation of drug by intestinal microbiota that has been inactivated in the liver. CPT-11 is an intravenous prodrug of the antineoplastic topoisomerase I inhibitor SN-38 for colorectal cancers (Vanhoefer et al., 2001). It is known that irinotecan needs to be hydrolyzed by a carboxylesterase in tissues and serum to produce SN-38 (de Jong et al., 2004), an active metabolite exerting its pharmacological effects. SN-38 is conjugated by hepatic UDP-glucuronosyltransferase 1A1 into the inactive SN-38-G (Kajinami et al., 2005). However, SN-38-G experiences biliary secretion into the intestines where it is deconjugated back to SN-38 by β-glucuronidase produced by bacteria, including *Escherichia coli*, *Bacteroides vulgatus*, and *Clostridium ramosum*. This reactivation leads to the dose-limiting adverse side effects, such as delayed diarrhea, weight loss, and suppression of the immune system (Wallace et al., 2010) Fig. 1. In line with SN-38, the enteropathic adverse reactions arise from protracted exposure to carboxylic acid-bearing non-steroidal anti-inflammatory drugs (NSAIDs) including **diclofenac**, **indomethacin** and **ketoprofen**. They are also related to the enterohepatic circulation of glucuronides and caused by reactivation of active metabolites by microbial β-glucuronidase (Saitta et al., 2014). Antibiotic treatment or application of inhibitors of microbial β-glucuronidase is reported to reduce the severe side effect inflicted by CPT-11

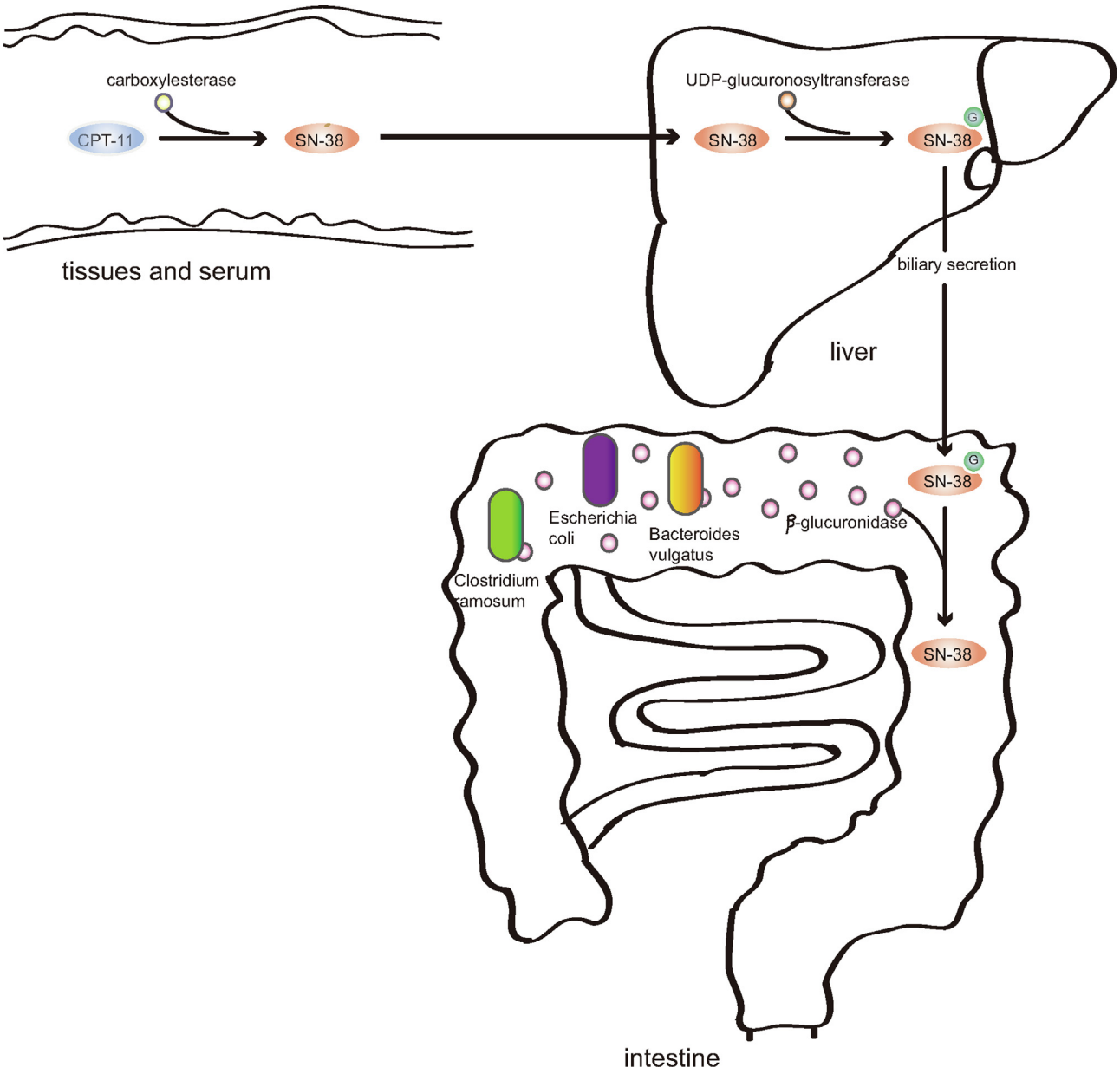

Fig. 1. Intestinal microflora participate in the enterohepatic recirculation of CPT-11, causing adverse side effects. (a) In tissues and serum, irinotecan is hydrolyzed by a carboxylesterase to produce SN-38, an active metabolite exerting its pharmacological effects. (b) In the liver, SN-38 is conjugated by UDP-glucuronosyltransferase 1A1 into the inactive SN-38-G. (c) SN-38-G experiences biliary secretion into the intestine. In the intestine, SN-38-G is deconjugated back to SN-38 by β-glucuronidase produced by bacteria, including Escherichia coli, Bacteroides vulgatus, and Clostridium ramosum.

(Roberts et al., 2013) and by these NSAIDs, especially indomethacin in animal experiment. A subsequent study demonstrated that the absence of bacterial de-gluconuronidation resulted in reduced indomethacin reabsorption into the circulation, with increased elimination and a shortened half-life to follow (Liang et al., 2015).

2.2.3. Affecting bile acid metabolism to modulate systemic drug absorption

Due to their potent competition with 3-hydroxy-3-methyl-glutaryl-Co A (HMG-CoA) reductase (Davidson and Toth, 2005)to reduce plasma levels of low-density lipoprotein cholesterol (LDL-C) (Postmus et al., 2014); **statins** are widely prescribed pro-drugs for treating hypercholesterolemia. Previously, great variations among individuals on therapeutic effects of statins are only partly attributed to genetic differences (Mangravite et al., 2006; Verschuren et al., 2012). Subsequent studies demonstrated that gut microbiota are also responsible for statins bioavailability (Kaddurahdaouk et al., 2011). Gut microbiota-derived bile acids and statins share transporters in the gut and liver, such as organic anion transporter SLCO1B1 (Niemi et al., 2011). The gene encoding SLCO1B1 contains a single nucleotide polymorphism, rs4149056, which is associated with plasma concentrations of simvastatin acid and seven bile acids (7α-hydroxycholesterol, cholic acid, taurocholic acid, glycocholic acid, taurochenodeoxycholic acid, lithocholic acid, taurolithocholic acid). The genetic polymorphism may cause competition between **simvastatin** and bile acids for hepatic uptake by SLCO1B1 transporter (Sayin et al., 2013). Concurrently, it is also shown that incubation of lovastatin with human or rat fecalase preparations produces four metabolites (Wallace et al., 2010), including active β-hydroxy acid metabolite that is known to inhibit HMG-CoA reductase (Yoo et al., 2014). Thus, gut microbiota

can influence the pharmacokinetics of simvastatin by competing with statins for absorbtion or co-metabolizing statins.

2.2.4. Affect the "components" of the host about drug metabolism

Emerging evidence indicates that the imbanlance of intestinal microbiota (germ-free mice and antibiotics-treated mice) alters expression levels of multiple drug-metabolizing enzymes and transporters in liver and kidney of mice, where most drugs are cleared. Among them, the decrease in CYP2B6 activity in human liver results in significant inter-individual differences in the metabolic activities towards cyclophosphamide, efavirenz and bupropio. Decreased protein expression level of BCRP also changes the pharmacokinetics of anticancer drugs, such as mitoxantrone and topotecan (Kuno et al., 2016). But, their related microbiota are unknown. The expression levels of drug-metabolizing enzymes (cytochromes, esterases, peptidases, phase I or II enzymes) and transporters (ATP-binding cassette, solute carrier family) in the gut are not only regulated by nuclear receptors (Gadaleta et al., 2015)but also by intestinal microbiota. Changes in drug-metabolizing enzymes and transporters in the gut have a direct impact on the first-pass effect of midazolam, verapamil, felodipine and cyclosporine, even the fate of oral drugs (acetaminophen (Wacher et al., 2001), fosamprenavir, insulin (Gavhane and Yadav, 2012).

2.2.5. Producing a unique metabolite inducing hepatic further metabolism

The involvement of gut microbiota in the metabolism of **nitrazepam**, a hypnotic, sedative, anticonvulsant and anxiolytic drug, into its teratogenicity was demonstrated in experiments with rats (Takeno and Sakai, 1991). Nitrazepam is transformed to 7-aminonitrazepam by nitroreductase from intestinal microbiota, followed by acetylation to 7-acetylaminonitrazepam in the liver (Takeno et al., 1993). Although reductive metabolism in rat liver is less potent than in gastrointestinal tract (Rafii, 1997), two metabolites are both teratogenic. The involvement of the gut microbiota in metabolism of above-mentioned drugs has been further demonstrated by studies in germ-free or antibiotic-treated rats. Metronidazole is the only drug with unchanged metabolism in these studies (Pierce et al., 2014). It is initially presumed that the specie involved in the metabolism of metronidazole is not sensitive to antibiotics. Currently metabolisms of many other drugs seem to also be related to the intestinal microbiota, but the specific bacteria or bacterial enzymes involved are unclear, and need to be further explored. Additionally, the mechanism by which the known intestinal microbiota affects drugs pharmacokinetics is by no means limited to the known. For example, the precise manner in which *Faecalibacterium prausnitzii* dictates **tacrolimus** dosing requirements is unknown (Lee et al., 2015).

3. The possible impact of gut microbes on immune checkpoint inhibitors

In addition to the important role of gut microbiota in preventing disease, regulating immunity and metabolizing chemical or Chinese herbal medicine, these microbes have been shown to affect the immunomodulatory effect and side effect of immunotherapy. In 2015, two researches first confirmed that the composition of intestinal microbes determines the effectiveness of cancer immunotherapy in mice. Namely, the effect of the antibody of Ipilimumab targeting the immune checkpoint blocker CTLA-4 required *Bacteroides thetaiotaomicron* and *Bacteroides Fragilis* (Vétizou et al., 2015), and *Bifidobacterium spp*. favored the efficacy of anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) monoclonal antibody (Sivan et al., 2015). Subsequent studies on human further confirmed the close relationship between intestinal bacteria and immunotherapy. Zivogel and his team revealed that gut microbiota, especially *Akkermansia muciniphila* which enhances the recruitment of CCR9 + CXCR3 + CD4+ T lymphocytes into tumor beds, has an impact on clinical benefit of immune checkpoint inhibitors targeting the PD-1/PD-L1 in patients with cancer (Routy et al., 2018). Another two studies published in the same issue of Science on melanoma patients treated with PD-1 blockade respectively show that beneficial strains are more abundant in the guts of blockade-responding patients. The bacteria involved in the former are bacteria of the Ruminococcaceae family (Gopalakrishnan et al., 2018), while the latter are *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium* (Matson et al., 2018). These gut microbes may induce dendritic cells to release some cytokines which recruit more effector T cells to focus around the tumor. Gut microbiota may also be the reason why immune checkpoint inhibitors have clinical benefits for only 20–30% of treated cancer patients (Botticelli et al., 2016; Wang et al., 2018a). Therefore, appropriate strains can assist the immune system in responding to these treatments. Manipulating the gut microbiota is expected to be a new strategy to increase the activity of immunotherapeutics, and may also be used to reduce their side effects. Three related results were obtained with germ-free mice or antibiotics-treated mice, which reported improved response to anti-PD-1 therapy in mice given feces from responsive cancer patients. The mice receiving fecal transplants from responding patients also showed enhanced systemic and antineoplastic immunity (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018). Notably, significant and rapid cure of refractory immune checkpoint inhibitors (ICI)-associated colitis has been derived from fecal microbiota transplantation (FMT) with changes in gut microbial composition and T cell composition within the colonic mucosa of two cancer patients (Wang et al., 2018b)). FMT benefits not only immunotherapy, but also other cancer treatments and reduces associated side effects, such as radiotherapy (Cui et al., 2017)and taking paclitaxel (Castelli et al., 2018). The list of immunological checkpoint inhibitors (Ayelet et al., 2015; Frankel et al., 2017; Wargo et al., 2017; Chaput et al., 2017) that are affected by the specific gut microbiota is showed in Table 2.

4. Existing limitations

It is known that intestinal microbes can modulate drug metabolism in several proposed ways including direct enzymatic effects on transform of drug molecules and affecting the host function to interfere with drug metabolism, such as changes in drug metabolizing enzymes, metabolic type and basal metabolism of host. Such studies accelerate the understanding of gut microbes and the correct application of drugs, but the animal models, germ-free mice and antibiotics-treated mice, have some limitations. Germ-free mice are abnormal mice with enlarged caecum, reduced villous thickness and villous capillary networks (Taguer and Maurice, 2016), and they are not equivalent to normal mice without gut floma. In terms of metabolism, germ-free mice consume more calories and secrete more lipids (Wostmann et al., 1983), which may make them more susceptible to low-grade inflammation. And germ-free mice show underdeveloped intestinal-associated lymphoid tissues, reduced production of secretory IgA and regulatory T cell, and imbalanced TH1-TH2 cell in immunity (Rooks and Garrett, 2016). Germ-free mice also have abnormalities in signal transduction. Endocrine small molecules, such as dopamine which is critical to the development of the enteric nervous system, in germ-free mice are decreased (Borre et al., 2014). Similarly antibiotics altenate not only intestinal microbiota but also the function of other organs in antibiotic-treated mice. Most experiments *in vitro* involve the incubation of drugs with bacterial suspensions

Table 2
Immunological checkpoint inhibitors that are affected by the specific gut microbiota.

Target	Specific agents	Clinical application	Bacterial Species involved	Mechanism	Ref.
PD-1	Pembrolizumab	Melanoma	*Dorea formicogenerans*	Unmentioned	Watanabe et al. (1995)
PD-1	Unidentified	Melanoma	*Clostridiales*	increasing tumor immune infiltrates and density of CD8 + T cells	Wostmann et al. (1983)
PD-1	Unidentified	Melanoma	*Ruminococcaceae*	increasing density of CD8 + T cells	Wadworth and Fitton (1991)
PD-1	Unidentified	Melanoma	*Bifidobacterium longum, Collinsella aerofaciens, Enterococcus faecium*	improving tumor control, augmenting T cell responses and enhancing efficacy of anti-PD-L1 therapy	Vanhoefer et al. (2001)
PD-L1	αPD-L1 mAb	Melanoma	Some *Bifidobacterium* species	enhancing CD8(+) T cell priming and accumulation around the tumor	Wilson and Nicholson (2017)
CTLA-4	Ipilimumab	Melanoma	*Faecalibacterium prausnitzii, Dorea formicigenerans*	reducing proportion of peripheral blood regulatory T cells	Wu et al. (2011)
CTLA-4	Ipilimumab	Melanoma	*Bacteroides thetaiotaomicron, Bacteroides fragilis*	induced TH1 immune responses in the tumor-draining lymph nodes and promoting the maturation of intratumoral DCs	Trinh et al. (2010)
PD-1/PD-L1	Unidentified	Non–small cell lung cancer, renal cell carcinoma and urothelial carcinoma	*Akkermansia muciniphila*	Enhancing the recruitment of CCR9 + CXCR3 + CD4 + T lymphocytes into tumor beds	Ünsalan et al. (2011)
CTLA-4 and PD-1	Ipilimumab plus nivolumab	Melanoma	*Fecalibacterium prausnitzii, Bacteroides thetaiotamicron, Holdemania filiformis*	Unmentioned	Watanabe et al. (1995)

mAb monoclonal antibody; *TH1* T helper 1; *DCs* dendritic cells.

prepared from rat or human cecal contents. Since the suspensions mix different bacteria that are in different positions and cannot contact each other in the gut *in vivo*, which may influence the order of different reactions, and some strains even cannot survive *in vitro*. So we can see that these operations do not accurately reflect the metabolism of the drug *in vivo*, although they allow us to discover the microbiota-mediated metabolites. Concurrently, the potential difference between *in vivo* and *in vitro* models of the gut microbiota should be taken into consideration when analyzing studies of drugs biotransformation, as some drugs are not metabolized *in vivo* but metabolized *in vitro*. These drugs are effectively absorbed before reaching the lower part of the intestine where containing more kinds of bacteria. Taken together, even if these models have certain reference value, it is very necessary for us to find more suitable models.

Given the wide variety of drugs affected by intestinal microbes, it is pivotal for personalized medicine to explore additional drugs affected by gut microbiota and their involved strains for further making mechanism clear. There is an overlap between different classes of drug metabolizing pathways. Thus, when exploring the unknown metabolic pathways of other drugs, it is conceivable that these pathways may be partially similar to the known pathways described above. Sometimes drug treatment outcomes of two individuals are different, although they all contain the related microorganisms and enzymes. Other factors may be involved in, e.g. microbial-induced host gene quantitative or qualitative changes, especially at the level of epigenetic regulation. Concurrently, although intestinal microbial regulation of microRNA in the brain (Hoban et al., 2017)and effect on drug metabolism enzymes and transporters in host liver and kidney (Kuno et al., 2016) have been confirmed, the mechanisms by which microbes cause these variations and the optimal treatments are in their initial stages.

5. Future directions

On the basis of existing research results, we propose these promising research points: (I) At present, there are only over 30 drugs that are known to be closely related to the intestinal microbiota, and we need to further clarify other drugs affected by the microbiota, and the mechanism involved. (II) In addition to germ-free mice and antibiotic-treated mice, studies on microbiota and drug metabolism require more scientific animal models. (III) There may be not only one kind strain involved in when intestinal microbiota affects drug metabolism and side effects, but may several "related" microbiota implicated in, or an equilibrium state of the whole microbiota related to. This conclusion may be different depending on the specific drugs taken. (IV) It is necessary to strengthen the *in vivo* study on the interaction of microbiota, host intestinal epithelial cells and drugs in the intestinal microenvironment, especially the microbical regulation of genes related to drug metabolism in the host. (V) By analyzing the relationship between individual intestinal microbiota traits (diversity, composition, metabolites) and drug metabolism, it is expected to develop a estimating system for bacterial population (before administration) related to drug use efficiency and side effects. (VI) When interfering with intestinal microbes, it is warranted to choose the right means based on the principle of completeness to restore intestinal microbiota balance, rather than only supplement what is short. Considering that FMT has made progress in the treatment of intestinal diseases (He et al., 2017; He et al., 2017; Johnsen et al., 2018), we can expect whether transplantation of normal human microbiota to patients with abnormal drug metabolism also has therapeutic effects. But, special attention should be paid during the operation to prevent infection which may endanger the patient's life. (VII) On the basis of clarifying the particular microbiota that affects the bioavailability of a drug, it may be considered to explore the strategy of taking the drug in combination with this related microbiota, but to ensure that this microbiota survives after entering the intestine without disturbing the overall microbiota balance (avoiding causing new problems), and acts on the same part of the intestinal tract with the drug. (VIII) Similarly, other means of regulating the microbiota of a patient may also be considered, such as co-administration of drug and prebiotics or synbiotics that are beneficial to the microbiota. It is necessary to explore new microbial inhibitors, microbial enzyme inhibitors or microbiota-derived molecules (active metabolites or microbial gene products)

which are equally beneficial to the drug, when the microbiota is not conducive to the metabolism of the drug. (IX) Co-administration of sorivudine and 5-fluorouracil is known to incite acute deaths. More drug-drug interactions involved in intestinal microbiota should be investigated. Answering these questions is conducive to the continued research of drugs and improving individualized medicine.

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Declaration of interest statement

Declarations of interest: none.

References

Abelardo, M., Ana Belén, F., José Antonio, M., Douwe, V.S., Reyes-Gavilán, C.G., Los, De, 2006. Two membrane proteins from Bifidobacterium breve UCC2003 constitute an ABC-type multidrug transporter. Microbiology 152, 3497–3505.
Akao, T., Kida, H., Kanaoka, M., Hattori, M., Kobashi, K., 1998. Drug metabolism: intestinal bacterial hydrolysis is required for the appearance of compound K in rat plasma after oral administration of ginsenoside Rb1 from Panax ginseng. J. Pharm. Pharmacol. 50, 1155–1160.
Artis, D., 2008. Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. Nat. Rev. Immunol. 8, 411–420.
Arumugam, M., Raes, J., Pelletier, E., Le, P.D., Yamada, T., Mende, D.R., Fernandes, G. R., Tap, J., Bruls, T., Batto, J.M., 2011. Enterotypes of the human gut microbiome. Nature 473, 174–180.
Ashida, N., Ijichi, K., Watanabe, Y., Machida, H., 1993. Metabolism of 5'-ether prodrugs of 1-beta-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil in rats. Biochem. Pharmacol. 46, 2201.
Ayelet, S., Leticia, C., Nathaniel, H., Williams, J.B., Keston, A.M., Earley, Z.M., Benyamin, F.W., Yuk Man, L., Bana, J., Maria-Luisa, A., 2015. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350, 1084–1089.
Behnsen, J., Deriu, E., Sassone-Corsi, M., Raffatellu, M., 2013. Probiotics: properties, examples, and specific applications. Cold Spring Harbor Perspect. Med. 3, a010074.
Benson, A.K., Kelly, S.A., Legge, R., Ma, F., Low, S.J., Kim, J., Min, Z., Oh, P.L., Nehrenberg, D., Hua, K., 2010. Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. PNAS 107, 18933.
Borre, Y.E., O'Keeffe, G.W., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2014. Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol. Med. 20, 509–518.
Botticelli, A., Zizzari, I., Mazzuca, F., Ascierto, P.A., Putignani, L., Marchetti, L., Napoletano, C., Nuti, M., Marchetti, P., 2016. Cross-talk between microbiota and immune fitness to steer and control response to anti PD-1/PDL-1 treatment. Oncotarget, 8.
Carmody, R.N., Turnbaugh, P.J., 2014. Host-microbial interactions in the metabolism of therapeutic and diet-derived xenobiotics. J. Clin. Investig. 124, 4173–4181.
Castelli, V., Palumbo, P., d'Angelo, M., Moorthy, N.K., Antonosante, A., Catanesi, M., Lombardi, F., Iannotta, D., Cinque, B., Benedetti, E., Ippoliti, R., Cifone, M.G., Cimini, A., 2018. Probiotic DSF counteracts chemotherapy induced neuropathic pain. Oncotarget 9, 27998–28008.
Chan, R.P., Pope, D.J., Gilbert, A.P., Sacra, P.J., Baron, J.H., Lennardjones, J.E., 1983. Studies of two novel sulfasalazine analogs, ipsalazide and balsalazide. Dig. Dis. Sci. 28, 609–615.
Chaput, N., Lepage, P., Coutzac, C., Soularue, E., Le, R.K., Monot, C., Boselli, L., Routier, E., Cassard, L., Collins, M., 2017. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 28, 1368.
Clayton, T.A., Baker, D., Lindon, J.C., Everett, J.R., Nicholson, J.K., 2009. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. Proc. Natl. Acad. Sci. U S A 106, 14728–14733.
Clemente, J.C., Ursell, L.K., Parfrey, L.W., Knight, R., 2012. The impact of the gut microbiota on human health: an integrative view. Cell 148, 1258–1270.
Costello, E.K., Lauber, C.L., Hamady, M., Fierer, N., Gordon, J.I., Knight, R., 2009. Bacterial community variation in human body habitats across space and time. Science, 1694–1697.
Cui, M., Xiao, H., Li, Y., Zhou, L., Zhao, S., Luo, D., Zheng, Q., Dong, J., Zhao, Y., Zhang, X., Zhang, J., Lu, L., Wang, H., Fan, S., 2017. Faecal microbiota transplantation protects against radiation-induced toxicity. EMBO Mol. Med. 9, 448–461.
Davidson, A.L., Chen, J., 2004. ATP-binding cassette transporters in bacteria. Annu. Rev. Biochem. 73, 241–268.
Davidson, M.H., Toth, P.P., 2005. Comparative effects of lipid-lowering therapies. Prog. Cardiovasc. Dis. 47, 73–104.
de Jong, F.A., Marsh, S., Mathijssen, R.H., King, C., Verweij, J., Sparreboom, A., Mcleod, H.L., 2004. ABCG2 pharmacogenetics: ethnic differences in allele frequency and assessment of influence on irinotecan disposition. Clin. Cancer Res. 10, 5889–5894.
Deloménie, C., Fouix, S., Longuemaux, S., Brahimi, N.M., Bizet, C., Picard, B., Denamur, E., Dupret, J.M., 2001. Identification and functional characterization of arylamine N-acetyltransferases in eubacteria: evidence for highly selective acetylation of 5-aminosalicylic acid. J. Bacteriol. 183, 3417–3427.
Dollive, S., Chen, Y.Y., Grunberg, S., Bittinger, K., Hoffmann, C., Vandivier, L., Cuff, C., Lewis, J.D., Wu, G.D., Bushman, F.D., 2013. Fungi of the murine gut: episodic variation and proliferation during antibiotic treatment. PLoS ONE 8, e71806.
Eckburg, P.B., Bik, E.M., Bernstein, C.N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K.E., Relman, D.A., 2005. Diversity of the human intestinal microbial flora. Science 308, 1635.
Elkington, S.G., Floch, M.H., Conn, H.O., 1969. Lactulose in the treatment of chronic portal-systemic encephalopathy. A double-blind clinical trial. N. Engl. J. Med. 281, 408.
Ferreira, C.L., Salminen, S., Grzeskowiak, L., Brizuela, M.A., Sanchez, L., Carneiro, H., Bonnet, M., 2011. Terminology concepts of probiotic and prebiotic and their role in human and animal health. Revista De Salud Animal.
Ferreira, C.M., Vieira, A.T., Vinolo, M.A.R., Oliveira, F.A., Rui, C., Martins, F.D.S., 2014. The central role of the gut microbiota in chronic inflammatory diseases. J. Immunol. Res. 2014.
Fiddian-Green, R.G., 2006. Helicobacter pylori eradication and L-dopa absorption in patients with PD and motor fluctuations. Neurology 66, 1824–1829.
Forslund, K., Hildebrand, F., Nielsen, T., Falony, G., Le, C.E., Sunagawa, S., Prifti, E., Vieirasilva, S., Gudmundsdottir, V., Krogh, P.H., 2017. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature 545, 116.
Fouts, J.R., Kamm, J.J., Brodie, B.B., 1957. Enzymatic reduction of prontosil and other azo dyes. J. Pharmacol. Exp. Ther. 120, 291–300.
Frankel, A.E., Coughlin, L.A., Kim, J., Froehlich, T.W., Xie, Y., Frenkel, E.P., Koh, A.Y., 2017. Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia (New York, NY) 19, 848–855.
Gadaleta, R.M., Cariello, M., Sabbà, C., Moschetta, A., 2015. Tissue-specific actions of FXR in metabolism and cancer. BBA 1851, 30–39.
Gamage, N., Barnett, A., Hempel, N., Duggleby, R.G., Windmill, K.F., Martin, J.L., Mcmanus, M.E., 2006. Human sulfotransferases and their role in chemical metabolism. Toxicol. Sci. 90, 5–22.
Gavhane, Y.N., Yadav, A.V., 2012. Loss of orally administered drugs in GI tract. Saudi Pharm. J. 20, 331–344.
Gingell, R., Bridges, J.W., 1973. Intestinal Azo-reduction and Glucuronide Conjugation of Prontosil. Xenobiotica; Fate Foreign Compd. Biol. Syst. 3, 599.
Gingell, R., Bridges, J.W., Williams, R.T., 1971. The role of the gut flora in the metabolism of prontosil and neoprontosil in the rat. Xenobiotica 1, 143–156.
Goldin, B.R., Peppercorn, M.A., Goldman, P., 1973. Contributions of host and intestinal microflora in the metabolism of L-dopa by the rat. J. Pharmacol. Exp. Ther. 186, 160.
Gong, S., Tian, L., Zeng, L., Luo, H., Yang, X., Na, L., Chen, X., Liu, Z., Rui, L., Win, S., 2018. Gut microbiota mediates diurnal variation of acetaminophen induced acute liver injury in mice. J. Hepatol. 69. S0168827818301466.
Gopalakrishnan, V., Spencer, C.N., Nezi, L., Reuben, A., Andrews, M.C., Karpinets, T.V., Prieto, P.A., Vicente, D., Hoffman, K., Wei, S.C., 2018. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359, 97.
Gopalakrishnan, V., Spencer, C.N., Nezi, L., Reuben, A., Andrews, M.C., Karpinets, T.V., Prieto, P.A., Vicente, D., Hoffman, K., Wei, S.C., Cogdill, A.P., Zhao, L., Hudgens, C. W., Hutchinson, D.S., Manzo, T., Petaccia de Macedo, M., Cotechini, T., Kumar, T., Chen, W.S., Reddy, S.M., Szczepaniak Sloane, R., Galloway-Pena, J., Jiang, H., Chen, P.L., Shpall, E.J., Rezvani, K., Alousi, A.M., Chemaly, R.F., Shelburne, S., Vence, L.M., Okhuysen, P.C., Jensen, V.B., Swennes, A.G., McAllister, F., Marcelo Riquelme Sanchez, E., Zhang, Y., Le Chatelier, E., Zitvogel, L., Pons, N., Austin-Breneman, J.L., Haydu, L.E., Burton, E.M., Gardner, J.M., Sirmans, E., Hu, J., Lazar, A.J., Tsujikawa, T., Diab, A., Tawbi, H., Glitza, I.C., Hwu, W.J., Patel, S.P., Woodman, S.E., Amaria, R.N., Davies, M.A., Gershenwald, J.E., Hwu, P., Lee, J.E., Zhang, J., Coussens, L.M., Cooper, Z.A., Futreal, P.A., Daniel, C.R., Ajami, N.J., Petrosino, J.F., Tetzlaff, M.T., Sharma, P., Allison, J.P., Jenq, R.R., Wargo, J.A., 2018. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359, 97–103.
Grundmann, O., 2010. The gut microbiome and pre-systemic metabolism: current state and evolving research. J. Drug Metab. Toxicol. 1 (104), 2.
Haiser, H.J., Gootenberg, D.B., Chatman, K., Sirasani, G., Balskus, E.P., Turnbaugh, P.J., 2014. Predicting and manipulating cardiac drug inactivation by the human gut bacterium eggerthella lenta. Science 341, 295–298.
Haiser, H.J., Seim, K.L., Balskus, E.P., Turnbaugh, P.J., 2014. Mechanistic insight into digoxin inactivation by Eggerthella lenta augments our understanding of its pharmacokinetics. Gut Microbes 5, 233–238.

Haiser, H.J., Turnbaugh, P.J., 2012. Is it time for a metagenomic basis of therapeutics?. Science 336, 1253–1255.
Hashim, H., Azmin, S., Razlan, H., Yahya, N.W., Tan, H.J., Manaf, M.R.A., Ibrahim, N. M., 2014. Eradication of helicobacter pylori infection improves levodopa action, clinical symptoms and quality of life in patients with Parkinson's disease. PLoS ONE 9, e112330.
Hattori, M., Namba, T., Akao, T., Kobashi, K., 1980. Metabolism of sennosides by human intestinal bacteria. Planta Med. 40, 172–179.
Hattori, M., Sakamoto, T., Kobashi, K., Namba, T., 1983. Metabolism of glycyrrhizin by human intestinal flora. Planta Med. 48, 38.
Hayllar, J., Bjarnason, I., 1991. Sulphasalazine in ulcerative colitis: in memoriam?. Gut 32, 462.
He, Z., Cui, B.T., Zhang, T., Li, P., Long, C.Y., Ji, G.Z., Zhang, F.M., 2017. Fecal microbiota transplantation cured epilepsy in a case with Crohn's disease: the first report. World J. Gastroenterol. 23, 3565–3568.
He, Z., Li, P., Zhu, J., Cui, B., Xu, L., Xiang, J., Zhang, T., Long, C., Huang, G., Ji, G., Nie, Y., Wu, K., Fan, D., Zhang, F., 2017. Multiple fresh fecal microbiota transplants induces and maintains clinical remission in Crohn's disease complicated with inflammatory mass. Sci. Rep. 7, 4753.
Hoban, A.E., Stilling, R.M., Moloney, G.M., Moloney, R.D., Shanahan, F., Dinan, T.G., Cryan, J.F., Clarke, G., 2017. Microbial regulation of microRNA expression in the amygdala and prefrontal cortex. Microbiome 5, 102.
Hogezand, R.A.V., Kennis, H.M., Schaik, A.V., Koopman, J.P., Hees, P.A.M.V., Tongeren, J.H.M.V., 1992. Bacterial acetylation of 5-aminosalicylic acid in faecal suspensions cultured under aerobic and anaerobic conditions. Eur. J. Clin. Pharmacol. 43, 189–192.
Houston, J.B., Day, J., Walker, J., 1982. Azo reduction of sulphasalazine in healthy volunteers. Br. J. Clin. Pharmacol. 14, 395–398.
Jeong, H.G., Kang, M.J., Kim, H.G., Oh, D.G., Kim, J.S., Lee, S.K., Jeong, T.C., 2013. Role of intestinal microflora in xenobiotic-induced toxicity. Mol. Nutr. Food Res. 57, 84–99.
Jernberg, C., Löfmark, S., Edlund, C., Jansson, J.K., 2010. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology 156, 3216–3223.
Joh, E.H., Kim, D.H., 2010. A sensitive liquid chromatography–electrospray tandem mass spectrometric method for lancemaside A and its metabolites in plasma and a pharmacokinetic study in mice. J. Chromatogr. B 878, 1875–1880.
Johnsen, P.H., Hilpüsch, F., Cavanagh, J.P., Leikanger, I.S., Kolstad, C., Valle, P.C., Goll, R., 2018. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. Lancet Gastroenterol. Hepatol. 3, 17–24.
Kaddurahdaouk, R., Baillie, R.A., Zhu, H., Zeng, Z.B., Wiest, M.M., Nguyen, U.T., Wojnoonski, K., Watkins, S.M., Trupp, M., Krauss, R.M., 2011. Enteric microbiome metabolites correlate with response to simvastatin treatment. PLoS ONE 6, e25482.
Kajinami, K., Akao, H., Polisecki, E., Schaefer, E.J., 2005. Pharmacogenomics of statin responsiveness. Am. J. Cardiol. 96, 65–70.
Kim, D.H., 2015. Gut microbiota-mediated drug-antibiotic interactions. Drug Metabol. Disposit. Biol. Fate Chem. 43, 1581.
Kim, D.H., Hong, S.W., Kim, B.T., Bae, E.A., Park, H.Y., Han, M.J., 2000. Biotransformation of glycyrrhizin by human intestinal bacteria and its relation to biological activities. Arch. Pharmacal Res. 23, 172.
Kim, D.H., Hyun, S.H., Shim, S.B., Kobashi, K., 1992. The role of intestinal bacteria in the transformation of sodium picosulfate. Jpn. J. Pharmacol. 59, 1.
Kim, D.H., Jung, E.A., Sohng, I.S., Han, J.A., Kim, T.H., Han, M.J., 1998. Intestinal bacterial metabolism of flavonoids and its relation to some biological activities. Arch. Pharmacal Res. 21, 17.
Kim, D.H., Kobashi, K., 1986. The role of intestinal flora in metabolism of phenolic sulfate esters. Biochem. Pharmacol. 35, 3507.
Kim, K.A., Jung, I.H., Park, S.H., Ahn, Y.T., Huh, C.S., Kim, D.H., 2013. Comparative analysis of the gut microbiota in people with different levels of ginsenoside Rb1 degradation to compound K. PLoS ONE 8. e62409–e62409.
Kim, Y.C., Lee, S.J., 1998. Temporal variation in hepatotoxicity and metabolism of acetaminophen in mice. Toxicology 128, 53–61.
Kinross, J.M., Darzi, A.W., Nicholson, J.K., 2011. Gut microbiome-host interactions in health and disease. Genome Med. 3, 14.
Kitamura, S., Sugihara, K., Kuwasako, M., Tatsumi, K., 1997. The role of mammalian intestinal bacteria in the reductive metabolism of zonisamide. J. Pharm. Pharmacol. 49, 253.
Klaassen, C.D., Cui, J.Y., 2015. Review: mechanisms of how the intestinal microbiota alters the effects of drugs and bile acids. Drug Metabol. Disposit. Biol. Fate Chem. 43, 1505–1521.
Klotz, U., 1985. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. Clin. Pharmacokinet. 10, 285.
Koch, R.L., Goldman, P., 1979. The anaerobic metabolism of metronidazole forms N-(2-hydroxyethyl)-oxamic acid. J. Pharmacol. Exp. Ther. 208, 406.
Kourtesi, C., Ball, A.R., Huang, Y.Y., Jachak, S.M., Vera, D.M.A., Khondkar, P., Gibbons, S., Hamblin, M.R., Tegos, G.P., 2013. Microbial efflux systems and inhibitors: approaches to drug discovery and the challenge of clinical implementation. Open Microbiol. J. 7, 34–52.
Kuno, T., Hirayama-Kurogi, M., Ito, S., Ohtsuki, S., 2016. Effect of intestinal flora on protein expression of drug-metabolizing enzymes and transporters in the liver and kidney of germ-free and antibiotics-treated mice. Mol. Pharm. 13, 2691–2701.
Kuno, T., Hirayamakurogi, M., Ito, S., Ohtsuki, S., 2016. Effect of intestinal flora on protein expression of drug-metabolizing enzymes and transporters in liver and kidney of germ-free and antibiotics-treated mice. Mol. Pharm. 13, 2691.
Lakshminarayanan, B., Stanton, C., O'Toole, P.W., Ross, R.P., 2014. Compositional dynamics of the human intestinal microbiota with aging: implications for health. J. Nutrit. Health Aging 18, 773.
Larson, A.M., Poison, J., Fontana, R.F., Davern, T.J., Lalani, E., Hynan, L.S., 2012. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study (vol 42, pg 1364, 2005). Austr. Prescrib. 35. 162–162.
Lederberg, J., 2000. Infectious history. Science 288, 287–293.
Lee, J.R., Muthukumar, T., Dadhania, D., Taur, Y., Jenq, R.R., Toussaint, N.C., Ling, L., Pamer, E., Suthanthiran, M., 2015. Gut microbiota and tacrolimus dosing in kidney transplantation. PLoS ONE 10, e0122399.
Ley, R.E., Bã□Ckhed, F., Turnbaugh, P., Lozupone, C.A., Knight, R.D., Gordon, J.I., 2005. Obesity alters gut microbial ecology. PNAS 102, 11070–11075.
Ley, R.E., Peterson, D.A., Gordon, J.I., 2006. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 124, 837–848.
Li, H., Jia, W., 2013. Cometabolism of microbes and host: implications for drug metabolism and drug-induced toxicity. Clin. Pharmacol. Ther. 94, 574–581.
Li, X.Z., Nikaido, H., 2004. Efflux-mediated drug resistance in bacteria. Drugs 64, 159–204.
Liang, X., Bittinger, K., Li, X., Abernethy, D.R., Bushman, F.D., Fitzgerald, G.A., 2015. Bidirectional interactions between indomethacin and the murine intestinal microbiota. Elife 4, e08973.
Lindenbaum, J., Rund, D.G., Butler Jr., V.P., Tse-Eng, D., Saha, J.R., 1981. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. N. Engl. J. Med. 305, 789–794.
Löfmark, S., Edlund, C., Nord, C.E., 2010. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin. Infect. Dis. 50 (Suppl 1), S16–S23.
Mangravite, L.M., Thorn, C.F., Krauss, R.M., 2006. Clinical implications of pharmacogenomics of statin treatment. Pharmacogenomics J. 6, 360.
Mani, S., Boelsterli, U.A., Redinbo, M.R., 2014. Understanding and modulating mammalian-microbial communication for improved human health. Annu. Rev. Pharmacol. Toxicol. 54, 559–580.
Martinez, M.N., Amidon, G.L., 2013. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. J. Clin. Pharmacol. 42, 620–643.
Matson, V., Fessler, J., Bao, R., Chongsuwat, T., Zha, Y., Alegre, M.L., Luke, J.J., Gajewski, T.F., 2018. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 359, 104–108.
Mikov, M., Lee, H.J., Fawcett, J.P., 2006. The influence of probiotic treatment on sulfasalazine metabolism in rat gut contents. Asian J. Pharmacokinet. Pharmacodynam. 6, 337–342.
Moore, V., 2008. The gastrointestinal microbiota as a site for the biotransformation of drugs. Int. J. Pharm. 363, 1–25.
Morita, N., Umemoto, E., Fujita, S., Hayashi, A., Kikuta, J., Kimura, I., Haneda, T., Imai, T., Inoue, A., Mimuro, H., Maeda, Y., Kayama, H., Okumura, R., Aoki, J., Okada, N., Kida, T., Ishii, M., Nabeshima, R., Takeda, K., 2019. GPR31-dependent dendrite protrusion of intestinal CX3CR1(+) cells by bacterial metabolites. Nature.
Nakayama, H., Kinouchi, T., Kataoka, K., Akimoto, S., Matsuda, Y., Ohnishi, Y., 1997. Intestinal anaerobic bacteria hydrolyse sorivudine, producing the high blood concentration of 5-(E)-(2-bromovinyl)uracil that increases the level and toxicity of 5-fluorouracil. Pharmacogenetics 7, 35–43.
Niemi, M., Pasanen, M.K., Neuvonen, P.J., 2011. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharmacol. Rev. 63, 157–181.
Okuda, H., Ogura, K., Kato, A., Takubo, H., Watabe, T., 1998. A possible mechanism of eighteen patient deaths caused by interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. J. Pharmacol. Exp. Ther. 287, 791.
Peppercorn, M.A., Goldman, P., 1973. Distribution studies of salicylazosulfapyridine and its metabolites. Gastroenterology 64, 240–245.
Perreten, V., Schwarz, F.V., Teuber, M., Levy, S.B., 2001. Mdt(A), a new efflux protein conferring multiple antibiotic resistance in Lactococcus lactis and Escherichia coli. Antimicrob. Agents Chemother. 45, 1109–1114.
Pierantozzi, M., Pietroiusti, A., Galante, A., Sancesario, G., Lunardi, G., Fedele, E., Giacomini, P., Stanzione, P., 2001. Helicobacter pylori-induced reduction of acute levodopa absorption in Parkinson's disease patients. Ann. Neurol. 50, 686–687.
Pierce, D., Corcoran, M., Martin, P., Barrett, K., Inglis, S., Preston, P., Thompson, T.N., Willsie, S.K., 2014. Effect of MMX® mesalamine coadministration on the pharmacokinetics of amoxicillin, ciprofloxacin XR, metronidazole, and sulfamethoxazole: results from four randomized clinical trials. Drug Design Dev. Therapy 8, 529–543.
Possamai, L.A., Mcphail, M.J., Khamri, W., Wu, B., Concas, D., Harrison, M., Williams, R., Cox, R.D., Cox, I.J., Anstee, Q.M., 2015. The role of intestinal microbiota in murine models of acetaminophen-induced hepatotoxicity. Liver Int. Off. J. Int. Assoc. Study Liver 35, 764–773.
Postmus, I., Trompet, S., Deshmukh, H.A., Barnes, M.R., Li, X., Warren, H.R., Chasman, D.I., Zhou, K., Arsenault, B.J., Donnelly, L.A., 2014. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. Nat. Commun. 5, 5068.
Putman, M., Van Veen, H.W., Konings, W.N., 2000. Molecular properties of bacterial multidrug transporters. Microbiol. Mol. Biol. Rev. Mmbr. 64, 672.

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65.
Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D.R., 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65.
Rafii, F., 1997. Reduction of nitrazepam by Clostridium leptum, a nitroreductase-producing bacterium isolated from the human intestinal tract. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 25 (Suppl 2), S121.
Ramakrishna, B.S., 2013. Role of the gut microbiota in human nutrition and metabolism. J. Gastroenterol. Hepatol. 28, 9–17.
Roberts, A.B., Wallace, B.D., Venkatesh, M.K., Mani, S., Redinbo, M.R., 2013. Molecular insights into microbial β-glucuronidase inhibition to abrogate CPT-11 toxicity. Mol. Pharmacol. 84, 208–217.
Roberts, M.S., Magnusson, B.M., Burczynski, F.J., Weiss, M., 2002. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. Clin. Pharmacokinet. 41, 751.
Robertson, L.W., Chandrasekaran, A., Reuning, R.H., Hui, J., Rawal, B.D., 1986. Reduction of digoxin to 20R-dihydrodigoxin by cultures of Eubacterium lentum. Appl. Environ. Microbiol. 51, 1300.
Rooks, M.G., Garrett, W.S., 2016. Gut microbiota, metabolites and host immunity. Nat. Rev. Immunol. 16, 341.
Routy, B., Le, C.E., Derosa, L., Cpm, D., Alou, M.T., Daillère, R., Fluckiger, A., Messaoudene, M., Rauber, C., Roberti, M.P., 2018. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359, 91.
Routy, B., Le Chatelier, E., Derosa, L., Duong, C.P.M., Alou, M.T., Daillère, R., Fluckiger, A., Messaoudene, M., Rauber, C., Roberti, M.P., Fidelle, M., Flament, C., Poirier-Colame, V., Opolon, P., Klein, C., Iribarren, K., Mondragón, L., Jacquelot, N., Qu, B., Ferrere, G., Clémenson, C., Mezquita, L., Masip, J.R., Naltet, C., Brosseau, S., Kaderbhai, C., Richard, C., Rizvi, H., Levenez, F., Galleron, N., Quinquis, B., Pons, N., Ryffel, B., Minard-Colin, V., Gonin, P., Soria, J.C., Deutsch, E., Loriot, Y., Ghiringhelli, F., Zalcman, G., Goldwasser, F., Escudier, B., Hellmann, M.D., Eggermont, A., Raoult, D., Albiges, L., Kroemer, G., Zitvogel, L., 2018. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359, 91–97.
Saha, J.R., Butler Jr., V.P., Neu, H.C., Lindenbaum, J., 1983. Digoxin-inactivating bacteria: identification in human gut flora. Science 220, 325–327.
Saitta, K.S., Zhang, C., Lee, K.K., Fujimoto, K., Redinbo, M.R., Boelsterli, U.A., 2014. Bacterial β-glucuronidase inhibition protects mice against enteropathy induced by indomethacin, ketoprofen or diclofenac: mode of action and pharmacokinetics. Xenobiotica 44, 28–35.
Sayin, S.I., Wahlström, A., Felin, J., Jäntti, S., Marschall, H.U., Bamberg, K., Angelin, B., Hyötyläinen, T., Orešič, M., Bäckhed, F., 2013. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metab. 17, 225–235.
Sender, R., Fuchs, S., Milo, R., 2016. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 164, 337–340.
Sepehr, E., Cooke, G.M., Robertson, P., Gilani, G.S., 2009. Effect of glycosidation of isoflavones on their bioavailability and pharmacokinetics in aged male rats. Mol. Nutr. Food Res. 53, 16–26.
Shu, Y.Z., Kingston, D.G., Van Tassell, R.L., Wilkins, T.D., 1991. Metabolism of levamisole, an anti-colon cancer drug, by human intestinal bacteria. Xenobiotica 21, 737–750.
Singh, V., Yeoh, B.S., Vijay-Kumar, M., 2016. Gut microbiome as a novel cardiovascular therapeutic target. Curr. Opin. Pharmacol. 27, 8–12.
Sivan, A., Corrales, L., Hubert, N., Williams, J.B., Aquinomichaels, K., Earley, Z.M., Benyamin, F.W., Lei, Y.M., Jabri, B., Alegre, M.L., 2015. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy. Science 350, 1084–1089.
Sommer, F., Bäckhed, F., 2013. The gut microbiota–masters of host development and physiology. Nat. Rev. Microbiol. 11, 227–238.
Spanogiannopoulos, P., Bess, E.N., Carmody, R.N., Turnbaugh, P.J., 2016. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nat. Rev. Microbiol. 14, 273–287.
Taguer, M., Maurice, C.F., 2016. The complex interplay of diet, xenobiotics, and microbial metabolism in the gut: Implications for clinical outcomes. Clin. Pharmacol. Ther. 99, 588–599.
Takeno, S., Hirano, Y., Kitamura, A., Sakai, T., 1993. Comparative developmental toxicity and metabolism of nitrazepam in rats and mice. Toxicol. Appl. Pharmacol. 121, 233–238.
Takeno, S., Sakai, T., 1991. Involvement of the intestinal microflora in nitrazepam-induced teratogenicity in rats and its relationship to nitroreduction. Teratology 44, 209–214.
Tao, J.H., Duan, J.A., Jiang, S., Qian, Y.Y., Qian, D.W., 2016. Biotransformation and metabolic profile of buddleoside with human intestinal microflora by ultrahigh-performance liquid chromatography coupled to hybrid linear ion trap/orbitrap mass spectrometer. J. Chromatogr. Bs 1009–1010, 163–169.
Tilg, H., Kaser, A., 2011. Gut microbiome, obesity, and metabolic dysfunction. J. Clin. Investig. 121, 2126–2132.
Torres, C., Galián, C., Freiberg, C., Fantino, J.R., Jault, J.M., 2009. The YheI/YheH heterodimer from Bacillus subtilis is a multidrug ABC transporter. BBA – Biomembranes 1788, 615–622.
Trinh, H., Joh, E., Kwak, H., Baek, N., Kim, D., 2010. Anti-pruritic effect of baicalin and its metabolites, baicalein and oroxylin A, in mice. 中国药理学报 31, 718–724.
Turnbaugh, P.J., Quince, C., Faith, J.J., Mchardy, A.C., Yatsunenko, T., Niazi, F., Affourtit, J., Egholm, M., Henrissat, B., Knight, R., 2010. Organismal, genetic, and transcriptional variation in the deeply sequenced gut microbiomes of identical twins. PNAS 107, 7503–7508.
Ünsalan, S., Çıkla, P., Küçükgüzel, Ş., Rollas, S., Şahin, F., Bayrak, Ö., 2011. Synthesis and characterization of triazenes derived from sulfonamides. Marmara Pharmaceut. J. 15, 11–17.
Vétizou, M., Pitt, J.M., Daillère, R., Lepage, P., Waldschmitt, N., Flament, C., Rusakiewicz, S., Routy, B., Roberti, M.P., Duong, C.P.M., 2015. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350, 1079.
Vanhoefer, U., Harstrick, A., Achterrath, W., Cao, S., Seeber, S., Rustum, Y.M., 2001. Irinotecan in the treatment of colorectal cancer: clinical overview. J. Clin. Oncol. 19, 1501–1518.
Verschuren, J.J.W., Trompet, S., Wessels, J.A.M., Guchelaar, H.J., De Maat, M.P.M., Simoons, M.L., Jukema, J.W., 2012. A systematic review on pharmacogenetics in cardiovascular disease: is it ready for clinical application?. Eur. Heart J. 33, 165.
Wacher, V.J., Salphati, L., Benet, L.Z., 2001. Active secretion and enterocytic drug metabolism barriers to drug absorption. Adv. Drug Deliv. Rev. 46, 89–102.
Wacher, V.J., Salphati, L., Benet, L.Z., 2001. Active secretion and enterocytic drug metabolism barriers to drug absorption 1. Adv. Drug Deliv. Rev. 46, 89–102.
Wadworth, A.N., Fitton, A., 1991. Olsalazine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in inflammatory bowel disease. Drugs 41, 647–664.
Wallace, B.D., Wang, H., Lane, K.T., Scott, J.E., Orans, J., Koo, J.S., Venkatesh, M., Jobin, C., Yeh, L.A., Mani, S., 2010. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science 330, 831–835.
Wang, Y., Ma, R., Liu, F., Lee, S.A., Zhang, L., 2018a. Modulation of gut microbiota: a novel paradigm of enhancing the efficacy of programmed death-1 and programmed death ligand-1 blockade therapy. Front. Immunol. 9, 374.
Wang, Y., Wiesnoski, D.H., Helmink, B.A., Gopalakrishnan, V., Choi, K., DuPont, H.L., Jiang, Z.D., Abu-Sbeih, H., Sanchez, C.A., Chang, C.C., Parra, E.R., Francisco-Cruz, A., Raju, G.S., Stroehlein, J.R., Campbell, M.T., Gao, J., Subudhi, S.K., Maru, D.M., Blando, J.M., Lazar, A.J., Allison, J.P., Sharma, P., Tetzlaff, M.T., Wargo, J.A., Jenq, R. R., 2018b. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat. Med. 24, 1804–1808.
Wargo, J.A., Gopalakrishnan, V., Spencer, C., Karpinets, T., Reuben, A., Andrews, M.C., Tetzlaff, M.T., Lazar, A., Hwu, P., Hwu, W.-J., 2017. Association of the diversity and composition of the gut microbiome with responses and survival (PFS) in metastatic melanoma (MM) patients (pts) on anti-PD-1 therapy. Am. Soc. Clin. Oncol.
Watanabe, K., Yamashita, S., Furuno, K., Kawasaki, H., Gomita, Y., 1995. Metabolism of omeprazole by gut flora in rats. J. Pharm. Sci. 84, 516–517.
Wilson, I.D., Nicholson, J.K., 2017. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Transl. Res.: J. Lab. Clin. Med. 179, 204–222.
Wostmann, B.S., Larkin, C., Moriarty, A., Bruckner-Kardoss, E., 1983. Dietary intake, energy metabolism, and excretory losses of adult male germfree Wistar rats. Lab. Anim. Sci. 33, 46–50.
Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.Y., Keilbaugh, S.A., Bewtra, M., Knights, D., Walters, W.A., Knight, R., 2011. Linking long-term dietary patterns with gut microbial enterotypes. Science 334, 105–108.
Xu, J., Chen, H.B., Li, S.L., 2017. Understanding the molecular mechanisms of the interplay between herbal medicines and gut microbiota. Med. Res. Rev. 37, 1140.
Yoo, D.H., Kim, I.S., Van Le, T.K., Jung, I.H., Yoo, H.H., Kim, D.H., 2014. Gut microbiota-mediated drug interactions between lovastatin and antibiotics. Drug Metab. Dispos. 42, 1508–1513.
Zhang, J., Min, R.W.M., Le, K., Zhou, S., Aghajan, M., Than, T.A., Win, S., Kaplowitz, N., 2017. The role of MAP2 kinases and p38 kinase in acute murine liver injury models. Cell Death Dis. 8, e2903.
Zhao, L., 2013. The gut microbiota and obesity: from correlation to causality. Nat. Rev. Microbiol. 11, 639.