Published in final edited form as:

Expert Opin Drug Metab Toxicol. 2016 ; 12(1): 31–40. doi:10.1517/17425255.2016.1121234.

The influence of gut microbiota on drug metabolism and toxicity

Prof. Houkai Li^{1,*}, Jiaojiao He¹, and Prof. Wei Jia^{1,2,*}

¹Center for Chinese Medical Therapy and Systems Biology, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

²Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii, 96813, USA

Abstract

Introduction—Gut microbiota plays critical roles in drug metabolism. The individual variation of gut microbiota contributes to the interindividual differences towards drug therapy including drug-induced toxicity and efficacy. Accordingly, the investigation and elucidation of gut microbial impacts on drug metabolism and toxicity will not only facilitate the way of personalized medicine, but also improve the rational drug design.

Areas covered—This review provide an overview on the microbiota-host cometabolism on drug metabolism and summarize 30 clinical drugs which are co-metabolized by host and gut microbiota. Moreover, this review is specifically focused on elucidating the gut microbial modulation on some clinical drugs, in which the gut microbial influences on drug metabolism, drug-induced toxicity and efficacy are intensively discussed.

Expert opinion—The gut microbial contribution to drug metabolism and toxicity is increasingly recognized, but remains largely unexplored due to the extremely complex relationship between gut microbiota and host. The mechanistic elucidation of gut microbiota in drug metabolism is critical before any practical progress in drug design or personalized medicine could be made by modulating human gut microbiota, which is predominantly relied on the technical innovations such as metagenomics and metabolomics, as well as the integration of multi-disciplinary knowledge.

1. Introduction

The gut microbiome is the collective genome of the whole microbes inhabiting in mammalian gastrointestinal tract, which contains over 1000 species bacteria and about 10 times the number of the host body cells ^{1, 2}. The gut microbiota has been regarded as an indispensable “metabolic organ” in regard to its critical functions in maintaining human health and involvement of various diseases ³. Meanwhile, the gut microbiota also plays

*Authors for correspondence: Houkai Li, houkai1976@126.com; Tel& Fax: 86-21-51322748 Wei Jia, wjia@cc.hawaii.edu; Tel& Fax: (808) 564-5823.

Declaration of interest

Dr. Houkai Li was supported by the grants from The Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning (No. A1-R140201) from Shanghai Municipal Education Commission, and Shanghai Pujiang Program (14PJD031) from the Science and Technology Commission of Shanghai Municipality.

crucial roles in drug metabolism by activating or inactivating the pharmacological property of drugs ⁴. Although the human gastrointestinal tract is mainly dominated by several types of bacteria phyla such as *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, the entire composition of human gut microbiota is highly variable ⁵, which contributes to the individually different responses to identical drug therapy in together with genetic polymorphism. However, in the past decades, extensive investigations have been largely focused on the host genetic background for bridging the association between host genetics and drug responses, whereas the roles of gut microbiota were underestimated owing to the complexity of gut microbiota and the difficulty in culture of gut bacteria *in vitro* ⁶.

In recent years, the microbial genomics has progressed from culture-dependent to culture-independent strategies (i.e. metagenomics), which facilitates the identification of roles of gut microbiota in diseases and drug metabolism ⁷. A new term “pharmacomicrobiomics” was coined to denote the effects of gut microbiota variations on pharmacokinetics and pharmacodynamics ⁶. To date, extensive efforts have been made to describe the effects of gut microbiota on pharmacokinetics, where gut microbiota could impact drug metabolism through several well-established ways including production of microbial metabolites to interfere with drug metabolism ⁸, production of microbial enzymes to transform drug molecules ^{9, 10}, and modification of drug metabolizing genes or enzymes in host liver or intestine tissues ⁷. However, given the extreme complexity between gut microbiota and host, the recognition of the gut microbial impacts on drug metabolism is still on the way and is now being accelerated by the striking innovation of systemic approaches such as metagenomics, metabolomics as well. On the other hand, the gut microbial impacts on pharmacodynamics are attracting more and more attention in recent years, due to the exiting progresses in uncovering the gut microbial modulations on drug efficacy.

In this review, we will first provide an overview of the microbiota-host cometabolism focusing on the main drug-metabolizing enzymes in liver, and the gut microbial impacts on drug metabolism. Second, we will discuss some new progresses in gut microbial-modulated drug metabolism in recent years, and summarize 30 drugs which are co-metabolized by gut microbiota and provide information about the type of microbial transformation, microbial-related products, influence on drug efficacy or toxicity, as well as the related bacteria species if available, which are responsible for the drug metabolism. Third, we will discuss the effects of gut microbial modulation on drug efficacy of recent studies, in which the gut microbiota is recognized as a critical factor for influencing the therapeutic outcome of some clinical drugs. The elucidation of these microbial contributions to the variations in drug responses will pave the way towards personalized therapy.

1. Microbiota-host cometabolism on drug metabolism and toxicity

2.1 Host and microbiota drug-metabolizing enzymes

Human beings are living with indispensable symbiotics over the whole life, which shapes the capability of detoxifying xenobiotics (including drugs, dietary compounds) through microbiota-host cometabolism. The host detoxification systems include phase I and phase II reactions. The phase I metabolism, including oxidation, reduction, hydroxylation, etc, is mainly mediated by cytochrome P450 (CYP) enzymes in liver, gut and other tissues, which

is to facilitate the excretion of xenobiotics in urine by increasing the polarity of foreign compounds. The phase II metabolism is the conjugation reaction, including glucuronidation and sulfonation. The foreign compounds are conjugated with endogenous metabolites by host enzyme transfer systems to increase their urinary excretion. The phase II enzymes include sulfotransferase (SULT), uridine 5'-diphospho-glucuronosyltransferase /UDP-glucuronosyltransferase (UGT), N-acetyltransferase (NAT) and glutathione S-transferase (GST) ¹¹. Over 70% of prescribed top 200 drugs are metabolized in liver, whereas about 25% are eliminated in kidney ¹¹, and about 50% of drugs are metabolized through P450 enzyme system highlighting the significance of the P450 enzyme systems in drug metabolism.

In addition to the host drug metabolism system, the gut microbiota also plays important roles in drug metabolism through secretion of microbial drug-metabolizing enzymes or microbiota-host cometabolism. Although, the impacts of gut microbiota on drug metabolism have been investigated for decades, the gut microbial impacts on only about 40 drugs or natural products have been reported so far ⁴. According to the well-established evidence of gut microbial influence on pharmacokinetics, the gut microbiota usually modulates the oral drug bioavailability or half-life of drugs via microbiota-host cometabolism by altering the capacity of drug-metabolizing enzymes or expression of genes involved in drug metabolism in host tissues ⁷. Moreover, the individual composition or function of gut microbiota is apt to be influenced by environmental factors such as diets, and antibiotics, or the healthy status of host because lots of diseases are associated with the gut dysbiosis or the vice versa ¹². Consequently, the individually different responses towards drug therapy are indispensably associated with the variations of gut microbiota ¹³. Most drugs are metabolized by host or microbiota-host cometabolism into active, inactive or toxic metabolites. About 30 therapeutic drugs which are metabolized by microbiota-host cometabolism are systemically summarized in Table 1. The following are several examples of clinical drugs with well-established evidence of microbial-modulation on their metabolism and toxicity.

2.2 Microbiota variation influences acetaminophen metabolism and acetaminophen-induced hepatotoxicity

Acetaminophen is a widely used analgesic and antipyretic medicine. However, the overdose of acetaminophen-induced hepatotoxicity is the most common cases in USA and UK ^{14, 15}. Acetaminophen is deactivated mainly by glucuronidation and sulfation to conjugated metabolites, and a small part of acetaminophen could be transformed to N-acetyl-p-benzoquinone imine by P450 enzymes, which is supposed to be the toxic metabolite of acetaminophen. With metabolomics approach, Clayton et al. have observed that individuals with a high level of predose urinary p-cresol, a microbial metabolite ¹⁶, show low postdose urinary ratios of acetaminophen sulfate to acetaminophen glucuronide ⁸, suggesting the microbial contribution on acetaminophen metabolism. Moreover, Lee et al. evaluate the effects of intestinal microbiota on acetaminophen metabolism in antibiotic-treated rats. They find that antibiotic-treated rats have higher level of acetaminophen glutathione conjugates in blood than untreated rats ¹⁷, which further suggests the gut microbial impacts on acetaminophen metabolism. Since p-cresol and acetaminophen are competitive substrates for cytosolic sulfotransferase ¹⁸, the high level of p-cresol may compete with acetaminophen for

binding with cytosolic sulfotransferase, and consequently alters the bioavailability of acetaminophen and its metabolites leading to the individual variation in acetaminophen metabolism and its hepatotoxicity. On the other hand, Possamai et al recently report that no significant differences in the extent of hepatocellular injury induced by acetaminophen between germ free and conventional housed mice. However, they observe that germ free mice show a milder acute liver failure and differential acetaminophen metabolism compared to conventional house mice¹⁹, suggesting the variations in gut microbiota do not fully explain the differential susceptibility to acetaminophen-induced liver injury, at least in mice. Given the physiological differences between animals and human, the influence of gut microbial metabolism on acetaminophen-induced hepatotoxicity needs further investigation.

2.3 Microbial metabolism on digoxin

Digoxin is a cardiac glycoside which is used for chronic heart failure therapy. It is also a well-established drug that the cardiac activity of digoxin is influenced by gut microbial metabolism, which metabolizes the parent compound into inactive metabolite, dihydrodigoxin by reducing the lactone ring of digoxin^{20,21}. Additionally, the gut microbial metabolism of digoxin is further demonstrated by the observation that antibiotic pretreatment reduces the secretion of dihydrodigoxin in urine and increases the level of digoxin in blood²², as well as the identification of digoxin-metabolizing gut bacteria, *Eggertherilla lenta*²³. Recently, a further investigation reveals a cytochrome-encoding operon in a common gut bacteria *Eggerthella lenta*, which is transcriptionally activated by digoxin. The identified cytochrome-encoding operon, also named cardiac glycoside reductase (*cgr*) operon, is supposed to be a predictor of the inactivation of digoxin because a significant correlation between “*cgr*ratio” (*cgr* abundance normalized by *E. lenta* 16S rDNA level) and *ex vivo* digoxin inactivation in healthy volunteers is observed⁹. Accordingly, the elucidation of the mechanisms underlying the gut microbial metabolism on digoxin augments the understanding on gut microbial impacts on pharmacokinetics, and paves the way for clinical application of reducing drug toxicity by manipulating gut microbiota.

1.4 Microbiota depletion reduces the side effect of irinotecan

Irinotecan (CPT-11) is a chemotherapeutic drug for colorectal cancers²⁴, which is intravenously used in clinic. CPT-11 is transformed by carboxylesterases in host tissues into active form SN-38, an inhibitor of topoisomerase I in tumor cells. SN-38 is conjugated into SN-38-G by hepatic UDP-glucuronosyltransferases before secreting into intestine. However, the nontoxic SN-38-G could be converted to SN-38 by the β -glucuronidase of gut bacteria leading to the severe intestinal side effect of diarrhea²⁵. Antibiotic treatment could significantly reduce the intestinal side effect of CPT-11 by suppressing the gut microbiota²⁶. Moreover, researchers have found out a potent inhibitor of β -glucuronidase that could effectively decrease the CPT-11-induced diarrhea and protect intestinal tissue by reducing cellular inflammation²⁷. Since CPT-11 is an intravenously delivered drug, the understanding on the gut microbial modulation on its intestinal side effect provides evidence of the profound impacts of gut microbiota on drug metabolism, in addition to the direct influence on orally administered drugs.

2. Gut microbiota influence on drug efficacy

Besides the well-evidenced microbial impacts on drug metabolism and toxicity, the intricate relationship between gut microbiota and host highlights the significance of gut microbiota on drug efficacy. In recent years, increasing evidence indicates that the variation of therapeutic effects of many drugs is associated with the differences in gut microbiota, which warrants the potential of gut microbiota-targeted manipulation for increasing drug efficacy.

3.1 Gut microbiota modulates the effect of antitumor chemotherapeutics

The commensal gut microbiota is profoundly involved in modulation of mammalian immunity²⁸. The antitumor chemotherapeutics usually cause the gut dysbiosis leading to severe intestinal side effects, as well as the modulation on host immune responses. Cyclophosphamide (CTX) is a widely used antitumor drug by inducing immunogenic cancer cell death^{29, 30}, subverting immunosuppressive T cells³¹ and promoting T_H 1 and T_H17 cells control tumor cell growth³². Recently, researchers demonstrate that CTX can alter the composition of gut microbiota and induce the translocation of several species of Gram-positive bacteria into secondary lymphoid organs. Then, these bacteria stimulate the generation of a specific subset of “pathogenic” T helper17 (pT_H17) cells and memory T_H1 immune responses. Moreover, tumor-bearing germ free mice or mice treated with antibiotics to deplete Gram-positive bacteria show a reduction in pT_H17 responses and resistance to the antitumor effect of CTX³³. In a similar study, researchers find that the disruption of gut microbiota impairs the therapeutic responses of subcutaneous tumors to a CpG-oligonucleotide immunotherapy and platinum chemotherapy. Meanwhile, germ free or antibiotic-treated mice show poor responses to therapy³⁴. As a result, the gut microbiota is also an important factor for influencing the efficacy of some antitumor chemotherapeutics, which highlights the potential of gut microbiota-targeted intervention for increasing the efficacy of antitumor chemotherapy.

3.2 Microbiota variation contributes to therapeutic difference of statin

Statins are the most frequently prescribed drugs for reducing plasma levels of LDL cholesterol and risk of cardiovascular disease by inhibiting 3-hydroxy-3-methyl-glutaryl-Co A (HMG-CoA) reductase³⁵. However, the efficacy of statins in reducing LDL-C varies greatly among individuals³⁶, whereas the reason is little known. Kaddurah-Daouk et al. investigate the correlation between baseline metabolites and therapeutic efficacy of simvastatin with targeted metabolomics³⁷. Their data indicate the baseline levels of several secondary bile acids, which are gut microbial-derived, could predict the magnitude of LDL-C lowering effect of simvastatin. Moreover, these microbial-derived secondary bile acids also correlate with the plasma levels of simvastatin, suggesting probable gut microbial impacts on the bioavailability of simvastatin. Similarly, a recent study indicates that incubation of lovastatin with human or rat fecalase preparations produces four metabolites. Moreover, the plasma concentration of the active hydroxyl acid metabolite of lovastatin is significantly lower in antibiotic-treated rats than controls³⁸. These results demonstrate that the oral lovastatin is also co-metabolized by gut microbiota, which may contribute to the variation in efficacy of lovastatin among individuals because of the differences in gut microbiota.

Expert opinion

Interindividual variation in response to same drug therapy is a very common phenomenon in clinic, which is predominantly regarded as a consequence of genetic diversity previously. However, the increasing evidence of gut microbiota involvement in drug metabolism shed light on the crucial roles of gut microbiota in determining the therapeutic outcomes in together with the host metabolism. Although we have made exciting progress in uncovering the intricate relationship between gut microbiota and drug metabolism during past decades, especially in the recent years because of technical innovation, there is still a long way to go before we can utilize the knowledge of gut microbiota for rational drug design, and personalized medicine, in which a more potent drug activity and lower drug-induced toxicity are expected. Currently, most of our endeavors are directing to the accumulation of knowledge on identification of roles and elucidation of mechanisms underlying the gut microbiota-involved drug metabolism and toxicity. Although the ultimate goal is prospective, there are some big challenges in front of us.

First, it is still a great challenge to identify the specific roles of gut bacteria in modulating drug metabolism. Antibiotic-treated animal models are frequently used for investigating the involvement of gut microbiota in drug metabolism and toxicity. Moreover, a more specific relationship between certain species of bacteria and drug metabolism can be discovered by using different antibiotics or their combination with different antibacterial spectrums. For example, vancomycin is usually used for elimination of Gram-positive bacteria, whereas a combination of ampicillin, neomycin, metronidazole and vancomycin is used for gut sterilization to produce a pseudo-germ free animal model³⁹. Compared to antibiotic-treated animal model, the germ free or gnotobiotic animals are better for investigating the contribution of specific bacteria in drug metabolism. However, both germ free and gnotobiotic animals are not only expensive, but also have strict requirements in animal house facilities, which greatly hinds their application. Accordingly, we envisage that antibiotic-treated animals will serve as a practical model for identifying the roles of gut microbiota in drug metabolism in most studies. However, more attention should be paid to distinguish the impacts on drug metabolism between antibiotic itself and antibiotic-induced alteration of gut microbiota. In addition, we should also bear in mind the existence of potential direct drug-drug interaction in intestine between unabsorbed antibiotics and investigated drugs, which may mislead our understanding on the role of gut microbiota in drug metabolism.

Second, the elucidation of gut microbial roles in drug metabolism largely relies on the technical innovations. The variable regions of bacteria 16S rDNA provide the opportunity for identification of bacteria species by 16S rDNA-based gene sequencing technique. However, the identification power of 16S rDNA-based gene sequencing is still very limited due to the extremely high similarity in sequence of 16S rDNA among bacteria within same family or even genus. Compared to the 16S rDNA sequencing, metagenomics is more powerful in microbial diversity study by providing unbiased sequence information of the whole gut microbiota. However, there is also limitation in application of metagenomics currently due to the relatively high price of sequencing and requirement of bioinformatics work on the enormous data of metagenomics. Therefore, other omics approach such as metabolomics is increasing adopted for combined analysis on gut microbiota-related

metabolic profiling or targeted metabolic analysis of specific microbial-associated metabolic pathways. It is estimated at least 10% of metabolites in plasma are gut microbiota-related ⁴⁰, in which more and more evidence has been achieved for bridging the gut microbiota-related metabolites with certain species of bacteria ⁴¹. As a result, it is prospective to investigate the role of gut microbiota in drug metabolism by using combined approaches such as metabolomics and metagenomics.

Third, the mechanisms underlying gut microbial modulation on drug metabolism are complicated and elusive. Currently, the effect of gut microbial-mediated drug metabolism has been well characterized in only about 40 clinical drugs. Given the thousands of clinical drugs, it is an urgent and challenging task for us to determine the roles of gut microbiota in drug metabolism and drug-induced toxicity. Moreover, the increasing application of antibiotics and their frequent combination with other medicines make the patients at the risk of unexpected drug-induced toxicity or compromising of drug efficacy. There are many ways for gut microbial modulation on drug metabolism such as direct secretion of drug metabolizing enzymes in intestine, completion for receptors or transporters in host tissues with drugs via production of bacterial metabolite, and microbial modulation on activity of drug metabolizing enzymes in host tissues which alters their capability in drug metabolism. Accordingly, the study on gut microbiota needs the efficient cooperation among scientists from different disciplines such as pharmacology, toxicology, microbiology, molecular biology, bioinformatics, and analytical chemistry, in addition to the instrumental innovation such as metagenomics and metabolomics. Based on the sustained enthusiasm on gut microbiota study and technical improvement, we believe that at least dozens of drugs which are co-metabolized by gut microbiota will be well-evidenced in the coming five to ten years, which will also facilitate the rational drug design by producing drugs with more potent and lower toxicity.

Bibliography

Papers of special note have been highlighted as either of interest

(•) or of considerable interest

(••) to readers.

1. Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. *Science*. 2006 Jun 2; 312(5778):1355–9. [PubMed: 16741115]
2. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010 Mar 4; 464(7285):59–65. [PubMed: 20203603]
- 3•. Jia W, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. *Nat Rev Drug Discov*. 2008 Feb; 7(2):123–9. This review provides an overview of gut microbiota involvement in diseases development and hypothesizes gut microbiota as a potential drug target. [PubMed: 18239669]
- 4••. Kang MJ, Kim HG, Kim JS, Oh do G, Um YJ, Seo CS, et al. The effect of gut microbiota on drug metabolism. *Expert opinion on drug metabolism & toxicology*. 2013 Oct; 9(10):1295–308. This review systemically summarized the gut microbiota modulation on many natural products and synthetic drugs. [PubMed: 24033282]
5. Rajilic-Stojanovic M, Smidt H, de Vos WM. Diversity of the human gastrointestinal tract microbiota revisited. *Environ Microbiol*. 2007 Sep; 9(9):2125–36. [PubMed: 17686012]

- 6•. Saad R, Rizkallah MR, Aziz RK. Gut Pharmacomicrobiomics: the tip of an iceberg of complex interactions between drugs and gut-associated microbes. *Gut Pathog.* 2012; 4(1):16. This paper discussed the complicated relationship between host and gut microbes, and coined the term of “pharmacomicrobiomics”. [PubMed: 23194438]
- 7••. Haiser HJ, Turnbaugh PJ. Developing a metagenomic view of xenobiotic metabolism. *Pharmacol Res.* 2013 Mar; 69(1):21–31. In this paper, the authors summarized the roles of gut microbiota in xenobiotic metabolism with some important examples. [PubMed: 22902524]
8. Clayton TA, Baker D, Lindon JC, Everett JR, Nicholson JK. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism. *Proceedings of the National Academy of Sciences of the United States of America.* 2009 Aug 25; 106(34):14728–33. [PubMed: 19667173]
9. Haiser HJ, Gootenberg DB, Chatman K, Sirasani G, Balskus EP, Turnbaugh PJ. Predicting and manipulating cardiac drug inactivation by the human gut bacterium *Eggerthella lenta*. *Science.* 2013 Jul 19; 341(6143):295–8. [PubMed: 23869020]
10. Westman EL, Canova MJ, Radhi IJ, Koteva K, Kireeva I, Waglechner N, et al. Bacterial inactivation of the anticancer drug doxorubicin. *Chem Biol.* 2012 Oct 26; 19(10):1255–64. [PubMed: 23102220]
11. Di L. The role of drug metabolizing enzymes in clearance. *Expert opinion on drug metabolism & toxicology.* 2014 Mar; 10(3):379–93. [PubMed: 24392841]
12. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. *Nat Rev Genet.* 2012 Apr; 13(4):260–70. [PubMed: 22411464]
- 13••. Li H, Jia W. Cometabolism of microbes and host: implications for drug metabolism and drug-induced toxicity. *Clin Pharmacol Ther.* 2013 Nov; 94(5):574–81. This review discussed the cometabolism between host and microbiota, and summarized the drugs that were metabolized by gut microbiota. [PubMed: 23933971]
14. Davidson DG, Eastham WN. Acute liver necrosis following overdose of paracetamol. *Br Med J.* 1966 Aug 27; 2(5512):497–9. [PubMed: 5913083]
15. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology.* 2005 Dec; 42(6):1364–72. [PubMed: 16317692]
16. Smith EA, Macfarlane GT. Formation of Phenolic and Indolic Compounds by Anaerobic Bacteria in the Human Large Intestine. *Microb Ecol.* 1997 Apr; 33(3):180–8. [PubMed: 9115181]
17. Lee SH, An JH, Lee HJ, Jung BH. Evaluation of pharmacokinetic differences of acetaminophen in pseudo germ-free rats. *Biopharm Drug Dispos.* 2012 Sep; 33(6):292–303. [PubMed: 22806334]
18. Gamage N, Barnett A, Hempel N, Duggleby RG, Windmill KF, Martin JL, et al. Human sulfotransferases and their role in chemical metabolism. *Toxicol Sci.* 2006 Mar; 90(1):5–22. [PubMed: 16322073]
19. Possamai LA, McPhail MJ, Khamri W, Wu B, Concas D, Harrison M, et al. The role of intestinal microbiota in murine models of acetaminophen-induced hepatotoxicity. *Liver Int.* 2015 Mar; 35(3):764–73. [PubMed: 25244648]
20. Jacobs WAH. The relationship between the structure and the biological action of the cardiac glucosides. *Journal of Biological Chemistry.* 1927; 74:787–93.
21. Vick RLKJJ, Acheson GH. Effects of dihydroouabain, dihydrodigoxin and dihydrodigitoxin on the heart-lung preparation of the dog. *J Pharmacol Exp Ther.* 1957; 121:330–39. [PubMed: 13481854]
22. Lindenbaum J, Rund DG, Butler VP Jr, Tse-Eng D, Saha JR. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *The New England journal of medicine.* 1981 Oct 1; 305(14):789–94. [PubMed: 7266632]
23. Saha JR, Butler VP Jr, Neu HC, Lindenbaum J. Digoxin-inactivating bacteria: identification in human gut flora. *Science.* 1983 Apr 15; 220(4594):325–7. [PubMed: 6836275]
24. Vanhoefter U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM. Irinotecan in the treatment of colorectal cancer: clinical overview. *J Clin Oncol.* 2001 Mar 1; 19(5):1501–18. [PubMed: 11230497]

25. Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh AS, Keefe DM. Faecal microflora and beta-glucuronidase expression are altered in an irinotecan-induced diarrhea model in rats. *Cancer Biol Ther.* 2008 Dec; 7(12):1919–25. [PubMed: 18927500]
26. Takasuna K, Hagiwara T, Hirohashi M, Kato M, Nomura M, Nagai E, et al. Involvement of beta-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (CPT-11) in rats. *Cancer Res.* 1996 Aug 15; 56(16):3752–7. [PubMed: 8706020]
27. Wallace BD, Wang H, Lane KT, Scott JE, Orans J, Koo JS, et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. *Science.* 2010 Nov 5; 330(6005):831–5. [PubMed: 21051639]
28. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science.* 2012 Jun 8; 336(6086):1268–73. [PubMed: 22674334]
29. Sistigu A, Viaud S, Chaput N, Bracci L, Proietti E, Zitvogel L. Immunomodulatory effects of cyclophosphamide and implementations for vaccine design. *Semin Immunopathol.* 2011 Jul; 33(4):369–83. [PubMed: 21611872]
30. Schiavoni G, Sistigu A, Valentini M, Mattei F, Sestili P, Spadaro F, et al. Cyclophosphamide synergizes with type I interferons through systemic dendritic cell reactivation and induction of immunogenic tumor apoptosis. *Cancer Res.* 2011 Feb 1; 71(3):768–78. [PubMed: 21156650]
31. Ghiringhelli F, Larmonier N, Schmitt E, Parcellier A, Cathelin D, Garrido C, et al. CD4+CD25+ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of established tumors to be curative. *Eur J Immunol.* 2004 Feb; 34(2):336–44. [PubMed: 14768038]
32. Viaud S, Flament C, Zoubir M, Pautier P, LeCesne A, Ribrag V, et al. Cyclophosphamide induces differentiation of Th17 cells in cancer patients. *Cancer Res.* 2011 Feb 1; 71(3):661–5. [PubMed: 21148486]
- 33•. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science.* 2013 Nov 22; 342(6161):971–6. This paper provides evidence for gut microbial impacts on drug efficacy such as cyclophosphamide. [PubMed: 24264990]
34. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science.* 2013 Nov 22; 342(6161):967–70. [PubMed: 24264989]
35. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004 Jul 13; 110(2):227–39. [PubMed: 15249516]
36. Barber MJ, Mangravite LM, Hyde CL, Chasman DI, Smith JD, McCarty CA, et al. Genome-wide association of lipid-lowering response to statins in combined study populations. *PLoS One.* 2010; 5(3):e9763. [PubMed: 20339536]
37. Kaddurah-Daouk R, Baillie RA, Zhu H, Zeng ZB, Wiest MM, Nguyen UT, et al. Enteric microbiome metabolites correlate with response to simvastatin treatment. *PLoS One.* 2011; 6(10):e25482. [PubMed: 22022402]
- 38•. Yoo DH, Kim IS, Van Le TK, Jung IH, Yoo HH, Kim DH. Gut microbiota-mediated drug interactions between lovastatin and antibiotics. *Drug metabolism and disposition: the biological fate of chemicals.* 2014 Sep; 42(9):1508–13. This paper provides evidence for gut microbial impacts on drug metabolism such as lovastatin. [PubMed: 24947972]
39. Dapito DH, Mencin A, Gwak GY, Pradere JP, Jang MK, Mederacke I, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. *Cancer Cell.* 2012 Apr 17; 21(4):504–16. [PubMed: 22516259]
40. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proceedings of the National Academy of Sciences of the United States of America.* 2009 Mar 10; 106(10):3698–703. [PubMed: 19234110]
- 41•. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. *Science.* 2012 Jun 8; 336(6086):1262–7. This review discussed the intricate relationship between host and gut microbiota. [PubMed: 22674330]

42. Goldin BR, Peppercorn MA, Goldman P. Contributions of host and intestinal microflora in the metabolism of L-dopa by the rat. *The Journal of pharmacology and experimental therapeutics*. 1973 Jul; 186(1):160–6. [PubMed: 4723308]
43. Koch RL, Goldman P. The anaerobic metabolism of metronidazole forms N-(2-hydroxyethyl)-oxamic acid. *The Journal of pharmacology and experimental therapeutics*. 1979 Mar; 208(3):406–10. [PubMed: 430360]
44. Aura AM, Mattila I, Hyotylainen T, Gopalacharyulu P, Bounsaythip C, Oresic M, et al. Drug metabolome of the simvastatin formed by human intestinal microbiota in vitro. *Molecular bioSystems*. 2011 Feb; 7(2):437–46. [PubMed: 21060933]
45. Mikov M, Caldwell J, Dolphin CT, Smith RL. The role of intestinal microflora in the formation of the methylthio adduct metabolites of paracetamol. *Studies in neomycin-pretreated and germ-free mice. Biochemical pharmacology*. 1988 Apr 15; 37(8):1445–9. [PubMed: 3358777]
46. Shu YZ, Kingston DG, Van Tassell RL, Wilkins TD. Metabolism of levamisole, an anti-colon cancer drug, by human intestinal bacteria. *Xenobiotica; the fate of foreign compounds in biological systems*. 1991 Jun; 21(6):737–50. [PubMed: 1949905]
47. Jin MJ, Kim U, Kim IS, Kim Y, Kim DH, Han SB, et al. Effects of gut microflora on pharmacokinetics of hesperidin: a study on non-antibiotic and pseudo-germ-free rats. *Journal of toxicology and environmental health Part A*. 2010; 73(21–22):1441–50. [PubMed: 20954071]
48. Lee NK, Choi SH, Park SH, Park EK, Kim DH. Antiallergic activity of hesperidin is activated by intestinal microflora. *Pharmacology*. 2004 Aug; 71(4):174–80. [PubMed: 15240993]
49. Caldwell J, Hawksworth GM. The demethylation of methamphetamine by intestinal microflora. *The Journal of pharmacy and pharmacology*. 1973 May; 25(5):422–4. [PubMed: 4146404]
50. Basit AW, Newton JM, Lacey LF. Susceptibility of the H₂-receptor antagonists cimetidine, famotidine and nizatidine, to metabolism by the gastrointestinal microflora. *International journal of pharmaceutics*. 2002 Apr 26; 237(1–2):23–33. [PubMed: 11955801]
51. Watanabe K, Yamashita S, Furuno K, Kawasaki H, Gomita Y. Metabolism of omeprazole by gut flora in rats. *Journal of pharmaceutical sciences*. 1995 Apr; 84(4):516–7. [PubMed: 7629748]
52. Meuldermans W, Hendrickx J, Mannens G, Lavrijsen K, Janssen C, Bracke J, et al. The metabolism and excretion of risperidone after oral administration in rats and dogs. *Drug metabolism and disposition: the biological fate of chemicals*. 1994 Jan-Feb; 22(1):129–38. [PubMed: 7512019]
53. Wadworth AN, Fitton A. Olsalazine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in inflammatory bowel disease. *Drugs*. 1991 Apr; 41(4):647–64. [PubMed: 1711964]
54. Strong HA, Renwick AG, George CF, Liu YF, Hill MJ. The reduction of sulphinyprazole and sulindac by intestinal bacteria. *Xenobiotica; the fate of foreign compounds in biological systems*. 1987 Jun; 17(6):685–96. [PubMed: 3630204]
55. Holt R. The bacterial degradation of chloramphenicol. *Lancet*. 1967 Jun 10; 1(7502):1259–60. [PubMed: 4165044]
56. Tozaki H, Emi Y, Horisaka E, Fujita T, Yamamoto A, Muranishi S. Metabolism of peptide drugs by the microorganisms in rat cecal contents. *Biological & pharmaceutical bulletin*. 1995 Jun; 18(6): 929–31. [PubMed: 7550138]
57. Shim SB, Kim NJ, Kim DH. Beta-glucuronidase inhibitory activity and hepatoprotective effect of 18 beta-glycyrrhetic acid from the rhizomes of *Glycyrrhiza uralensis*. *Planta medica*. 2000 Feb; 66(1):40–3. [PubMed: 10705732]
58. Akao T, Hayashi T, Kobashi K, Kanaoka M, Kato H, Kobayashi M, et al. Intestinal Bacterial Hydrolysis Is Indispensable To Absorption Of 18-Beta-Glycyrrhetic Acid after Oral-Administration Of Glycyrrhizin In Rats. *Journal Of Pharmacy And Pharmacology*. 1994 Feb; 46(2):135–37. [PubMed: 8021802]
59. Takeno S, Sakai T. Involvement of the intestinal microflora in nitrazepam-induced teratogenicity in rats and its relationship to nitroreduction. *Teratology*. 1991 Aug; 44(2):209–14. [PubMed: 1925980]

60. Harris BE, Manning BW, Federle TW, Diasio RB. Conversion of 5-fluorocytosine to 5-fluorouracil by human intestinal microflora. *Antimicrobial agents and chemotherapy*. 1986 Jan; 29(1):44–8. [PubMed: 3729334]
61. Lavrijsen K, van Dyck D, van Houdt J, Hendrickx J, Monbaliu J, Woestenborghs R, et al. Reduction of the prodrug loperamide oxide to its active drug loperamide in the gut of rats, dogs, and humans. *Drug metabolism and disposition: the biological fate of chemicals*. 1995 Mar; 23(3):354–62. [PubMed: 7628301]
62. Tralau T, Sowada J, Luch A. Insights on the human microbiome and its xenobiotic metabolism: what is known about its effects on human physiology? *Expert opinion on drug metabolism & toxicology*. 2015 Mar; 11(3):411–25. [PubMed: 25476418]
63. Nakayama H, Kinouchi T, Kataoka K, Akimoto S, Matsuda Y, Ohnishi Y. 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*. 1997 Feb; 7(1):35–43. [PubMed: 9110360]
64. Mao B, Li D, Zhao J, Liu X, Gu Z, Chen YQ, et al. In vitro fermentation of lactulose by human gut bacteria. *Journal of agricultural and food chemistry*. 2014 Nov 12; 62(45):10970–7. [PubMed: 25340538]
65. Trinh HT, Joh EH, Kwak HY, Baek NI, Kim DH. Anti-pruritic effect of baicalin and its metabolites, baicalein and oroxylin A, in mice. *Acta pharmacologica Sinica*. 2010 Jun; 31(6):718–24. [PubMed: 20453872]
66. Kang MJ, Ko GS, Oh do G, Kim JS, Noh K, Kang W, et al. Role of metabolism by intestinal microbiota in pharmacokinetics of oral baicalin. *Archives of pharmacol research*. 2014 Mar; 37(3):371–8. [PubMed: 23771520]
67. Matthies A, Clavel T, Gutschow M, Engst W, Haller D, Blaut M, et al. Conversion of daidzein and genistein by an anaerobic bacterium newly isolated from the mouse intestine. *Applied and environmental microbiology*. 2008 Aug; 74(15):4847–52. [PubMed: 18539813]
68. Renouf M, Hendrich S. *Bacteroides uniformis* Is a Putative Bacterial Species Associated with the Degradation of the Isoflavone Genistein in Human Feces. *J Nutr*. 2011 Jun; 141(6):1120–26. [PubMed: 21525249]
69. Akao T, Kida H, Kanaoka M, Hattori M, Kobashi K. Intestinal bacterial hydrolysis is required for the appearance of compound K in rat plasma after oral administration of ginsenoside Rb-1 from *Panax ginseng*. *Journal Of Pharmacy And Pharmacology*. 1998 Oct; 50(10):1155–60. [PubMed: 9821663]
70. Matthies A, Loh G, Blaut M, Braune A. Daidzein and Genistein Are Converted to Equol and 5-Hydroxy-Equol by Human Intestinal *Slackia isoflavoniconvertens* in Gnotobiotic Rats. *J Nutr*. 2012 Jan; 142(1):40–46. [PubMed: 22113864]
71. Schneider H, Simmering R, Hartmann L, Pforte H, Blaut M. Degradation of quercetin-3-glucoside in gnotobiotic rats associated with human intestinal bacteria. *Journal of applied microbiology*. 2000 Dec; 89(6):1027–37. [PubMed: 11123476]

Article highlights

- The intricate gut microbiome is hypothesized as a “metabolic organ” within host. It is not only involved in many diseases development, but also plays critical roles in drug metabolism through microbiota-host cometabolism.
- Currently, there are dozens of clinical drugs that have been demonstrated to be co-metabolized by host and gut microbiota. Nevertheless, the specific roles and mechanisms underlying gut microbial modulation on drug metabolism are still largely unexplored due to the complexity of gut microbiota itself and its relationship with host metabolism.
- The interindividual variation of gut microbiota contributes to the therapeutic outcomes in clinic. The investigation of the gut microbial impacts on drug therapy provides novel evidence for gut microbial modulation on drug efficacy, which sheds light on the role of gut microbiota in personalized medicine.
- The progress on gut microbiota study mainly relies on technical innovations. Metabolomics is an essential approach for investigating the involvement of gut microbiota in drug metabolism by discovering the gut microbial-related metabolites, in addition to the bacteria identification with metagenomics.
- The mechanistic elucidation of gut microbiota in drug metabolism and toxicity will facilitate the rational drug design and provide important evidence for gut microbiota-targeted therapy.

Table 1

Drugs that are co-metabolized by gut microbiota

Drugs	Clinical application	Type of microbial metabolism	Microbial-related products	Influence on drug efficacy or toxicity	Related bacteria (if available)	Ref
Digoxin	Treatment for heart disease	Reduction	Dihydrodigoxin and dihydrodigoxigenin	Decreased cardiac activity	<i>Eggerthella lenta</i>	9, 22
L-Dopa	Treatment for parkinson's disease	Dehydroxylation	m-tyrosine, m-tyramine, m-hydroxyphenylacetic acid	Decreased activity		42
Metronidazole	Anti-anaerobic bacteria drug	Reduction	N-(2-hydroxyethyl)-oxamic acid and acetamide	Probably increase its liver toxicity		43
Simvastatin	Hypolipidemic drug and prevention of cardiovascular disease	Hydrolysis, demethylation, hydroxylation/dehydroxylation and β -oxidation	Lactic acid, 3-hydroxybutanoic acid, cyclohexanecarboxylic acid, 2-hydroxyvaleric acid	Altering its lipids-lowering activity		44
Lovastatin		Hydrolysis	Demethylbutyryl metabolite, hydroxylated metabolite, hydroxy acid metabolite			38
Acetaminophen	Anti-analgesic drug	O-Sulfation; C-S cleavage of acetaminophen-3-cysteine	Acetaminophen sulfate and glucuronide	Decreased activity or increased cellular toxicity	<i>Clostridium difficile</i>	8, 45
Levamisole	A typical anthelmintic drug that is also used for anti-colon cancer treatment	Thiazole ring opening	Formation of three thiazole ring-opened metabolites, namely, levametabol-I, II and III	Increased activity	<i>Bacteroides</i> and <i>Clostridium spp.</i>	46
Hesperidin	Anti-allergic agent	Deglycosylation	Hesperetin	Increased activity		47, 48
Glyceryl trinitrate	Treatment for angina pectoris	Denitration	Glyceryl-1,3-dinitrate, glyceryl-1,2-dinitrate, glyceryl-1-mononitrate, and glyceryl-2-mononitrate	Decreased activity		7
Methamphetamine	Sympathomimetic stimulant	Demethylation	Amphetamine, norephedrine and an unknown metabolite	Decreased activity	<i>Lactobacilli</i> , <i>Enterococci</i> , and <i>Clostridia</i>	49
Nizatidine, Ranitidine	H ₂ -receptor antagonist for peptic ulcer disease therapy	N-Oxide bond cleavage		Decreased intestinal absorption and systemic bioavailability		50
Omeprazole	Gastric ulcer	Reduction	Production of corresponding sulfide metabolites	Decreased activity	Anaerobic bacteria such as <i>Bacteroides</i> strains	51
Risperidone	anti-psychotic drug	Ring cleavage and hydroxylation	Benzisoxazole ring scission or hydroxylation	Inducting symptoms of Parkinson's disease		52
Olsalazine	Treatment for inflammatory diseases such as ulcerative colitis, Crohn's disease and rheumatoid arthritis	Azo reduction	5-aminosalicylic acid	Increased activity or causing side effects such as anorexia, nausea		53
Sulindac, Sulfapyrazone	Anti-inflammatory agent	Reduction	Formation of their sulfide products--sulindac sulfide, sulfinpyrazone sulfide	Increased activity		54

Drugs	Clinical application	Type of microbial metabolism	Microbial-related products	Influence on drug efficacy or toxicity	Related bacteria (if available)	Ref
Chloramphenicol	Antibacterial agent	Amine formation and hydrolysis	<i>p</i> -aminophenyl-2-amino-1, 3-propanediol	Inducing bone marrow aplasia		55
Insulin	Treatment for type 1 diabetes mellitus	Proteolysis	Peptides	Decreased activity		56
Glycyrrhizin	Anti-inflammation and hepatoprotective activity	Hydrolysis	18- β -glycyrrhetic acid	Increased activity	<i>Eubacterium. sp.</i> strain GLH	57, 58
Nitrazepam	A hypnotic drug used in the treatment of moderate to severe insomnia	Nitroreduction	7-aminonitrazepam	Inducing teratogenicity		59
Flucytosine	Antifungal drug	Deamination	5-fluorouracil	Increased activity or toxicity		60
Loperamide oxide	Anti-diarrhea	Reduction	Loperamide	Increased activity		61
Indomethacin	Anti-inflammatory drug	Deconjugation		Decreased activity, and increased side effects such as diarrhoea, anorexia, or weight loss		62
3,4-dihydroxyphenylalanine	Treatment for Parkinson's disease	Dehydroxylation	m-tyramine and m-hydroxyphenylacetic acid	Increased activity		13
Sorivudine	Antiviral drug	Hydrolysis	(E)-5-(2-bromovinyl)uracil	(E)-5-(2-bromovinyl)uracil can inactivate a key liver enzyme, leading to lethal toxicity of 5-fluorouracil when coadministered with 5-fluorouracil		13, 63
Lactulose	Prebiotic	Hydrolysis	Monosaccharides	Stimulating the growth of beneficial bacteria such as <i>Bifidobacteria</i> and <i>Lactobacilli</i>	Utilized by <i>Cronobacter sakazakii</i> , <i>Enterococcus casseliflavus</i> , <i>Enterococcus faecalis</i> , and <i>Klebsiella pneumoniae</i>	62, 64
Baicalin	An herbal extract with multiple biological functions such as anti-inflammation, prevention of diabetes mellitus, and anti-tumor effect	Hydrolysis, deglycosylation	Baicalin and oxoxylin A	Increased activity		4, 65, 66
Genistein	An herbal extract with multiple biological functions such as prevention of obesity and type 2 diabetes	Hydrogenation	Production of 5-hydroxyequol via dihydrogenation		<i>Bacteroides uniformis</i>	67, 68
Ginsenoside Rb1	An herbal extract with multiple biological functions such as anti-	Hydrolysis	Compound K	Increased activity	<i>Bacteroides</i> and <i>Bifidobacterium</i>	4, 69

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Drugs	Clinical application	Type of microbial metabolism	Microbial-related products	Influence on drug efficacy or toxicity	Related bacteria (if available)	Ref
Daidzein	inflammation, and anti-tumor actions A phytoestrogen used for treatment hormone-dependent and age-related diseases, including osteoporosis, menopausal symptoms, cardiovascular diseases, and obesity	Reduction, phenolic ring opening	Dihydrodaidzein, equol, or O-desmethylanolensin(ODMA)	Increased activity	an Anaerobic Bacterium(Mt1B8); <i>Enterolignans</i> and <i>Clostridium</i> <i>sp</i> HGH 136	4, 67, 70
Quercetin-3-glucoside	Protection against cardiovascular disease and tumors	Deglycosylation	Butyrate, acetate, 3,4-dihydroxyphenylacetic acid		<i>Eubacterium ramulus</i> and <i>Enterococcus casseliflavus</i>	71