

## GUT MICROBIOTA-MEDIATED DRUG METABOLISM: IMPACT ON PHARMACOKINETICS AND PERSONALIZED THERAPEUTICS

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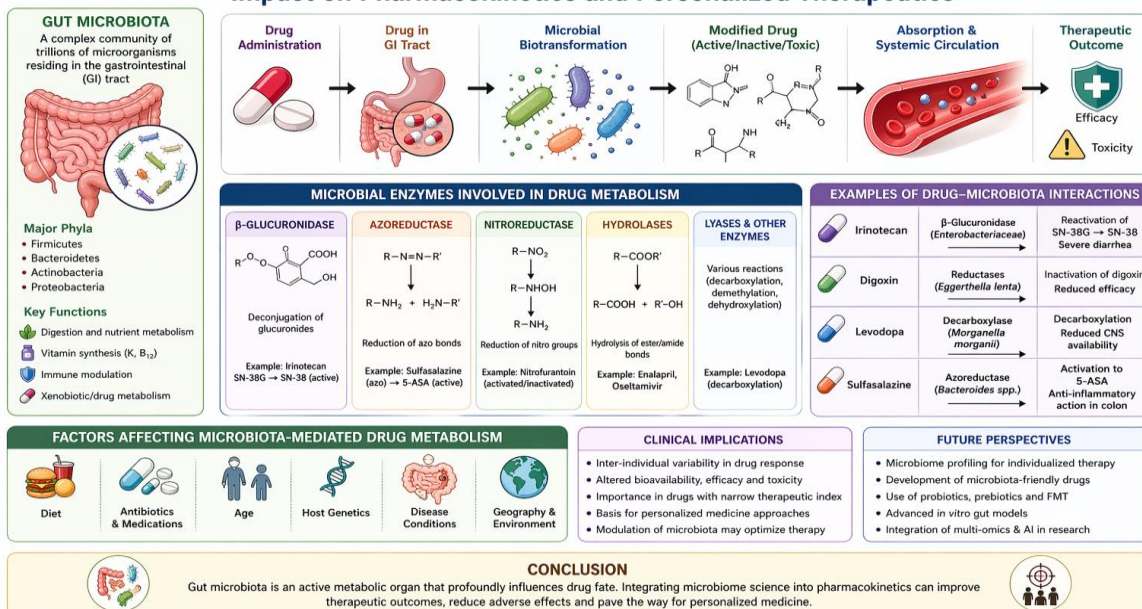
### ABSTRACT

The gut microbiota plays an important role in drug metabolism and pharmacokinetics by influencing drug absorption, bioavailability, and toxicity through various microbial enzymatic reactions.<sup>[1–3]</sup> Increasing evidence suggests that microbiota-mediated drug metabolism contributes significantly to interindividual variability in therapeutic response and adverse drug reactions.<sup>[4,5]</sup> Gut microorganisms can activate prodrugs, inactivate therapeutic agents, generate toxic metabolites, and regulate host metabolic enzymes.<sup>[6,7]</sup> Advances in pharmacomicrobiomics and microbiome research have highlighted the importance of integrating microbial profiling into personalized medicine.<sup>[8,9]</sup> Understanding drug–microbiota interactions may improve therapeutic outcomes, minimize adverse effects, and facilitate precision-based pharmacotherapy.<sup>[10]</sup>

**KEYWORDS:** Gut microbiota; Drug metabolism; Pharmacokinetics; Microbiome; Personalized medicine.

### GRAPHICAL ABSTRACT

## Gut Microbiota-Mediated Drug Metabolism: Impact on Pharmacokinetics and Personalized Therapeutics



## 1. INTRODUCTION

The human gastrointestinal tract contains trillions of microorganisms collectively known as the gut microbiota, which contribute significantly to host metabolism, immunity, and xenobiotic biotransformation.<sup>[6,8]</sup> Traditionally, drug metabolism has been primarily associated with hepatic enzymes, particularly the cytochrome P450 enzyme system. However, recent evidence demonstrates that intestinal microbiota also plays an important role in drug metabolism through hydrolysis, reduction, deconjugation, decarboxylation, and demethylation reactions.<sup>[1,2]</sup>

These microbial transformations may activate prodrugs, inactivate therapeutic compounds, alter drug bioavailability, or generate toxic metabolites.<sup>[3,7]</sup> Consequently, gut microbiota significantly influences pharmacokinetics, therapeutic efficacy, and adverse drug reactions.<sup>[4,5]</sup> The emerging field of pharmacomicrobiomics investigates the interactions between drugs and microbial communities to optimize pharmacotherapy and support personalized medicine approaches.<sup>[9,10]</sup>

## 2. Composition and Function of Gut Microbiota

The human gut contains approximately  $10^{13}$ – $10^{14}$  microorganisms representing more than 1,000 bacterial species.<sup>[11,16]</sup> The microbial population varies across individuals depending on genetics, diet, age, lifestyle, antibiotic exposure, and disease conditions.<sup>[12-14]</sup>

### 2.1 Major Phyla of Gut Microbiota

#### Firmicutes

Firmicutes constitute one of the largest bacterial phyla in the human intestine and include genera such as *Lactobacillus*, *Clostridium*, and *Enterococcus*. These bacteria are involved in carbohydrate fermentation and short-chain fatty acid production.<sup>[13,14]</sup>

#### Bacteroidetes

Bacteroidetes include *Bacteroides* and *Prevotella* species that contribute to polysaccharide digestion and nutrient metabolism.<sup>[15]</sup>

#### Actinobacteria

This phylum includes beneficial genera such as *Bifidobacterium*, which support intestinal health and immune modulation.<sup>[12,19]</sup>

#### Proteobacteria

Proteobacteria include *Escherichia*, *Salmonella*, and *Helicobacter* species. Excessive growth of these organisms is associated with dysbiosis and inflammatory disorders.<sup>[18,19]</sup>

### 2.2 Physiological Functions

The gut microbiota contributes to.

- Digestion and nutrient metabolism<sup>[15]</sup>

- Vitamin synthesis including vitamin K and B vitamins<sup>[20]</sup>
- Immune modulation<sup>[19]</sup>
- Maintenance of intestinal barrier integrity<sup>[13]</sup>
- Protection against pathogens<sup>[18]</sup>
- Metabolism of xenobiotics and drugs.<sup>[17]</sup>

Disruption of microbial homeostasis, known as dysbiosis, has been associated with obesity, diabetes, inflammatory bowel disease, cancer, and altered drug metabolism.<sup>[10,12,14]</sup>

## 3. Gut Microbiota and Drug Metabolism

Gut microbiota influences drug metabolism through direct enzymatic transformation and indirect modulation of host metabolic pathways.<sup>[1,2]</sup>

### 3.1 Microbial Enzymes Involved in Drug Metabolism

#### $\beta$ -Glucuronidase

This enzyme deconjugates glucuronide metabolites, leading to reactivation of drugs within the intestine.<sup>[2,5]</sup>

#### Azoreductase

Azoreductase enzymes reduce azo bonds in drugs such as sulfasalazine.<sup>[4]</sup>

#### Nitroreductase

Nitroreductases participate in the reduction of nitro-containing drugs.<sup>[7]</sup>

#### Hydrolases

Hydrolases catalyze ester and amide hydrolysis reactions.<sup>[6]</sup>

#### Demethylases and Decarboxylases

These enzymes alter drug structure and activity through removal of methyl and carboxyl groups.<sup>[7,9]</sup>

## 4. Mechanisms of Microbiota-Mediated Drug Metabolism

### 4.1 Drug Activation

Certain prodrugs require microbial enzymes for activation. Sulfasalazine is activated in the colon by bacterial azoreductases, releasing 5-aminosalicylic acid.<sup>[4,5]</sup>

### 4.2 Drug Inactivation

Some bacteria metabolize drugs into inactive forms. *Eggerthella lenta* inactivates digoxin through reduction reactions, thereby reducing therapeutic efficacy.<sup>[3,7]</sup>

### 4.3 Toxic Metabolite Formation

Microbial  $\beta$ -glucuronidase reactivates irinotecan metabolites in the intestine, causing severe diarrhea and gastrointestinal toxicity.<sup>[1,9]</sup>

**4.4 Modulation of Host Enzymes**

Gut microbiota regulates host cytochrome P450 enzymes and influences hepatic drug metabolism.<sup>[6,8]</sup>

**5. Clinically Important Drug–Microbiota Interactions**

**5.1 Irinotecan**

Irinotecan is metabolized into SN-38, which undergoes glucuronidation in the liver. Intestinal microbial  $\beta$ -glucuronidase deconjugates SN-38G back to active SN-38, resulting in intestinal toxicity.<sup>[1,9]</sup>

**5.2 Digoxin**

*Eggerthella lenta* reduces digoxin into inactive metabolites, lowering its therapeutic activity.<sup>[3,7]</sup>

**5.3 Levodopa**

Gut bacterial decarboxylases metabolize levodopa before absorption, reducing its availability in the central nervous system.<sup>[2,4]</sup>

**5.4 Sulfasalazine**

Bacterial azoreductases activate sulfasalazine into sulfapyridine and 5-aminosalicylic acid.<sup>[5]</sup>

**5.5 Metformin**

Metformin alters gut microbial composition and increases beneficial bacterial populations associated with glucose metabolism.<sup>[10,14]</sup>

**Table 1: Clinically Important Drug–Microbiota Interaction.**

Drug	Microbial Interaction	Clinical Consequence
Irinotecan	$\beta$ -glucuronidase-mediated reactivation	Gastrointestinal toxicity
Digoxin	Reduction by <i>Eggerthella lenta</i>	Reduced therapeutic efficacy
Levodopa	Bacterial decarboxylation	Reduced CNS availability
Sulfasalazine	Azoreductase-mediated activation	Therapeutic activation
Metformin	Alters microbial composition	Improved glucose metabolism

**6. Factors Affecting Gut Microbiota-Mediated Drug Metabolism**

**6.1 Diet**

Dietary habits significantly alter gut microbial diversity and metabolic activity.<sup>[15,18]</sup>

**6.2 Antibiotics**

Antibiotics disrupt microbial homeostasis and reduce microbial diversity.<sup>[1,12]</sup>

**6.3 Age**

Microbial composition changes considerably across infancy, adulthood, and aging.<sup>[13,17]</sup>

**6.4 Genetics**

Host genetics influence microbiome composition and microbial metabolic functions<sup>[12,16]</sup>

**6.5 Disease Conditions**

Inflammatory bowel disease, obesity, diabetes, and liver disorders alter microbial composition and functionality<sup>[10,19]</sup>

**7. Pharmacokinetic Implications**

Gut microbiota significantly affects

- Drug absorption.<sup>[1,4]</sup>
- Distribution<sup>[5]</sup>
- Metabolism<sup>[2,6]</sup>
- Excretion<sup>[7]</sup>
- Bioavailability<sup>[3]</sup>
- Plasma drug concentration.<sup>[9]</sup>

Microbial metabolism contributes substantially to interindividual variability in therapeutic response and adverse effects.<sup>[8,10]</sup>

**8. Pharmacomicrobiomics and Personalized Medicine**

**8.1 Personalized Therapeutics**

Microbiome profiling may help predict drug response and optimize individualized dosing regimens.<sup>[2,3]</sup>

**8.2 Microbiota-Based Therapeutics**

Approaches include

- Probiotics
- Prebiotics
- Synbiotics
- Fecal microbiota transplantation
- Microbiome-targeted therapeutics.<sup>[10,19]</sup>

**8.3 Artificial Intelligence and Multi-Omics**

Advanced computational approaches, artificial intelligence, metagenomics, metabolomics, and transcriptomics support precision medicine and microbiome-guided therapeutics.<sup>[8,16]</sup>

**9. Challenges and Future Perspectives**

**9.1 Complexity of Microbial Ecosystems**

The gut microbiome exhibits substantial interindividual variability, making prediction of drug responses challenging.<sup>[17,18]</sup>

## 9.2 Standardization Issues

Lack of standardized microbiome analysis methods limits clinical implementation and reproducibility.<sup>[9,10]</sup>

## 9.3 Drug Development Challenges

Integrating microbiome data into pharmaceutical development requires extensive clinical validation and regulatory frameworks.<sup>[3,4]</sup>

Future research should focus on microbiome biomarkers, precision therapeutics, personalized drug development, microbiota-targeted interventions, and AI-assisted pharmacomicrobiomics.<sup>[8,9]</sup>

## 10. CONCLUSION

Gut microbiota represents an important metabolic organ that significantly influences drug metabolism, pharmacokinetics, and therapeutic outcomes.<sup>[1,2]</sup> Microbial enzymes can activate, inactivate, or toxify drugs, thereby affecting efficacy and safety.<sup>[3,7]</sup> Advances in pharmacomicrobiomics and microbiome research have improved understanding of interindividual variability in drug response.<sup>[4,8]</sup> Integration of microbiome science into pharmaceutical research may enhance precision medicine, optimize drug therapy, and minimize adverse effects.<sup>[9,10]</sup> Future investigations should emphasize microbiome-based diagnostics, personalized therapeutics, and microbiota-targeted interventions for improved healthcare outcomes.<sup>[16,19]</sup>

## 11. DISCUSSION

The present review highlights the critical role of gut microbiota in modulating drug metabolism and influencing pharmacokinetic behavior. Traditionally, hepatic enzymes were considered the principal mediators of xenobiotic metabolism; however, growing evidence demonstrates that intestinal microorganisms also possess extensive metabolic capabilities that directly affect therapeutic efficacy and toxicity.<sup>[1,2]</sup> The gut microbiota acts as a dynamic metabolic organ capable of transforming drugs through hydrolysis, reduction, deconjugation, demethylation, and decarboxylation reactions.<sup>[3,7]</sup>

One of the most important findings from recent studies is the contribution of microbiota-mediated metabolism to interindividual variability in drug response. Differences in microbial composition among individuals may explain why patients receiving the same dose of a drug often exhibit varying therapeutic outcomes and adverse reactions.<sup>[4,8]</sup> For example, *Eggerthella lenta* can inactivate digoxin, thereby reducing its pharmacological activity, while bacterial  $\beta$ -glucuronidase reactivates irinotecan metabolites and contributes to severe gastrointestinal toxicity.<sup>[1,3]</sup> These findings emphasize the

importance of considering microbial composition during drug therapy and dose optimization.

The review also demonstrates that gut microbiota significantly influences drug absorption and bioavailability. Microbial metabolism occurring before systemic absorption can alter the chemical structure and pharmacological properties of drugs.<sup>[5,6]</sup> In the case of levodopa, bacterial decarboxylases metabolize the drug within the gastrointestinal tract, reducing its availability to the central nervous system and potentially compromising treatment outcomes in patients with Parkinson's disease.<sup>[2,4]</sup> Similarly, microbial activation of sulfasalazine illustrates the beneficial role of bacterial enzymes in prodrug activation and therapeutic effectiveness.

Another important aspect discussed is the bidirectional interaction between drugs and microbiota. While microbiota alters drug metabolism, several drugs also modify microbial composition and functionality. Metformin, for instance, has been shown to increase beneficial bacterial populations associated with improved glucose metabolism and anti-inflammatory effects.<sup>[10,14]</sup> Antibiotics can disrupt microbial diversity and induce dysbiosis, which may subsequently alter metabolism of concurrently administered drugs.<sup>[12,18]</sup> These interactions suggest that microbiota should be considered an important determinant of pharmacotherapy outcomes.

Pharmacomicrobiomics has emerged as a promising field for personalized medicine by integrating microbiome profiling with pharmacokinetic and pharmacodynamic data. Advances in metagenomics, metabolomics, transcriptomics, and artificial intelligence have improved understanding of host-microbiome-drug interactions and may support development of individualized therapeutic strategies.<sup>[8,16]</sup> Microbiome-based interventions such as probiotics, prebiotics, synbiotics, fecal microbiota transplantation, and microbiota-targeted therapeutics may further enhance treatment efficacy and reduce adverse drug reactions.

Despite substantial progress, several challenges remain in translating microbiome research into clinical practice. The gut microbiome is highly complex and exhibits significant interindividual variability influenced by diet, age, genetics, environmental exposure, disease states, and antibiotic use.<sup>[13,17]</sup> Furthermore, lack of standardized analytical techniques and limited large-scale clinical studies hinder routine application of microbiome-guided therapeutics. Additional research is required to identify reliable microbial biomarkers and establish clinically validated microbiome-based therapeutic approaches.

Overall, the evidence presented in this review supports the growing recognition of gut microbiota as a major determinant of drug metabolism and pharmacokinetics. Integrating microbiome science into pharmaceutical research and clinical practice may improve therapeutic

precision, minimize adverse effects, and contribute to the advancement of personalized medicine.

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#### Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

**Ethical Approval** Not applicable. This article is a review based on previously published literature and does not involve studies with human participants or animals.

#### Author Contributions

All authors contributed significantly to the conception, literature review, manuscript drafting, critical revision, and final approval of the manuscript.

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