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GUT MICROBIOTA–DRUG INTERACTIONS: IMPLICATIONS FOR PHARMACOKINETICS AND PERSONALIZED MEDICINE

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Abstract:

The human gastrointestinal tract contains a complex microbial ecosystem that contributes to nutrition, immune regulation, intestinal barrier integrity, and host metabolism. Increasing evidence indicates that gut microorganisms also influence the pharmacokinetics, pharmacodynamics, efficacy, and toxicity of pharmaceutical agents. Gut bacteria can directly transform drugs through enzymatic reactions, bioaccumulation, and deconjugation, while microbial metabolites can indirectly regulate host metabolic enzymes, intestinal transporters, bile acid pathways, and immune responses. Consequently, differences in microbiota composition and functional capacity may contribute to inter-individual variability in drug response. The relationship is bidirectional because pharmaceutical agents can also alter the composition and metabolic activity of the gut microbiota. The emerging field of pharmacomicrobiomics investigates these interactions and provides a potential framework for microbiome-informed personalized medicine. This review discusses the influence of gut microbiota on drug absorption, metabolism, bioavailability, enterohepatic circulation, therapeutic efficacy, and adverse drug reactions. Important examples involving digoxin, metformin, levodopa, irinotecan, and other drugs are considered. Current evidence suggests that integration of microbiome profiling with pharmacogenomics, metabolomics, pharmacokinetics, and clinical information may improve understanding of individual treatment responses. However, substantial challenges remain, including microbiome variability, methodological heterogeneity, differences between experimental and human studies, and limited clinical validation. Future research may establish microbiome-derived biomarkers and microbiota-targeted interventions for safer and more individualized pharmacotherapy.

Keywords: *Gut Microbiota, Pharmacomicrobiomics, Drug Metabolism, Pharmacokinetics, Pharmacodynamics, Microbiome, Personalized Medicine, Drug–Microbiota Interactions.*

1. Introduction

The human gastrointestinal tract harbors a highly diverse microbial ecosystem consisting of bacteria, archaea, fungi, viruses, and other microorganisms. These microbial communities contribute to digestion, nutrient utilization, immune regulation, intestinal barrier maintenance, and protection against pathogens. In addition to

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these physiological functions, the gut microbiota interacts with numerous exogenous substances, including pharmaceutical compounds. Increasing evidence indicates that these interactions can influence drug pharmacokinetics, pharmacodynamics, efficacy, and toxicity (1, 2).

Pharmacokinetics describes the processes of absorption, distribution, metabolism, and excretion (ADME) that determine the concentration and duration of a drug in the body. Traditionally, hepatic enzymes, intestinal enzymes, renal function, transport proteins, genetics, age, diet, and disease status have been considered major determinants of pharmacokinetic variability. However, the intestinal microbiota represents an additional metabolic compartment that can modify drugs before or after absorption (2, 3).

The term pharmacomicrobiomics describes the study of relationships between microbial variation and drug response. It extends conventional pharmacogenomics by considering microbial genes, enzymes, metabolites, and community composition as additional factors contributing to inter-individual differences in pharmacotherapy (4).

The gut microbiota can directly transform pharmaceutical compounds or indirectly influence host metabolic enzymes and transporters. Conversely, drugs can alter microbial composition and function, creating a bidirectional relationship between the host microbiome and pharmaceutical agents.

Inter-individual variability in drug response is an important clinical problem. Patients receiving the same drug at the same dose may show different therapeutic responses or adverse reactions. Host genetic variation explains part of this variability, but it does not completely account for differences in treatment outcomes. Microbiome composition and functional capacity may provide an additional explanation for some of this variability (4, 5).

2. Gut microbiota and drug pharmacokinetics

2.1 Influence on drug absorption

The gastrointestinal tract is a major site of exposure for orally administered medicines. Gut microorganisms can influence drug absorption by changing intestinal pH, bile acid metabolism, epithelial permeability, mucus properties, and the activity of intestinal transport proteins.

Microbial metabolites, including short-chain fatty acids, secondary bile acids, and indole derivatives, can influence host signaling pathways and transporter expression. Recent evidence indicates that microbial communities and their metabolites may regulate transporters such as P-glycoprotein, breast cancer resistance protein, and multidrug resistance-associated proteins, potentially altering oral drug exposure (6).

Microbial bioaccumulation is another possible mechanism. Certain bacteria can take up drugs into their cells without chemically transforming them. Klünemann *et al.* demonstrated numerous bacteria–drug interactions and showed that bioaccumulation can account for some drug depletion from the surrounding environment (7).

2.2 Microbial drug metabolism

Gut bacteria contain a large collection of enzymes capable of transforming pharmaceutical compounds. Microbial reactions may include hydrolysis, reduction, deconjugation, decarboxylation, acetylation, and other chemical modifications. These transformations can activate prodrugs, inactivate active drugs, or generate metabolites with altered pharmacological properties (8).

Microbial drug metabolism may occur before systemic absorption or during enterohepatic circulation. Consequently, the intestinal microbiota can influence the amount of active drug reaching the circulation. The extent of this effect may differ between individuals because the abundance and metabolic activity of relevant microbial species vary between people.

2.3 Bioavailability and enterohepatic circulation

Some pharmaceutical compounds undergo hepatic conjugation and are subsequently secreted into the intestinal tract through bile. Microbial enzymes can remove conjugated groups from these metabolites and thereby facilitate their reabsorption. This process can modify enterohepatic circulation and alter systemic drug exposure.

The microbiota may therefore affect bioavailability not only by directly transforming a drug but also by modifying the recycling of drug metabolites. These mechanisms are particularly relevant for compounds that remain in prolonged contact with intestinal microorganisms (9).

3. Mechanisms of microbiota–drug interactions

Gut microbiota–drug interactions can broadly be divided into direct and indirect mechanisms.

Direct mechanisms involve physical or chemical interaction between microorganisms and drugs. These include enzymatic biotransformation, hydrolysis, reduction, deconjugation, bioaccumulation, and degradation. Microbial genes encoding drug-transforming enzymes have been identified for numerous pharmaceutical compounds (10).

Indirect mechanisms occur when microbiota-derived molecules affect host physiological processes. Microbial metabolites may regulate hepatic or intestinal drug-metabolizing enzymes, transport proteins, bile acid signaling, inflammatory pathways, and immune responses. Such mechanisms can influence both pharmacokinetics and pharmacodynamics (2). Microbial metabolism is therefore not simply an additional pathway of drug elimination. It can influence the biological activity of a pharmaceutical compound and may sometimes produce metabolites with greater or different biological activity.

4. Bidirectional effects of drugs on the gut microbiota

The relationship between drugs and microbiota is reciprocal. Pharmaceutical compounds can alter microbial abundance, diversity, metabolic pathways, and community structure.

Antibiotics have particularly strong effects because they directly inhibit susceptible bacteria. However, non-antibiotic medications can also affect intestinal microorganisms. Maier *et al.* screened more than 1,000 marketed drugs against representative gut bacteria and found that a substantial proportion of drugs with human targets affected bacterial growth *in vitro* (11). Similarly, Vich Vila *et al.* reported associations between commonly used medications and alterations in gut microbiota composition and metabolic function (12).

Drug-induced microbial changes may have secondary consequences. A medication can alter microbial metabolites, which may subsequently affect intestinal barrier function, host metabolism, inflammation, or the pharmacological response to another medicine. This creates the possibility of indirect drug–drug interactions mediated through the microbiome.

5. Clinically relevant examples

5.1 Digoxin

Digoxin is one of the classic examples of microbiota-mediated drug metabolism. Certain intestinal bacteria, particularly *Eggerthella lenta*, can transform digoxin and reduce its pharmacological activity. This example demonstrates how differences in bacterial abundance and metabolic capacity may contribute to differences in drug exposure and response.

5.2 Metformin

Metformin is widely used for the treatment of type 2 diabetes, and its effects are associated with changes in the intestinal environment and microbiota. The relationship is complex because metformin can alter microbial composition while microbial changes may also contribute to some of its metabolic effects. Current evidence supports further investigation of microbiome characteristics as potential determinants of response.

5.3 Levodopa

Levodopa is used in Parkinson's disease and represents another important example of microbial involvement in drug metabolism. Specific intestinal microorganisms can metabolize levodopa, potentially influencing the amount of drug available for absorption and subsequent conversion to dopamine. Recent pharmacomicrobiomics research continues to examine this interaction and its implications for treatment variability.

5.4 Irinotecan

Irinotecan is an anticancer drug whose toxicity can be influenced by intestinal microbial β-glucuronidase activity. Microbial conversion of inactive glucuronide metabolites back into active compounds in the intestine has been associated with intestinal toxicity. This example has encouraged investigation of selective microbial enzyme inhibition as a potential strategy for reducing adverse effects.

6. Gut microbiota and personalized medicine

Personalized medicine aims to tailor treatment according to characteristics of individual patients. Pharmacogenomics has already demonstrated that genetic variation can influence drug metabolism and response. However, the microbiome provides another layer of biological variability.

Individuals differ substantially in microbial composition and functional capacity because of diet, age, geography, lifestyle, disease, environmental exposure, and medication history. Therefore, two individuals with similar human genetic profiles may still possess different microbial metabolic capabilities.

Pharmacomicrobiomics attempts to integrate these microbial characteristics into pharmacological decision-making. Metagenomic sequencing can identify microbial genes, while metabolomics can identify microbial products that may be associated with drug metabolism. Integration of these data with host genomic and clinical information could improve prediction of drug response (4, 5).

However, microbiome-guided prescribing is still an emerging concept. Current evidence is insufficient to recommend routine microbiome-based dosing for most medicines. Large, standardized clinical studies are required before such approaches can become part of routine pharmacotherapy.

7. Microbiome-based therapeutic strategies

The recognition that microbiota can affect pharmaceutical responses has stimulated interest in microbiome-targeted interventions. Potential approaches include dietary modification, probiotics, prebiotics, synbiotics, fecal microbiota transplantation, bacteriophage-based approaches, and selective inhibition of microbial enzymes.

An important strategy is the selective inhibition of microbial enzymes that produce undesirable drug metabolites. Such an approach may reduce drug toxicity while avoiding broad disruption of the beneficial microbiota.

Microbiome-aware drug development is another emerging concept. Instead of considering the microbiota only after a drug has been developed, microbial metabolism can be incorporated into drug discovery, formulation, pharmacokinetic assessment, and safety evaluation (5).

8. Current challenges

Several limitations currently restrict clinical translation of pharmacomicrobiomics.

First, microbiome composition differs considerably between individuals. Diet, age, geographical location, lifestyle, disease, antibiotics, and other medications can all influence microbial communities.

Second, taxonomic composition alone may not adequately predict drug metabolism. Two individuals may possess similar bacterial species but different functional genes or levels of enzyme expression.

Third, many experimental observations have been obtained using isolated bacterial cultures, artificial communities, animal models, or *in vitro* systems. These models provide valuable mechanistic information but may not fully reproduce the complexity of the human gastrointestinal environment.

Fourth, microbiome studies use different sample collection procedures, sequencing platforms, bioinformatic pipelines, and analytical methods. Such methodological heterogeneity can make direct comparison between studies difficult.

Therefore, future clinical studies should combine standardized microbiome profiling with pharmacokinetic measurements, metabolomics, pharmacogenomics, and clinically relevant treatment outcomes.

9. Future perspectives

Future research in pharmacomicrobiomics is likely to focus on identifying microbial biomarkers that can predict drug response or toxicity. Functional metagenomics, metabolomics, machine learning, and systems pharmacology may help identify relationships between microbial genes, metabolites, drug exposure, and clinical outcomes.

Microbiome-informed drug development may also provide opportunities to design pharmaceutical compounds that are less susceptible to undesirable microbial transformation. Conversely, drugs could potentially be designed to exploit specific microbial metabolic pathways for activation.

Recent research emphasizes that successful clinical translation will require integration of human and microbial genomic information with multi-omics and pharmacological data (4, 5).

10. Conclusion

Gut microbiota–drug interactions represent an important interdisciplinary field connecting microbiology, pharmacology, biotechnology, and personalized medicine. Gut microorganisms can directly transform drugs through enzymatic reactions and bioaccumulation and can indirectly influence drug absorption, metabolism, transport, bioavailability, toxicity, and therapeutic response. At the same time, pharmaceutical agents can alter the composition and metabolic function of the gut microbiota. This bidirectional relationship may contribute to inter-individual variability in drug response that cannot be explained entirely by host genetics.

Pharmacomicrobiomics therefore offers a promising framework for understanding individual differences in pharmacotherapy. However, routine microbiome-guided prescribing requires stronger clinical evidence, standardized analytical approaches, and validated biomarkers. Future integration of microbiome profiling with pharmacogenomics, metabolomics, pharmacokinetics, and clinical data may support safer and more individualized drug therapy.

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