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Original Research Article

Beyond hepatic drug metabolism: Integrating microbiota-driven biotransformation, host-microbe interactions, and pharmacokinetic variability

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Abstract

Purpose: *To evaluate current knowledge on microbiota-driven drug metabolism, focusing on microbial biotransformation mechanisms, host–microbe co-metabolism, and their clinical implications.*
Method: *A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar for studies published between 2020 and 2026, following PRISMA guidelines.*
Results: *Findings reveal that gut microbes influence drug metabolism through enzymatic processes including reduction, hydrolysis, and deconjugation, as well as through indirect mechanisms such as modulation of host metabolic enzymes and drug transporters. Clinically relevant examples include microbial inactivation of digoxin by Eggerthella lenta, reactivation of irinotecan via bacterial β-glucuronidases leading to gastrointestinal toxicity, and microbial activation of sulfasalazine through azoreductase activity. Additionally, microbial metabolites such as short-chain fatty acids and bile acids regulate host enzyme expression, further shaping drug disposition and response. Despite these advances, substantial interindividual variability in microbiome composition remains a major challenge in predicting drug response and toxicity.*
Conclusion: *Microbiota-driven drug metabolism represents a critical component of precision medicine. Integrating microbiome-informed strategies into clinical practice may enhance drug efficacy, reduce adverse effects, and enable more personalized therapeutic interventions. Emerging approaches, including artificial intelligence-based modeling, microbiome profiling, and gene-editing technologies, offer promising avenues for improving therapeutic precision but require further clinical validation.*

Keywords: *Biotransformation, Cytochrome P450, Drug metabolism, Gut microbiota, Pharmacogenomics*

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INTRODUCTION

The human gastrointestinal tract harbors a complex and diverse microbial community that plays an essential role in numerous physiological processes, including the biotransformation of xenobiotics such as therapeutic agents and dietary constituents [1,2]. Although the liver is recognized as the principal organ responsible for xenobiotic metabolism, accumulating evidence demonstrates that intestinal microorganisms also contribute substantially to drug disposition through enzymatic reactions such as reduction, hydrolysis, and deconjugation [1,3]. These

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microbial activities can modify the pharmacokinetic behavior of drugs by influencing their bioavailability, therapeutic effectiveness, and toxicity, thereby contributing to the considerable variability observed in individual treatment responses [1,4]. Although significant advances have been made in microbiome research, important questions remain regarding the mechanisms through which gut microorganisms regulate host drug metabolism and ultimately influence clinical outcomes and human health [1,5].

The gut microbiota constitutes a complex and dynamic microbial community that exists in a symbiotic relationship with its host and plays an essential role in maintaining normal physiological functions [5,6]. Beyond supporting metabolic homeostasis, this microbial community contributes to immune regulation, preservation of intestinal barrier integrity, and overall host well-being. Colonization of the gastrointestinal tract begins early in life and continues to evolve throughout adulthood under the influence of factors such as diet, environmental exposures, lifestyle, medication use, and disease status [3,7]. The adult intestine harbors an enormous microbial population, estimated to exceed one hundred trillion cells, with a collective metabolic capacity that greatly expands the biochemical capabilities of the human host [6,8]. Consequently, intestinal microorganisms are capable of transforming numerous therapeutic compounds by activating prodrugs, inactivating active medications, or generating metabolites with altered biological activity (Table 1) [3,7]. Differences in microbial composition and metabolic function among individuals therefore represent an important source of variability in drug response [6]. This functional diversity is further supported by the enormous genetic repertoire of the gut microbiome, which contains substantially more genes than the human genome [6,8]. Growing evidence indicates that the gut microbiome performs a wide range of biological functions that extend far beyond drug metabolism. These include nutrient utilization, maintenance of intestinal barrier function, modulation of immune responses, and the biosynthesis of bioactive metabolites such as short-chain fatty acids that influence host physiology [8,9]. The composition of the intestinal microbiota is closely associated with immune system maturation and regulation, emphasizing its importance in maintaining normal physiological processes throughout life [7,10]. In addition, advances in high throughput sequencing technologies have markedly improved the characterization of microbial communities, providing deeper insights into the complex interactions between intestinal microorganisms and their host as well as their influence on therapeutic responses [4]. Collectively, the human microbiome comprises bacteria, archaea, fungi, viruses, and other microorganisms that inhabit multiple body sites and function as an integrated ecological network [10,11]. Among these microbial habitats, the gastrointestinal tract contains the greatest microbial diversity, harboring hundreds of bacterial species whose collective genomes and metabolic activities exert profound effects on host physiology, health, and drug metabolism [11].

METHODS

Study design

This systematic review examined the role of the gut microbiota in drug metabolism, with emphasis on microbe-drug interactions, microbial biotransformation, and their effects on drug efficacy, toxicity, and personalized medicine. Relevant studies were systematically analyzed to evaluate current evidence on microbial contributions to drug metabolism, identify approaches for minimizing adverse microbiota drug interactions, and highlight areas that require further research. This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a structured, transparent, and reproducible approach throughout the review process.

A total of 1,725 records were retrieved from the database searches (Pubmed, Scopus, sciencedirect, web of Science, Google scholar). After the removal of 700 duplicate records, 1,025 records remained for screening based on their titles and abstracts. Of these, 900 records were excluded, leaving 125 full-text publications for eligibility assessment. Following full-text assessment, 76 publications were excluded for the following reasons: 27 were outside the scope of the review, 24 provided insufficient details, and 25 were considered to have limited methodological rigour. Ultimately, 49 studies met the eligibility criteria and were included in the qualitative synthesis. The complete study identification, screening, eligibility assessment, and inclusion process is presented in the PRISMA flow diagram (Figure 1).

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they examined the contribution of the gut microbiota to drug metabolism,

pharmacokinetics, or microbiota-drug interactions including the biotransformation of xenobiotics and the therapeutic application of probiotics. The review included original research articles and high quality review papers published in peer-reviewed English language journals between 2020 and 2026. Publications were excluded if they did not address drug metabolism, microbial enzymatic biotransformation, microbiome engineering, drug efficacy, or therapeutic interventions. Conference abstracts, editorials, letters to the editor, studies with inadequate methodological descriptions, articles without accessible full texts, and publications in languages other than English were also excluded.

Search strategies

Studies relevant to this review were scrupulously identified via a comprehensive search of multiple databases, including Google Scholar, PubMed, Web of Science, ScienceDirect, and Scopus, to identify scholarly articles relevant to this study published between January 2020 and March 2026. Database-specific search strategies were developed using a combination of free-text terms and controlled vocabulary (MeSH terms), structured with Boolean operators (AND, OR). The primary search terms included in the search strategy used the following keywords: ("gut microbiota" OR "microbiome") AND ("drug metabolism" OR "pharmacomicrobiomics") AND ("drug efficacy" OR "drug toxicity"). The search terms were combined using Boolean operators to retrieve relevant studies. The reference lists of eligible articles were also examined to identify additional studies that met the inclusion criteria. Only peer-reviewed articles published in English between 2020 and March 2026 were included. Both original research articles and review papers were considered, regardless of study design.

Screening and selection process

All records identified through the literature search were imported into Zotero; duplicate entries were identified and removed before screening commenced. The remaining citations were transferred to Rayyan to support the study selection process. Two reviewers independently assessed the titles and abstracts of all retrieved articles without knowledge of each other's decisions. After this stage, the reviewers compared their assessments and resolved differences through discussion. The full-text versions of studies considered potentially eligible were then independently evaluated by the same reviewers. Any disagreements arising during the full-text assessment were settled through discussion or, when necessary, by consultation with the third reviewer. Studies that satisfied the predefined eligibility criteria were included in the final review.

Quality appraisal

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), which is designed to evaluate the quality of observational studies. The NOS was applied only to observational studies and assessed three domains: selection of study participants, comparability of study groups, and ascertainment of outcomes or exposures. Each study was assigned a score ranging from 0 to 9, with higher scores indicating better methodological quality. Studies scoring 7–9 were classified as high quality, those scoring 4–6 as moderate quality, and those scoring 0–3 as low quality. Where review articles were eligible for inclusion, their methodological quality was assessed separately using an appropriate critical appraisal tool for reviews rather than the NOS.

Data extraction

Information relevant to the objectives of this review was collected from each eligible study using a standardized data extraction approach. The extracted information included publication year, study design, methodological quality, and the main biological focus of the investigation. Where reported, details on therapeutic targets, interventions, and study outcomes were also recorded. The information extracted was compiled into a summary table to enable comparison of findings across the included studies.

Data synthesis

Because of the diversity in study designs, methodologies, and statistical approaches, a meta-analysis was not performed, and pooled effect sizes were not calculated. Instead, a qualitative comparative synthesis was conducted to summarize and interpret the findings across studies, focusing on the magnitude and direction of reported outcomes related to therapeutic resistance and drug metabolism.

RESULTS

Microbial modulation of drug metabolism

Drug metabolism is a complex process that affects how the body interacts with administered drugs to enhance their elimination [12].

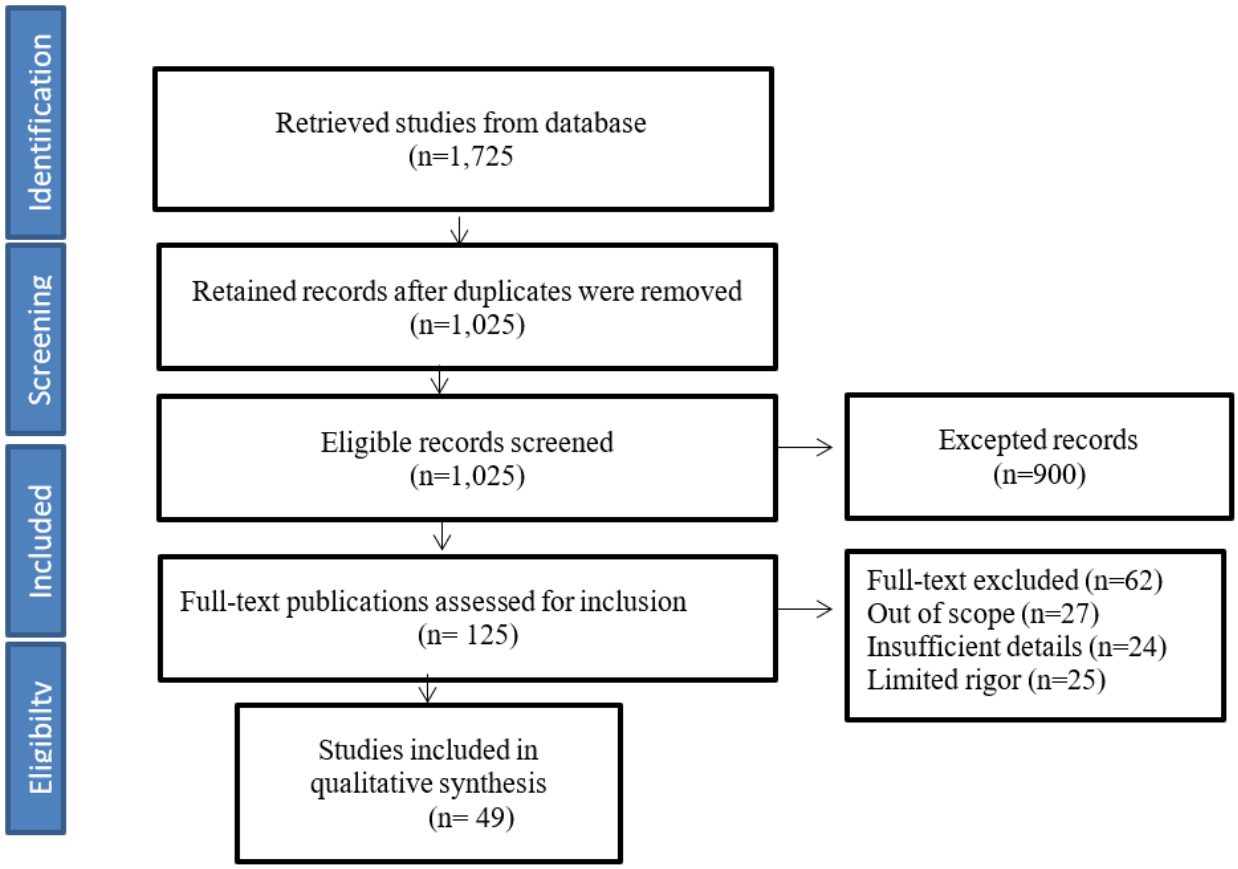


Figure 1: PRISMA 2020 flow diagram illustrating the study selection process

It occurs in many tissues, mainly in the liver and also takes place in the kidney and by the gut microbiota. Locally, liver enzymes (hepatic) are involved in drug metabolism, especially those that belong to the family cytochrome P450 (CYP) [13]. The enzymes are capable of metabolizing drugs into active or inactive metabolites, impacting how long they will work, how they will work and potential toxicity. The action takes place in the liver and is recognized as a major mechanism of drug metabolism [14]. The gut microbiota harbors numerous enzymes that aid in drug metabolism and bioactivation processes, including hydrolysis, reduction, and deconjugation reactions that influence drug bioavailability and activity [15]. In reductive metabolism, specific bacteria, such as Eggerthella lenta, reduce the therapeutic efficacy of drugs such as digoxin [11]. Bacterial beta-glucuronidases hydrolyze glucuronidated medications by changing their pharmacodynamics. For example, irinotecan, a chemotherapy drug, undergoes bacterial beta-glucuronidase-mediated reactivation, leading to gastrointestinal toxicity [16]. In deconjugation, medications such as sulfasalazine, which are used to mitigate the effects of inflammatory bowel disease, require bacterial azoreductase to release its active moiety, 5-aminosalicylic acid [17]. Beyond direct microbial biotransformation of drugs, gut microorganisms can indirectly influence drug metabolism by regulating host metabolic enzymes [13]. Microbial-derived metabolites, including short-chain fatty acids (SCFAs) and bile acids, affect the expression and functional activity of hepatic enzymes, particularly members of the cytochrome P450 (CYP450) family that are responsible for the metabolism of numerous therapeutic agents [14]. Among these metabolites, butyrate has been shown to regulate CYP3A4 expression, thereby modifying the metabolism of drugs such as statins and immunosuppressive agents [18]. Microbial modification of bile acids affects nuclear receptor signaling, influencing hepatic enzyme expression and altering drug detoxification pathways [19]. Microbial metabolism of drugs is a key determinant of drug efficacy, safety, and interindividual variability [20]. It is very important to understand the interaction of drugs because it will facilitate precision drug approaches, enhancing healing outcomes while limiting adverse effects [21].

Drug metabolisms

Drug metabolism is the biochemical process through which enzymes transform drugs and

other xenobiotics into metabolites, influencing their pharmacological activity, toxicity, and elimination from the body [10].

The liver plays a central role in drug metabolism because it contains abundant drug-metabolizing enzymes, including the cytochrome P450 (CYP450) family, which catalyses many Phase I biotransformation reactions [22]. These reactions can convert drugs into more water-soluble metabolites, although they may also produce pharmacologically active or toxic metabolites. Drug metabolites produced by metabolic biotransformations may be poisonous, inactive, or active. Medications are classified as xenobiotics since they are substances that are not manufactured by the body [23]. Because they are frequently hydrophobic, xenobiotics need to be detoxified by certain metabolic processes in order to be excreted effectively [9]. The metabolism of drugs is made up of these biological activities. The metabolic breakdown of drugs involves specialized enzymes. Cytochrome P450 enzymes are involved in approximately 90% of drug metabolism reactions [3]. Due to mechanism-based enzyme inhibition and drug-to-drug interactions, cytochrome P450s, a superfamily of major biological catalysts involved in host drug metabolism, are implicated in numerous clinical examples of toxicity and adverse drug responses [24].

Drug metabolism is commonly described in terms of Phase I and Phase II reactions (Figure 2). Phase I reactions include oxidation, reduction, and hydrolysis, many of which are catalysed by cytochrome P450 (CYP) enzymes, whereas Phase II reactions involve conjugation with endogenous molecules to facilitate the elimination of drugs and their metabolites [25].

During phase I biotransformation, compounds undergo oxidation, reduction, or hydrolysis, resulting in the addition or exposure of polar functional groups, including hydroxyl (-OH), carboxyl (-COOH), amino (-NH_2), and sulfhydryl (-SH). This process enhances their water solubility and promotes subsequent excretion [26]. Phase II drug metabolism consists of conjugation reactions in which metabolites generated during phase I are linked to endogenous polar molecules [27]. These reactions are catalyzed by conjugating enzymes such as glutathione S-transferases (GSTs), sulfotransferases (SULTs), and uridine diphosphate glucuronosyltransferases (UGTs). The resulting conjugates are generally more water-soluble, allowing xenobiotics and their metabolites to be more readily excreted from the body [28]. Before being identified by efflux transporters and pushed out of cells, the conjugated medications may undergo additional processing. Reactive metabolites, which are harmful to the human body, can also be produced by the same metabolic process. This is known as drug bioactivation and is especially dependent on key structural characteristics of these substances [20].

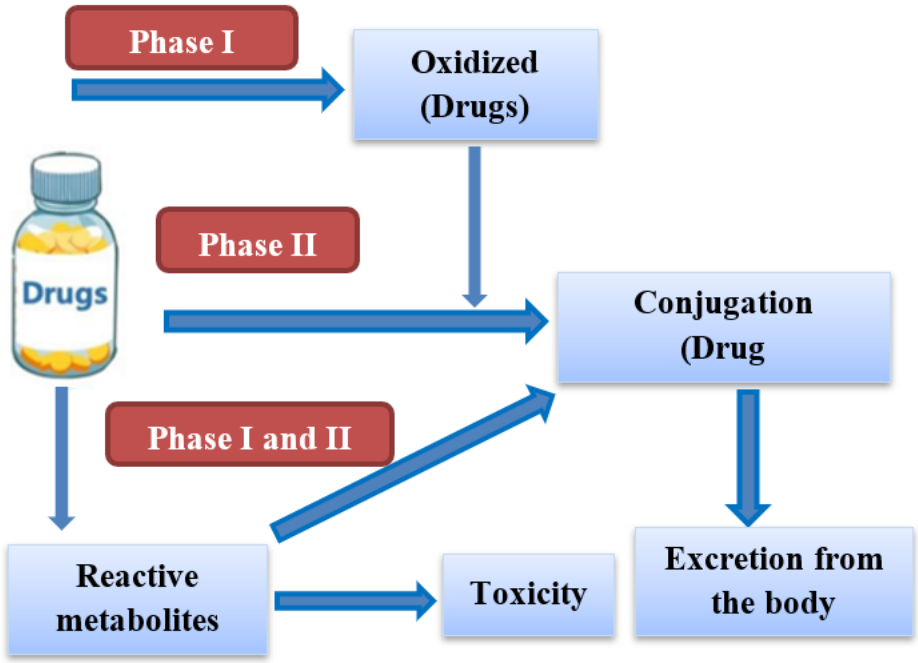


Figure 2: General pathways of drug metabolism [6,21]

Phase I of drug metabolism: functionalization

Phase I drug metabolism reactions are non-synthetic (functionalization) processes that either introduce new hydrophilic functional groups or expose pre-existing ones within drug molecules [29]. These reactions, including oxidation, reduction, and hydrolysis, primarily increase the polarity of lipophilic compounds, facilitating their subsequent metabolism or excretion [26]. During these processes, functional groups such as hydroxyl, amino, or carboxyl moieties are either introduced or exposed on the parent molecule, creating reactive sites for further biotransformation. Phase I metabolism is predominantly catalyzed by cytochrome P450 (CYP450) enzymes, which serve as the principal enzymatic system responsible for oxidative drug metabolism [19]. Among the phase I reactions, oxidation occurs most frequently, with enzymes of the cytochrome P450 superfamily carrying out the majority of these metabolic transformations [27]. Although less common than oxidation, reduction and hydrolysis also contribute to phase I drug metabolism and participate in the biotransformation of selected therapeutic compounds [30]. The products of phase I reactions may remain active or be further processed in phase II [28].

Phase II of Drug Metabolism: Conjugation

In Phase II drug metabolism, the body conjugates drugs or their Phase I metabolites with endogenous molecules such as sulfate, glucuronic acid, or glutathione, resulting in more water-soluble compounds that facilitate excretion [29]. Glucuronidation is one of the most common phase II reactions, facilitated by UDP-glucuronosyltransferases [31]. Sulfation is another important reaction, often involving sulfotransferase enzymes [5]. Conjugation reactions render the metabolite more hydrophilic and thus easier to excrete through urine or bile [15].

Drug metabolism by the gut microbiota varies among bacterial species and can substantially influence treatment outcomes. For example, *Eggerthella lenta* inactivates digoxin through microbial metabolism, thereby reducing its therapeutic activity. In contrast, the presence of *Akkermansia muciniphila* has been associated with improved responses to cancer immunotherapy by promoting T-cell-mediated immune function [10]. Microbial biotransformation may also generate metabolites that contribute to adverse drug reactions and increased toxicity. Recent advances in artificial intelligence have enabled the development of computational models that predict drug microbiome interactions, providing valuable insights for optimizing treatment efficacy and addressing antimicrobial resistance. Personalized medicine based on microbiome analysis offers improved outcomes by tailoring treatments (Table 1).

Table 1: Diverse ways microbiomes interact with drugs, influencing their effectiveness and potential side effects

Study	Key finding	References
Effect of gut microbes on medication effectiveness	Medications like digoxin and sulfasalazine are metabolized by gut microbiomes, thereby modulating their bioavailability and therapeutic effects. Bacteria like *Eggerthella lenta* can inactivate digoxin, reducing its effectiveness.	[4]
Gut Microbiomes and Immune Checkpoint Inhibitors	*Akkermansia muciniphila* present in the gut improves the effectiveness of immune checkpoint inhibitors in cancer treatment by supporting T-cells	[3,32]
The impact of microbes in drug toxicity	Specific microbes like *Clostridium spp.* convert prodrugs into noxious substances, intensifying medication side effects.	[33,34]
Artificial intelligence (AI) is used to predict drug-microbiome interactions	'An artificial intelligence-based model predicts how gut microbes break down drugs such as antibiotics and statins and how their effectiveness and resistance profiles are altered.	[35]
Microbiome and Personalized Medicine	Personalized drug regimens based on microbiome analysis enhance treatment outcomes by mitigating adverse effects and improving drug efficacy, particularly in antibiotics and chemotherapeutic agents.	[3,5,20]

Factors influencing drug metabolism

Several factors influence the extent of drug metabolism, including diet, sex, genetic variation, age, and concomitant medication use [21].

Genetic polymorphisms in drug-metabolizing enzymes, mainly in the cytochrome P450 group, can lead to variations in metabolism [10]. Age differences also play a role in biological actions; newborns and older people exhibit different digestion rates [10]. Drug interactions, where one drug interferes with the metabolism of another, can lead to altered drug levels and potential adverse effects.

Direct metabolism by microbial enzymes

Bacteria possess several biological catalysts proficient at metabolizing drugs. For instance, bacterial azoreductases activate the inactive drug sulfasalazine into its active form, 5-aminosalicylic acid, which exerts anti-inflammatory effects in the colon [5,12]. Conversely, certain microbes can inactivate drugs; *Eggerthella lenta* produces a cardiac glycoside reductase (Table 2) that reduces digoxin, diminishing its therapeutic efficacy [31]. The abundant glucuronides in the human intestine are processed by bacterial β-glucuronidase enzymes to produce glucuronic acids from conjugated compounds.

Modification of drug metabolites

Drug metabolites can be transmogrified by microbial biological catalysts, impacting their reabsorption and activity. A noteworthy example is the deconjugation of glucuronidated drug metabolites by bacterial β-glucuronidases. This method can lead to the reactivation of drugs like irinotecan, resulting in adverse effects such as diarrhea [5].

Competition for metabolic pathways

Gut microbial metabolites can influence drug disposition by competing with medications for the same host metabolic pathways. One example is *p*-cresol, a bacterial metabolite that competes with acetaminophen for sulfation by sulfotransferase 1A1 (SULT1A1). This competition may reduce acetaminophen metabolism and alter both its therapeutic activity and potential for toxicity [4,27].

Sequestration and binding

Interaction between intestinal microorganisms and orally administered drugs can influence drug absorption. *Helicobacter pylori*, for instance, has been reported to reduce the availability of L-DOPA, a key therapy for Parkinson's disease, thereby potentially compromising its clinical efficacy [10].

Table 2: Microbes and their roles in drug breakdown

Microbes	Impact on drug metabolism	Examples	References
Coprococcus	Activation of certain prodrugs through microbial metabolism and involvement in bile acid transformation.	Cyclophosphamide, Bilirubin	[36,37]
Bacteroides	Metabolism of chemical compounds due to reaction with water and reduction reactions.	Digoxin, Sulfasalazine	[38]
Lactobacillus	Conjugation and conversion.	Chloramphenicol, Estrogens	**[5,39]**
Escherichia coli	Decrease and conversion of nitroaromatic complexes.	Nitrofurantoin, Sulfasalazine	
Enterococcus	Hydrolysis and deconjugation.	Sulfonamides, Bile Acids	[2,40]
Prevotella	Depletion of complex carbohydrates.	NSAIDs, Statins	[41]
Akkermansia muciniphila	Modulates absorbency and immune response.	Metformin, Immunotherapy	[10,30]
Ruminococcus	Fermentation and drug bioavailability.	L-Dopa, Statins	[7,41]
Methanobrevibacter	Methanogenesis and antibiotic modulation.	Antibiotics, TMAO	[5,22]
Faecalibacterium prausnitzii	Short-chain fatty acid production and anti-inflammatory effects.	Prodrugs, Immune-modulating drugs	**[14]**

Production of metabolites influencing drug action

Gut bacteria produce a wide range of metabolites that influence host metabolic processes involved in drug disposition. Among these, butyrate has been shown to regulate the expression of drug-metabolizing enzymes, thereby modifying the metabolism of certain medications [22].

Impact on drug transporters

Interaction between the gut microbiota and host transport proteins contributes to variability in drug disposition. Microbial metabolites have been reported to regulate the expression of *P-glycoprotein*, an important drug efflux transporter, thereby influencing the absorption and pharmacokinetics of several medications [34].

Influence on host immune system

The gut microbiota communicates closely with the host immune system, and these interactions can influence drug metabolism. Microbial signals regulate immune pathways that, in turn, affect the expression and activity of cytochrome P450 enzymes, which are responsible for the biotransformation of many therapeutic agents. As a result, immune-mediated changes driven by the gut microbiota may alter the pharmacokinetic properties of certain drugs [33,40].

Interindividual variability

The composition of the gut microbiota varies significantly between individuals, leading to differences in drug metabolism and response. This variability can influence the efficacy and toxicity of medications, underscoring the importance of considering the gut microbiome in personalized medicine [15,24].

Prospects of drug metabolism

There is rapid advancement in drug metabolism, motivated by developing technologies and a deeper understanding of host-microbe interactions [30]. Scientific advancement and investigation are likely to focus on drug customization for patients, the use of artificial intelligence in drug breakdown, the influence of the gut microbiome and technological advancement models**.** Further research in pharmacogenomics and gene sequencing will facilitate more individualized drug healing effects, limiting harmfulness and improving drug therapies [10]. With the knowledge of genetic polymorphisms in enzymes that metabolize drugs, especially in the cytochrome P450 family, health workers can modify drugs for particular patients, improving the therapeutic outcome [3,4]. There is a need for further research into the use of artificial intelligence and machine learning models in predicting drug metabolic pathways, toxicity risks, and drug-drug interactions [9]. AI-driven simulations of enzyme-drug interactions can accelerate drug discovery and improve the safety profile of pharmaceuticals before clinical trials [4]. CRISPR-Cas9 technology offers new possibilities in modifying genes related to drug metabolism**,** potentially addressing drug resistance and metabolic disorders [13,42]. Future studies may focus on genetic engineering to enhance drug metabolism efficiency**,** leading to the development of customized therapeutics [10].

Growing evidence indicates that the gut microbiota is a major determinant of drug metabolism, influencing both therapeutic efficacy and the risk of adverse drug reactions through diverse microbial enzymatic activities [24,43]. Future investigations should focus on identifying microbial enzymes involved in drug biotransformation and determining how differences in microbial composition contribute to variability in drug response among individuals [10]. Depending on the metabolic pathway involved, microbial enzymes may activate prodrugs, inactivate therapeutic compounds, or generate metabolites with altered pharmacological properties, thereby influencing treatment outcomes [27].

Advances in microbiome research are expected to support the development of microbiome-directed therapeutic strategies aimed at improving drug efficacy while minimizing toxicity [38]. At the same time, emerging experimental platforms, including organ-on-a-chip systems and three-dimensional (3D) bioprinted tissues, offer more physiologically relevant alternatives to conventional animal models for investigating drug metabolism and host microbiota interactions [5]. These technologies more closely reproduce human biological environments, thereby improving the prediction of drug metabolism and therapeutic responses [10].

The contribution of the gut microbiota to antimicrobial resistance and resistance to anticancer therapies remains an important area of investigation. Future studies should prioritize the characterization of microbial metabolic pathways associated with drug resistance to identify novel therapeutic targets and improve treatment outcomes [24]. Furthermore, integrating metabolomics, proteomics, and genomics will provide a more comprehensive

understanding of host microbiota interactions during drug metabolism [26]. Such multi-omics approaches are expected to strengthen drug safety evaluation, facilitate the identification of new therapeutic targets of metabolic disorders, including diabetes and cardiovascular diseases, and advance the implementation of precision pharmacology [9,36].

Drug metabolism is governed not only by hepatic phase I and phase II metabolic enzymes [19,29] but also by the diverse biochemical activities of the gut microbiota, which contribute significantly to the biotransformation of numerous therapeutic agents [36]. Although cytochrome P450 enzymes remain central to xenobiotic biotransformation, intestinal microorganisms contribute through reactions such as reduction, hydrolysis, deconjugation, and other biochemical transformations that can modify drug activity. In addition to these direct effects, microbial metabolites, including short-chain fatty acids and bile acids, regulate the expression of host metabolic enzymes, thereby influencing drug absorption, distribution, metabolism, and elimination [35].

Drug metabolism is shaped by multiple interacting factors, including genetic variation, dietary habits, environmental exposures, and the composition of the gut microbiome. Differences in microbial communities between individuals partly explain why patients receiving the same medication may experience different therapeutic responses or adverse effects [26]. Evidence from studies involving drugs such as digoxin, irinotecan, and sulfasalazine highlights the importance of considering microbiome composition when selecting or optimizing pharmacological therapy [10]. These findings support the growing role of microbiome-informed strategies in precision medicine.

Rapid advances in biotechnology are creating new opportunities to better understand and manipulate drug microbiome interactions. Artificial intelligence is increasingly being used to predict microbial metabolic pathways, identify potential drug microbe interactions, and improve the early stages of drug development [9]. At the same time, CRISPR-based genome editing offers the possibility of modifying microbial genes involved in drug metabolism, with the long-term goal of reducing treatment-related toxicity and improving therapeutic outcomes.

Progress in personalized medicine will depend on combining microbiome research with pharmacogenomics and other emerging omics diagnostic tools, targeted microbial interventions, and therapeutic strategies that account for an individual's microbial composition when selecting drug therapy [15]. A more comprehensive understanding of host microbiota interactions will improve the prediction of drug response, strengthen medication safety, and contribute to the design of more effective and individualized treatment strategies.

CONCLUSION

The growing body of evidence demonstrates that the gut microbiota is an important contributor to interindividual differences in drug response. By activating, inactivating, or chemically modifying therapeutic compounds, intestinal microorganisms can alter drug bioavailability, pharmacokinetics, therapeutic efficacy, and the likelihood of adverse drug reactions. These findings highlight the close relationship between host metabolism and the gut microbiome and emphasize the need to better understand the mechanisms through which microbial communities influence drug disposition and clinical outcomes.

The available evidence indicates that the gut microbiota should be regarded as an integral component of drug metabolism rather than a passive bystander. Incorporating microbiome research into pharmacological studies may improve the prediction of drug response, support the design of individualized treatment strategies, and enhance medication safety. Continued progress in this field is expected to strengthen precision medicine by enabling therapies that better reflect each patient's biological and microbial characteristics.

DECLARATIONS

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Ethical approval

Not applicable.

Availability of data and materials

Not applicable

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

Samuel Ebiloma conducted the literature search, drafted the manuscript, and coordinated the study. Okoronkwo Christopher Uche and Chibundo supervised and critically revised the work.

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