International Journal of Basic & Clinical Pharmacology
Deshmukh AR et al. Int J Basic Clin Pharmacol. 2026 Jul;15(4):768-774
https://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20261967

Systematic Review

The role of gut microbiota in drug metabolism: implications for personalized medicine: a systematic review

Abhiraj R. Deshmukh, Nainish B. Mehta*, Girish S. Joshi, Prathamesh S. Sawant

Department of Pharmacology, Topiwala National Medical College and BYL Nair hospital, Mumbai, Maharashtra, India

Received: 21 March 2026
Revised: 18 April 2026
Accepted: 29 April 2026

***Correspondence:**
Dr. Nainish B. Mehta,
Email: nainishmehta@gmail.com

ABSTRACT

Interindividual variability in drug response remains a significant challenge in clinical pharmacology. Emerging evidence suggests that the gut microbiota contributes to variability in drug metabolism, efficacy, and toxicity. A systematic search of PubMed, Scopus, Nature Portfolio, and relevant pharmacology journals was conducted for studies published between January 2019 and August 2025 using predefined keywords related to pharmacomicrobiomics and drug-microbiota interactions. Peer-reviewed human and animal studies evaluating mechanistic or clinical implications were included. Study selection and reporting followed PRISMA 2020 guidelines. Risk of bias was assessed using the Cochrane RoB 2 tool for randomized trials, the Newcastle-Ottawa Scale for observational studies, and SYRCLE's tool for animal studies. Data were synthesized qualitatively due to methodological heterogeneity. Of 2,847 identified records, 158 studies met inclusion criteria. Clinically significant microbiota-drug interactions were observed across multiple drug classes including cardiac glycosides, anti-inflammatory agents, chemotherapeutics, antidepressants, immunosuppressants, and immunotherapies. Mechanisms included direct microbial biotransformation, metabolite reactivation, modulation of host metabolic pathways, and immune-mediated effects. These interactions were associated with altered pharmacokinetics and variable therapeutic outcomes. The gut microbiota is an important determinant of drug response variability. Incorporating microbiome-based insights into pharmacotherapy may enhance individualized treatment strategies. Further well-designed clinical studies are needed to support routine clinical implementation.

Keywords: Gut microbiota, drug metabolism, Precision medicine, drug response, Interindividual variability

INTRODUCTION

The variability in drug response among individuals remains one of the most persistent challenges in clinical pharmacology. Differences in age, genetics, disease states, and environmental factors have traditionally been used to explain interindividual variability; however, these factors alone fail to fully account for the observed differences in drug efficacy and toxicity.[1,2] In recent years, the human gut microbiota has emerged as a crucial and previously underappreciated determinant of drug disposition and response.[3]

The human gastrointestinal tract harbours a dense and diverse microbial ecosystem comprising trillions of microorganisms and millions of genes, collectively referred to as gut microbiome. This microbial community functions as a dynamic metabolic organ capable of influencing host physiology through enzymatic activity, immune modulation, and signalling along gut-brain axis. Beyond its established role in nutrition and immunity, accumulating evidence demonstrates that gut microbiota can directly and indirectly modify pharmacokinetics and pharmacodynamics of numerous drugs.[4,5,6]

Microbial enzymes can activate prodrugs, inactivate active compounds, or generate toxic metabolites, thereby altering therapeutic outcomes. Classical examples include the bacterial reduction of digoxin to inactive dihydrodigoxin[7] and the azoreductase-mediated activation of sulfasalazine

to 5-aminosalicylic acid.[8] Additionally, the gut microbiota can influence host drug-metabolizing enzymes, modulate drug transporters, and affect enterohepatic circulation.[9] Such interactions contribute to variability in bioavailability, efficacy, and adverse drug reactions.

Concept of pharmacomicrobiomics integrates microbiome science with pharmacology to explain and predict drug response variability based on microbial composition and function.[10] Advances in sequencing technologies and bioinformatics have accelerated research in this field, revealing clinically relevant microbiota-drug interactions across diverse therapeutic areas, including oncology, psychiatry, cardiology, and immunology.[11-13] These findings have significant implications for personalized medicine, as microbiome-informed therapies may optimize treatment efficacy while minimizing toxicity.

Despite growing interest, existing evidence is fragmented across experimental, observational, and clinical studies. A comprehensive synthesis of current knowledge is essential to delineate established mechanisms, identify clinically relevant interactions, and highlight gaps for future research. Therefore, this systematic review aims to critically evaluate role of gut microbiota in drug metabolism and discuss its implications for advancement of personalized medicine. While pharmacogenomics has advanced precision medicine, it explains only a fraction of interindividual variability in drug response. A critical gap persists in accounting for environmentally modifiable and functionally dynamic contributors. In this context, gut microbiota introduces a unique dimension, unlike the static human genome, microbiome is highly adaptable, influenced by diet, drugs, and disease states. This raises an important conceptual shift: variability in drug response may not solely be predicted but potentially modulated through microbiome-targeted interventions. Despite increasing recognition, integration of microbiome data into clinical pharmacology remains limited, necessitating a critical synthesis of current evidence with emphasis on translational applicability.

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[14]

Search strategy

A comprehensive literature search was performed across PubMed, Scopus, Nature Portfolio, and selected pharmacology and microbiology journals. The search covered studies published between January 2019 and August 2025. The following keywords and Medical Subject Headings (MeSH) terms were used in various combinations: pharmacomicrobiomics, gut microbiota, drug metabolism, microbiome-drug interactions, and personalized medicine.[15] Reference lists of relevant articles were also manually screened to identify additional eligible studies.

Inclusion criteria

Peer-reviewed human or animal studies evaluating interactions between gut microbiota and pharmaceutical agents; studies reporting relevant mechanistic insights, pharmacokinetic or pharmacodynamic outcomes, or clinical implications related to our study and articles published in English were included.

Exclusion criteria

Studies limited solely to dietary substances or nutraceuticals, lacked specific microbiota-drug interaction data, consisted of case reports, editorials, or letters with insufficient methodological detail and failed to provide clinically or mechanistically relevant outcomes were excluded from the study. Reviews were considered for background context but excluded from qualitative synthesis.

Study selection and data extraction

Two reviewers independently screened titles and abstracts for eligibility. Full-text articles retrieved for potentially relevant studies and assessed for inclusion. Discrepancies were resolved through discussion and consensus. Data extracted included study design, population characteristics, drug class evaluated, microbial species/ functional pathways involved, proposed mechanisms, and reported clinical or pharmacological outcomes.

Data synthesis and quality assessment

Given the heterogeneity in study designs, populations, microbiome assessment techniques, and pharmacokinetic/pharmacodynamic endpoints, a qualitative narrative synthesis was performed. Studies were grouped according to therapeutic class and principal mechanism of microbiota interaction.

Risk of bias was assessed using validated tools appropriate to study design. Randomized controlled trials were evaluated using the Cochrane risk of bias 2 (RoB 2) tool. Observational cohort and case-control studies were assessed using the Newcastle-Ottawa Scale (NOS). Animal experimental studies were evaluated using SYRCLE's risk-of-bias tool. Two reviewers independently performed quality assessment, and disagreements were resolved through consensus discussion. Studies were categorized as low, moderate, or high risk of bias based on predefined scoring thresholds.[16-18]

A quantitative meta-analysis was not undertaken due to substantial clinical and methodological heterogeneity, variability in microbiome sequencing methodologies, and inconsistent reporting of pharmacokinetic parameters such as AUC, C_{max}, and clearance.

Additionally, an interpretive synthesis approach was adopted to identify recurring mechanistic patterns and emerging translational themes across heterogeneous studies, enabling integration of mechanistic and clinical evidence beyond descriptive aggregation.

RESULTS

Study selection and characteristics

The systematic search identified a total of 2,847 records across all databases. After removal of duplicates and initial screening of titles and abstracts, 312 articles were retrieved for full-text assessment. Of these, 158 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. The included studies comprised a heterogeneous mix of observational studies, randomized controlled trials, and experimental human and animal studies. The majority were observational in design, reflecting the emerging and exploratory nature of pharmacomicrobiomics research.

The studies originated from 23 countries and collectively represented a wide range of therapeutic areas. Sample sizes varied substantially, ranging from fewer than 30 participants in mechanistic studies to over 2,000 participants in large observational cohorts. Most studies evaluated adult populations, with limited data available in pediatric settings.

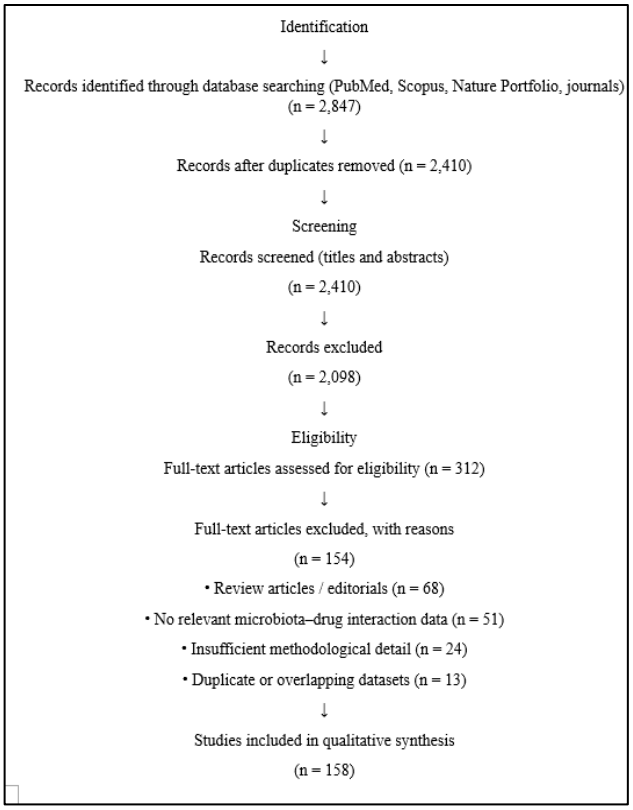

Figure 1: PRISMA flow diagram of study selection.

Table 1: Characteristics of included studies (n=156).

Parameters	Findings
Total records identified	2,847
Full-text articles assessed	312
Studies included	158
Countries represented	23
Study design distribution	Observational studies (62.8%), randomized controlled trials (14.74%) and case–control studies (7.7%).
Population type	Predominantly adults
Major therapeutic areas	Cardiology, oncology, psychiatry, transplant medicine, immunotherapy

Table 2: Major drug classes and mechanisms of microbiota interaction.

Drug/class	Key microbial factor	Mechanism of interaction	Pharmacological impact	Clinical relevance
Digoxin	Eggerthella lenta	CGR operon-mediated reduction to dihydrodigoxin	Reduced systemic exposure	Possible dose adjustment required
Sulfasalazine	Colonic bacteria	Azoreductase-mediated cleavage	Prodrug activation to 5-ASA	Essential for therapeutic efficacy
Irinotecan	β-glucuronidase-producing bacteria	Deconjugation of SN-38 glucuronide	Reactivation of toxic metabolite	Increased gastrointestinal toxicity
SSRIs	Altered microbial diversity	Gut-brain axis modulation[20]	Variable pharmacodynamic response	Differences in antidepressant efficacy
Tacrolimus	Microbiome composition variability	Altered intestinal metabolism/absorption[21]	Variable AUC and dose requirement	Challenges in therapeutic drug monitoring
Anti-PD-1 inhibitors	Microbial diversity and specific taxa	Immune system modulation	Altered treatment response	Impact on immunotherapy outcomes

Table 3: Risk-of-bias assessment summary of included studies (n=158).

Study design	Number of studies	Low risk (%)	Moderate risk (%)	High risk (%)	Common sources of bias
Randomized controlled trials	23	61.9	28.6	9.5	Lack of allocation concealment, incomplete blinding
Observational cohort studies	98	54.1	36.7	9.2	Confounding, inadequate adjustment for covariates
Case-control studies	12	50.0	41.7	8.3	Selection bias, recall bias
Animal experimental studies	25	48.0	40.0	12.0	Lack of randomization and blinding

Distribution of study designs

Observational studies constituted the largest proportion of included literature (approximately 62.8%), followed by randomized controlled trials (14.74%) and case–control studies (7.7%). This distribution highlights the predominance of hypothesis-generating and real-world evidence in this field, with comparatively fewer interventional trials assessing microbiome-guided therapeutic strategies.

Clinically relevant drug-microbiota interactions

Cardiac glycosides

Several studies demonstrated that specific gut bacterial species, particularly Eggerthella lenta, are capable of reducing digoxin to its inactive metabolite, dihydrodigoxin. This microbial biotransformation was associated with reduced systemic exposure and diminished therapeutic efficacy of digoxin, necessitating dose adjustments in affected individuals. The mechanism involves the cardiac glycoside reductase (CGR) operon expressed by certain bacterial strains.

Anti-inflammatory agents

Sulfasalazine, a prodrug widely used in inflammatory bowel disease and rheumatological conditions, was consistently shown to undergo bacterial azoreduction in the colon, resulting in the release of its active moiety, 5-aminosalicylic acid. The presence and activity of bacterial azoreductase enzymes were essential for therapeutic activation, underscoring the dependence of drug efficacy on gut microbial composition.

Chemotherapeutic agents

In the case of irinotecan, gut microbial β-glucuronidase enzymes were implicated in the reactivation of its inactive metabolite, SN-38 glucuronide, back to the toxic SN-38 form within the intestine. This process was strongly associated with increased gastrointestinal toxicity, particularly delayed-onset diarrhea, without contributing to antitumor efficacy. Modulation of microbial β-glucuronidase activity emerged as a potential strategy to reduce adverse effects.

Antidepressants

Emerging evidence suggested that baseline gut microbiome profiles may influence response to selective serotonin reuptake inhibitors (SSRIs). Several studies reported associations between microbial diversity, specific bacterial taxa, and antidepressant treatment outcomes. These effects were proposed to be mediated through modulation of the gut–brain axis, neurotransmitter availability, and immune signaling, although direct microbial metabolism of SSRIs appeared to be limited.

Immunosuppressants

Tacrolimus pharmacokinetics were shown to be influenced by gut microbiome composition, with interindividual variability in drug exposure partially attributed to microbial effects on intestinal metabolism and absorption. While specific mechanisms remain incompletely understood, alterations in microbial diversity and functional capacity were consistently associated with changes in tacrolimus dose requirements.

Immunotherapy

Multiple studies evaluating immune checkpoint inhibitors, particularly anti-PD-1 therapies, demonstrated that gut microbiome diversity and the presence of specific bacterial taxa were associated with differential treatment responses. Patients with favorable microbiome profiles exhibited enhanced therapeutic efficacy and improved survival outcomes, likely mediated through microbiota-driven modulation of host immune responses.

Importantly, a recurring pattern across studies was the context-dependent nature of microbiota–drug interactions, where the same drug exhibited variable effects depending on microbial composition and functional gene expression. This highlights that taxonomic profiling alone may be insufficient, and functional microbiomics may be more relevant for predicting drug response. Furthermore, a disproportionate reliance on observational data suggests that current evidence is more associative than causative,

underscoring the need for mechanistically driven clinical trials.

DISCUSSION

This systematic review consolidates current evidence supporting the gut microbiota as a significant determinant of interindividual variability in drug response. The findings reinforce pharmacomicrobiomics as an emerging extension of precision medicine, complementing pharmacogenomics by incorporating microbial enzymatic capacity, metabolic potential, and immune-modulatory effects into therapeutic decision-making.

Across diverse therapeutic classes, consistent mechanistic themes emerged. Direct microbial biotransformation-such as reduction, hydrolysis, and deconjugation-demonstrates that the gut microbiota can function as an additional metabolic compartment parallel to hepatic metabolism. The reduction of digoxin by Eggerthella lenta and the azoreductase-mediated activation of sulfasalazine exemplify clinically meaningful microbial contributions to drug bioavailability and efficacy. Importantly, these effects are not merely theoretical but have demonstrated pharmacokinetic consequences, including altered systemic exposure and variability in therapeutic response.

Beyond direct metabolism, modulation of enterohepatic circulation and metabolite reactivation appears central to drug toxicity. Irinotecan-induced gastrointestinal toxicity, mediated through bacterial β-glucuronidase activity, highlights how microbial enzymatic processes may selectively influence adverse drug reactions without enhancing therapeutic benefit. Such findings open avenues for targeted microbiota-modulating strategies aimed at improving tolerability while preserving efficacy.

In neuropsychiatric and immunological therapeutics, the microbiota exerts influence primarily through indirect pharmacodynamic mechanisms. Modulation of the gut–brain axis, immune signaling pathways, and inflammatory tone suggests that microbial composition may determine therapeutic responsiveness independent of plasma drug concentration. This distinction is clinically relevant, as it implies that conventional therapeutic drug monitoring may not fully capture determinants of treatment success.

Integration of microbiome science with classical pharmacokinetics offers a more comprehensive framework for understanding variability in parameters such as AUC, Cmax, clearance, and dose–response relationships. While host genetic polymorphisms in cytochrome P450 enzymes account for hepatic metabolic variability, microbial enzymes contribute additional intestinal-level variability that may partially explain unexplained interindividual differences observed in clinical practice.[20-22,25]

Nevertheless, the predominance of observational designs underscores that pharmacomicrobiomics remains an evolving field. Standardization of microbiome sequencing techniques, harmonization of outcome reporting, and incorporation of microbiome profiling into prospective interventional trials are necessary to translate current insights into routine clinical application.[24]

Another critical consideration is the bidirectional nature of drug-microbiome interactions. While microbiota influence drug metabolism, drugs themselves can alter microbial composition, creating feedback loops that may evolve over the course of therapy. This temporal variability is largely overlooked in current studies and represents a significant gap in understanding longitudinal treatment outcomes.

Collectively, the evidence supports a paradigm shift in clinical pharmacology: drug response should be conceptualized as a product of host-microbiome interaction rather than host factors alone. Future therapeutic strategies may integrate microbial profiling, targeted modulation, and traditional pharmacogenomics to achieve truly individualized pharmacotherapy.

From a clinical perspective, the feasibility of integrating microbiome profiling into routine practice remains uncertain. However, targeted strategies such as microbiome modulation (e.g., probiotics, antibiotics, enzyme inhibitors, or fecal microbiota transplantation) may offer practical avenues for optimizing drug response, particularly in oncology and immunotherapy.

Strengths

This systematic review possesses several methodological and scientific strengths. First, it was conducted in strict accordance with PRISMA 2020 guidelines, incorporating a structured search strategy, predefined eligibility criteria, independent dual-reviewer screening, and formal risk-of-bias assessment using validated tools tailored to study design. Such methodological rigor enhances transparency, reproducibility, and credibility of findings.

Second, the review integrates evidence across multiple therapeutic domains including cardiology, oncology, psychiatry, transplant medicine, and immunotherapy providing a comprehensive and interdisciplinary perspective on pharmacomicrobiomics. By synthesizing both mechanistic and clinical studies, it bridges the gap between experimental microbiome research and applied clinical pharmacology.

Third, inclusion of structured risk-of-bias evaluation allows contextual interpretation of findings, distinguishing hypothesis-generating evidence from higher-quality interventional data. This strengthens the validity of conclusions and reduces the likelihood of overinterpretation.

Finally, the review emphasizes clinically relevant pharmacokinetic parameters such as AUC, Cmax, clearance, and therapeutic drug monitoring implications,

thereby aligning microbiome science with core principles of clinical pharmacology and personalized medicine.

Limitations

This review has several limitations. First, the heterogeneity of included studies in terms of design, population characteristics, and outcome measures precluded quantitative meta-analysis. Second, a substantial proportion of evidence was derived from observational and experimental studies, limiting causal inference. Third, variability in microbiome assessment techniques and lack of standardized reporting across studies complicate direct comparisons. Finally, most studies focused on adult populations, highlighting a paucity of data in pediatric and geriatric patients.

CONCLUSION

The gut microbiota represents a dynamic and modifiable determinant of drug response, extending beyond traditional pharmacokinetic frameworks. Current evidence supports its role in influencing drug metabolism, efficacy, and toxicity across multiple therapeutic domains. However, translation into clinical practice remains constrained by methodological variability and limited interventional data. Moving forward, integration of microbiome science with pharmacology has the potential to transform personalized medicine from a predictive to a modifiable paradigm, enabling not only tailored therapy but also targeted optimization of treatment outcomes.

Future directions

Future research should prioritize well-designed, prospective clinical trials incorporating microbiome profiling alongside pharmacokinetic and pharmacodynamic endpoints. Standardization of sequencing methodologies, functional annotation, and reporting frameworks is essential to enable reproducibility and clinical translation. Integration of multi-omics approaches, including metagenomics, metabolomics, and pharmacogenomics, may provide a more comprehensive understanding of host-microbiome-drug interactions. Additionally, development of predictive models incorporating microbial signatures could facilitate personalized dosing strategies. Ultimately, bridging the gap between experimental findings and clinical implementation will determine the success of pharmacomicrobiomics in precision medicine.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533.
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;464(7285):59-65.
3. Pant A, Maiti TK, Mahajan D, Das B. Human gut microbiota and drug metabolism. Microb Ecol. 2023;86(1):97-111.
4. Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ. The microbial pharmacists within us. Nat Rev Microbiol. 2016;14(5):273-87.
5. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism. Nature. 2019;570(7762):462-7.
6. Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism. Transl Res. 2017;179:204-22.
7. Haiser HJ, Gootenberg DB, Chatman K, Sirasani G, Balskus EP, Turnbaugh PJ. Cardiac drug inactivation by Eggerthella lenta. Science. 2013;341(6143):295-8.
8. Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy. Nat Rev Gastroenterol Hepatol. 2017;14(6):356-65.
9. Yoo DH, Kim IS, Van Le TK, Jung IH, Yoo HH. Gut microbiota-mediated drug interactions. Drug Metab Dispos. 2014;42(9):1508-13.
10. Doestzada M, Vila AV, Zhernakova A, Koonen DPY, Weersma RK, Touw DJ, et al. Pharmacomicrobiomics and personalized medicine. Protein Cell. 2018;9(5):432-45.
11. Javdan B, Lopez JG, Chankhamjon P, Lee YJ, Hull R, Wu Q, et al. Personalized mapping of drug metabolism. Cell. 2020;181(7):1661-79.
12. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, et al. Gut microbiome and PD-1 therapy. Science. 2018;359(6371):91-7.
13. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Bifidobacterium and immunotherapy efficacy. Science. 2015;350(6264):1084-9.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 statement. BMJ. 2021;372:n71.
15. Weersma RK, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome. Gut. 2020;69(8):1510-9.
16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2 tool. BMJ. 2019;366:l4898.
17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle–Ottawa Scale. Ottawa Hospital Research Institute. Researchgate. 2000.
18. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE risk-of-bias tool. BMC Med Res Methodol. 2014;14:43.
19. Wallace BD, Wang H, Lane KT, Scott JE, Orans J, Koo JS, et al. Inhibiting bacterial enzymes to reduce toxicity. Science. 2010;330(6005):831-5.

20. Clarke G, Sandhu KV, Griffin BT, Dinan TG, Cryan JF, Hyland NP. Xenobiotic–microbiome interactions. Pharmacol Rev. 2019;71(2):198-224.
21. Enright EF, Gahan CGM, Joyce SA, Griffin BT. Gut microbiota and clinical outcomes. Yale J Biol Med. 2016;89(3):375-82.
22. Tremlett H, Bauer KC, Appel-Cresswell S, Finlay BB, Waubant E. Gut microbiome and neurological disease. Ann Neurol. 2017;81(3):369-82.
23. Koppel N, Rekdal VM, Balskus EP. Chemical transformation of xenobiotics. Science. 2017;356(6344):eaag2770.
24. Valdes AM, Walter J, Segal E, Spector TD. Gut microbiota in health and disease. BMJ. 2018;361:k2179.
25. Bejaoui S, D'Amico F, Turroni S. Role of the gut microbiome in shaping drug response in immunocompromised hosts. Clin Microbiol Infect. 2026;S1198-743X(26)00104-7.

Cite this article as: Deshmukh AR, Mehta NB, Joshi GS, Sawant PS. The role of gut microbiota in drug metabolism: implications for personalized medicine: a systematic review. Int J Basic Clin Pharmacol 2026;15:768-74.