HEALTH ENGINEERING
e-ISSN 3007-2689
Open Access
Review

Leveraging machine learning to unravel drug–microbiome interactions in the gut

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Cite This: *Health Engineering*, **2026**, *2*, 9460012

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ABSTRACT: The human gut microbiome (HGM) is a complex, highly diverse microbial ecosystem with extensive enzymatic and metabolic capacity. The HGM plays a pivotal role in drug biotransformation, thereby modulating the therapeutic efficacy and pharmacokinetic profiles. Considerable interindividual variability in gut microbiota composition can produce differential metabolic activity, resulting in variable therapeutic responses to the same drug across individuals. In contrast, orally administered drugs can also affect HGM diversity and composition, impacting host health. Despite its importance, the systematic investigation of drug–microbiome interactions (DMIs) presents substantial experimental challenges. In recent years, machine learning (ML) has emerged as a powerful tool in biological and health sciences, offering advanced capabilities in pattern recognition and discovery of hidden relationships. This progress opens new avenues for DMI research. This review provides an overview of recent advances in HGM-mediated drug biotransformation and drug-induced HGM modification, with particular emphasis on ML applications in these areas. We aim to elucidate the critical role of ML in the systematic exploration and mechanistic understanding of DMI, highlighting its importance as a key future research direction.

KEYWORDS: human gut microbiome, drug–microbiome interactions, drug discovery, machine learning

1 Introduction

The human gut microbiome (HGM) is a structurally complex and highly diverse microbial ecosystem, with a gene count exceeding that of the human genome by more than 100-fold, thereby conferring substantial metabolic potential to the host [1,2]. Recent evidence indicates that HGM markedly contributes to dietary component digestion and transformation and influences the metabolism of orally administered drugs [3–5]. Specifically, HGM can catalyze previously unrecognized reactions of drugs, potentially resulting in reduced therapeutic efficacy or increased toxicity [6,7]. These HGM-mediated effects provide an important biological basis for interindividual variability observed in drug responses [8]. In contrast, drug intake can reshape HGM diversity and community structure, thereby exerting widespread effects on the host's metabolic homeostasis and overall physiological health [9–12]. Therefore, drug–microbiome interactions (DMIs) present new perspectives and targets for drug discovery and precision medicine [13–15].

Despite rapid advances in this field, systematic elucidation of the mechanisms underlying DMI remains a notable challenge [16]. Multiple host-related factors—including dietary composition, genetic background, and immune status—often confound *in vivo* studies, complicating the isolation and accurate attribution of the effects of HGM on drug metabolism. *In vitro* models offer greater experimental control and reproducibility; however, such models typically include limited microbial diversity and fail to capture HGM complexity [17]. Moreover, conventional experimental approaches are often resource-intensive and time-consuming. As a complementary strategy, machine learning (ML) approaches have emerged as valuable tools owing to their capacity to process high-dimensional data and uncover latent patterns. Recent advances in ML have facilitated remarkable breakthroughs in various biomedical fields, including protein structure prediction [18,19], gene annotation [20,21], and enzyme-related parameter prediction [22,23], demonstrating its potential to decipher complex biological relationships. By integrating large-scale screening datasets with multilevel molecular and genomic features, ML-based models can learn and predict potential DMI based on chemical structures and microbial functional profiles [6,24]. This review summarizes the current progress in HGM-mediated drug biotransformation and drug-induced HGM disruption alongside the latest applications of ML in both areas.

Received: June 17, 2025; **Revised:** September 27, 2025
Accepted: October 27, 2025

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2 Drug biotransformation by the HGM

HGM markedly contributes to drug biotransformation through diverse enzymatic reactions—including acetylation, demethylation, dihydroxylation, deacetylation, deamination, azoreduction, hydrolysis, and reduction—thereby influencing the drug efficacy [25,26]. Table 1 gives a summary of exemplary drugs that are susceptible to various types of direct transformation by the HGM, together with the representative metabolizing microbes and responsible genes for each drug. Substantial interindividual variability in HGM composition frequently results in distinct therapeutic responses to the same drug across populations [27]. For example, digoxin is a widely used cardiac glycoside for treating heart failure and arrhythmias. As early as 1981, researchers discovered that the gut microbiota metabolized digoxin, with the inactive transformed metabolite dihydrodigoxin detectable in feces [41,42]. Haiser et al. detected that *Eggerthella lenta* DSM2243 contained a *cgr* gene cluster composed of *cgr1* and *cgr2*, encoding heme-dependent monooxygenases that specifically catalyze digoxin reduction at the C-12 position [43,44]. In addition, *cgr2* could catalyze the reduction of several other cardiac glycosides used clinically, including digitoxin, digoxigenin, ouabain, and ouabagenin [37].

Levodopa (L-DOPA) serves as a crucial therapeutic agent for Parkinson's disease and other neurological disorders, with its metabolism influenced by HGM-mediated pathways. Maini et al. identified that *Enterococcus faecalis* produces a pyridoxal phosphate–dependent tyrosine decarboxylase, which converts L-DOPA to dopamine. Then, the dopamine is further metabolized to m-tyramine by the action of a molybdenum-dependent dehydroxylase from *E. lenta* [29]. Multiple studies have shown that tyrosine decarboxylase activity in fecal samples is closely associated with L-DOPA levels, clinical phenotypes, and treatment responses in patients with Parkinson's disease [29,45].

Acarbose, an α-glucosidase inhibitor widely used to treat type II diabetes [46], contains a biosynthetic gene cluster encoding a kinase, AcbK, which catalyzes acarbose O6A-hydroxyl phosphorylation, resulting in drug inactivation [47]. Balaich et al. reported a widespread distribution of AcbK homologs across the HGM. Their clinical studies further revealed that the presence of AcbK homologs in the HGM affects acarbose therapeutic efficacy, with implications for the clinical evaluation of its long-term drug use [47]. In addition, Tian et al. identified *Klebsiella grimontii* TD1 as an acarbose-degrading bacterium, the HGM abundance of which was markedly associated with acarbose resistance in patients [31].

Chondroitin sulfate is commonly used as a symptomatic slow-

Table 1 Examples of drugs susceptible to direct transformation by the HGM

Drugs	Degradation type	Representative metabolizing microbes	Responsible gene	Ref
5-Aminosalicylic acid	Acetylation	*Faecalibacterium*	*nat*	[27]
Caffeine	Demethylation	*Pseudomonas*	*ndmA*	[28]
Levodopa	Decarboxylation	*Enterococcus*	*tyrDC*	[29]
Diltiazem	Deacetylation	*Bacteroides*	*bt4096*	[3]
Gemcitabine	Deamination	*Klebsiella*	*cdd*	[30]
Acarbose	Hydrolysis	*Klebsiella*	*apg*	[31]
Chondroitin sulfate	Hydrolysis	*Bacteroides*	*cslA*	[32]
Balsalazide	Azoreduction	*Escherichia*	*azoR*	[33]
Olsalazine	Azoreduction	*Escherichia*	*azoR*	[33]
Sulfasalazine	Azoreduction	*Escherichia*	*azoR*	[33]
Ampicillin	Hydrolysis	*Escherichia*	*ampC*	[34]
Brivudine	Hydrolysis	*Escherichia*	*pdp*	[34]
Diclofenac	Hydrolysis	*Escherichia*	*uidA*	[35]
Indomethacin	Hydrolysis	*Escherichia*	*uidA*	[35]
Ketoprofen	Hydrolysis	*Escherichia*	*uidA*	[35]
SN-38(active metabolite of irinotecan)	Hydrolysis	*Escherichia*	*uidA*	[36]
5-Fluorouracil	Reduction	*Escherichia*	*preTA*	[12]
Digoxin	Reduction	*Eggerthella*	*cgr*	[37]
Digitoxin	Reduction	*Eggerthella*	*cgr*	[34]
Digoxigenin	Reduction	*Eggerthella*	*cgr*	[34]
Ouabagenin	Reduction	*Eggerthella*	*cgr*	[34]
Ouabain	Reduction	*Eggerthella*	*cgr*	[34]
5-Fluorocytosine	Reduction	*Escherichia*	*codA*	[38]
Clonazepam	Reduction	*Clostridium*	*nfsB*	[39]
Nitrazepam	Reduction	*Clostridium*	*nfsB*	[39]
Everolimus	Reduction	*Clostridium*	*CLOSPO_00137*	[40]

acting drug or dietary supplement for providing relief in osteoarthritis [48]. Wang et al. demonstrated that specific HGM microorganisms possess chondroitin sulfate–degrading capability. Key degrading strains include *Bacteroides salyersiae*, *B. finegoldii*, *B. xylanisolvens*, *B. thetaiotaomicron*, and *B. ovatus*. These anaerobic bacteria secrete glycoside hydrolases that degrade the action of chondroitin sulfate stepwise into unsaturated chondroitin sulfate oligosaccharides and short-chain fatty acids, thereby affecting its bioavailability and pharmacological effects [32].

Beyond individual cases where strains and enzymes are well characterized for drug inactivation, researchers have also conducted large-scale experiments to explore the broader impact of the HGM on drug biotransformation, investigating how different gut microorganisms influence the metabolism of numerous drugs. Zimmermann et al. conducted a full-factorial coculture experiment involving 76 representative gut bacterial strains and 271 clinically used drugs, finding that at least one bacterial strain could metabolize ~65% drugs [3]. Metabolic activity correlated with distinct chemical substructures (e.g., esters, amides, nitro, azo, and lactones), and the study pioneered a combinatorial pooling combined with gain-of-function genetic screening strategy to identify 30 microbiome-encoded enzymes catalyzing 20 drug conversions [3]. Javdan et al. simulated the *in vivo* gut environment using an optimized *in vitro* culture system and performed a systematic metabolic screen of 575 orally administered drugs. They identified notable gut microbiota–mediated metabolic alterations in 57 drugs [4]. This work highlighted pronounced interindividual variability in metabolic capacity and identified novel metabolites, underscoring the value of community-level assays for predicting drug bioavailability [4]. Furthermore, Wu et al. constructed a synthetic microbial community comprising 30 typical gut microbial species and screened 127 G protein–coupled receptor (GPCR)–targeting drugs under anaerobic conditions for 24 h. They observed that 30 drugs were metabolized, with 12 drugs showing high levels of metabolism, characterized by ≥80% drug depletion [5]. They demonstrated that such metabolism can markedly alter GPCR activity and discovered unconventional pathways, such as sulfur-based thionaphthene formation and amino acid–derived tricyclic conjugations [5]. Collectively, these large-scale studies integrate methodological innovation with mechanistic insights, advancing our understanding of how the HGM shapes drug metabolism and its clinical implications.

3 Diverse outcomes of gut microbial drug biotransformation

As microbial enzymatic activity within the HGM can reduce the efficacy of various drugs, HGM-mediated drug biotransformation can also enhance drug toxicity (Fig. 1) [6,49]. For example, the anticancer prodrug irinotecan is initially activated by host carboxylesterases into SN-38, an active metabolite with cytotoxicity, which is expected to be detoxified in the liver via glucuronidation to form SN-38G. However, this detoxified product can be reactivated in the intestinal tract by HGM-generated β-glucuronidases, resulting in SN-38 release and subsequent gastrointestinal side effects such as diarrhea [50]. In addition, β-glucuronidases participate in the reactivation of nonsteroidal anti-inflammatory drugs, contributing to aglycone accumulation. These aglycones are associated with mitochondrial damage and endoplasmic reticulum stress, which can promote intestinal barrier dysfunction and trigger local inflammatory responses [35].

Gut microbial biotransformation can also yield beneficial effects [49], for example, the use of azo prodrugs, where the active drug is covalently linked to an azo group, forming a stable compound that avoids absorption in the upper gastrointestinal tract [51]. This design enables colon-specific drug release, where gut microbiota–derived azoreductases cleave the azo bond to liberate the active compound. Sulfasalazine, a drug commonly used to treat ulcerative colitis, also follows this strategy. Its active component, 5-aminosalicylic acid, becomes effective only after microbial azo reduction in the colon [52]. Other azo prodrugs, such as olsalazine, ipsalazide, and balsalazide, have also been developed to improve targeted delivery and treatment outcomes [53,54].

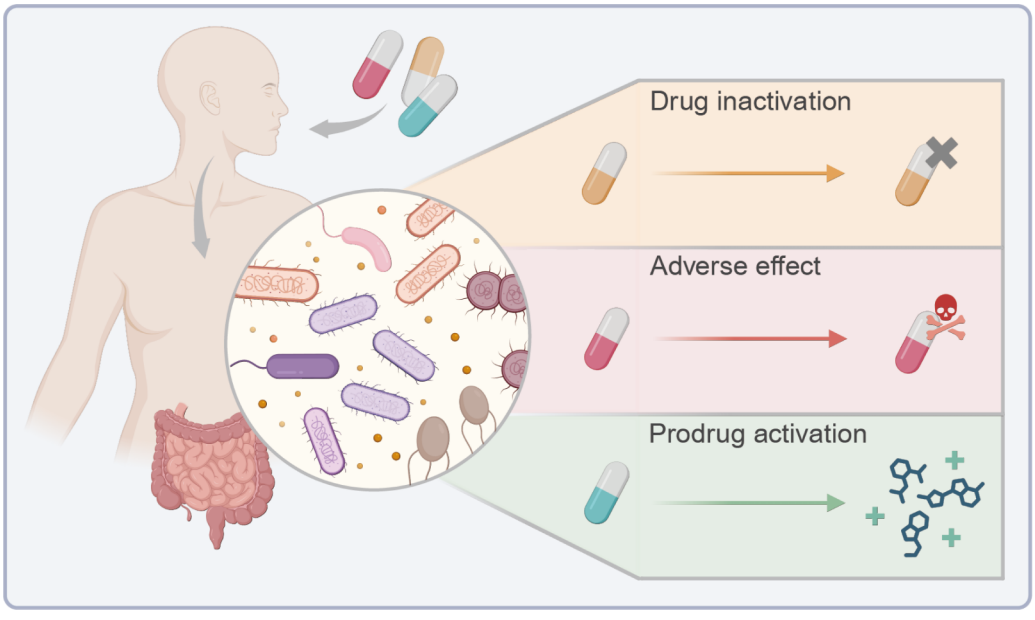

Figure 1 Drug biotransformation by the HGM and the diverse outcomes of microbial drug metabolism. The HGM enzymatically transforms drugs, leading to altered efficacy or induction of adverse effects. Created in BioRender.

4 Computational prediction of HGM-mediated drug biotransformation

Identifying the specific microbial strains and genes involved in drug biotransformation—and characterizing the associated biochemical reactions and metabolic products within the HGM—presents a notable challenge. In this regard, computational approaches integrating ML, cheminformatics, and metagenomics are increasingly recognized as powerful tools for elucidating HGM-mediated drug biotransformation (Figs. 2a and 2b) [6].

Several predictive models have been developed to identify gut microbial genera capable of drug degradation (Table 2). One of the earliest and most representative methods is DrugBug, which constructs two random forest (RF) models to predict the first- and second-level Enzyme Commission (EC) numbers for a given substrate. This is followed by molecular similarity-based inference to identify the potential microbial genus responsible for the reaction. DrugBug has successfully identified several known DMIs, including digoxin metabolism by *Eggerthella* [55]. GutBug expands upon DrugBug by increasing the training dataset size and employing an ensemble modeling strategy to predict EC numbers. It then applies a k-nearest neighbor (KNN) search to produce potential associations among reactions, enzymes, and microbial strains. In benchmarking tasks involving 27 representative small molecules, GutBug achieved prediction accuracies of 0.78–0.97, demonstrating strong generalization performance [56]. In addition, MDM-Pred was developed based on three Naïve Bayes classifiers to address three tasks: 1) whether a drug can be metabolized by gut

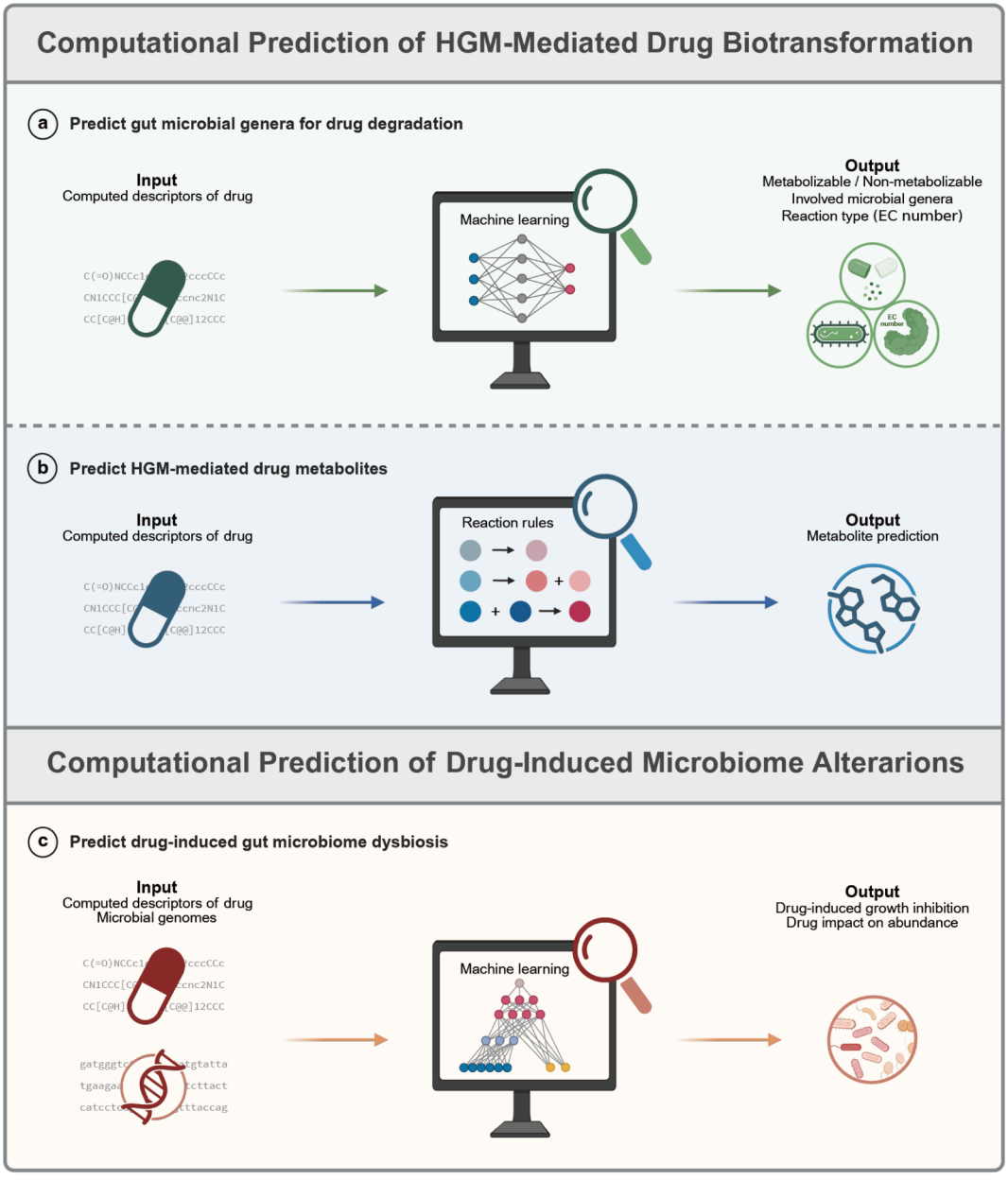

Figure 2 Machine learning predictions of DMI in the HGM. (a) Drug-degrading microbial genera prediction: Input drug descriptors (e.g., SMILES) are processed to predict drug metabolizability, involved microbial genera, and types of associated biotransformation reactions. (b) HGM-mediated drug metabolite prediction: Drug structural features are analyzed to predict potential microbial metabolites. (c) Drug-induced dysbiosis prediction: Combined drug properties and microbial genomic data predict growth inhibition patterns and shifts in genome abundance, identifying dysbiotic risks. Created in BioRender.

Table 2 Computational prediction models for HGM-mediated drug biotransformation

Methods	Input	Output	Model framework	Feature
DrugBug [55]	SMILES	1. Predicted EC numbers 2. Gut microbial genera potentially capable of metabolizing the drug	Random forest	1. Based on a database of metabolic enzymes from 491 gut microbial strains 2. Uses molecular similarity to infer responsible microbes 3. Genus-level predictions
GutBug [56]	Molecular structure	1. Predicted EC numbers, enzyme names, and corresponding microbial strains 2. Reaction centers 3. Microbial abundance data	Module 1: RF/ANN for EC top-level class Module 2: RF + Label Powerset for EC subclass Module 3: Tanimoto similarity + KNN for full EC + RDM	1. Integrates enzyme prediction with population-level strain abundance 2. Multimodule ensemble design 3. Structural similarity–driven 4. Applicable to genus- and strain-level predictions
MDM-Pred [57]	SMILES	1. Metabolic tendency 2. Microbial genera 3. Biotransformation type	PASS (improved Naïve Bayes classifier)	1. Learns statistical associations between molecular features and microbial degradability, taxa, and reaction type 2. Multitask classification
McCoubrey et al. [58]	SMILES	Whether the drug is likely to be metabolized by HGM	Extra Trees	1. Learns statistical associations between molecular features and gut microbial metabolism susceptibility 2. Binary classification 3. Trained on large-scale *in vitro* screening data
SIMMER [59]	Reaction SMILES	Catalytic enzymes and their associated gut microbial species	SVM	1. Uses MetaCyc database and protein sequence alignment 2. Enzyme-level resolution and suitable when specific degradation reactions are known 3. Rule-based + sequence homology
BioTransformer [60]	SMILES	Predicted degradation pathways of the drug	Random forest	1. Integrates curated reaction rules with ML 2. Includes multiple modules for different xenobiotic transformation contexts 3. Rule-based simulation
MicrobeRX [61]	SMILES	Potential HGM-derived metabolites	Transformer	1. Reaction rule-based inference using Recon3D and AGORA2 2. Suitable for strain-level metabolite prediction 3. Outperforms BioTransformer in benchmark datasets
MicrobeFDT [62]	SMILES	1. List of structurally similar drugs 2. Possible enzymes 3. Potential toxicity risk	SVM	1. Structural similarity-driven 2. Predicts drug-metabolizing enzymes and toxicity by drug similarity

Note: ANN, artificial neural network; PASS, Prediction of Activity Spectra for Substances; RDM, reaction centre, difference region, matched region; RF, random forest; SVM, support vector machine.

microbes, 2) the potential microbial genera involved, and 3) the corresponding reaction type. This method achieved independent accuracy scores of 0.85, 0.92, or 0.92 in cross-validation experiments [57]. SIMMER, another predictive tool, incorporates comprehensive reaction-level information by representing reactions with substrates, products, and cofactors [63]. It also integrates protein sequence similarity searches to identify candidate catalytic enzymes and their microbial origins [59]. In a benchmark involving 33 experimentally validated positive reactions, the recall and accuracy of SIMMER were higher than those of DrugBug [59]. However, its strong reliance on known degradation reactions limits its applicability when specific degradation reactions are unavailable.

Beyond the aforementioned approaches, other studies have explored DMI from different perspectives (Table 2). One research avenue focuses on characterizing the biochemical reactions and metabolic products of HGM-mediated drugs. Tools in this category typically rely on reaction rules to simulate and infer potential metabolic products. BioTransformer, a predictive platform for drug metabolism, integrates reaction rules extracted from curated biochemical reaction databases with ML strategies [60]. It comprises five functional modules designed to simulate CYP450-mediated biotransformation, EC number-based enzymatic reactions, Phase II conjugation reactions, HGM degradation, and environmental microbial biotransformation, enabling the modeling of biotransformation pathways of xenobiotics under different metabolic contexts [60]. In contrast, MicrobeRX adopts a more systematic strategy for constructing reaction rules, combining the human genome-scale metabolic model (GEM), Recon3D [64], with 6,286 strain-level gut microbial GEMs from the AGORA2 [65]. Using a validation dataset comprising 485 drugs from DrugBank [66] and their corresponding 1,274 metabolic products (comprising 1,144 unique molecular structures), MicrobeRX demonstrated great predictive performance, correctly identifying 66.0% of the parent drugs and 63.7% of their metabolites, thereby outperforming BioTransformer in terms of predictive performance [61]. In addition, McCoubrey et al. developed 11 classification models for this task and identified the Extra Trees algorithm as optimal, achieving an AUROC of approximately 75.1% on an independent test dataset [58]. MicrobeFDT is built on the core assumption that structural similarity reflects functional relatedness. By integrating

the chemical fingerprint profiles of approximately 10,000 compounds, including foods, drugs, and endogenous metabolites, it constructs an interaction network to predict HGM-mediated drug biotransformation and assess potential toxicity risks [62].

5 Drug-induced HGM alterations

Drugs can markedly alter the HGM composition and function (Fig. 3) [11]. Antibiotics are particularly noteworthy owing to their inherent mechanisms of action [67]. Several studies have shown that antibiotics, including macrolides, lincosamides, β-lactams, and fluoroquinolones, can markedly reduce gut microbiota diversity. In addition, antibiotics can cause compositional imbalances within the microbial community. For instance, they may increase Firmicutes-to-Bacteroidetes ratio, a shift associated with obesity, or disrupt the early colonization of key symbiotic bacteria in infants, potentially resulting in long-term impairments in immune development and metabolic function.

By reducing microbiota diversity and disrupting community structure, drugs can induce detrimental effects, including immune system dysfunction, metabolic disorders, and neurological impairments.

Some drugs can induce widespread perturbations in the HGM [68]. High-throughput *in vitro* screening by Maier et al. revealed that more than 27% of non-antibiotic drugs inhibited the growth of at least one gut bacterial strain [9]. Subsequently, Garcia-Santamarina et al. constructed a synthetic gut microbial community comprising 32 representative strains and demonstrated that 74% of the drug-induced perturbations observed at the single-strain level were consistent at the community level [10]. The remaining drugs exhibited pronounced cross-protective effects within the microbial community, suggesting that microbial consortia possess a certain degree of adaptability to drug-induced disturbances [10].

Several commonly used non-antibiotic drugs have been confirmed to substantially alter HGM composition and impact host health. For example, several antipsychotic drugs, including clozapine, olanzapine, risperidone, and chlorpromazine, reduce microbiota diversity in the female HGM [69]. The antineoplastic agent methotrexate decreases the abundance of Bacteroidetes and increases that of Actinobacteria, potentially indirectly modulating host immune responses [70]. Moreover, calcium-channel blockers considerably influence microbial community composition [9]. Proton pump inhibitors, commonly prescribed for acid-related gastrointestinal disorders, reduce gut microbiota diversity, decrease the abundance of beneficial commensal bacteria, and facilitate the overgrowth of oral-derived microorganisms within the HGM, potentially increasing susceptibility to infections and disrupting metabolic homeostasis [71]. However, metformin treatment could increase *Akkermansia muciniphila* abundance, improve gut epithelial integrity, and alter bile acid metabolism, all of which may contribute to its antidiabetic effects [72]. Additionally, statins may have beneficial effects on metabolic syndrome, possibly by enhancing HGM diversity and promoting probiotic taxa proliferation [73].

6 Computational predictions of drug-induced HGM alterations

Host genetics, diet, and environmental exposures influence HGM composition and function, complicating isolation and attribution of drug-specific effects [8,74]. Furthermore, *in vitro* culture systems are limited in their ability to accurately recapitulate the complexity and dynamic interactions of the gut microbial ecosystem [75]. Alternatively, computational approaches have been adopted for elucidating drug-induced alterations in the HGM (Fig. 2c) [6]. To investigate the principles governing DMI, McCoubrey et al. developed 13 traditional ML models based on the large-scale *in vitro* screening dataset established by Maier et al. [9], aiming to predict whether a given drug would inhibit the growth of 40 representative bacterial strains. Among them, the Extra Trees algorithm demonstrated the best performance, achieving an average AUROC of 0.85 and an F1 score of 0.66 in cross-validation [76]. Algavi et al. proposed an approach that combines molecular

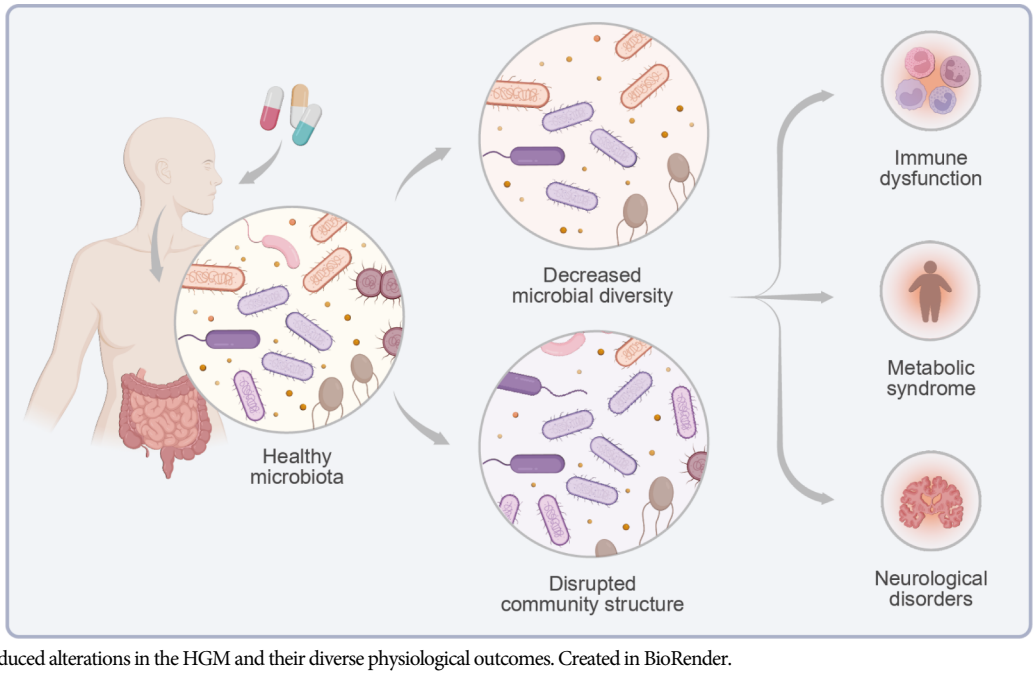

Figure 3 Drug-induced alterations in the HGM and their diverse physiological outcomes. Created in BioRender.

Table 3 Computational prediction models for drug-induced HGM alterations

Methods	Input	Output	Model framework	Feature
McCoubrey et al. [76]	Molecular structure of the drug	Predict whether the drug inhibits the growth of 40 gut microbes	Extra Trees	Developed 13 models; Extra Trees showed best performance (AUROC = 0.85)
Algavi et al. [77]	SMILES and microbial genomes	Predict whether the drug inhibits the growth of a specific strain	Random forest	Combines drug fingerprints with KEGG pathway abundance from genomes
IDMA-MLDA [78]	SMILES and microbial genomes	Predict the drug's impact on the abundance of specific strains	Hypergraph-based	Multiview learning; graph classification; addresses class imbalance

fingerprints of drugs with the abundance profiles of KEGG metabolic pathways derived from microbial genomes to predict drug-induced growth inhibition of specific microbial strains [77]. Their results suggest a potential synergistic relationship between the structural features of drugs and the metabolic capacities of microorganisms [77].

To address challenges such as class imbalance, feature heterogeneity, and intrinsic DMI complexity, recent research works have introduced a novel predictive framework called the Impact of Drugs on Microbial Abundance via Multi-view Learning and Data Augmentation (IDMA-MLDA) [78]. This approach formulates the prediction task as a graph-based node classification problem by incorporating high-order topological relationships among microbial species, chemical structure graphs of drugs, and microbe similarity networks. Furthermore, a data augmentation strategy based on majority-class compensation was employed to alleviate the severe imbalance between "abundance increasing" and "abundance decreasing" samples. The experimental results demonstrate that IDMA-MLDA outperforms previous models in terms of prediction accuracy, model robustness, and sensitivity to minority classes, offering a promising computational tool for elucidating drug-induced disruptions of the HGM [78]. A comparison of the different models in terms of their input, output, framework, and feature, is given in (Table 3).

7 Conclusion

The HGM, one of the largest metabolic organs in the human body, has been recently identified as a key contributor to the biotransformation of orally administered drugs owing to its vast metabolic potential [79,80]. HGM-mediated biotransformation markedly influences drug efficacy and pharmacokinetic profiles and is a major contributor to interindividual variability in drug responses. In turn, drug administration can alter HGM diversity and composition. Reduced microbiota diversity is strongly associated with various health risks, including immune dysfunction, metabolic syndrome, and neurological disorders [6,81]. Therefore, systematic investigation of bidirectional drug–HGM interactions offers substantial theoretical and practical value for drug screening, clinical validation, and the development of personalized treatment strategies.

The HGM is highly complex, with substantial interindividual differences in species composition, metabolic capacity, and functional redundancy. Traditional experimental methods often fail to capture dynamic variability and interindividual heterogeneity. In contrast, computational modeling offers a promising alternative for elucidating DMI, particularly through large-scale data integration and systematic analyses. Nevertheless, several challenges remain. Many existing models rely on few large-scale experimental datasets, which often have restricted microbial coverage and fail to fully represent the inherent HGM community structure. More critically, many current studies overlook essential variables such as microbial strain-level abundance, despite substantial interindividual and environmental variation in microbiota composition. This oversight constrains model generalizability and real-world applicability.

Furthermore, current research tends to oversimplify DMI as static processes, modeling "HGM-mediated biotransformation" and "drug-induced disruption of the HGM" separately, while overlooking their coupled mechanisms and dynamic feedback loops. Although the HGM metabolizes a drug, the drug may simultaneously alter HGM composition and function. This newly established microecological state can, in turn, influence subsequent drug metabolism pathways and their efficiencies. Failure of these models to capture such bidirectional regulation may introduce systematic biases between training data and real-world human conditions, thereby undermining predictive accuracy and clinical translatability.

In summary, future research on DMI should incorporate more dynamic and longitudinal data sources along with integrative multiomic approaches. Combining advanced modeling techniques, such as systems biology [13,82], graph-based modeling [83], and causal inference, will enable more accurate reconstruction of *in vivo* DMI networks. Importantly, these models' predictive capacity can be leveraged in clinical settings by integrating their outputs into electronic health records. This could facilitate the early identification of patients at high risk of HGM-mediated adverse events, guide individualized dosing adjustments to minimize microbiome disruption, and inform microbiome-targeted cotherapy design. Realizing this potential will require rigorous clinical validation, seamless interoperability with healthcare data systems, and strict adherence to regulatory and ethical standards. Nevertheless, it presents a tangible pathway from the algorithm to bedside, which could ultimately improve patient outcomes and treatment strategies.

Acknowledgements

None.

Author contribution statement

K.W. and C.L. drafted the manuscript. C.L. prepared the figures. F.L., R.W., C.Z., H.G., X.Z., X.H., Y.Y., and D.L. critically revised the manuscript. All authors approved the final version of the manuscript.

Consent

Not applicable.

Data availability

Not applicable.

Declaration of competing interest

Can Yang Zhang is the Executive Editor-in-Chief of this journal, but he was not but he is not involved in the peer-review or decision of this article. All the other contributing authors report no conflicts of interest in this work.

Ethical approval

Not applicable.

Funding

This work was financially supported by the National Key R&D Program of China (Grant No. 2024YFA0920300), Shenzhen Medical Research Fund (Grant No. A2403013), National Natural Science Foundation (Grant Nos. 22478223 and 62532017), Guangdong S&T Program (Grant Nos. 2024B1111150001 and 2024B1111140001), Tsinghua Shenzhen International Graduate School Cross-disciplinary Research and Innovation Fund (Grant No. JC2024004) and Department of Chemical Engineering-iBHE Joint Cooperation Fund (Grant No. DCE-iBHE-2023-1).

Use of AI statement

During the preparation of this work, K.W. and C.L. used ChatGPT to enhance the clarity and fluency of English language. All authors have subsequently reviewed and revised the content as necessary and take full responsibility for the integrity and accuracy of the final manuscript.

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