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Unlocking therapeutic impacts of the gut microbiota with computational tools

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Abstract

The human gut microbiota, particularly the intestinal microbiota, shapes host physiology, disease risk, and therapeutic outcomes through complex metabolic and enzymatic activities. Recent advances in molecular omics, metabolomics, enzyme bioinformatics, and artificial intelligence (AI) have created unprecedented opportunities to elucidate its therapeutic roles to further enable precision microbiome medicine for personalized prevention, diagnosis, and treatment. In this review, we highlight emerging applications that leverage molecular omics and metabolomics technologies to dissect gut microbial functions, along with developments in enzyme bioinformatics and AI tools that reveal gut microbial species, enzymes, and metabolic pathways impacting human health. Finally, we discuss perspectives on data standardization, functional annotation, and interpretability, and how emerging tools are accelerating translational microbiome research.

Introduction

The human gut microbiota, especially those inhabiting the large intestine, forms one of the body's most complex and influential ecosystems. Trillions of microorganisms, including bacteria, archaea, fungi, and viruses, make up this diverse community. These microbes expand the genetic capacity of the human host, providing what is often called a 'second genome' [1].

Their roles in human health are multifaceted: they ferment indigestible dietary fibers into short-chain fatty acids; synthesize essential vitamins; modulate bile acid metabolism; help

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The authors declare no conflict of interest.

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develop the immune system; and even influence neurological signaling through the gut–brain axis [2]. When this ecosystem is disrupted — by antibiotics, diet, lifestyle, or genetic predisposition, it has been linked to a wide array of diseases, ranging from metabolic syndrome and cardiovascular disease to autoimmune and neuropsychiatric disorders [3-5]. Consequently, the gut microbiome has become central to precision medicine, where treatments are tailored to an individual's biological profile [6].

Yet, linking microbial composition to host physiology remains a formidable challenge, despite the significance of the gut microbiota [7]. The diversity among gut microbes is extraordinary. Not only does it vary from one person to another, but it also fluctuates within the same individual over time, making it difficult to identify consistent biomarkers or therapeutic targets [8]. Many gut microbes remain uncultivable using traditional laboratory methods. Additionally, reductionist approaches that focus on single species or pathways often fail to capture the emergent properties of entire microbial communities [9]. To address this, researchers need approaches that can integrate complexity across multiple levels, as host–microbe interplay is mediated by diet, genetics, and environmental factors.

This review highlights how computational approaches are reshaping our understanding of the gut microbiome and its therapeutic impacts (Figure 1). Building on the challenges and opportunities outlined above, we will discuss the applications of molecular omics, metabolomics, enzyme-based bioinformatics, and artificial intelligence (AI)-driven prediction models in elucidating the roles of intestinal microbiota in health and disease, with a focus on advances reported since 2020. Finally, we will discuss current challenges and future perspectives in applying computational tools to microbiome research.

Molecular omics strategies in microbiome research

Advances in molecular omics technologies, namely metagenomic, meta-transcriptomic, and metaproteomic, have transformed gut microbiome research from descriptive surveys of community composition into mechanistic investigations of how microbial activities modulate host metabolism and inform the development of novel therapeutic strategies [10]. Following this paradigm shift, computational tools have provided the foundation for this transformation by enabling the analysis of massive datasets generated from molecular omics experiments [11,12].

Using computational pipelines, raw DNA sequencing reads can be processed to identify microbial taxa, annotate functional genes, and reconstruct metagenome-assembled genomes [12], offering a genome-centric view of microbial community potential. Tools such as metaGEM exemplify the reconstruction of genomescale, flux balance analysis–ready metabolic models directly from metagenomes, thereby supporting community-level modeling and the generation of mechanistic hypotheses for disease-associated microbiomes [13]. In addition, bioinformatics analysis of the human gut microbiome enables assessment of the distribution of specific enzymes. For example, bioinformatics analysis identified widespread distribution of homologues of *Enterocloster bolteae* DesE, an enzyme shown to reduce ketone groups in drugs such as nabumetone and tacrolimus, highlighting how computational approaches can map xenobiotic-modifying activities across the gut

microbiota [14]. Comparative metagenomics further allows the identification of key gut microbes, genes, and metabolic pathways that are differentially enriched in health- and disease-associated populations. For instance, a large-scale meta-analysis of over 11,000 global metagenomes identified the genus CAG-170 as a candidate biomarker of health, notable for its ability to produce vitamin B12 despite lacking genes for arginine biosynthesis [15]. In parallel, another large-scale metagenomic analysis of 378 end-stage renal disease patients and 290 healthy controls revealed extensive gut microbiome alterations, identifying 348 differentially abundant species and disease-associated functional pathways, linking microbial composition to chronic kidney disease progression [16].

Beyond studies focused solely on (meta) genomics, (meta) transcriptomics, and (meta) proteomics can illuminate how gut microbial proteins and pathways translate into physiological outcomes. For instance, meta-transcriptomic analyses have identified a catechol dehydroxylase in the human gut bacterium *Gordonibacter pamelaeae* that dehydroxylates hydra caffeic acid [17]. Stamboulian et al. demonstrated the power of metaproteomic for species-level functional annotation and developed GutBac, an online resource to study the human gut microbiome [18]. Other studies have used multiple omics strategies to elucidate host–microbiome interactions. For example, Qin et al. integrated 16S rRNA, metagenomic, and transcriptomic analyses of tumor and normal mucosal tissues from 19 patients with colon cancer. Their work revealed distinct microbial and gene expression profiles, *Campylobacter jejuni* enrichment linked to bile secretion and immune modulation, and novel microbial taxa associated with patient survival [19].

Metabolomics and its role in functional insights into the gut microbiome

The gut microbiota possesses extensive biosynthetic capacity, producing hundreds of small molecules that can modulate host physiology. To systematically explore this potential, gutSMASH was developed for large-scale detection of primary metabolic gene clusters, identifying nearly 19,890 clusters across 4240 high-quality microbial genomes, thereby providing foundational insights into how specific taxa contribute to the chemical landscape of the microbiome [20]. While gutSMASH can predict the biosynthetic potential of gut microbes, metabolomics provides a direct readout of their functional output. By profiling small molecules in stools, metabolomics can directly capture the end products of gut microbial metabolism [21,22]. For instance, Zimmermann et al. [23] and Javdan et al. [24] used metabolomics to comprehensively map drug metabolism by the gut microbiome, identifying novel drug-microbiome interactions that vary between microbes and individuals. Another systematic comparative metabolomics analysis of 127 G-protein-coupled receptor-targeted drugs revealed that human gut commensals extensively reshape drug structures and their activities, uncovering both intrinsic and collaborative metabolic processes across taxa [25]. Beyond providing a snapshot of gut microbial metabolism, integrating metabolomic data with host phenotypes can provide a holistic understanding of microbiome–host interactions. For example, metabolomic profiling has revealed that baicalin, a small-molecule drug for hepatitis, can overcome anti-PD-1 immunotherapy resistance by modulating gut microbial metabolism of short-chain fatty acids [26]. Using similar strategies, the roles of nobiletin in the prevention and intervention of metabolic-associated fatty liver disease have also been demonstrated [27]. Furthermore, gut

microbiota–mediated regulation of ginsenosides, bile acids, and short-chain fatty acids has also been implicated in alleviating fatigue-related metabolic abnormalities [28]. Extending beyond metabolic disorders, metabolomic analyses have further linked the early stages of Parkinson's disease with the abundance of alanine, betaine, and nicotinamide. Both metabolites can be directly processed by gut microbes and are found at reduced levels in patient samples, underscoring the potential contribution of gut dysbiosis to Parkinson's disease pathogenesis [29].

Integrating metabolomics with molecular omics data provides an additional layer of insight, enhancing the ability to pinpoint the microbial metabolic pathways most relevant to host health [30]. For example, using a combination of gut microbiota sequencing and metabolomics, researchers found that leonurine modulates microbial composition and metabolic capacity, notably enhancing AdoCbl biosynthesis and methionine regeneration from homocysteine, which may confer cardioprotective effects [31]. A recent study leveraging stool metagenomics and metabolomics from 1429 participants of the Framingham Heart Study revealed key microbial pathways implicated in cardiovascular disease, including those involved in flavonoid, γ-butyrobetaine, and cholesterol metabolism. Notably, cholesterol-metabolizing functions were conserved across diverse *Oscillibacter sp.*, underscoring the potential for microbiome-informed risk stratification in cardiovascular disease [32]. Besides its therapeutic effects on cardiovascular health, the gut microbiota has also been implicated in inflammatory and metabolic disorders through multi-omics investigations. For instance, Mehta et al. identified thiolases and acyl-CoA N-acyltransferases of the gut microbiota as contributors to treatment failure in patients with inflammatory bowel disease (IBD) [33], while Vich Vila et al. reviewed how metabolomics led to the identification of microbially derived metabolites for IBD prognosis and therapy [34]. Moreover, butyrate and its gut microbial producers (*Clostridium spp.*) have been identified as metabolic and microbial biomarkers in patients with myalgic encephalomyelitis [35]. In addition, Xia et al. have reported that short-chain fatty acid production within the gut microbiota may disrupt lipid metabolism in childhood obesity [36]. The association between gut microbiota and brain function has also been elucidated through multi-omics studies that highlight the underlying gut microbial metabolic pathways. For example, researchers have demonstrated the interplay between metabolome and gut microbes by a significant increase in pyruvate and a decrease in citrate in individuals with major depressive disorder [37]. Furthermore, the gut microbial bioconversion of dietary tyrosine to 4-ethylphenol has been shown to alter gene expression in the brain, leading to anxiety-like behaviors in mouse models [5].

Beyond individual case studies, integrative computational frameworks and curated datasets are emerging as powerful tools for uncovering complex microbiome–disease relationships from multi-omics data. For example, Muller et al. developed 'MintTea', a powerful yet universal intermediate-integration computational framework that combines metabolomics and molecular omics data to identify robust, disease-associated microbiome signatures across molecular processes [38]. Applying this approach to cohorts with metabolic syndrome and colorectal cancer, MintTea revealed modules linking microbial species, metabolites, and host pathways, illustrating the power of integrated analyses to generate systems-level hypotheses of microbiome–disease interactions. In parallel, the

gutMGene database has been developed to systematically compile experimentally validated relationships among gut microbes, microbial metabolites, host target genes, and associated diseases and therapeutic interventions. It provides an interactive platform for exploring microbial gene metabolite interactions, investigating microbial roles in disease onset and progression, and predicting potential microbiome-based drug candidates [39].

Advances in mass spectrometry-based platforms and the associated computational tools have further enhanced sensitivity and reproducibility in profiling microbial metabolites over the past 5 years [40]. Molecular networking of untargeted mass spectrometry data has been developed to facilitate the discovery of novel metabolites, providing new opportunities for dissecting microbiome–host interactions [41]. Furthermore, Han et al. developed a microbiome-focused metabolomics pipeline that effectively links microbial composition to host interactions by leveraging a mass spectrometry-based reference library to detect anaerobic biochemical activities. This platform provides publicly accessible resources to facilitate microbiome–metabolite association studies [42]. Beyond metabolite identification, another computational tool, LOCATE (Latent variables of microbiome and metabolites relations), has been developed to predict metabolite concentrations, whose fluctuations can also influence host metabolism [43].

Together with the comprehensive review by Puig-Castellví et al. [44], which summarized advances in integrating metabolomics and metagenomics data for the human gut microbiome and their clinical applications, these studies underscore the central role of metabolomics in elucidating the functional consequences of gut microbiome activity in health and disease.

Bioinformatics of enzymes and their role in gut microbiome function and therapeutics

While metabolomics provides insights into the biochemical outputs of the gut microbiome, enzyme-focused bioinformatics allows researchers to pinpoint the specific catalysts responsible for these transformations. This section focuses on the use of computational and bioinformatic tools to predict gut microbial enzyme function from primary sequences. Such approaches help elucidate how the gut microbiota produces or bio-transforms bioactive compounds with therapeutic relevance. By characterizing these enzymes, researchers can achieve a molecular-level understanding of host–microbe interactions and potentially engineer microbial consortia with tailored enzymatic activities for targeted interventions.

Several predictive platforms have been developed to support this effort. GutBug, for example, uses machine learning to predict the enzyme commission numbers of bacterial enzymes and the microbes that harbor them, based on specific chemical substrates [45]. It provides actionable insights beyond basic enzyme identification, enabling the informed design of prebiotics, nutraceutical products, personalized dietary strategies, and drug development approaches. Its predictive performance is constrained by limitations in the training data, reliance on structure-based inference, and a lack of quantitative metabolic context. These constraints are common across current microbiome biotransformation prediction tools and highlight the need for experimental validation alongside computational

predictions. MicrobeRX extends this concept by integrating 3650 drug metabolic reactions from DrugBank with over 4000 microbial and 5400 human reactions, linking the genetic and chemical landscapes of the gut microbiome through modules for metabolite visualization and enzymatic or taxonomic analysis. Its broad utility across biomedical and industrial applications has been demonstrated by the successful identification of 5878 structurally diverse metabolites generated by microbial enzymes from 1083 orally administered drugs [46]. By linking genomic data with predicted chemical transformations, MicrobeRX unlocks the gut microbiome's chemical potential, making it a valuable resource for research and innovation in human health, food science, pharmaceuticals, and environmental safety. Like many metabolite prediction tools, MicrobeRX can struggle when the underlying reaction mechanisms or enzymes have not been fully characterized, so even experimentally observed metabolites may remain hard to predict with high confidence. Although constrained by current knowledge gaps, MicrobeRX offers a scalable framework that can be updated with new reaction data, enhancing its capacity to predict previously uncharacterized metabolites. Cui et al. have developed EZSpecificity, an advanced graph neural network that can understand the three-dimensional shapes of molecules and uses a cross-attention system to learn how enzymes and their substrates interact [47]. It serves as a versatile tool with broad relevance to biocatalysis, synthetic biology, enzyme engineering, and drug discovery, and its future incorporation of dynamic binding information is expected to further improve its predictive capabilities. EZSpecificity demonstrated 91.7% accuracy in identifying the correct reactive substrate, a substantial improvement over the 58.3% accuracy achieved by the leading existing enzyme-substrate prediction model. The INTEDE database integrates interactions among microbiome-derived enzymes, xenobiotics, and host drug-metabolizing enzymes [48]. Similarly, collaborative initiatives such as those led by Medicen have highlighted how enzyme-focused microbiome tools can be directly integrated into drug discovery and development pipelines, accelerating translation into therapeutics. Likewise, computational models such as 'similarity algorithms that identify microbiome enzymatic reactions (SIMMER)' combine chemical and protein similarity algorithms to predict the responsible species and enzymes for specific reactions; this approach has already been applied to the metabolism of methotrexate, an anti-arthritic drug [49]. Beyond drug metabolism, enzyme bioinformatics has also shed light on microbial enzymes involved in bile acid transformations. To bridge the gap, more than 40 enzymes are predicted to mediate these reactions, and a few of them have been experimentally validated. AI-assisted pipelines such as BEAUT have been developed to more accurately identify gut microbial bile acid–metabolizing enzymes [50]. Collectively, these advances demonstrate how enzyme bioinformatics can contribute to microbiome studies by revealing the molecular machinery behind microbial metabolism, a concept further expanded by Jia et al. in their review of emerging technologies for enzyme discovery and mining from the gut microbiota [51].

Artificial intelligence for gut microbiota study

AI and machine learning (ML) have become indispensable in microbiome research, enabling the analysis of complex, high-dimensional datasets and the generation of predictive insights. By integrating molecular omics, metabolomics, and clinical phenotypes, AI models can capture nonlinear relationships between the gut microbiome and host health, surpassing

conventional statistical methods [52-54]. For example, Wang et al. demonstrated the complex interplay between the gut microbiota and the tumor microenvironment by applying multi-omics integrative clustering and machine learning models to datasets from 274 colorectal cancer patients [55]. Moghaddam et al. introduced an ML framework for integrating transcriptomic, metabolomic, and lipidomic datasets into multimodal networks to link microbial metabolites to immune regulation in aging metabolism [56]. Moreover, researchers have also looked at the application of ML to predict the stability of xenobiotics within gut bacteria. For instance, an ML platform called MoleculeX has been used to predict the metabolic capacity of *Clostridium sporogenes* against small molecules, which can significantly reduce experimental burden by guiding targeted validation [57]. In addition, ML has been used to analyze gut microbiota in precision oncology to enhance noninvasive tools for risk prediction and management of colorectal cancer [58]. More applications of AI tailored to microbiome research can be found in review articles by Wu et al. [59], Chetty and Blekhman [60], Abavisani et al. [61], D'Urso et al. [62], Li et al. [63], and Wan [64]. As AI-driven methods continue to evolve as essential for unraveling the complexity of host–microbiome interactions and for guiding precision medicine strategies, ethical and methodological considerations are also emerging and have been reviewed by Alexandrescu et al. [65] and Patil et al. [66].

Conclusion and future perspectives

Gut microbiome research is rapidly evolving toward the integration of computational and experimental approaches. The current emergence of advanced computational approaches, such as molecular omics, metabolomics, enzyme-based bioinformatics, and AI, is beginning to enable a mechanistic understanding of the therapeutic effects of the gut. By unlocking the therapeutic impacts of the gut microbiota through computational innovation, we move closer to realizing the promise of precision medicine, where microbiome-informed strategies can be routinely applied for disease prevention, diagnosis, and therapeutics. However, despite recent advances, several challenges remain. Current molecular omics often generate data that cannot be easily mapped back to the native microenvironment, limiting mechanistic interpretation. Although computational tools are improving at reconstructing complete genomes from metagenomes, extrapolating from genome-level information to higher-order host–microbe interactions still requires significant manual curation, creating a bottleneck for mechanistic understanding. While powerful tools exist for time-series and multi-omics integration, the lack of standardization in workflows and reporting continues to hinder reproducibility and broader adoption [11]. The establishment of more comprehensive, curated public databases will further strengthen computational analyses and support robust cross-study comparisons. Looking ahead, artificial intelligence holds great promise for addressing these challenges and advancing the field. The development of open-source, user-friendly computational platforms, ideally supported by intuitive graphical interfaces, will be essential to make these tools accessible to the broader biomedical community. Equally important will be efforts to improve model interpretability and to promote interdisciplinary training that bridges biology, medicine, and computational sciences, ensuring that computational advances translate into meaningful clinical applications.

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Data Availability

No data were used for the research described in the article.

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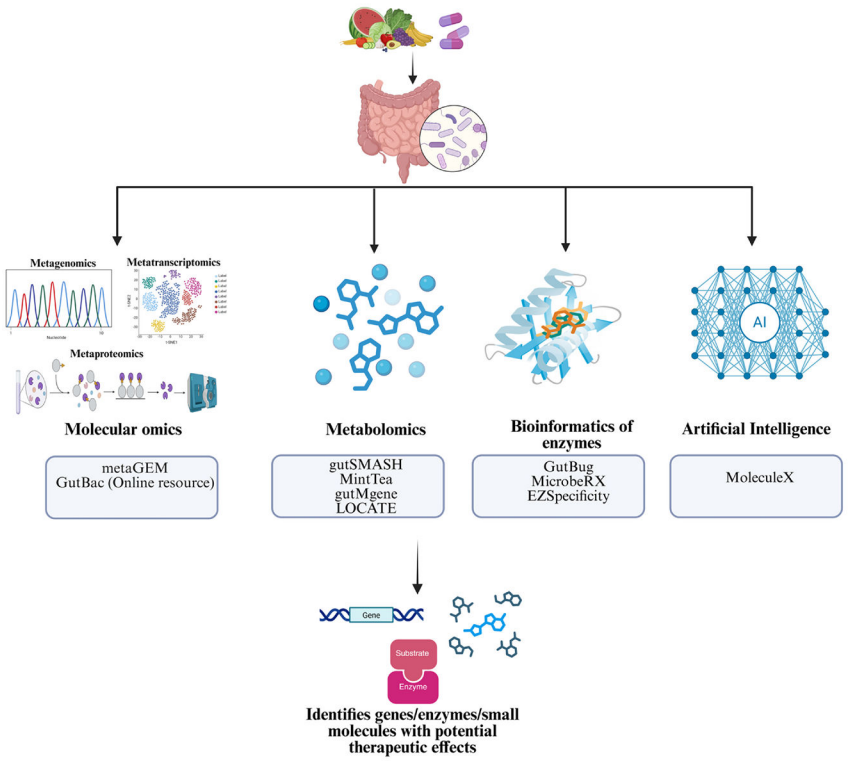

Figure 1.

Integration of computational tools for probing the therapeutic impacts of gut microbiota. Representative newly developed computational tools are shown in the box below each corresponding section. Biorender.com was used to prepare this figure.