Pharmacomicrobiomics: Bidirectional Drug-Microbiome Interactions, Clinical Translation and Precision Therapeutics

Atharva Dahibhate[1], *Pradnya Deolekar[2], Kavitha Dongerkery[3], Prateek DT[4], BalajiKiran D P[5], Srirambabu V[6], Moulik Chandibhamar[7], Shubham Sagar[8]

[1-4,6-8]Department of Pharmacology, D Y School of Medicine, Navi Mumbai

[5]Department of Pharmacology, Malla Reddy Medical College for women's, Hyderabad

***Corresponding Author**

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ABSTRACT

Inter-individual variability in drug efficacy and toxicity is only partly explained by dose, organ function, pharmacogenomics and adherence. The intestinal microbiome adds a dynamic, environmentally responsive metabolic layer that can directly transform drugs, sequester them within microbial biomass, reactivate conjugated metabolites, alter enterohepatic cycling, and regulate host enzymes, transporters and immune pathways. Conversely, antibiotics and many non-antibiotic medicines reshape microbial community structure and function, creating bidirectional feedback that may modify subsequent pharmacological responses. This narrative review synthesizes mechanistic and clinical evidence across drug absorption, distribution, metabolism and excretion, with focused discussion of microbial bioaccumulation, sulfasalazine activation, irinotecan-associated diarrhoea, digoxin inactivation, immune-checkpoint inhibitor response, psychotropic drugs, the gut–liver axis and inflammatory bowel disease. The strongest causal examples arise from defined microbial enzymes and genes—such as bacterial β-glucuronidases and the cardiac glycoside reductase operon—whereas many taxonomic associations remain context-dependent and incompletely reproducible. Meta-analyses consistently associate peri-immunotherapy antibiotic exposure with poorer outcomes, but confounding by infection severity, cancer burden and co-medication limits causal interpretation. Translation will require standardized sampling, shotgun metagenomics and functional assays, longitudinal designs, external validation, and interventional trials of enzyme inhibitors, diet, defined microbial consortia or faecal microbiota transplantation. Pharmacomicrobiomics should therefore be viewed as a complement to pharmacogenomics and therapeutic drug monitoring rather than a replacement. A function-first, mechanism-led approach may ultimately support microbiome-informed dose selection, toxicity prevention and treatment stratification.

INTRODUCTION

Pharmacomicrobiomics examines how variation in the human microbiome influences drug disposition, pharmacodynamics, efficacy and adverse effects, and how medicines in turn alter microbial ecology. The concept extends classical pharmacology from the host genome to the combined host–microbial "meta-genome," recognizing the gut microbiota as a metabolically active organ with substantial inter-individual variability [1–4]. Unlike immutable germline variants, microbiome features can change over days to months with diet, antibiotics, geography, disease activity and co-medications. This plasticity creates both a source of noise and a potentially modifiable therapeutic target.

For this review, the section sequence was derived from the accompanying pharmacomicrobiomics seminar: definition and gut microbiome overview; drug accumulation and transformation; microbial and host-mediated effects on ADME; drug-induced microbiome alteration; enterohepatic recycling and transporters; oncology and immune-checkpoint inhibitors; CNS drugs and the gut–brain axis; the gut–liver axis; and IBD therapeutics. Literature was prioritized from PubMed-indexed mechanistic studies, major reviews, systematic reviews and meta-analyses, with emphasis on human data and clinically interpretable outcomes. Because this is not a

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prospectively registered systematic review, the search was purposive rather than exhaustive, and no pooled estimates were recalculated.

The gut microbiome as a metabolic organ

The human gastrointestinal tract contains a dense and spatially heterogeneous community of bacteria, archaea, fungi, viruses and bacteriophages. Contemporary estimates emphasize microbial gene content and functional capacity rather than a fixed organism count, because biomass varies markedly by anatomic site and between individuals [5,6]. The colon harbours the greatest density and predominantly anaerobic metabolism. Microbial functions relevant to pharmacology include fermentation of non-digestible carbohydrates, production of short-chain fatty acids (SCFAs), transformation of bile acids, metabolism of amino acids and xenobiotics, colonization resistance, maintenance of epithelial barrier integrity and education of mucosal immunity [5–7].

The "metabolic organ" analogy is useful but incomplete. Unlike the liver, the microbiome is not a single stable tissue: its enzymatic repertoire is distributed across strains, can be horizontally transferred, and is shaped by ecological interactions. Consequently, the presence of a species does not guarantee a particular drug-metabolizing phenotype. Strain-level genes, transcriptional state, substrate availability and community context can be more predictive than relative abundance alone [8,9]. This distinction underpins the shift from taxonomy-first studies toward functional metagenomics, metatranscriptomics and targeted enzyme assays.

Drug accumulation, sequestration and transformation by gut microbes

Microbial effects on medicines are not limited to enzymatic biotransformation. A large in vitro survey showed that numerous therapeutic drugs accumulate within gut bacterial cells without necessarily being chemically modified. Such bioaccumulation can alter bacterial metabolism and, in defined communities, change drug availability to the host [10]. Mechanisms include passive partitioning, active uptake, binding to cell-wall or membrane components, adsorption to biofilms and intracellular trapping. The pharmacokinetic consequence depends on whether the process is reversible, the magnitude of microbial biomass, gastrointestinal transit and whether the sequestered drug is later released.

Bioaccumulation challenges the conventional assumption that reduced luminal drug concentration always reflects chemical degradation. It may delay absorption, increase faecal elimination or create a luminal reservoir. However, evidence for clinically important effects in humans remains limited. In vitro drug–bacterium interaction maps should therefore be considered hypothesis-generating until validated by physiologically relevant gut models and human pharmacokinetic studies.

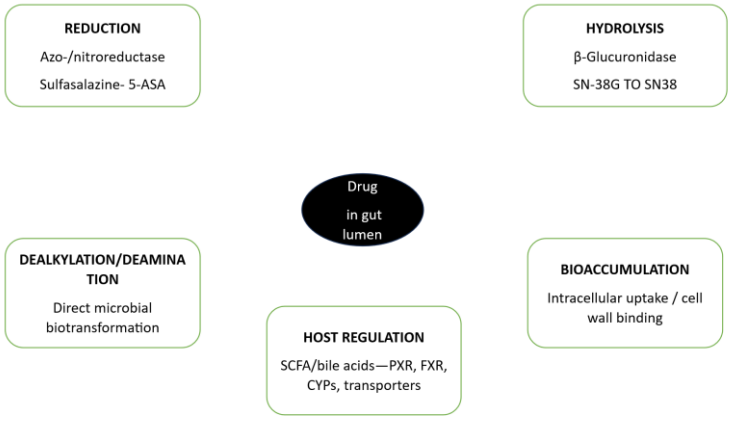

Figure 1. Principal mechanisms by which gut microbes modify drug exposure and response. Original diagram created for this review based on references 2–4, 8–10, 15 and 19.

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Mechanism	Representative example	Potential pharmacological consequence	Strength of evidence
Direct reduction	Digoxin reduction by cgr-positive Eggerthella lenta	Lower active drug exposure and variable response	Mechanistic human-isolate and gnotobiotic evidence
Azo-bond cleavage	Sulfasalazine activation to 5-aminosalicylic acid	Site-selective colonic prodrug activation	Established clinical pharmacology
Deconjugation	SN-38G reactivation by bacterial β-glucuronidases	Higher colonic SN-38 and delayed diarrhoea	Strong mechanistic/preclinical; translational
Bioaccumulation	Intracellular uptake of diverse drugs by gut bacteria	Sequestration, delayed availability, altered microbial metabolism	Broad in vitro evidence; limited clinical validation
Indirect host regulation	SCFA/bile-acid signalling through nuclear receptors	Changes in CYPs, transporters and inflammatory response	Biologically plausible; variable human evidence

Microbial contribution to drug metabolism

Reductive reactions and azo-prodrug activation

The anaerobic colonic environment favours reductive reactions that are uncommon in oxygenated host tissues. Bacterial azoreductases, nitroreductases and related flavoproteins can reduce azo, nitro and other functional groups [2,3,11]. Sulfasalazine is the classic therapeutic example: colonic bacterial azoreductases cleave its azo bond, releasing 5-aminosalicylic acid (5-ASA), which acts locally in ulcerative colitis, and sulfapyridine, which is largely absorbed and contributes to systemic adverse effects [11]. The dependence on microbial cleavage explains why sulfasalazine behaves as a colon-targeted prodrug and why changes in transit or microbiota could theoretically affect activation.

Other microbial transformations include deamination, dehydroxylation, demethylation, decarboxylation and hydrogenation. The clinical importance of a reaction depends on whether the microbial metabolite is absorbed, active, toxic, or subsequently processed by host enzymes. A useful conceptual model is "combinatorial metabolism," in which host and microbial reactions occur sequentially and jointly determine final exposure [3,12].

Hydrolysis, β-glucuronidase and enterohepatic recycling

Host glucuronidation usually increases polarity and facilitates biliary or urinary elimination. In the intestine, microbial β-glucuronidases can hydrolyse glucuronide conjugates, regenerating the parent aglycone. The released compound may be reabsorbed, prolonging half-life and systemic exposure, or may damage the intestinal mucosa locally [13–15]. This mechanism is relevant to endogenous molecules such as bilirubin and steroid hormones as well as several drugs and metabolites.

Bacterial β-glucuronidases are structurally diverse, and enzyme activity is not reliably inferred from broad taxonomic labels. Functional assays or gene-family characterization are therefore preferable. Selective inhibitors that spare mammalian glucuronidases and do not kill bacteria have reduced intestinal toxicity in animal models, illustrating a precision strategy that targets microbial chemistry without causing broad dysbiosis [14,15].

Irinotecan-associated gastrointestinal toxicity

Irinotecan is converted by carboxylesterases to SN-38, a potent topoisomerase-I inhibitor. Hepatic UGT1A1 glucuronidates SN-38 to SN-38G, which is secreted into bile. In the colon, bacterial β-glucuronidases can regenerate SN-38, increasing epithelial exposure and contributing to delayed diarrhoea and mucosal injury [14–

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16]. Host UGT1A1 genotype remains an important determinant of systemic neutropenia and diarrhoea, but microbial deconjugation provides an additional, potentially modifiable layer.

Preclinical studies of selective microbial β-glucuronidase inhibitors demonstrated reduced gastrointestinal damage without compromising antitumour activity or broadly eliminating commensals [14,15]. Translation to routine care has been slower because irinotecan toxicity is multifactorial, the relevant enzymes vary across individuals, and clinical-grade inhibitors require proof of safety and absence of pharmacokinetic interference. Nevertheless, this remains one of the clearest examples of mechanism-directed pharmacomicrobiomics.

Digoxin inactivation by Eggerthella lenta

A subset of Eggerthella lenta strains reduces digoxin to less active dihydrodigoxin. The phenotype is associated with the cardiac glycoside reductase (cgr) operon rather than simple species presence [17,18]. Expression is induced by digoxin and influenced by environmental factors, including arginine availability. In gnotobiotic mice, dietary protein altered microbial digoxin metabolism and systemic/urinary drug concentrations [17]. These findings provide a model of how a microbial gene marker and diet could jointly predict drug exposure.

Clinical application is not yet established. Digoxin dosing is already guided by indication, renal function, interacting drugs, age and serum concentration when appropriate. A validated stool cgr assay could eventually refine interpretation in unexplained low exposure, but prospective studies must show incremental value beyond therapeutic drug monitoring. The digoxin example also cautions against citing newly described "digoxin-induced dysbiosis" as evidence of inactivation; the established mechanism is microbial reduction by cgr-positive strains, not a general dysbiosis effect.

Effects of the microbiome on pharmacokinetics parameters

Absorption and luminal availability

The microbiome can alter absorption by transforming the parent drug, changing luminal pH and bile-acid composition, modifying intestinal barrier function, regulating mucus, and sequestering molecules in microbial biomass. Microbial metabolites may also influence epithelial transporters and tight-junction proteins. These effects are likely to be most relevant for orally administered drugs with incomplete proximal absorption, prolonged intestinal residence or enterohepatic cycling [2–4,10].

Direct evidence for a "microbiome effect" on distribution is comparatively sparse. Apparent distribution may change secondarily when microbial metabolism alters systemic exposure, plasma-protein binding through metabolite competition, inflammation or tissue transporter expression. Claims that gut microbes directly control volume of distribution should therefore be made cautiously unless supported by pharmacokinetic modelling.

Regulation of host enzymes and transporters

Microbial metabolites—including SCFAs, indoles and primary/secondary bile acids—engage host receptors such as pregnane X receptor (PXR), farnesoid X receptor (FXR), aryl hydrocarbon receptor and G-protein-coupled receptors. These pathways can modulate intestinal and hepatic CYP enzymes, conjugating enzymes and transporters such as P-glycoprotein (ABCB1/MDR1), MRP2 and selected organic anion transporters [3,19,20]. The direction and magnitude of regulation are context dependent and differ across germ-free, antibiotic-treated and conventionally colonized animals.

For clinical pharmacology, indirect regulation is harder to attribute than direct microbial metabolism because host disease, inflammation, diet and medications affect the same pathways. Well-designed studies should measure drug concentrations, microbial functions and host enzyme/transporter phenotypes longitudinally rather than inferring pharmacokinetic effects from microbiome composition alone.

Excretion and enterohepatic cycling

Microbial deconjugation can reduce net faecal elimination by regenerating absorbable parent compounds, increasing area under the concentration–time curve and prolonging exposure. Conversely, irreversible microbial metabolism or sequestration can increase faecal loss. Bile-acid-mediated regulation of FXR and transporter

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networks may further modify biliary secretion and renal handling indirectly [13,19,20]. These processes blur the traditional separation of hepatic, renal and intestinal excretion and support a whole-body view of clearance.

Drug-induced changes in microbiome diversity and function

Antibiotics and ecological disruption

Antibiotics are the most obvious modifiers of the gut microbiome. Their effects depend on spectrum, route, biliary/faecal excretion, duration, repeated exposure and baseline ecology. Common consequences include loss of diversity, depletion of obligate anaerobes, expansion of resistant organisms and reduced colonization resistance. The resulting ecological vacancy is central to Clostridioides difficile infection, particularly after exposure to clindamycin, cephalosporins, fluoroquinolones and broad-spectrum penicillins, although individual risk is shaped by age, hospitalization and comorbidity [21]. Recovery may be incomplete and strain-specific.

From a pharmacomicrobiomic perspective, antibiotics can remove drug-metabolizing functions, alter microbial metabolites and affect response to unrelated therapies. However, antibiotic exposure is often a marker of infection or frailty; observational associations must therefore address confounding by indication.

Non-antibiotic medicines

A large screen of marketed drugs showed that many non-antibiotic compounds inhibit the growth of at least one gut bacterial strain in vitro, suggesting that direct antimicrobial-like effects extend beyond antibiotics [22]. Human cohort and crossover studies have linked proton-pump inhibitors (PPIs), metformin, antipsychotics and other medicines to reproducible microbial signatures [23–25]. PPIs alter gastric acidity and increase oral taxa in the intestine; metformin-associated signatures can confound attempts to define a “type 2 diabetes microbiome” [23,24].

Causality and clinical meaning vary. A microbiome shift may mediate efficacy, contribute to adverse effects, reflect the treated disease, or be biologically neutral. For example, metformin increases several SCFA-associated taxa in some cohorts and can affect bile-acid metabolism, but gastrointestinal intolerance and therapeutic response cannot yet be predicted reliably from stool profiles. For antipsychotics, dysbiosis has been proposed as one contributor to weight gain and metabolic dysfunction, but diet, sedation and disease-related factors remain important.

Drug/class	Reported microbiome effect	Potential clinical relevance	Limitation
Antibiotics	Reduced diversity; loss of colonization resistance	C. difficile infection; altered response to other drugs	Strong confounding by infection and exposure heterogeneity
PPIs	Higher oral taxa in stool; altered community composition	Enteric infection risk; possible interaction with ICI outcomes	Acid suppression, indication and comorbidity confounding
Metformin	Treatment-associated taxonomic and functional signature	May contribute to metabolic effects and GI intolerance	Diabetes itself strongly confounds cross-sectional comparisons
Antipsychotics	Taxonomic shifts in animal and human studies	Possible contribution to weight gain/metabolic syndrome	Small cohorts; lifestyle and disease effects
SSRIs and other psychotropics	Drug-specific antimicrobial and ecological effects	Potential variability in response/tolerability	Sparse longitudinal human evidence

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Microbial metabolites as pharmacodynamic mediators

Short-chain fatty acids

Acetate, propionate and butyrate are produced during microbial fermentation of dietary substrates. They serve as energy substrates and signalling molecules, modulate epithelial integrity, influence histone deacetylation, and engage receptors including FFAR2 and FFAR3 [6,7]. Butyrate is a major fuel for colonocytes and supports barrier function. Changes in SCFA production can therefore influence inflammation, immunity and metabolism even when the drug itself is not microbially transformed.

SCFAs should not be treated as uniformly beneficial. Effects depend on concentration, site, host metabolic state and receptor context. Stool concentration is an imperfect proxy for production because most SCFAs are absorbed. Studies linking SCFAs to treatment response should ideally combine dietary assessment, targeted metabolomics and functional microbial profiling.

Bile acids, tryptophan metabolites and immune signalling

Gut microbes convert primary bile acids into secondary species that signal through FXR and TGR5, affecting lipid and glucose metabolism, barrier function and hepatic transporter expression [19,20]. Tryptophan-derived indoles can activate the aryl hydrocarbon receptor and modulate mucosal immunity. These pathways provide plausible links between the microbiome and systemic pharmacodynamics, including anticancer immunity and CNS effects, but their redundancy and diet dependence complicate biomarker development.

Cancer immunotherapy and the gut microbiome

Immune checkpoints and biological rationale

CTLA-4 limits early T-cell activation, whereas PD-1/PD-L1 signalling restrains activated T cells in peripheral tissues. Antibodies targeting CTLA-4, PD-1 or PD-L1 restore antitumour immunity across melanoma, non-small-cell lung cancer, renal-cell carcinoma and many other malignancies, but durable benefit is restricted to a subset of patients and immune-related adverse events can affect almost any organ [26]. The microbiome may influence this balance through dendritic-cell maturation, cytokine production, microbial metabolites, antigen mimicry, barrier integrity and trafficking of effector T cells.

Association studies and candidate organisms

Landmark studies reported associations between response to checkpoint blockade and taxa including Akkermansia muciniphila, Bifidobacterium species, Faecalibacterium and other Firmicutes, with transfer experiments in mice supporting causality in selected settings [27–30]. Yet cross-cohort taxonomic concordance is modest. Differences in tumour type, geography, diet, sequencing platform, sample processing, prior therapy and statistical pipelines generate heterogeneous “responder” signatures. Functional pathways and community ecology may be more transferable than a universal list of favourable species.

Recent longitudinal work strengthens the concept that stable microbial functions and microbe-derived antigens may support response, while also illustrating that baseline snapshots can miss dynamic features [31]. Accordingly, microbiome biomarkers for ICIs should be externally validated and evaluated against established clinical variables such as tumour mutational burden, PD-L1 expression, performance status and treatment line.

Antibiotics, PPIs and treatment outcomes

Multiple systematic reviews and meta-analyses associate antibiotic exposure around ICI initiation with worse overall survival, progression-free survival and response. One broad meta-analysis of 48 studies and 12,794 patients reported shorter overall and progression-free survival among antibiotic-exposed patients [32]. More recent tumour-specific meta-analyses have reproduced the direction of association in urothelial and gastrointestinal cancers [33,34]. PPI exposure has also been associated with poorer outcomes in meta-analysis [35].

These estimates should not be interpreted as proof that all antibiotics or PPIs directly cause ICI failure. Infection severity, hospitalisation, corticosteroid exposure, frailty, tumour burden and indication for acid suppression may confound results. Clinically necessary antibiotics should not be withheld. A prudent implication is antimicrobial stewardship, avoidance of unnecessary broad-spectrum exposure, and prospective collection of medication timing in ICI trials.

Microbiome-directed interventions

Interventional strategies include dietary modulation, probiotics, prebiotics, defined bacterial consortia and faecal microbiota transplantation (FMT). Early clinical studies in melanoma have shown that FMT from ICI responders can restore sensitivity in a subset of anti-PD-1-refractory patients, with accompanying immune and microbiome changes [36,37]. These studies are proof-of-concept rather than routine-care evidence. Donor selection, pathogen transmission, standardisation, durability and regulatory oversight remain major issues. Commercial probiotics cannot be assumed to reproduce the effects of complex responder communities and, in some settings, may delay microbiome recovery after antibiotics.

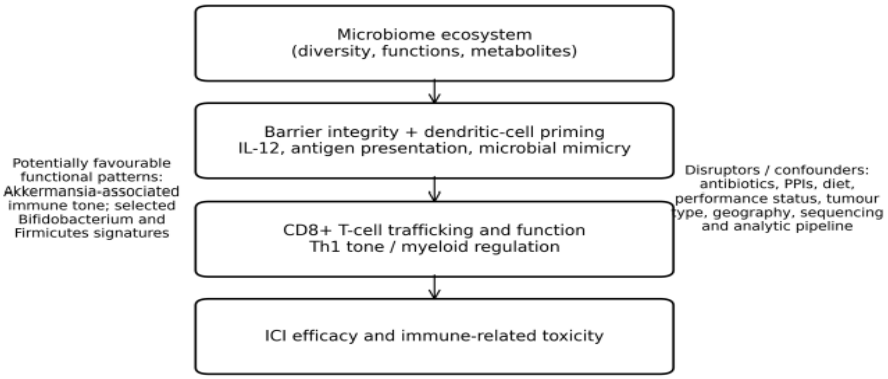

Figure 2. Mechanistic pathways and major confounders linking the gut microbiome to immune-checkpoint inhibitor efficacy and toxicity. [27–37].

Microbiome and central nervous system drugs

The microbiota–gut–brain axis

The microbiota–gut–brain axis integrates neural, endocrine, immune and metabolic communication between the gut, enteric nervous system and central nervous system. Proposed mediators include vagal signalling, cytokines, microbial SCFAs, bile acids and tryptophan metabolites [38]. Although gut bacteria can synthesize or consume neuroactive molecules in vitro, peripheral production does not imply direct delivery of neurotransmitters to the brain; barrier transport and host metabolism must be considered.

Psycho-pharmacomicrobiomics

Psychotropic drugs can alter gut microbial composition through direct antimicrobial activity, changes in motility, appetite and diet, or host metabolic effects. Conversely, baseline microbial features may influence treatment response or adverse effects. A 2024 systematic review and meta-analysis of psycho-pharmacomicrobiomics concluded that psychotropics are associated with microbiome changes, but the human evidence is heterogeneous and insufficient for clinical stratification [39]. A subsequent systematic review in bipolar disorder likewise found a small, methodologically diverse evidence base [40].

Antipsychotic-associated weight gain is the most developed clinical hypothesis, supported by animal transfer studies and small human cohorts. For antidepressants, associations with microbial diversity and taxa are inconsistent, and there is no validated microbiome test for selecting an SSRI or predicting response. Future trials should separate medication effects from diagnosis, diet, smoking, constipation, obesity and polypharmacy, and should include pre-treatment samples and repeated follow-up.

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The gut–liver axis and metabolic pharmacology

Portal circulation exposes the liver to microbial metabolites and products, while bile acids and biliary drug metabolites shape the intestinal environment. SCFAs can influence AMP-activated protein kinase, PPAR signalling and lipogenesis; microbial bile-acid transformations regulate FXR/TGR5 pathways; and barrier disruption can increase portal endotoxin exposure and inflammatory signalling [19,20,41]. These pathways are relevant to steatotic liver disease, insulin resistance and drug handling.

Pharmacomicrobiomic interpretation in liver disease is challenging because hepatic dysfunction itself changes bile flow, intestinal permeability, diet and medication exposure. Thus, microbiome associations may be cause, consequence or both. Mechanistic studies should quantify bile acids, microbial functions and hepatic enzyme/transporter phenotypes alongside standard liver tests and pharmacokinetics.

Inflammatory bowel disease: disease biology and therapeutic response

Dysbiosis, barrier dysfunction and mucosal immunity

IBD arises from interactions among host susceptibility, environmental exposures, intestinal microbes and dysregulated mucosal immunity. Common findings include reduced diversity, depletion of butyrate-producing obligate anaerobes, expansion of facultative anaerobes, altered bile-acid metabolism and impaired barrier function [42,43]. However, no single microbial signature defines ulcerative colitis or Crohn disease, and inflammation, diet and treatment substantially reshape the microbiome.

Mechanistically, reduced SCFA production may compromise epithelial energy supply and tight junctions; altered microbial antigens and metabolites may promote Th1/Th17 activity; and impaired host sensing pathways, including NOD2-related mechanisms, may reduce bacterial handling. These processes can amplify inflammation and influence drug response, but causality differs between patients and disease stages.

Microbiome interactions with IBD therapy

Sulfasalazine is an established example of microbiome-dependent prodrug activation. Beyond this, microbiome profiles have been explored as predictors of response to biologics, corticosteroids, thiopurines and dietary therapy, but no test is yet standard. Mycophenolate is not an IBD therapy but illustrates how microbial deconjugation can produce gastrointestinal toxicity in immunosuppressed patients, reinforcing the broader relevance of intestinal enzyme activity.

Probiotics have evidence in selected contexts, particularly some formulations for ulcerative colitis and pouchitis, but efficacy is strain- and indication-specific; evidence in Crohn disease is limited [42–44]. FMT is effective for recurrent C. difficile infection and is under study in ulcerative colitis, where trials show variable induction of remission. It should remain protocolized because donor factors, processing, dosing and safety strongly affect outcomes.

Figure 3. Systemic axes through which the gut microbiome may modify drug response in CNS, hepatic and inflammatory disease. Original diagram based on references 6, 7, 19, 20 and 38–43.

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Methodological challenges and standards for high-quality studies

The field is vulnerable to overinterpretation because microbiome datasets are high-dimensional, compositional and highly sensitive to technical choices. A credible pharmacomicrobiomic study should define the drug exposure window, collect pre-treatment samples, document diet and co-medications, and use longitudinal pharmacokinetic or clinical endpoints. Shotgun metagenomics offers better strain and functional resolution than 16S rRNA sequencing, but gene presence should be complemented by transcript, protein, enzyme or metabolite measurements when mechanism is central.

- Pre-analytical control: standardized stool collection, stabilisation, storage time, extraction method and batch randomisation.
- Clinical phenotyping: exact dose, formulation, adherence, organ function, interacting drugs, disease severity and relevant pharmacogenetic variants.
- Functional validation: anaerobic culture, microbial isolates, enzyme assays, ex vivo communities, gnotobiotic models and targeted metabolomics.
- Statistical rigor: compositional methods, correction for multiple testing, prespecified hypotheses, internal validation and independent external replication.
- Causal inference: negative controls, careful confounding assessment and, ultimately, randomized microbiome-directed interventions.
- Reporting: transparent pipelines, data/code sharing, taxonomic nomenclature, absolute abundance where feasible and clinically meaningful effect sizes.

Clinical translation and precision therapeutics

Potential clinical applications include prediction of efficacy, identification of toxicity risk, microbiome-aware dose adjustment, avoidance of unnecessary microbiome-disrupting co-medications, and targeted manipulation of microbial enzymes or communities. The most near-term strategies are likely to be function-specific rather than broad attempts to create a universally “healthy” microbiome. Examples include measuring a defined microbial gene such as cgr, inhibiting bacterial β-glucuronidase, or using validated responder-derived consortia in a specified cancer setting.

A practical precision framework would integrate host pharmacogenomics, renal/hepatic function, therapeutic drug monitoring, microbiome functional markers and environmental context. Before implementation, a microbiome test must show analytical validity, clinical validity and clinical utility: it should be reproducible, improve prediction beyond existing variables, and change management in a way that improves outcomes. At present, routine microbiome-guided prescribing is not recommended outside research protocols.

Translational strategy	Example	Development status	Requirement
Microbial biomarker	cgr operon for digoxin reduction	Mechanistically compelling; not routine	Prospective incremental-value study
Enzyme inhibitor	Selective bacterial β-glucuronidase inhibition	Strong preclinical rationale	Human safety and efficacy trials
Ecological intervention	FMT/defined consortia with ICIs	Early proof-of-concept	Standardised donor/product and randomized trials

Medication stewardship	Avoid unnecessary antibiotics/PPIs during ICI therapy	Clinically reasonable	Do not withhold indicated treatment; prospective validation
Dietary modulation	Protein/arginine or fibre-driven functional change	Context-specific experimental evidence	Controlled, drug-specific human trials

CONCLUSION

Pharmacomicrobiomics provides a mechanistic explanation for part of the residual variability in drug response after conventional clinical and genetic factors are considered. Gut microbes can directly transform drugs, reactivate conjugated metabolites, sequester molecules, regulate host enzymes and transporters, and alter immune or metabolic pharmacodynamics. Drugs simultaneously reshape the microbiome, creating feedback that is particularly relevant to antibiotics, PPIs, metformin, psychotropics and cancer therapy. The most convincing examples are gene- and enzyme-defined, whereas broad taxonomic associations often lack reproducibility. Translation should therefore prioritize mechanistic function, longitudinal pharmacology and rigorous causal validation. Used alongside—not instead of—pharmacogenomics and therapeutic drug monitoring, microbiome information may eventually enable safer and more precise therapeutics.

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