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Gut Microbiome-Drug Interactions in Pharmacokinetics, Pharmacodynamics, and Precision Therapeutics

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Abstract: Interindividual variability in drug response remains a major challenge in pharmacotherapy and cannot be fully explained by host genetics alone. Research increasingly implicates intestinal microbial activity in differences in drug exposure, treatment effects, and toxicity through its interactions with pharmacokinetic and pharmacodynamic pathways. Drawing on a structured selection of literature, this narrative review examines mechanistic, translational, and clinical findings on drug–microbiome interactions and their implications for precision treatment. The review discusses microbial drug biotransformation, pre-absorptive drug loss, enterohepatic recirculation, metabolic competition, and microbially mediated prodrug activation, with representative examples including digoxin, levodopa, tacrolimus, irinotecan, and mycophenolate. It also evaluates microbiome-derived metabolites and immune signaling pathways that may alter host response states, while distinguishing direct pharmacodynamic modulation from broader physiological effects. In addition, the review examines drug-induced ecological perturbations, microbiome-informed predictive modeling, and microbiome-modulating approaches, including dietary, probiotic, synbiotic, postbiotic, and regulated ecosystem-repair strategies. Current evidence is strongest for selected pharmacokinetic interactions with defined microbial mechanisms and measurable exposure-related outcomes. Whether microbiome-directed interventions will improve routine care remains uncertain, as available clinical evidence is limited and highly context-dependent. Overall, pharmacomicrobiomics provides a useful framework for understanding drug-response variability. Still, clinical translation requires stronger functional biomarkers, controlled intervention studies, external validation, and careful distinction between established, emerging, and hypothesis-generating evidence.

Keywords: pharmacomicrobiomics; gut microbiome; drug-microbiome interactions; pharmacokinetics; pharmacodynamics; precision therapeutics; microbiome-targeted interventions.

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1. Introduction

Variation in response between patients continues to complicate pharmacotherapy. Patients receiving the same medication may experience different outcomes, ranging from adequate therapeutic benefit to treatment failure or serious adverse drug reactions. Traditionally, researchers have attributed this variability largely to host-related factors, particularly genetic polymorphisms affecting drug-metabolizing enzymes, transporters, and

targets. However, pharmacogenomics alone does not fully account for the observed differences in drug exposure, efficacy, and toxicity across patients [1]. This limitation has encouraged a broader pharmacological framework in which drug response is viewed as the result of interactions among host genetics, physiology, environment, diet, medications, and the gut microbiome.

The intestinal microbiome is relevant to this broader view of drug response: its varied metabolic functions operate at the interface between orally administered medicines and the host. Gut microorganisms have enzymatic systems that can modify xenobiotics before absorption, during enterohepatic recirculation, or by competing with host metabolic pathways [1,2]. These microbial activities may alter drug activation, inactivation, systemic exposure, and toxicity. Large-scale experimental screening has strengthened this view by showing that numerous orally administered drugs can be chemically transformed by human gut bacteria, with microbial gene content contributing to differences in drug-metabolizing capacity [3]. These findings suggest that the microbiome is not merely associated with pharmacological variability but may directly shape pharmacokinetic outcomes.

The relationship between medicines and the intestinal microbiome works in both directions. While gut microorganisms can modify drugs, medications can also reshape microbial community structure, metabolic activity, and ecological stability. These drug-induced microbiome changes may influence host physiology, intestinal barrier function, immune tone, and susceptibility to adverse outcomes. However, not every drug-induced change in microbial composition should be interpreted as a clinically meaningful feedback loop. A feedback relationship is more convincing when the altered microbiome can be linked to subsequent changes in drug response, toxicity, host outcomes, or treatment tolerance. This distinction matters because pharmacomicrobiomics still contains evidence of varying maturity, from well-defined microbial drug metabolism to broader host physiological associations that are less directly linked to clinical drug response.

Microbial metabolites and signaling molecules can change the host environment in which a medicine exerts its effects, potentially influencing pharmacodynamic responses. Short-chain fatty acids, bile acid derivatives, indole metabolites, and microbial-associated molecular patterns can regulate immune function, epithelial barrier integrity, inflammatory tone, and host signaling pathways [2]. These effects are pharmacologically relevant, but they should be interpreted carefully. Some microbial signals may directly modify drug responsiveness, whereas others influence broader host physiology and only indirectly affect therapeutic outcomes. A clear distinction between direct pharmacodynamic modulation and indirect host-state regulation is therefore necessary to avoid overstating the clinical implications of mechanistic findings.

These mechanistic findings have also prompted interest in interventions intended to modify microbial activity. Dietary strategies, prebiotics, probiotics, synbiotics, postbiotics, live biotherapeutics, and regulated ecosystem-repair approaches have been proposed as ways to modify microbial functions relevant to drug response. Nevertheless, the clinical evidence supporting the broad use of dietary supplements or probiotics to improve drug efficacy remains limited and context-dependent [4–6]. Many interventions demonstrate effects on microbial composition or metabolites, but fewer have been tested against controlled pharmacokinetic, pharmacodynamic, toxicity, or clinical response endpoints. Therefore, microbiome-modulating strategies should be positioned as emerging and indication-specific approaches rather than broadly established tools for precision pharmacotherapy.

The pressing question is which drug–microbiome interactions can be measured reliably, reproduced across settings, and ultimately used to inform clinical decisions. Current evidence is strongest where specific microbial enzymes or functions are linked to measurable pharmacokinetic consequences, such as altered drug exposure or toxicity. Evidence is more preliminary when based mainly on taxonomic associations, indirect physiological effects, or uncontrolled intervention data. This uneven maturity creates a need for a structured synthesis that separates established mechanisms from promising translational signals and hypothesis-generating concepts.

This narrative review examines drug–microbiome interactions in pharmacokinetics, pharmacodynamics, ecological change, predictive modeling, and microbiome-directed interventions. The review does not aim to function as a systematic review or meta-analysis. Instead, it offers a concept-driven, evidence-aware synthesis of key mechanisms, translational opportunities, and limitations in pharmacomicrobiomics. It distinguishes direct microbial effects on drug disposition or response from broader microbiome-associated host physiological changes and evaluates which areas are closest to clinical implementation within microbiome-aware precision therapeutics.

2. Review Approach and Literature Selection

This narrative review drew on a structured selection of literature. The review was not designed as a systematic review or meta-analysis; however, the search strategy, eligibility criteria, and study selection process are described to improve transparency. No formal risk of bias assessment, pooled effect estimation, or PRISMA-based flow diagram was performed.

Literature searches were conducted in PubMed and Scopus in April 2026. Search terms combined keywords related to microbiome-drug interactions and translational pharmacology, including “pharmacomicrobiomics,” “gut microbiome,” “gut microbiota,” “drug metabolism,” “pharmacokinetics,” “pharmacodynamics,” “drug efficacy,” “drug toxicity,” “microbial β-glucuronidase,” “irinotecan,” “digoxin,” “levodopa,” “tacrolimus,” “mycophenolate,” “immune checkpoint inhibitor,” “fecal microbiota transplantation,” “predictive modeling,” “PBPK,” “prebiotic,” “probiotic,” “synbiotic,” “postbiotic,” and “drug response.”

Eligible sources included original experimental studies, mechanistic microbiology studies, human translational studies, clinical cohort studies, early-phase clinical trials, randomized controlled trials where available, pharmacokinetic or pharmacodynamic investigations, predictive modeling studies, consensus statements, and high-quality reviews used for contextual framing. Only English-language articles with accessible full text were considered. Conference abstracts, editorials, commentaries without primary data, non-peer-reviewed sources, and articles without accessible full text were excluded.

Studies were included when they examined microbial drug metabolism, linked microbiome features to pharmacokinetic or pharmacodynamic outcomes, evaluated drug-induced microbial changes relevant to toxicity or treatment response, assessed microbiome-based predictors of drug response, or investigated microbiome-modulating interventions with pharmacological relevance. Studies were excluded when they focused only on general microbiome-disease associations without a clear pharmacological link, relied solely on taxonomic descriptions without functional or clinical relevance, or made broad supplement or probiotic claims without drug-response endpoints.

Screening began with titles and abstracts; potentially relevant records were then assessed in full text. Priority was given to studies with mechanistic relevance, translational significance, clinical applicability, and measurable pharmacological endpoints, including drug exposure, toxicity, treatment response, immune modulation, or host-facing metabolites. Evidence was synthesized narratively into major themes: microbial pharmacokinetics, microbial pharmacodynamics and host signaling, ecological feedback, translational pharmacomicrobiomics, systems integration and predictive modeling, and microbiome-modulating interventions. Particular attention was given to distinguishing established or relatively advanced translational evidence from early clinical, mechanistic, or hypothesis-generating evidence.

3. The Microbial Pharmacokinetic Interface

Descriptions of oral drug disposition usually focus on host absorption, distribution, hepatic metabolism, and elimination. However, growing evidence indicates that the gut microbiome represents an additional metabolic layer that can significantly influence drug disposition before systemic circulation is achieved. Located at the interface between orally administered compounds and the host, intestinal microorganisms possess extensive enzymatic repertoires that can transform xenobiotics, thereby modifying drug bioavailability, metabolic pathways, and systemic exposure. In this sense, the microbial pharmacokinetic interface can be understood across several recurring mechanisms, including direct drug biotransformation, pre-absorptive loss of active compound, enzyme-mediated reactivation during enterohepatic recirculation, competition with host metabolic pathways, and deliberate microbial activation of prodrugs. Together, these mechanisms indicate that microbial effects on drug disposition extend beyond isolated drug-specific interactions.

Initial mechanistic evidence came from work showing that particular intestinal bacterial species can chemically modify medicines. One of the most well-characterized examples involves the cardiac glycoside digoxin. The gut bacterium *Eggerthella lenta* has been shown to convert digoxin into inactive metabolites via a cytochrome-encoding operon specifically induced by the drug. Functional studies have demonstrated that microbial inactivation of digoxin significantly alters systemic drug concentrations and that dietary factors, such as arginine availability, can modulate this metabolic activity *in vivo* [7]. These findings illustrate how strain-level microbial enzymatic activity can directly influence pharmacokinetics by reducing the fraction of active drug available for systemic absorption.

Related bacterial transformations have also been described for other medicines of clinical importance. For example, the Parkinson's disease medication levodopa (L-DOPA) can undergo metabolic conversion by gut microorganisms before being absorbed by the host. An interspecies microbial pathway has been identified in which *Enterococcus faecalis* decarboxylates levodopa to dopamine via a tyrosine decarboxylase, followed by conversion of dopamine to m-tyramine by *Eggerthella lenta*. This microbial metabolic cascade reduces the amount of intact levodopa available for transport across the intestinal barrier, thereby potentially diminishing therapeutic efficacy. Importantly, inhibition of this bacterial pathway has been shown to increase levodopa bioavailability in experimental models, highlighting the microbiome as a modifiable determinant of drug pharmacokinetics [8].

Beyond altering drug activation or inactivation, gut bacteria may also introduce previously unrecognized elimination pathways for certain pharmaceuticals. Tacrolimus, a widely used immunosuppressant with a narrow therapeutic index, exhibits highly variable oral

bioavailability among transplant recipients. Investigations into this variability revealed that several gut commensal bacteria, particularly members of the *Clostridiales* order, including *Faecalibacterium prausnitzii*, can metabolize tacrolimus into a keto-reduction product (M1) with markedly reduced immunosuppressive activity. Detection of this metabolite in both bacterial cultures and stool samples from transplant recipients suggests that microbial metabolism represents a previously underrecognized route of tacrolimus elimination that may contribute to variability in systemic drug exposure [9].

Beyond direct drug transformation, the gut microbiome also plays a critical role in modulating enterohepatic recirculation of xenobiotics. A prominent example involves the chemotherapeutic agent irinotecan (CPT-11), whose dose-limiting toxicity is severe gastrointestinal injury. After hepatic metabolism, irinotecan is converted into an inactive glucuronide conjugate that is excreted into the intestine. However, bacterial β-glucuronidases can deconjugate this metabolite, thereby regenerating the active compound in the gut lumen and increasing intestinal toxicity. Inhibiting microbial β-glucuronidase activity has been shown to alleviate irinotecan-induced toxicity in animal models without disrupting the commensal microbial community, suggesting that targeted modulation of microbial enzymes may improve drug safety profiles [10].

A similar microbiome-mediated mechanism has been observed in the pharmacokinetics of the immunosuppressant mycophenolate mofetil. Mycophenolic acid undergoes glucuronidation in the liver, producing metabolites that can be reconverted into active drug through bacterial β-glucuronidase activity in the intestine. Clinical pharmacomicrobiomics studies in transplant recipients have demonstrated that variations in gut microbial composition are associated with differences in enterohepatic recirculation and systemic exposure to mycophenolic acid. Higher abundance of certain *Bacteroides* species has been correlated with increased drug exposure, suggesting that microbiome composition may influence both therapeutic efficacy and the risk of toxicity [11,12]. Together with irinotecan, this example illustrates that microbial enzyme activity can shape pharmacokinetic variability not only by inactivating drugs, but also by restoring active compounds at clinically relevant sites.

Intestinal microbes may influence drug disposition without transforming the drug itself, notably through competition involving host metabolic pathways. Pharmacometabonomic studies have demonstrated that microbial metabolites can influence host drug metabolism by competing for enzymatic capacity. For instance, elevated levels of the microbial metabolite p-cresol sulfate have been associated with reduced sulfation of acetaminophen in humans. Because sulfation is a major pathway of acetaminophen metabolism, increased microbial production of competing substrates may alter the balance between detoxification pathways, thereby affecting systemic drug metabolism [13]. This example is especially important because it shows that microbiome effects on pharmacokinetics do not always require direct drug transformation; they may also emerge through competition at the level of host biochemistry.

For selected prodrugs, metabolism by intestinal microorganisms is an intended step in drug activation. Several anti-inflammatory medications used in inflammatory bowel disease are designed as prodrugs that rely on bacterial metabolism in the colon. Azo-bonded compounds such as sulfasalazine, balsalazide, and olsalazine are cleaved by colonic bacterial enzymes to release the active drug 5-aminosalicylic acid directly at the site of inflammation. Experimental studies using human fecal microbiota confirm that bacterial azo-reduction plays a central role in this activation process, showing how microbial metabolism can be deliberately integrated into pharmacokinetic design [14].

Work on individual bacterial strains has been extended by experimental approaches that examine drug transformation across whole microbial communities. The development of the Microbiome-Derived Metabolism (MDM) screening framework has demonstrated that the capacity of human gut microbiota to metabolize drugs varies significantly between individuals. By combining ex vivo culturing of subject-specific microbial communities with functional metagenomic screening, this approach has identified numerous previously unrecognized drug-microbiome metabolic interactions and revealed that microbiome gene content can predict drug metabolic outcomes. These findings provide strong evidence that the microbiome acts as a personalized pharmacokinetic modifier, potentially influencing drug responses across populations [15].

The clinical implications of these examples differ considerably. Interactions supported by measurable human pharmacokinetic variability or toxicity, such as those involving tacrolimus, mycophenolate, and irinotecan, currently offer the clearest relevance for clinical translation. In contrast, others remain more informative as mechanistic models of microbiome-dependent drug transformation. As a result, the contribution of the microbiome to precision dosing is likely to be most immediate in settings where microbial activity can be directly linked to exposure-related endpoints.

Tacrolimus and mycophenolate offer particularly plausible routes to clinical application: both are immunosuppressants whose exposure varies appreciably, and therapeutic drug monitoring is already established. Irinotecan is also highly translational because bacterial β-glucuronidase activity is mechanistically linked to dose-limiting gastrointestinal toxicity and represents a defined enzymatic target for toxicity mitigation. By contrast, digoxin and levodopa remain highly valuable mechanistic models. Still, broader clinical implementation will require stronger prospective evidence linking microbiome-based assessment or intervention to improved dosing, efficacy, or safety outcomes.

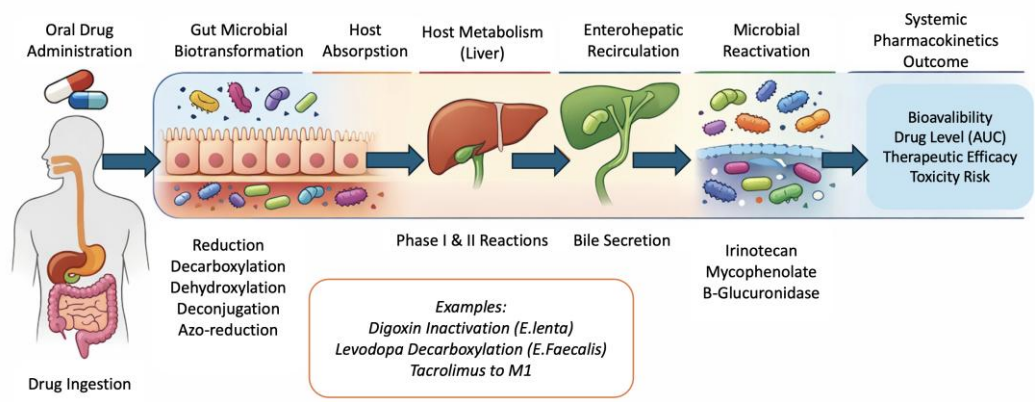


Figure 1. Microbial modulation of drug pharmacokinetics in the gastrointestinal tract**.**
After oral administration, pharmaceutical compounds encounter gut microbial communities that can transform xenobiotics through diverse enzymatic reactions. Microbial metabolism can lead to drug activation, inactivation, or altered bioavailability before host absorption. In addition, bacterial enzymes contribute to enterohepatic recirculation by deconjugating drug metabolites, thereby influencing systemic drug exposure and toxicity. These microbiome-mediated processes represent a key source of interindividual variability in pharmacokinetics and therapeutic outcomes [7–10,12].

Across these examples, intestinal microorganisms affect drug disposition through several distinct routes: direct transformation, loss before absorption, metabolic competition, reactivation during enterohepatic cycling, and activation of selected prodrugs. Through these

mechanisms, microbial communities can modulate drug bioavailability, systemic exposure, and toxicity profiles. Importantly, because microbiome composition varies substantially among individuals and can be modified by diet, lifestyle, and therapeutic interventions, the intestinal ecosystem should be understood not as a passive background for absorption but as an active pharmacokinetic interface with direct relevance to precision pharmacotherapy (Figure 1). Integrating microbiome profiling into pharmacokinetic modeling provides new opportunities to predict drug responses, refine dosing strategies, and improve therapeutic outcomes in the era of personalized medicine.

4. Microbial Pharmacodynamics and Host Signaling

In conventional pharmacology, pharmacodynamics describes how a medicine interacts with its targets to produce benefit or harm. However, accumulating mechanistic evidence indicates that the gut microbiome can also modify pharmacodynamic responses, even when systemic drug exposure is broadly comparable, by altering the physiological context in which drugs act. In this sense, the microbiome functions not merely as a metabolic modifier of drug availability but as an upstream regulator of the host response state, capable of reshaping tissue sensitivity, inflammatory set points, barrier integrity, and immune readiness. Conceptually, these effects can be understood across four convergent domains: bioactive metabolite signaling, epigenetic and immune reprogramming, barrier and xenobiotic-sensor modulation, and systemic immune priming.

Distinguish direct microbial effects on drug responsiveness from indirect influences arising from changes in host physiology. Microbiome-related variability in drug response may extend beyond drug metabolism to changes in the host state that amplify, dampen, or redirect therapeutic outcomes.

Short-chain fatty acids (SCFAs) produced by intestinal microorganisms provide one connection between dietary fermentation and regulation of host immunity. Butyrate and propionate promote peripheral regulatory T-cell (Treg) differentiation by inhibiting histone deacetylases (HDACs) and inducing FOXP3 expression through enhancer-dependent mechanisms, thereby shifting intestinal immunity toward tolerance and limiting inflammatory pathology [16,17]. Beyond Treg induction, SCFAs also influence mucosal effector function. Microbiota-derived SCFAs enhance IL-22 production by CD4+ T cells and innate lymphoid cells via GPR41 signaling and HDAC inhibition, thereby activating the AHR and HIF1α pathways to support barrier protection and reduce intestinal inflammation [18]. These observations suggest that SCFAs may act as host-state modulators that influence the inflammatory context in which drugs operate. However, their direct role in modifying specific drug responses remains dependent on the therapeutic setting.

Microbial modification of bile acids provides another route through which intestinal organisms influence host signaling relevant to pharmacological responses. Microbial metabolism converts primary bile acids into a diverse pool of secondary bile acids and related derivatives that signal through nuclear and G protein-coupled receptors, with important downstream effects on immune balance. Screening studies have identified lithocholic acid derivatives with opposing actions on adaptive immunity: 3-oxoLCA suppresses TH17 differentiation by directly binding RORγt, whereas isoalloLCA enhances Treg differentiation through mitochondrial reactive oxygen species and FOXP3 regulatory elements [19]. Complementary in vivo studies further show that microbial and dietary factors shape the colonic bile acid pool and regulate RORγ+ FOXP3+ Treg homeostasis, thereby influencing

susceptibility to inflammatory colitis through bile acid-sensing host pathways [20]. These findings are pharmacodynamically relevant mainly because they shift immune balance and the inflammatory disease context, which may then influence responses to immunosuppressants, biologics, and diet-based interventions, rather than because they universally modify drug responses directly.

Microbial products of tryptophan metabolism offer another example of small molecules that can alter host signaling in ways relevant to treatment responses. Commensal lactobacilli can convert tryptophan into indole derivatives that engage the aryl hydrocarbon receptor (AHR), thereby promoting IL-22 transcription, strengthening mucosal protection, reinforcing colonization resistance, and limiting inflammation [21]. Microbial indoles also signal through xenobiotic sensors in the gut. For example, indole-3-propionic acid can activate pregnane X receptor (PXR), downregulate epithelial inflammatory signaling, and improve barrier integrity through pathways that intersect with TLR4 signaling [22]. These mechanisms are best interpreted as indirect pharmacodynamic influences when they affect barrier function, mucosal inflammatory tone, local drug tolerance, symptom burden, or the risk of gastrointestinal adverse events, particularly in chronic inflammatory disorders and complex medication settings.

Signals of microbial origin can prime systemic immunity, potentially affecting responses to medicines in tissues outside the intestine. Peptidoglycan derived from the microbiota can translocate systemically and prime neutrophil function through NOD1 signaling, demonstrating a defined route by which commensal organisms tune systemic innate immunity [23]. This baseline immune priming may indirectly shape therapies that depend on intact innate-adaptive crosstalk, including infection-related outcomes during immunosuppression and the efficacy-toxicity balance of immunomodulatory regimens.

Cancer immunotherapy illustrates this relationship particularly clearly because response depends on the prevailing immune state, antigen presentation, and T-cell activity. In melanoma patients treated with anti-PD-1 therapy, baseline gut microbiome diversity and the relative abundance of specific taxa, including members of the Ruminococcaceae family, have been associated with clinical response and with enhanced systemic and intratumoral immunity in responders and in gnotobiotic transfer models [24]. Independent cohorts have similarly reported associations between commensal composition and anti-PD-1 efficacy, with fecal transfer experiments supporting a mechanistic contribution [25]. In epithelial tumors, abnormal microbiome composition has been linked to primary resistance to PD-1 blockade, and antibiotic exposure has been associated with reduced clinical benefit. In contrast, supplementation with Akkermansia muciniphila restored anti-PD-1 activity in preclinical transfer models through IL-12-dependent immune pathways [26]. Preclinical work further demonstrates that Bifidobacterium can enhance antitumor immunity and synergize with checkpoint blockade, supporting the concept that microbiome modulation can shift pharmacodynamic responsiveness to immunotherapy [27]. Compared with the broader metabolite-mediated pathways discussed above, cancer immunotherapy provides a more direct example of microbiome-linked pharmacodynamic modulation because microbial community features and immune signaling have been associated with differential response to a defined drug class.

These studies suggest that the microbial community may contribute to differences in response or resistance to checkpoint blockade, although the extent of this contribution varies across settings. Nevertheless, the strength and reproducibility of these associations vary across

cohorts, and researchers are still actively defining the precise microbial functions that causally determine immunotherapy responsiveness.

Microbial signaling may also intersect with neural pathways relevant to centrally acting treatments and neuropsychiatric outcomes. Indole produced by tryptophanase-expressing microbes has been shown to promote adult hippocampal neurogenesis through AHR-dependent mechanisms, linking microbial metabolism to brain plasticity and suggesting plausible routes by which microbiome state could modulate responses to neuroactive therapeutics [28]. Although the translational boundaries of this evidence remain to be defined, this observation offers a mechanistic template for integrating microbial metabolites into pharmacodynamic models of central nervous system outcomes. At present, the relevance of these pathways to variability in therapeutic response remains more conceptual than clinically established.

These findings indicate that the microbiome may influence host responsiveness through mechanisms beyond drug metabolism. Through bioactive metabolite signaling, immune and epigenetic reprogramming, barrier modulation, and systemic immune priming, the microbiome can influence the context in which therapies exert benefit or toxicity. However, this influence should be interpreted along a continuum. Some mechanisms may directly affect drug responsiveness, as immunotherapy suggests most clearly, whereas others primarily modify host physiology and may only indirectly shape therapeutic outcomes. At the same time, the evidentiary maturity across these signaling pathways is not uniform. While some microbiome-derived metabolites have well-characterized host targets and strong experimental support, others remain better understood as mechanistic frameworks than as clinically validated determinants of drug response. This perspective strengthens the rationale for microbiome-informed patient stratification and targeted interventions to improve drug efficacy while reducing treatment-related adverse effects. For clarity, the principal microbiome-derived metabolites and signaling axes discussed in this section are summarized in Table 1.

Table 1. Representative microbiome-derived metabolites and host signaling pathways relevant to pharmacodynamic modulation.

Microbial metabolite / signal	Major host pathway or target	Pharmacodynamic implication	Representative evidence
Butyrate, propionate (SCFAs)	HDAC inhibition; FOXP3 induction; GPR41 signaling; IL-22/AHR/HIF1α axis	Promotes immune tolerance, strengthens barrier protection, and may improve responsiveness to anti-inflammatory and immunomodulatory therapies	[16–18]
Secondary bile acids (e.g., 3-oxoLCA, isoalloLCA)	RORγt modulation; mitochondrial ROS; FOXP3 regulatory signaling	Shifts TH17-Treg balance and may alter response to biologics, immunosuppressants, and inflammation-directed therapies	[19,20]
Indole derivatives	AHR activation	Enhances IL-22 signaling, mucosal defense, and colonization resistance; may improve tissue-level tolerance to therapy	[21]
Indole-3-propionic acid	PXR activation; interaction with TLR4-linked inflammatory pathways	Reduces epithelial inflammatory signaling, supports barrier integrity, and may lower gastrointestinal adverse-event risk	[22]
Peptidoglycan	NOD1 signaling	Primes systemic innate immunity and may influence the efficacy-toxicity balance of immunomodulatory therapies	[23]
Microbiome-associated immune signaling in immunotherapy-responsive communities	Enhanced antigen presentation, IL-12-linked immune activation, improved T-cell fitness	May increase responsiveness to immune checkpoint blockade	[24–27]

Microbial metabolite / signal	Major host pathway or target	Pharmacodynamic implication	Representative evidence
Indole from tryptophanase-expressing microbes	AHR-dependent neuroactive signaling	Suggests a plausible microbiome contribution to pharmacodynamic variability in neuroactive therapeutics	[28]

5. Drug-Microbiome Ecological Feedback Loops

5.1. Non-antibiotic drugs as ecological perturbants.

Drug-microbiome interactions extend beyond microbially mediated drug metabolism and host signaling. Medicines can disturb intestinal microbial ecosystems, changing community composition, metabolic networks, and species competition, with possible consequences for later drug responses. In this sense, drug-microbiome ecological feedback loops arise when a medication changes the intestinal ecosystem, the altered ecosystem modifies host physiology or microbial function, and this new ecological state then influences the response to the same drug or to co-administered therapies. However, not all drug-induced microbiome changes should be interpreted as feedback loops; this term is used here only when the altered microbial state is linked to subsequent changes in drug response, toxicity, host outcomes, or treatment tolerance. A foundational ecological observation is that many non-antibiotic, human-targeted drugs directly inhibit the growth of gut bacteria. In a large in vitro screen of more than 1,000 marketed drugs tested against 40 representative gut bacterial strains, approximately 24% of human-targeted compounds inhibited at least one strain, with certain drug classes, notably antipsychotics, overrepresented. Susceptibility patterns to human-targeted drugs correlated with antibiotic susceptibility across bacterial species, implying shared resistance mechanisms and suggesting that non-antibiotics may contribute to selection pressures shaping resistance ecology [29]. From an ecosystem perspective, common medications may therefore function as community filters, suppressing specific taxa, enabling competitive release of others, and reconfiguring microbial interaction networks. At this stage, such findings mainly establish ecological perturbation; their classification as feedback loops requires additional evidence that these microbial shifts subsequently modify pharmacological or clinical outcomes.

5.2. Polypharmacy and community-level remodeling.

In clinical care, these ecological effects are complicated by the frequent co-use of multiple medicines. Population-scale metagenomic studies comparing medication users versus non-users indicate that widely prescribed drugs are associated with shifts in microbial taxonomy, functional potential, and the resistome. After adjustment for multiple concurrent medications, proton pump inhibitors (PPIs), metformin, antibiotics, and laxatives consistently emerge among the strongest correlates of microbiome variation, underscoring that medications can be dominant ecological drivers and major confounders in human microbiome research [30]. This aligns with bidirectional frameworks emphasizing that apparent dysbiosis signatures may reflect treatment exposure rather than disease mechanisms, and that robust inference therefore requires explicit correction for medication use [2]. Under these conditions, feedback loops may layer: one drug reshapes the ecosystem, the altered ecosystem changes host physiology and tolerance, and these shifts then modify responses to other therapies administered sequentially or in combination. Nevertheless, interpret population-level associations cautiously, because

medication-associated microbial differences do not, by themselves, prove that an altered microbiome feeds back to change drug efficacy or toxicity.

5.3. Loss of colonization resistance.

One of the most clinically actionable ecological feedback loops involves disruption of colonization resistance. In drug-perturbed communities, pathogenic *Gammaproteobacteria* can be more resistant to non-antibiotics than commensals, facilitating post-treatment expansion. Using synthetic and human stool-derived communities, a substantial fraction of tested non-antibiotics increased the growth of enteropathogens such as *Salmonella Typhimurium*, and these in vitro effects translated into higher intestinal pathogen burdens in vivo. Mechanistically, non-antibiotics promoted pathogen proliferation by inhibiting commensals, altering microbial interactions, and enhancing pathogen access to metabolic niches. In terfenadine-treated mice, drug-induced disruption of colonization resistance accelerated disease onset and increased inflammation in infected mice [31]. This establishes a complete ecological loop in which drug exposure perturbs commensal structure, ecological niches open, pathogens expand, and inflammation intensifies, thereby worsening outcomes and potentially shifting the benefit-risk profile of concurrent therapies.

5.4. Metformin and beneficial ecological feedback.

Drug-related changes in the microbial ecosystem do not invariably worsen clinical outcomes. Metformin provides a mechanistically important example in which drug-induced microbiome remodeling appears to contribute to therapeutic benefit. In a randomized, double-blind study of treatment type 2 diabetes, metformin induced marked changes in gut microbiome composition, and fecal transfer from metformin-treated donors improved glucose tolerance in germ-free mice, supporting microbiome-mediated contributions to antidiabetic effects [32]. Complementary analyses that disentangle type 2 diabetes signatures from metformin signatures demonstrate that medication exposure can dominate microbiome profiles and may also help explain gastrointestinal adverse effects through compositional and functional shifts [33]. Collectively, these findings illustrate a bidirectional loop in which metformin reshapes microbial functions, microbial outputs feed back to metabolic outcomes and tolerability, and these outcomes then influence adherence and long-term treatment trajectories. This example is stronger than purely associative drug-microbiome observations because microbial transfer experiments provide functional support that the drug-altered microbiome can contribute to host metabolic outcomes.

5.5. Acid suppression and ecological filtering.

A medicine can also alter microbial ecology indirectly by changing host conditions that determine which organisms survive and establish themselves. Long-term PPI therapy reduces gastric acidity and is linked to characteristic dysbiosis patterns, including enrichment of oral taxa in the gut, a process often described as oralization. In cirrhosis, gut-derived biomarkers associated with long-term PPI use have been linked to intestinal inflammation, barrier dysfunction, bacterial translocation, and increased mortality risk, providing an example in which host-environment alteration drives ecosystem remodeling with clinically meaningful consequences [34]. This mechanism emphasizes that microbial feedback loops do not always require direct microbial transformation of the drug; alteration of ecological constraints alone

may be sufficient to reshape the community and downstream host responses. However, because many PPI findings are observational and strongly influenced by disease severity, co-medication, and clinical context, this should be presented as an indirect ecological pathway rather than definitive proof of a drug-response feedback loop.

5.6. Interruptible toxicity loops.

Toxicity provides a setting in which microbial disruption and mucosal injury may reinforce one another, worsening adverse effects and constraining treatment intensity. In irinotecan therapy, targeted inhibition of bacterial β-glucuronidase activity has been shown to protect intestinal epithelium while maintaining antitumor efficacy. Notably, β-glucuronidase inhibition also reduced irinotecan-associated blooms of *Enterobacteriaceae in vivo*, suggesting that enzyme-targeted strategies can stabilize community ecology while improving tolerability. By enabling dose intensification without compromising safety, such interventions can enhance overall therapeutic effectiveness [35]. This represents a high-value translational loop in which chemotherapy perturbs the gut ecosystem, dysbiosis and barrier injury exacerbate toxicity, and microbiome-directed intervention interrupts the cycle to improve outcomes.

5.7. Implications for microbiome-aware therapeutics.

For microbiome-directed therapeutic strategies, ecological feedback offers a way to relate changes in microbial function to clinically meaningful outcomes. If non-antibiotic drugs commonly act as selective pressures that reshape community structure and resistance ecology [29], and if real-world microbiomes are strongly shaped by polypharmacy [2,30], then nutraceutical or microbiome-supportive strategies that strengthen barrier function, preserve functional redundancy, or sustain beneficial metabolic outputs may plausibly buffer drug-induced perturbations and reduce risks related to dysbiosis, infection susceptibility, or treatment intolerance. At the same time, translational claims in this area should remain cautious and should explicitly account for medication confounding, ecological heterogeneity, and variability in exposure history. Accordingly, microbiome-supportive strategies should be framed as plausible modifiers of ecological resilience rather than established interventions to improve drug efficacy, unless controlled drug-response or toxicity data support them. Taken together, these examples show that drug-microbiome interactions frequently operate as ecological feedback loops rather than one-directional pharmacokinetic events. However, the term feedback loop should be reserved for situations in which drug-induced microbial changes are linked to subsequent effects on host outcomes, drug toxicity, treatment tolerance, or therapeutic response. In such systems, a drug perturbs microbial community structure and metabolism, reshapes ecology, and the resulting ecological state subsequently modifies the pharmacological response to the same or subsequent therapies. At the same time, ecological feedback should still be regarded as an emerging interpretive framework rather than a uniformly validated clinical model. The evidentiary maturity across these examples remains uneven, and some are currently more convincing as ecological analogies or mechanistic templates than as fully established feedback loops with direct clinical relevance**.** Clinically, an ecological loop becomes actionable when three conditions converge: the microbial shift is reproducible across patients, the resulting metabolic or immunological signal is measurable, and the ecological state is modifiable through interventions such as diet, probiotics, microbiome-targeted therapeutics, or rational drug selection. When these criteria are met,

microbiome ecology moves from descriptive observation toward practical precision pharmacology, opening opportunities to predict treatment response, mitigate toxicity, and intentionally reshape host-microbe dynamics to improve therapeutic outcomes.

6. Translational Pharmacomicrobiomics in Clinical Therapeutics

6.1. From association to intervention.

The translational aim of pharmacomicrobiomics is to determine whether observed drug–microbe relationships can guide dosing, improve treatment benefit, or limit adverse effects. This transition is increasingly plausible because converging lines of evidence now support microbiome effects on drug response, including mechanistic studies identifying specific microbes and enzymes, functional assays linking community gene content to metabolic capacity, and early clinical investigations that deliberately modify the gut ecosystem to alter treatment outcomes [7,9]. However, translational maturity in this field remains uneven across therapeutic domains. In practical terms, microbiome-drug interactions are most clinically credible when three conditions converge: a defined microbial mechanism, a measurable pharmacological consequence, and a feasible route for controlled intervention. When these conditions are met, pharmacomicrobiomics moves beyond associative relevance toward implementation-oriented precision therapeutics; when they remain incomplete, the field remains promising but not yet practice-ready. In this review, we consider translational maturity strongest when microbial activity can be linked to a measurable pharmacological endpoint in human settings and when that activity plausibly supports controlled therapeutic intervention. To apply this framework consistently, this review uses pragmatic evidence maturity categories rather than a formal clinical grading system: clinically established within a defined indication, advanced translational signal, early clinical promise, mechanistic proof-of-concept, and hypothesis-generating evidence.

6.2. Established translational signals.

The clearest translational examples involve identified microbial activities associated with measurable changes in drug exposure or toxicity. In transplantation pharmacotherapy, tacrolimus provides a prominent example. Commensal gut bacteria, including taxa within the order Clostridiales such as *Faecalibacterium prausnitzii*, can metabolize tacrolimus into a keto-reduction product (M1) with markedly reduced immunosuppressive activity. Detection of this metabolite in stool from tacrolimus-treated transplant recipients supports gut bacterial metabolism as a previously underrecognized elimination pathway that may contribute to low and variable tacrolimus exposure. These findings provide a strong mechanistic basis for incorporating microbiome-related features into therapeutic drug monitoring and for investigating whether microbiome-aware strategies could reduce interpatient variability in tacrolimus exposure [9]. Accordingly, tacrolimus is best interpreted as an advanced translational signal, because the mechanism is defined and clinically relevant, but routine microbiome-guided tacrolimus dosing has not yet been established.

Mycophenolate mofetil (MMF) illustrates a different interaction, involving enterohepatic recirculation. The liver glucuronidates mycophenolic acid (MPA) to MPAG and secretes it into the intestine, where microbial β-glucuronidase activity can reconvert MPAG to active MPA, increasing systemic exposure. In kidney transplant recipients, microbiome-derived reactivation rates of MPAG to MPA, measured ex vivo, correlate positively with the

degree of in vivo enterohepatic recirculation, directly linking microbial functional activity to pharmacokinetic variability. Metagenomic analyses further link this variability to specific microbial taxa and β-glucuronidase alleles, including variants associated with Faecalibacterium prausnitzii, and show that microbiome composition changes dynamically across transplant time points. Taken together, these findings support microbiome-informed dosing as a credible translational direction in immunosuppressive therapy, although prospective implementation studies are still needed. Even so, these examples are best regarded as relatively advanced translational signals rather than clinically established tools, because routine implementation still depends on prospective validation and integration into exposure-guided decision-making. Thus, MMF is similarly positioned as an advanced translational signal rather than a clinically established microbiome-guided dosing approach.

A related translational principle is illustrated by prior mechanistic work on digoxin, in which microbial drug metabolism by *Eggerthella lenta* was shown to be modifiable in vivo by dietary factors [7]. Although not yet a standardized clinical intervention, this example provides strong proof of concept that microbiome-mediated drug metabolism can itself be functionally manipulated, thereby strengthening the translational logic of pharmacomicrobiomics beyond observational association alone**.** In the evidence maturity framework used here, digoxin is best regarded as a mechanistic proof of concept because it demonstrates microbial drug metabolism and manipulability, but not routine clinical implementation.

6.3. Early phase clinical promise.

The clearest area of early-phase clinical promise is cancer immunotherapy, where modulation of the gut microbiome has been explored as a strategy to improve responses to immune checkpoint inhibitors (ICIs) and potentially mitigate immune-related adverse events. Here, the translational rationale is strong, but the field remains in a phase of feasibility testing rather than definitive implementation. Several fecal microbiota transplantation (FMT)-based clinical programs have now moved beyond preclinical plausibility into first-in-human translational studies. Within the proposed maturity categories, these studies best reflect early clinical promise rather than established clinical practice.

In metastatic renal cell carcinoma, the phase 1 PERFORM trial evaluated encapsulated healthy-donor FMT (LND101) in combination with standard ICI regimens in treatment-naïve patients. The trial met its primary safety endpoint, with no serious FMT-related toxicities or grade 4-5 immune-related adverse events; grade 3 events occurred in a subset of participants. Among evaluable patients, the reported objective response rate was encouraging, and mechanistic analyses suggested that improved alpha diversity, durable engraftment of donor-derived taxa, and anti-inflammatory metabolic functions were associated with reduced toxicity and improved response. These findings suggest that functional microbiome engraftment is feasible and biologically relevant in this setting, but the small cohort size and early-phase design preclude definitive conclusions about efficacy [36].

In advanced melanoma, the phase 1 MIMic trial investigated healthy-donor FMT followed by standard anti-PD-1 therapy as first-line treatment. In this small cohort, investigators reported encouraging safety and response findings; extended follow-up suggested prolonged progression-free and overall survival in some patients. These findings are promising because they imply that microbiome modulation may influence not only initial tumor response but also longer-term clinical durability. Nevertheless, the limited sample size and non-

definitive trial structure mean that these results remain hypothesis-generating rather than practice-changing [37].

A clinical study of FMT in advanced non-small cell lung cancer with secondary PD-1 resistance reported partial responses in some patients and differences in microbial diversity and taxonomic profiles among responders. Immune correlates were consistent with enhanced CD8+ T-cell infiltration and lower proportions of regulatory T cells in patients who responded. At the same time, outcomes were clearly influenced by baseline and concomitant medications, as proton pump inhibitor use and corticosteroid exposure during FMT were independently associated with shorter progression-free survival. This study, therefore, illustrates both the clinical promise of microbiome-based intervention and its sensitivity to the surrounding pharmacological context [38].

In oncology, attempts to modify the microbiome have reached early clinical testing, although efficacy evidence remains preliminary. At present, however, the most appropriate interpretation is not that these approaches are ready for routine use, but that they establish feasibility, biological relevance, and a strong rationale for larger controlled trials. Importantly, these studies should not yet be interpreted as a single mature translational class, because intervention formats, donor strategies, cancer settings, and concomitant treatment contexts remain highly heterogeneous. For this reason, FMT-based strategies in immunotherapy should be described as early clinical promise. In contrast, avoid claims of routine clinical utility until larger controlled studies demonstrate reproducible benefit.

6.4. Unresolved implementation barriers.

Important practical obstacles remain before pharmacomicrobiomic findings can be used consistently in clinical care. First, interindividual variability in microbiome composition and engraftment remains substantial, making intervention effects difficult to reproduce across patients and across studies. Second, trial designs remain heterogeneous with respect to donor selection, intervention format, timing, concomitant therapy, and endpoint definition, complicating cross-study comparisons and weakening generalizability. Third, concomitant medications that strongly perturb the microbiome, including proton pump inhibitors, corticosteroids, and antibiotics, remain major confounders in both oncology and non-oncology settings. These factors can independently alter community structure, functional output, and immune tone.

Clinical translation will also require moving beyond lists of associated microbial taxa to measurements of what those organisms actually do. Clinical implementation is unlikely to succeed if it relies primarily on compositional signatures without identifying the microbial enzymes, metabolites, or community functions that directly mediate drug response. For this reason, translational progress will depend on integrating mechanistic microbiology, exposure-response pharmacology, and clinically validated biomarkers rather than taxonomy alone. In practice, microbiome-aware intervention is most credible when a reproducible microbial function links to a measurable pharmacological endpoint. That function can be modified in a controlled manner. These barriers explain why many applications remain promising or translationally informative, but not yet ready for routine clinical decision-making.

6.5. Translational outlook.

Current studies show progress towards clinical application, but the readiness of different pharmacomicrobiomic approaches varies markedly. Microbiome-dependent metabolism of tacrolimus and mycophenolate represents a relatively well-established translational signal with direct pharmacokinetic relevance, as the responsible microbial functions are mechanistically interpretable and linked to measurable variability in exposure. Within the evidence maturity categories used in this review, these examples are best regarded as advanced translational signals. By contrast, microbiome modulation during immune checkpoint blockade remains a promising early-phase area rather than established clinical practice, despite a strong biological rationale and encouraging feasibility data. FMT-based immunotherapy studies are therefore positioned as early clinical promise. Across both domains, the central task is no longer to accumulate more association studies, but to define mechanism-linked microbial functions, develop interventions that reproducibly modify those functions, and link those changes to validated endpoints such as drug exposure, treatment response, and toxicity. Framed in this way, pharmacomicrobiomics is best understood not as a uniformly ready clinical platform, but as an emerging translational discipline whose implementation will depend on rigorous mechanistic validation, biomarker-guided stratification, and carefully controlled clinical testing. For clarity, Table 2 summarizes representative applications of translational pharmacomicrobiomics across different levels of clinical maturity.

Table 2. Evidence maturity categories for representative applications in translational pharmacomicrobiomics.

Drug / intervention domain	Microbiome-linked mechanism	Pharmacological or clinical relevance	Evidence maturity category	Current interpretation	Main limitation	Representative citations
Tacrolimus	Gut commensals, including taxa within *Clostridiales* such as *Faecalibacterium prausnitzii*, metabolize tacrolimus into the less active M1 metabolite	May contribute to low or variable tacrolimus exposure in transplant recipients	Advanced translational signal	Mechanistically defined and linked to measurable pharmacokinetic variability	Not yet validated as a routine microbiome-guided dosing strategy	[9]
Mycophenolate mofetil	Microbial β-glucuronidase activity reconverts MPAG to active MPA during enterohepatic recirculation	May contribute to variability in MPA exposure, efficacy, and toxicity risk	Advanced translational signal	Functionally linked to pharmacokinetic variability in transplant recipients	Requires prospective validation before use in exposure-guided dosing	[11,12]
Digoxin	*Eggerthella lenta* inactivates digoxin through a drug-inducible cytochrome-encoding operon	Can reduce the fraction of active digoxin available for systemic absorption	Mechanistic proof-of-concept	Strong mechanistic evidence for microbial drug inactivation	No standardized clinical microbiome-based dosing or intervention strategy	[7]

Drug / intervention domain	Microbiome-linked mechanism	Pharmacological or clinical relevance	Evidence maturity category	Current interpretation	Main limitation	Representative citations
Levodopa	*Enterococcus faecalis* converts levodopa to dopamine, followed by further microbial conversion by *Eggerthella lenta*	May reduce intestinal levodopa availability before host absorption	Mechanistic proof-of-concept	Mechanistically informative example of pre-absorptive drug metabolism	Patient-level contribution to clinical response variability requires further validation	[36]
Irinotecan	Bacterial β-glucuronidases deconjugate irinotecan metabolites and regenerate toxic active compounds in the gut lumen	Contributes to gastrointestinal toxicity and represents a specific microbial enzyme target	Advanced translational signal	Mechanistically linked to drug toxicity and toxicity-mitigation strategies	Selective enzyme-targeted approaches still require clinical validation for routine use	[37]
Immune checkpoint blockade with FMT in metastatic renal cell carcinoma	Donor microbiota engraftment may alter immune and metabolic functions during immunotherapy	May influence response and immune-related toxicity	Early clinical promise	Phase 1 evidence supports feasibility and biological relevance	Small cohort size and non-definitive efficacy evidence	[38]
Immune checkpoint blockade with FMT in advanced melanoma	Donor microbiome transfer may modify immune tone during anti-PD-1 therapy	May influence response to immune checkpoint blockade	Early clinical promise	Early clinical evidence suggests potential benefit	Requires larger controlled trials before clinical adoption	[39]
FMT in advanced NSCLC with secondary PD-1 resistance	Microbiome modulation is associated with increased diversity, responder-enriched taxa, and immune correlates	Partial responses have been reported in a subset of patients	Early clinical promise	Clinically suggestive but context-dependent	Interpretation is influenced by concomitant medications such as PPIs and corticosteroids	[40]
SER-109 for recurrent *Clostridioides difficile* infection	Standardized spore-based microbiome therapy restores colonization resistance after antibiotics	Reduces recurrence of *C. difficile* infection	Clinically established within a defined indication	Regulated microbiome therapy supported by controlled manufacturing and clinical endpoint validation	Indication-specific; not direct evidence for optimizing unrelated drug responses	[41,42]
Fermentable fibers / prebiotic strategies	Selective microbial utilization can increase saccharolytic fermentation and SCFA production	May modify microbiome-associated metabolic or immune context	Hypothesis-generating for drug-response optimization	Biologically plausible supportive approach, but not established for improving drug efficacy	Controlled evidence linking these interventions to improved drug efficacy or toxicity outcomes remains limited	[9]

Drug / intervention domain	Microbiome-linked mechanism	Pharmacological or clinical relevance	Evidence maturity category	Current interpretation	Main limitation	Representative citations
Probiotics, *Akkermansia muciniphila*, and supplement-associated modulation	Live microbial administration or supplement exposure may alter microbial and host metabolic or immune signaling	May influence selected metabolic or immunotherapy-related contexts	Hypothesis-generating for broad pharmacomicrobiomic use	Mechanistically plausible but heterogeneous	Effects are strain-, host-, disease-, and treatment-specific; controlled drug-response evidence remains limited	[11,12]

Note: Evidence maturity categories were used as a pragmatic interpretive framework for this narrative review and should not be interpreted as a formal clinical grading system. The categories were defined as follows: clinically established within a defined indication refers to evidence supporting use within a specific clinical indication or approved therapeutic context; advanced translational signal refers to a defined microbial mechanism linked to measurable pharmacokinetic, pharmacodynamic, toxicity, or exposure-related endpoints without routine clinical implementation; early clinical promise refers to feasibility, phase 1, pilot, or early human translational evidence with non-definitive efficacy; mechanistic proof-of-concept refers to experimental or preclinical evidence demonstrating plausible microbial mechanisms or functional manipulability without proven patient-level utility; and hypothesis-generating evidence refers to associative, indirect, ecological, or context-dependent evidence without validated drug-response endpoints.

7. Systems Integration and Predictive Modeling

Researchers are increasingly combining mechanistic and clinical data to examine whether the microbiome can improve individual-level prediction of drug effects and adverse reactions. This shift is necessary because single-mechanism examples, while highly informative, cannot, by themselves, capture the full variability observed in real clinical settings, where host genetics, diet, immune status, co-medications, microbial gene content, and ecological dynamics interact simultaneously to shape pharmacokinetics and pharmacodynamics. For this reason, systems-level approaches are increasingly needed to connect “who is there” (taxa), “what they can do” (functions), and “what they are doing now” (metabolites and host responses) into predictive models with translational relevance. In practice, these approaches combine longitudinal sampling, multi-omics integration, and statistical or machine-learning methods to convert microbiome variation into endpoints that may ultimately support therapeutic stratification, toxicity prediction, and microbiome-aware intervention design. However, the clinical value of these models depends not only on predictive accuracy within a study cohort, but also on their robustness across populations, sequencing platforms, analytical pipelines, and real-world clinical settings.

One prospective multicenter study examined microbiome-based prediction among patients with locally advanced rectal cancer treated with neoadjuvant immunotherapy and chemoradiotherapy. At baseline, microbial features differed between responders and non-responders, and researchers developed a species-level gut microbiome prediction model (SPEED) to predict pathological complete response (pCR). The model showed strong discrimination in the training cohort and retained predictive performance in an independent validation cohort, supporting the idea that microbiome-informed signatures may complement conventional clinical predictors for stratifying response to intensive multimodal regimens [43]. Importantly, the study also emphasized longitudinal sampling across time points, suggesting that predictive signals may be dynamic rather than static and that trajectories such as microbiome resilience, engraftment, or functional shifts may provide information beyond

baseline composition alone. This point is especially relevant in pharmacomicrobiomics, where drug exposure and microbiome state may co-evolve during treatment rather than remain fixed at baseline. Even in promising models, interpretation should remain cautious because small cohorts, high-dimensional microbial features, and multiple analytical choices can increase the risk of overfitting. Therefore, independent external validation across different populations and treatment settings is essential before microbiome-based prediction can inform clinical decisions.

Physiological and pharmacokinetic models offer a complementary approach that may make predictions easier to relate to underlying mechanisms. Building on evidence that gut bacteria can chemically transform drugs, expanded physiology-based pharmacokinetic (PBPK) models have been proposed that explicitly incorporate intestinal compartments with microbiome-associated drug-metabolizing activity. Such models may help simulate host and microbial contributions to systemic drug and metabolite exposure, estimate conditions under which microbial metabolism meaningfully alters serum profiles, and examine how variation in microbial activity, host physiology, and drug physicochemical properties interact to shape pharmacokinetic outcomes [44]. In this respect, PBPK extension is valuable not only as a predictive tool, but also as a mechanistically structured framework for testing how microbiome-dependent metabolism might alter exposure under conditions that are difficult to isolate in observational cohorts. Nevertheless, PBPK models that incorporate microbiome parameters remain constrained by limited quantitative data on strain-level abundance, enzyme activity, intestinal localization, temporal stability, and interindividual variability. These uncertainties may reduce model transportability if assumptions are not tested against measured pharmacokinetic outcomes.

Metabolomic measurements can connect microbial activity with biochemical signals detectable in the host. A foundational human pharmacometabolomics study showed that a predose urinary metabolic signature could predict postdose acetaminophen metabolism: higher baseline p-cresol sulfate, a microbiome-related cometabolite, was associated with altered acetaminophen sulfation capacity, consistent with competition for host sulfonation pathways [13]. This example remains important because it illustrates a clinically plausible workflow in which a pre-treatment biospecimen captures an integrated readout of microbial activity and host metabolic state, which can then be related to drug biotransformation pathways and safety-relevant metabolic partitioning. More recent systems frameworks extend similar strategies to targeted microbial metabolites, including bile acid derivatives, indoles, and short-chain fatty acids, as well as functional enzyme annotations derived from metagenomic data. These approaches are especially valuable because they bring prediction closer to host-facing biochemical signals rather than relying solely on taxonomic composition. At the same time, metabolomics and multi-omics models are vulnerable to batch effects, sample handling differences, dietary variation, medication confounding, and platform-specific measurement bias. Without standardized preprocessing, metadata capture, and cross-cohort validation, apparently strong signatures may reflect technical or population-specific patterns rather than generalizable pharmacological predictors.

Another approach brings drug properties, host biology, and microbial functions into a common modeling framework. Recent perspectives suggest viewing the microbiome as a modifiable pharmacological variable, both a source of drug metabolism and a target whose modulation may influence drug performance, motivating models that span bioavailability, absorption, metabolism, excretion, toxicity, and drug-driven microbiome remodeling [45].

From this perspective, predictive modeling should not be an endpoint in itself, but a decision-support component for hypothesis generation, translational interpretation, and designing microbiome-aware therapeutic strategies. The strongest systems models will therefore be those that do not merely classify patients by microbial signatures, but connect those signatures to defined functions, measurable pharmacological consequences, and modifiable intervention points. For clinical translation, these models must also generate outputs that are interpretable, reproducible, and actionable. A model that statistically predicts response may still have limited clinical utility if it does not indicate how treatment selection, dosing, monitoring, or microbiome-directed intervention should change.

Predictive algorithms, microbiome-extended PBPK models, and pharmacometabonomic approaches offer complementary ways to investigate variability in drug response. Their collective value lies in helping scale microbiome research from isolated mechanistic observations toward interpretable clinical prediction. Immediate priorities include standardizing longitudinal sampling and metadata for model comparability, incorporating microbial functional capacity rather than taxonomy alone, and pairing predictive performance with causal validation.

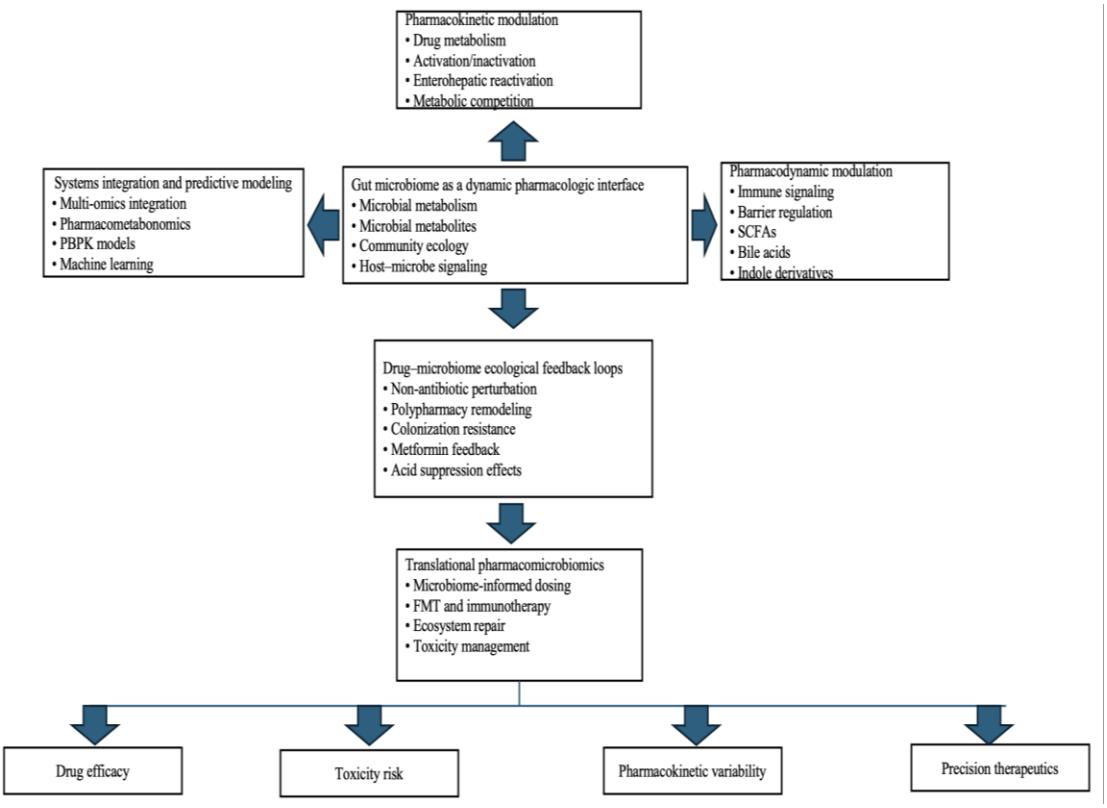


Figure 2. Conceptual framework of pharmacomicrobiomics linking microbial metabolism, ecological feedback, and translational therapeutics.

However, most predictive frameworks reported to date remain cohort-specific and have not yet been consistently validated across independent clinical populations. Major barriers include overfitting in small cohorts, limited external validation, batch effects across sequencing and metabolomics platforms, population specificity related to geography, diet, disease background, and medication exposure, and the difficulty of converting microbiome signatures into clinically usable decision tools. Moreover, although systems-level integration has improved mechanistic understanding, translating these models into clinically usable decision tools remains an ongoing challenge. Systems integration complements mechanistic

pharmacology by linking microbiome-associated processes to clinically testable models of efficacy, toxicity, and patient stratification across treatment settings.

Drug response can be shaped by several connected activities of the intestinal microbiome. Microbial metabolism alters pharmacokinetics, microbial metabolites influence host pharmacodynamic signaling, and drug exposure reshapes microbial community ecology through feedback loops. These processes interact with systems-level modeling approaches and support translational pharmacomicrobiomics, including microbiome-informed therapeutic strategies. Together, these mechanisms contribute to variation in drug efficacy, toxicity risk, pharmacokinetic variability, and precision therapeutics (Figure 2).

8. Microbiome-Modulating Interventions: Dietary, Biotherapeutic, and Ecosystem Repair Strategies

8.1. Rationale and scope.

Interventions targeting intestinal microorganisms aim to change their composition or function to improve treatment benefit, tolerability, or disease outcomes. Unlike conventional host-directed pharmacology, these strategies treat the intestinal ecosystem as a modifiable pharmacologic compartment in which changes in taxa, genes, and metabolites can shift host signaling, immune tone, and xenobiotic handling. These interventions encompass three broad, partially overlapping domains: dietary and metabolic modulation, live microbial or biotherapeutic modulation, and ecosystem repair strategies developed with drug-like control. This logic has accelerated the development of both consumer-facing dietary supplements, such as fermentable fibers and selected probiotics, and regulated microbiome therapeutics, such as standardized microbial consortia or spore-based products, that are increasingly evaluated using clinical frameworks more typical of pharmacological intervention. However, these intervention classes should not be interpreted as having equivalent evidentiary strength. Dietary supplements and probiotics may modify microbiome-associated functions, but broad claims that they improve drug efficacy require controlled drug-response data.

8.2. Prebiotics and fermentable fibers as metabolic levers.

Prebiotics are substrates selectively utilized by host microorganisms that confer a health benefit, emphasizing function over taxonomy alone [40,46]. In practice, fermentable fibers can increase saccharolytic fermentation, increase short-chain fatty acid (SCFA) production, and shift bile acid pools, thereby influencing epithelial barrier integrity and immunometabolic signaling. Controlled human studies show that targeted fiber-based interventions can measurably alter gut ecology and host metabolic phenotypes, supporting the idea of dietary pharmacomicrobiomics as a clinically actionable layer [40]. At the same time, the magnitude and direction of the response vary with baseline microbiome configuration, habitual diet, and concurrent medications, indicating that fiber-based interventions should be understood as context-dependent modulators of microbiome-linked pharmacology rather than uniform solutions. At present, evidence that prebiotics or fermentable fibers broadly improve drug efficacy remains limited unless supported by controlled studies with pharmacokinetic, pharmacodynamic, toxicity, or treatment-response endpoints.

8.3. Probiotics, next-generation probiotics, and live biotherapeutics.

Conventional probiotic products generally contain selected strains studied for particular indications; however, their persistence and biological activity can differ considerably between individuals. This variability has driven interest in next-generation probiotics, namely candidate commensals with stronger mechanistic rationale, and in higher-control live biotherapeutic products. A proof-of-concept exploratory human study of Akkermansia muciniphila, including pasteurized preparations, reported improvements in selected metabolic endpoints in overweight or obese participants, illustrating how a mechanistically motivated commensal can be advanced toward clinical evaluation when supported by human data [41]. In this respect, the translational value of live microbial interventions depends not simply on whether a strain can be administered, but also on whether its functional effect can be reproduced, mechanistically interpreted, and linked to meaningful host outcomes.

The potential clinical effects of microbiome changes are particularly relevant during cancer immunotherapy. Human translational data in melanoma indicate that diet quality, particularly higher dietary fiber intake, and over-the-counter probiotic exposure may be associated with differences in microbiome features and clinical outcomes during immune checkpoint blockade, reinforcing the potential clinical relevance of microbiome-targeted supplements. They should therefore be handled with indication-specific caution [42]. These findings should be interpreted with caution because supplement exposure and dietary patterns do not necessarily establish a causal improvement in drug response. This example is important because it shows that even ostensibly benign supplement practices may influence treatment-relevant ecology in ways that are not uniformly beneficial across disease settings. Probiotics should not be treated as a uniform translational class, as strain identity, colonization dynamics, and host-microbiome context can substantially alter both functional output and clinical reproducibility. Thus, probiotics should be discussed as indication- and strain-specific interventions, not as broadly applicable enhancers of pharmacotherapy.

8.4. Synbiotics and formulation principles.

Synbiotics combine live microorganisms with substrate(s) that host microorganisms are intended to use selectively and that confer a health benefit. The ISAPP consensus statement emphasizes that synbiotics should not be treated by default as a generic probiotic-plus-prebiotic mixture; instead, mechanistic alignment among components matters, and supporting evidence should align with the intended synbiotic type [4]. In complementary synbiotics, each component independently satisfies relevant criteria and contributes benefits. In contrast, synergistic synbiotics select the substrate specifically for use by the co-administered microorganism(s), enabling cooperative function [4]. These distinctions matter because they shift synbiotic design from empirical mixing to more precise formulation logic. However, when the intended outcome is improved drug response, synbiotic claims should be supported by drug-relevant endpoints rather than by compositional microbiome changes alone. However, the mechanisms proposed for many marketed synbiotic formulations have yet to be adequately validated, and their effects on drug-related outcomes remain uncertain.

8.5. Postbiotics and metabolite-forward supplementation.

Postbiotic interventions use inanimate microbial preparations or their components and, in some contexts, may be easier to standardize than live organisms. Conceptually, postbiotics

align well with pharmacology because they may offer greater dose control, product stability, and clearer exposure-response relationships than live organisms that variably engraft. However, efficacy will likely remain context-dependent, since host receptor expression, baseline microbiome ecology, and concurrent drug regimens can shape downstream signaling. The ISAPP consensus statement provides a standardized definition and scope for postbiotics, intended to improve interpretability and comparability across studies and products [47]. From a translational perspective, postbiotics are especially attractive when mechanistic reproducibility and formulation stability matter more than ecological engraftment. At the same time, most postbiotic strategies are supported primarily by mechanistic or early translational evidence, and indication-specific clinical validation remains limited. Therefore, postbiotics should be positioned as promising but not yet broadly validated tools for improving pharmacotherapy outcomes.

8.6. Regulated microbiome therapeutics as drug-like ecosystem repair.

A key translational milestone is the shift from heterogeneous fecal products toward standardized, quality-controlled microbiome therapeutics that can be evaluated and deployed with drug-like rigor. In recurrent *Clostridioides difficile* infection, a phase 3 randomized, double-blind, placebo-controlled trial showed that an oral microbiome therapy composed of purified Firmicutes spores (SER-109) reduced recurrence compared with placebo after standard-of-care antibiotics, along with evidence consistent with ecosystem repair and restored colonization resistance [39]. This trial is illustrative because it shows that microbiome intervention can function as a therapeutic modality with manufacturing control, defined dosing, and clinically meaningful endpoints. It therefore represents one of the clearest examples of microbiome-directed ecosystem repair moving into a domain that resembles conventional drug development. Nevertheless, this evidence is indication-specific and should not be generalized as proof that microbiome therapeutics broadly improve the efficacy of unrelated drugs.

8.7. Practical considerations for clinical translation.

Supplements and therapeutics intended to modify the microbiome warrant evaluation against the same standards used for other interventions that might alter treatment response. Patient selection and baseline microbiome context matter because responders and non-responders may differ substantially before intervention begins. Concurrent medications, including antibiotics, PPIs, metformin, corticosteroids, and immunosuppressants, may confound or even reverse intended effects by altering microbial composition and function independently of the intervention itself. Safety must remain indication-specific, particularly in immunocompromised or oncology populations, where unintended ecological shifts may carry disproportionate risk. In addition, endpoint selection should go beyond taxonomy and include functional readouts such as metabolites, pathway abundance, or immune correlates, because mechanistic effects often depend on microbial functions that compositional changes alone do not capture. For drug-response applications, the strongest studies should include controlled pharmacokinetic, pharmacodynamic, toxicity, or clinical treatment-response endpoints.

The evidence is too heterogeneous to treat all microbiome-modulating interventions as one equally validated group. Fermentable fibers, probiotics, synbiotics, and postbiotics can shift microbial function, but their effects are often context-dependent and inconsistently reproducible. By contrast, standardized microbiome therapeutics designed with manufacturing

controls and clinically validated endpoints more closely resemble drug-like ecosystem-repair strategies. In this hierarchy, dietary and supplement-based approaches primarily modify ecological context, whereas regulated microbiome therapeutics increasingly resemble targeted pharmacological interventions. The key translational challenge is to identify interventions that reproducibly modify defined microbial functions and produce measurable pharmacological effects under controlled conditions.

Recent studies further illustrate the development of microbiome-modulating materials, including microencapsulation systems designed to protect the viability of probiotic *Pichia kudriavzevii* and modified jack bean flour with prebiotic potential [48,49]. However, these studies should be interpreted as supportive evidence for protecting probiotic viability and developing prebiotic ingredients, rather than as direct evidence that probiotics or prebiotics broadly improve drug efficacy.

9. Conclusion

The reviewed evidence links intestinal microorganisms to differences in drug response, although the supporting mechanisms vary considerably in how well they have been established. The strongest evidence is for selected pharmacokinetic interactions in which defined microbial enzymes or functions link to measurable drug exposure or toxicity, such as tacrolimus, mycophenolate, irinotecan, digoxin, and levodopa. Through these mechanisms, the microbiota can influence drug biotransformation, enterohepatic recirculation, pre-absorptive drug loss, metabolic competition, and toxicity risk.

Evidence for clinical use is less developed in pharmacodynamics, cancer immunotherapy, microbiome-based prediction, and interventions designed to alter microbial function. In these areas, microbial metabolites, immune signaling, and ecological changes may shape the host response state and treatment tolerance. However, evidence strength varies, and many findings still require larger controlled studies, external validation, and clearer links to drug-response endpoints. More speculative or hypothesis-generating areas include broad claims that dietary supplements, probiotics, synbiotics, postbiotics, or generalized microbiome modulation can improve drug efficacy across clinical settings. Although these interventions may alter microbial composition or metabolic outputs, we should not infer routine use to improve pharmacotherapy without controlled pharmacokinetic, pharmacodynamic, toxicity, or clinical response data.

Future investigations should focus on microbial activities linked to treatment outcomes, not taxonomic associations alone. Integration of multi-omics data, pharmacokinetic modeling, predictive analytics, and controlled intervention studies will be essential to determine which microbiome-drug interactions are reproducible, measurable, and actionable. Thus, pharmacomicrobiomics should be viewed as an emerging precision pharmacology framework with established mechanisms in selected settings, promising translational applications in others, and several areas that remain preliminary. Its clinical value will depend on translating mechanistic insight into validated biomarkers, decision tools, and intervention strategies that improve drug efficacy, safety, or tolerability in defined patient populations.

Author Contributions

Conceptualization, R.T.I. and H.R.; methodology, R.T.I.; data curation, H.R.; writing-original draft preparation, R.T.I.; writing-review and editing, H.R.; supervision, H.R. and R.T.I. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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ChatGPT (OpenAI; GPT-6) was used to assist with grammar checking and readability improvement during final proofreading. All scientific content, analysis, and conclusions were developed by the authors.

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