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RESEARCH ARTICLE

Gut Microbiome Mediated Modulation of Drug Efficacy: Nutritional Interventions to Improve Pharmacotherapy Outcomes

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Abstract: The gut microbiome plays a pivotal role in determining the pharmacokinetics and pharmacodynamics of therapeutic agents. Microbial enzymes can activate, inactivate, or toxify drugs, thereby influencing their absorption, metabolism, and therapeutic efficacy. Interindividual variability in microbiome composition contributes to heterogeneity in drug responses, challenging the predictability of pharmacotherapy. Emerging evidence indicates that targeted nutritional strategies such as prebiotic supplementation, probiotic administration, synbiotic formulations, and precision dietary modulation can reshape the gut microbiome to optimize drug action and minimize adverse effects. Moreover, fiber-rich diets increase short-chain fatty acid production, which can modulate hepatic drug-metabolizing enzymes, while specific probiotic strains attenuate antibiotic-induced dysbiosis and preserve drug bioavailability. Nutritional interventions also hold promise in reducing microbiome-driven drug toxicity, such as irinotecan-induced diarrhea or digoxin inactivation. This review synthesizes current understanding of microbiome–drug interactions, highlighting key microbial pathways (e.g., β-glucuronidase activity, bile acid metabolism, reductive transformations) that influence drug fate. We further examine clinical evidence linking dietary modulation of the microbiome to improved therapeutic outcomes in oncology, cardiology, metabolic disorders, and neuropsychiatric disease. Finally, we discuss challenges in translating microbiome-nutrition insights into personalized medicine, including interindividual variability, temporal instability of the microbiome, and the need for integrated multi-omics approaches. By elucidating the nexus between diet, microbiota, and pharmacology, this review underscores the potential of nutritional interventions as adjuvants to precision pharmacotherapy.

Keywords: Gut microbiome Drug metabolism Nutritional interventions Pharmacotherapy Prebiotics and probiotics, Personalized medicine.

INTRODUCTION

The Microbiome as a Pharmacological Determinant

The human gastrointestinal tract harbors an immense and dynamic microbial ecosystem comprising archaea, fungi, bacteria, and viruses that collectively encode metabolic capacities exceeding those of the host genome (Cullin et al., 2021; Hillman et al., 2017). Once regarded primarily as a passive inhabitant of the gastrointestinal-tract, the microbiome is now recognized as a dynamic "Metabolic Organ" that interfaces with host physiology and exogenous compounds, including beneficial agents (Xiao et al., 2020). Advances in meta-genomics, meta-bolomics, and systems pharmacology have revealed that gut microbes can pro-foundly influence the absorption, distribution, metabolism, and excretion of drugs, thereby shaping their efficacy, toxicity, and interindividual variability in clinical response (Tan et al., 2024). This paradigm shift redefines pharmacology by expanding the concept of drug disposition beyond host genetics and organ function to include the collective genome and bio-chemical activity of the microbiota (Jia et al., 2008). Far beyond their classical parts in nutrient assimilation and immune maturation, these microbes participate in the bio-transformation of xenobiotics, including therapeutic medicines (Koppel et al., 2017; Pant et al., 2023). Microbial enzymes can directly metabolize orally administered compounds before they are absorbed (pre-systemic metabolism) or can indirectly influence drug pharmacokinetics by altering bile acid pools, gut barrier integrity, and host metabolic signaling pathways (Pereira De Sousa & Bernkop-Schnürch, 2014). Consequently, the gut microbiome has emerged as a critical yet underappreciated determinant of drug efficacy and toxicity (S. Wang et al., 2024).

The cardiac glycoside digoxin is in-activated by Eggerthella lenta via a cardiac glycoside reductase, leading to reduced therapeutic effect in colonized persons (Haiser et al., 2014). Likewise, the anti-neoplastic agent irinotecan undergoes microbial β-glucuronidase mediated reactivation in the colon,

producing severe gastrointestinal toxicity (Mahdy et al., 2023). Anti-biotics themselves can trigger a vicious cycle by perturbing the microbiome and thereby altering the pharma-cokinetics of co-administered medications, such as oral contraceptives or anti-coagulants (Torrent Rodríguez et al., 2024). These discoveries highlight the necessity of considering host microbe co-metabolism in modern pharmacology. At the molecular interface, the microbiome modulates pharmacokinetics through a repertoire of enzymatic reactions that rival hepatic metabolism. Microbial enzymes such as azoreductases, β-glucuronidases, nitroreductases, and sulfatases can activate prodrugs, inactivate active compounds, or generate toxic metabolites (Pant et al., 2023). The bacterial reactivation of the chemotherapeutic irinotecan via β-glucuronidase, the reductive activation of the anti-inflammatory drug sulfasalazine, and the metabolism of digoxin by E. lenta to an inactive dihydro metabolite exemplify how microbial enzymes can activate prodrugs, inactivate active compounds, or generate toxic metabolites (Currò, 2018; Haiser et al., 2014). In addition to straight bio-transformation, gut microbes influence host drug metabolizing enzymes and transporters through the production of signaling molecules like short-chain fatty acids (SCFAs), bile acid derivatives, and tryptophan catabolites, which can modulate nuclear receptors (e.g., pregnane X receptor (PXR), Farnesoid X Receptor (FXR), and aryl hydrocarbon receptor (AhR)) and alter hepatic cytochrome P450 expression (Liu et al., 2023; J. Wang & Zhou, 2025).

Beyond metabolism, the microbiome shapes pharmacodynamics by interacting with drug targets and host immune responses (Burke & Li, 2025). Microbial metabolites such as SCFAs, secondary bile acids, and indoles can modify receptor sensitivity, regulate inflammatory pathways, and influence the blood–brain barrier, thereby affecting the therapeutic outcomes of antibiotics, anticancer agents, immunotherapies, and neuroactive drugs (Anwer et al., 2025; Gasaly et al., 2021). For example, gut microbiota composition has been linked to the success of immune checkpoint inhibitors in cancer therapy, with specific taxa such as Bifidobacterium and Akkermansia enhancing antitumor immunity (X. Li et al., 2022; Simpson et al., 2023). These results underscore a bidirectional relationship in which drugs can also remodel the microbial ecosystem, sometimes leading to unintended consequences such as antibiotic resistance, or altered drug - drug interactions, and dysbiosis (Cusumano et al., 2025).

The clinical implications of these insights are profound. Inter-individual variability in drug response long attributed to genetic polymorphisms and environmental factors can now be partly explained by differences in microbial composition and function (Y. Li et al., 2016). Personalized pharmacotherapy may thus require integrating microbiome profiling with pharmacogenomics to predict drug efficacy and toxicity. Emerging strategies such as microbiota transplantation, targeted probiotics, prebiotics, and engineered microbial consortia hold promise for modulating the gut microbiome to optimize drug outcomes (Dash et al., 2024). Moreover, computational models and artificial intelligence are being leveraged to predict microbe–drug interactions and guide the rational design of microbiome-informed therapeutics (K. Wu et al., 2024). In this context, the microbiome is no longer a peripheral consideration but a central pharmacological determinant. Understanding its role in drug disposition and action offers a transformative framework for precision medicine, where therapeutic regimens are tailored not only to the patient's genome but also to their unique microbial landscape.

1.2. Nutritional Modulation as a Therapeutic Lever

Diet is one of the most powerful and modifiable factors shaping the composition and metabolic activity of the gut microbiome, thereby indirectly influencing drug pharmacokinetics and pharmacodynamics (Conlon & Bird, 2015). Nutritional interventions can act as therapeutic levers to enhance or mitigate microbiome-drug communications, offering a cost effective and patient-friendly strategy to optimize pharmacotherapy outcomes (Daoust et al., 2021). Unlike pharmacological agents that target specific receptors, dietary components exert broad systemic and local effects, providing a multifaceted means of modulating microbial ecology, host metabolism, and drug disposition (Lindell et al., 2022). While pharmacogenomics has advanced the personalization of drug therapy, genetic variation alone cannot completely explain interindividual differences in drug response (Evans & Johnson, 2001). Equally, diets rich in saturated fats and simple sugars favor bile-tolerant and pro-inflammatory species that may enhance drug toxicity. Probiotics (live beneficial microbes), prebiotics (fermentable substrates), and synbiotics (combinations) represent targeted nutritional tools capable of remodeling microbial communities to favor drug efficacy and reduce adverse effects (Habteweld & Asfaw, 2023).

The mechanistic basis for this influence lies in the ability of dietary components to serve as substrates for microbial fermentation, leading to the production of bioactive metabolites such as SCFAs, secondary bile acids, indoles, and phenolic compounds (L. S. Zhang & Davies, 2016). These metabolites can modulate host drug-metabolizing enzymes like cytochrome P450s, transporters such as P-glycoprotein, and nuclear receptors including PXR and FXR, ultimately affecting drug absorption, distribution, and clearance (Basińska-Ziobroń et al., 2025; Mohammed & Zalzala, 2025). At the same time, diet exerts selective pressure on microbial taxa, favoring species that enhance or diminish specific metabolic pathways. High fiber diets, for example, enrich SCFA-producing bacteria such as Faecalibacterium and Roseburia, which can regulate hepatic drug metabolism and improve intestinal barrier integrity, whereas high-protein diets may favor proteolytic species that produce metabolites capable of

altering drug activity or toxicity (Y. Zhao et al., 2025). Certain nutrients or bioactive compounds can also directly interact with drugs or alter gastric pH, influencing solubility and absorption (Chai et al., 2018). Poly-phenols such as quercetin and catechins can inhibit intestinal β-glucuronidase, potentially reducing the reactivation of drugs like irinotecan and mitigating gastrointestinal toxicity (Mahdy et al., 2023).

This dietary leverage opens therapeutic opportunities ranging from the use of prebiotics and fiber-enriched diets to promote beneficial microbes and improve gut barrier function, to probiotic-fortified foods that stabilize gut ecology and reduce side effects of antibiotics or chemotherapy (Holscher, 2017). Polyphenol-rich functional foods, including green tea catechins, resveratrol, and curcumin, exert prebiotic-like effects and modulate host xenobiotic metabolism (Plamada & Vodnar, 2022). Precision nutrition approaches that integrate metagenomic sequencing with dietary analytics are emerging, enabling the tailoring of dietary regimens to an individual's microbial profile to improve drug response, enhance immunotherapy efficacy, or reduce statin intolerance (Erikainen & Chan, 2019).

Nutritional modulation thus provides a non-invasive adjunct to pharmacological strategies, allowing clinicians to fine-tune drug outcomes by altering diet rather than drug structure or dose. Personalized dietary interventions can be incorporated into microbiome-informed precision medicine, where specific food-based therapies are co-designed with drug regimens to reduce adverse effects or enhance therapeutic benefit. Ongoing clinical trials are already investigating synbiotics, targeted dietary fibers, and fermented foods as co-therapies in cancer, metabolic diseases, and neuropsychiatric conditions. By strategically harnessing diet, researchers and clinicians can reshape the microbiome–drug interface to improve drug efficacy, reduce toxicity, and advance integrated nutrition–pharmacology interventions for precision medicine (Fig. 1).

This review aims to integrate mechanistic, preclinical, and clinical evidence on the interplay between the gut microbiome and drug efficacy, with a particular focus on nutritional interventions as modulators of this interface. We first summarize microbial pathways implicated in drug metabolism, including direct enzymatic transformations (reduction, hydrolysis, deconjugation) and indirect effects on host enzymes and transporters. Next, we discuss nutritional strategies ranging from fiber enrichment to probiotic and synbiotic formulations that can beneficially modulate these pathways. Finally, we explore clinical applications and emerging technologies, such as microbiome-based biomarkers and precision nutrition approaches, that promise to translate these insights into improved pharmacotherapy outcomes. By framing nutritional interventions as an accessible means to manipulate the microbiome–drug axis, we highlight an actionable frontier for precision medicine. Understanding how diet and targeted supplementation shape microbial drug metabolism will not only improve therapeutic efficacy but also reduce adverse drug reactions, a leading cause of morbidity and healthcare cost worldwide.

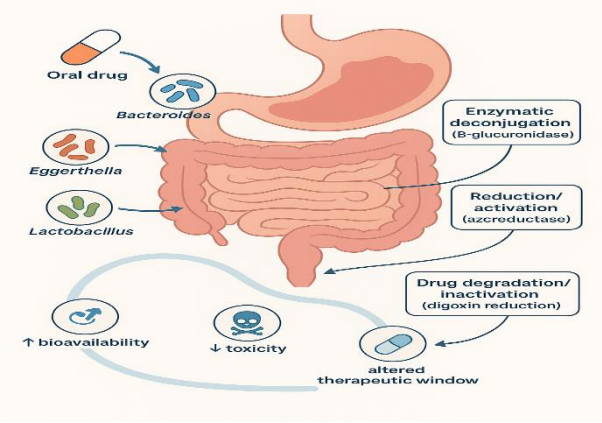

Figure 1. Conceptual Overview of Gut Microbiome–Drug Interactions

Mechanisms of Gut-Microbiome–Drug Interaction

The human gut microbiome plays a crucial role in modulating the pharmacokinetics and pharmacodynamics of orally administered drugs. This interaction occurs through multiple mechanisms, influencing drug absorption, metabolism, efficacy, and toxicity. Understanding these mechanisms is essential for optimizing therapeutic strategies and minimizing adverse effects. The gut microbiome influences drug efficacy through a multifaceted network of direct biochemical transformations, indirect host–microbe crosstalk, and immune-metabolic signaling. Understanding these pathways provides the mechanistic foundation for leveraging nutritional interventions to optimize pharmacotherapy (Fig. 2).

2.1. Direct Microbial Metabolism of Drugs

The gut microbiome exerts a profound influence on drug efficacy and safety through direct microbial metabolism, a process in which bacterial enzymes chemically transform drugs within the intestinal lumen (Feng et al., 2020; Pant et al., 2023). These transformations can result in activation, inactivation, or the production of toxic metabolites, significantly altering therapeutic outcomes. Common microbial reactions include reduction, hydrolysis, dehydroxylation, and deamination, reflecting the diverse enzymatic repertoire of gut bacteria (Krautkramer et al., 2021). Recently, Gao et al. (2022) reported that β-glucuronidase produced by certain bacterial species can hydrolyze drug-glucuronide conjugates, reversing host-mediated detoxification and reactivating compounds such as the chemotherapeutic irinotecan, which contributes to gastrointestinal toxicity. Similarly, nitro- and azo-containing drugs may undergo reductive cleavage by microbial reductases, producing metabolites with altered pharmacological activity (Ryan,

2017; Ryan et al., 2011). Hydrolytic reactions mediated by bacterial esterases and sulfatases can also convert prodrugs into their active forms or release free drugs from conjugated derivatives (Yang et al., 2011). Additionally, the microbial community can generate novel metabolites through reactions such as dehydroxylation and deamination, which may enhance or reduce drug potency (van Kessel et al., 2020; Venisetty & Ciddi, 2005). These direct metabolic processes are highly dependent on the composition and enzymatic capacity of an individual's gut microbiota, contributing to interpatient variability in drug response (Q. Zhao et al., 2023). Understanding the mechanisms and specific microbial enzymes involved in direct drug metabolism provides opportunities to predict and modulate therapeutic outcomes, for instance through targeted probiotic, prebiotic, or dietary interventions, thereby advancing precision pharmacotherapy (Feng et al., 2020; Shukla et al., 2024).

Several well-characterized examples highlight the clinical significance of direct microbial drug metabolism. The cardiac glycoside digoxin is partially inactivated by Eggerthella lenta through a specific cardiac glycoside reductase, reducing the drug's bioavailability and therapeutic effect (Haiser et al., 2014). The anti-inflammatory agent sulfasalazine, designed as a prodrug, requires bacterial azoreductases in the colon to cleave its azo bond and release the active 5-aminosalicylic acid, illustrating the beneficial aspect of microbial activation (Sousa et al., 2014). Similarly, the antidiabetic drug metformin undergoes microbial transformation that can influence its gastrointestinal tolerability and glucose-lowering efficacy (Szymczak-Pajor et al., 2025). Antibiotics such as chloramphenicol and rifampicin are susceptible to nitroreduction and deacetylation, respectively, by intestinal bacteria, potentially affecting drug potency and contributing to resistance development (Urban-Chmiel et al., 2022). Certain non-steroidal anti-inflammatory drugs (NSAIDs) are also reactivated in the gut following bacterial β-glucuronidase–mediated deconjugation, which can promote enterohepatic recirculation and increase mucosal injury (X. Wang et al., 2021). These examples underscore the bidirectional consequences of microbial metabolism either enabling therapeutic activation of prodrugs or generating toxic metabolites that compromise safety (J. Wang & Zhou, 2025). Recognizing these microbe–drug relationships is crucial for predicting interindividual variability, guiding dose adjustments, and designing interventions to manipulate the gut microbiome for improved pharmacological outcomes (Q. Zhao et al., 2023).

2.2. Indirect Modulation of Host Pharmacokinetics

The gut microbiome can influence drug disposition not only through direct chemical transformation but also by indirectly modulating host pharmacokinetics, thereby altering absorption, distribution, metabolism, and excretion (J. Zhang et al., 2018). Microbial metabolites such as short-chain fatty acids, secondary bile acids, and indole derivatives act as signaling molecules that regulate host gene expression involved in xenobiotic metabolism (Liu et al., 2023). These compounds can activate nuclear receptors, including the PXR, constitutive androstane receptor (CAR), and AhR, which in turn control the transcription of cytochrome P450 enzymes, UDP-glucuronosyltransferases, and drug transporters (Hakkola et al., 2018). Through this regulatory network, the microbiota can enhance or suppress hepatic and intestinal enzyme activity, thereby accelerating or slowing the metabolic clearance of numerous pharmaceuticals (Q. Zhao et al., 2023). In addition, microbial modulation of bile acid pools influences enterohepatic circulation and the solubilization of lipophilic drugs, indirectly affecting their systemic exposure. Changes in intestinal permeability and local inflammation, both shaped by microbiome composition, further impact drug absorption and first-pass metabolism (Pavlović et al., 2018). These effects are highly individualized, as differences in microbial diversity, dietary patterns, and antibiotic use can produce significant variability in the pharmacokinetic profiles of drugs that depend on host enzyme and transporter systems (Tsunoda et al., 2021). Even without direct metabolism, the microbiome can reshape the host's metabolic capacity (Tremaroli & Bäckhed, 2012). Understanding this indirect regulatory role of the gut microbiota is critical for predicting interpatient differences in drug efficacy and toxicity and offers new opportunities to optimize therapy through microbiome-targeted interventions.

2.2.1. Bile Acid Pool and Drug Solubility

Bile acids, synthesized from cholesterol in the liver and secreted into the intestine via bile, act as natural surfactants that emulsify dietary lipids and facilitate micelle formation (Šarenac & Mikov, 2018). The bile acid pool plays a pivotal role in determining the solubility, dissolution, and eventual absorption of orally administered drugs (Pavlović et al., 2018). Their amphipathic structure possessing both hydrophilic and hydrophobic domains enables them to solubilize lipophilic compounds, including poorly water-soluble drugs, within mixed micelles (Faustino et al., 2016). This process enhances the dissolution rate of drugs in the intestinal lumen and improves their bioavailability. The composition and size of the bile acid pool are not static; they are dynamically regulated by hepatic synthesis, intestinal reabsorption, and microbial metabolism (Larabi et al., 2023). Intestinal bacteria, particularly members of the genera Clostridium, Bacteroides, and Lactobacillus, deconjugate and transform primary bile acids (e.g., cholic acid, chenodeoxycholic acid) into secondary forms (e.g., deoxycholic acid, lithocholic acid) (Ridlon et al., 2006, Ridlon et al., 2020). These microbial conversions alter the hydrophobicity and critical micelle concentration of the bile acid pool, directly influencing the solubilization capacity for lipophilic drugs (Enright et al., 2017). For example, a

higher proportion of secondary bile acids typically increases micelle hydrophobicity, potentially improving solubilization of fat-soluble drugs but also risking precipitation if the balance between hydrophilic and hydrophobic bile acids is disrupted (Pavlović et al., 2018).

Dietary patterns and nutritional interventions can further modulate bile acid synthesis and microbial metabolism, thereby impacting drug solubility (P. Gao et al., 2024). High-fiber diets, for instance, bind bile acids and promote their fecal excretion, prompting hepatic synthesis of new bile acids and altering pool composition (Rowe & Winston, 2024). Conversely, diets rich in fat can increase bile acid secretion and favor a more hydrophobic bile acid profile, enhancing the micellar solubilization of certain lipophilic drugs (Faustino et al., 2016). Probiotic or prebiotic supplementation may shift gut microbial populations, influencing bile salt hydrolase activity and secondary bile acid formation, with downstream effects on the solubility and absorption of orally delivered pharmaceuticals (Enright et al., 2017). Clinically, disturbances in bile acid homeostasis such as those seen in liver disease, bile acid malabsorption, or gut dysbiosis can impair the solubility of bile-dependent drugs like cyclosporine, tacrolimus, and certain antifungal agents (Ticho et al., 2020). Understanding the interplay between the gut microbiome, bile acid pool, and drug solubility opens opportunities for tailored nutritional strategies to optimize pharmacotherapy outcomes. Interventions such as targeted prebiotics, bile acid sequestrants, or specific dietary fats may be leveraged to restore or enhance bile-mediated drug solubilization, ultimately improving drug efficacy and patient response.

2.2.2. Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids (SCFAs) are key microbial metabolites produced in the colon through the anaerobic fermentation of dietary fibers, resistant starches, and other indigestible carbohydrates (Disca et al., 2025; Topping & Clifton, 2001). The primary SCFAs acetate, propionate, and butyrate are generated in molar ratios of roughly 60:20:20, although these proportions vary with diet, microbiome composition, and intestinal transit time (Hernández et al., 2019). SCFAs serve as essential signaling molecules and energy sources, bridging the metabolic activities of the gut microbiota with host physiology (Den Besten et al., 2013). Their diverse functions extend beyond local gut effects, influencing drug metabolism, absorption, and pharmacodynamics. One of the primary ways SCFAs modulate drug efficacy is through the regulation of intestinal barrier integrity and luminal pH. By lowering the colonic pH, SCFAs enhance the ionization state and solubility of certain weakly basic drugs, which can increase their dissolution and passive diffusion across the epithelium (Dima et al., 2020). Butyrate, in particular, supports tight junction protein expression and strengthens the mucosal barrier, indirectly impacting drug permeability and protecting drugs from premature degradation (Knudsen et al., 2018). Moreover, SCFAs serve as energy substrates for colonocytes, supporting epithelial health and maintaining a physiological environment conducive to efficient drug absorption (Disca et al., 2025).

SCFAs also exert systemic effects that influence pharmacokinetics and pharmacodynamics. They act as ligands for G-protein-coupled receptors (e.g., GPR41, GPR43) and modulate histone deacetylase (HDAC) activity, thereby regulating gene expression in the liver and other tissues involved in drug metabolism (Liu et al., 2024). The propionate has been shown to influence hepatic gluconeogenesis and cytochrome P450 enzyme activity, potentially altering the biotransformation and clearance of drugs such as antidiabetics or statins (G. Y. Wang et al., 2023). Acetate can serve as a substrate for cholesterol and fatty acid synthesis, indirectly affecting bile acid production and the solubilization of lipophilic compounds (R. Wang et al., 2022).

Nutritional strategies play a critical role in shaping SCFA production. Diets rich in soluble fibers (e.g., inulin, pectin, β-glucans), resistant starch, and prebiotics promote the proliferation of SCFA-producing bacteria such as Faecalibacterium prausnitzii, Roseburia, and Bifidobacterium (Baky et al., 2024; de Oliveira et al., 2024). Increased SCFA output from these diets can improve the absorption and bioavailability of orally administered drugs while reducing interindividual variability in drug response (Wilkinson, 1997). Conversely, low-fiber, high-fat diets diminish SCFA production, potentially impairing drug solubility and metabolism. Supplementation with specific fibers, probiotics, or synbiotics offers a targeted approach to enhance SCFA generation and optimize pharmacotherapy outcomes (S. Zhang et al., 2021). Clinically, disruptions in SCFA production such as those occurring in inflammatory bowel disease, antibiotic-induced dysbiosis, or metabolic disorders can compromise drug efficacy by altering gut permeability, luminal pH, and host metabolic pathways (Cusumano et al., 2025; Duan et al., 2022). Understanding the dynamic interplay between SCFAs, the gut microbiome, and drug metabolism provides a foundation for designing dietary interventions aimed at improving therapeutic responses (Q. Zhao et al., 2023). Incorporating SCFA-promoting foods or supplements into patient care may help stabilize the gut environment, enhance drug solubility, and fine-tune pharmacokinetic profiles for better clinical outcomes.

2.2.3. Gut Barrier Integrity

Gut barrier integrity is a critical determinant of drug absorption, metabolism, and overall pharmacological efficacy. The intestinal barrier is a multi-layered defense system composed of the mucus layer, epithelial cells, tight junction proteins, immune components, and the resident microbiota (Guo et al., 2025). Its primary function is to regulate the selective permeability of

nutrients and xenobiotics, allowing beneficial compounds to pass into circulation while restricting the entry of pathogens and toxins (Patra et al., 2019). A healthy gut barrier ensures that orally administered drugs reach their intended absorption sites in a stable and predictable manner, whereas barrier dysfunction can lead to variable pharmacokinetics, altered bioavailability, and increased risk of adverse drug reactions (Dahlgren & Lennernäs, 2019).

The epithelial layer, formed by a single sheet of enterocytes, is sealed by tight junctions made up of proteins such as claudins, occludins, and zonula occludens. These tight junctions maintain paracellular permeability and control the passage of hydrophilic drugs that rely on passive diffusion (Slifer & Blikslager, 2020). Gut microbes play a central role in regulating these junctions. Commensal bacteria such as Lactobacillus and Bifidobacterium produce metabolites particularly SCFAs like butyrate that reinforce tight junction integrity by activating AMP-activated protein kinase (AMPK) and enhancing the expression of barrier-protective proteins (Peng et al., 2009). Conversely, dysbiosis, characterized by an overgrowth of pathobionts such as Escherichia coli or Clostridioides difficile, can trigger inflammation, disrupt tight junctions, and increase intestinal permeability ("leaky gut"), leading to uncontrolled drug absorption and unpredictable plasma concentrations (Petersen, 2022). A compromised gut barrier can significantly influence drug efficacy and toxicity. Increased permeability facilitates the translocation of lipopolysaccharides (LPS) and other microbial products into the bloodstream, activating immune pathways and hepatic cytochrome P450 enzymes that modify drug metabolism (Ghosh et al., 2020). This immune activation can either accelerate drug clearance or alter drug targets, reducing therapeutic effectiveness (Donald Harvey & Morgan, 2014). For example, in conditions such as inflammatory bowel disease, celiac disease, or chronic alcohol consumption, barrier dysfunction has been linked to altered pharmacokinetics of antibiotics, immunosuppressants, and antidiabetic medications (König et al., 2016).

Nutritional interventions are powerful modulators of gut barrier integrity and can indirectly influence pharmacotherapy outcomes. Diets rich in soluble fiber, resistant starch, and prebiotics promote the growth of SCFA-producing bacteria, increasing butyrate availability to strengthen epithelial junctions (Ali et al., 2022). Polyphenol-rich foods such as berries, green tea, and cocoa exert antioxidant and anti-inflammatory effects, helping preserve tight junction function (Kaulmann & Bohn, 2016). Fermented foods and probiotics (e.g., Lactobacillus rhamnosus, Bifidobacterium longum) enhance mucin production and reduce epithelial inflammation, creating a more stable environment for drug absorption (Sanz et al., 2008). Conversely, high-fat, high-sugar diets and excessive alcohol intake can disrupt the microbiota, deplete SCFAs, and impair barrier function, thereby reducing drug efficacy (Jamar et al., 2021). From a clinical perspective, preserving gut barrier integrity offers a promising strategy to improve pharmacotherapy outcomes. Personalized dietary plans incorporating prebiotics, probiotics, or postbiotics can help stabilize the intestinal environment, reduce inflammatory triggers, and ensure consistent drug absorption. Understanding the interplay between gut barrier health, microbial metabolites, and drug pharmacokinetics enables the development of nutrition-based adjunct therapies that enhance drug bioavailability, minimize variability in patient responses, and reduce the risk of side effects (Mousa et al., 2023).

2.3. Immune and Neuroendocrine Crosstalk

The gut microbiome exerts profound influence on both the immune and neuroendocrine systems, creating a bidirectional network that shapes drug efficacy, pharmacokinetics, and therapeutic outcomes (Tahri et al., 2025). This crosstalk often referred to as the gut immune brain axis integrates microbial metabolites, host immune signals, and neuroendocrine pathways to regulate systemic inflammation, stress responses, and metabolic homeostasis (Kasarello et al., 2023). Disruptions in this intricate communication can alter drug metabolism, modify target receptor sensitivity, and lead to interindividual variability in pharmacotherapy.

2.3.1. Microbiome–Immune Interactions and Drug Response

Gut microbes continuously interact with intestinal immune cells, shaping both innate and adaptive immunity. Commensal bacteria stimulate pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors, on epithelial and immune cells, promoting a balanced immune tone (Oviedo-Boyso et al., 2014). Microbial metabolites, including SCFAs like butyrate and propionate, regulate the differentiation of regulatory T cells (Tregs) and modulate cytokine production, dampening excessive inflammation (C. H. Kim et al., 2014). These immune-modulatory effects can directly influence drug efficacy. For example, anti-inflammatory microbial activity may enhance the action of immunosuppressants (e.g., corticosteroids) by reducing pro-inflammatory cytokines that otherwise accelerate drug clearance (Maseda et al., 2019). Conversely, chronic low-grade inflammation driven by gut dysbiosis can upregulate hepatic cytochrome P450 enzymes and efflux transporters such as P-glycoprotein, increasing drug metabolism and lowering therapeutic concentrations (Yin et al., 2023).

2.3.2. Neuroendocrine Regulation of Pharmacokinetics

The gut microbiome also communicates with the hypothalamic–pituitary–adrenal (HPA) axis and enteric nervous system through metabolites (e.g., SCFAs, tryptophan derivatives) and microbial neurochemicals (e.g., γ-aminobutyric acid, serotonin precursors) (Zhou

et al., 2025). Activation of the HPA axis under stress triggers the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, which can alter intestinal permeability, slow gastrointestinal transit, and affect drug absorption (Marwaha et al., 2025). Cortisol also regulates the expression of hepatic enzymes and transporters, modifying first-pass metabolism and drug clearance (K. Gao et al., 2020). Dysbiosis-driven changes in tryptophan metabolism can shift serotonin availability, indirectly influencing gut motility and the pharmacokinetics of drugs dependent on transit time, such as sustained-release formulations (Bosi et al., 2020).

2.3.3. Integrated Immune–Neuroendocrine Effects on Therapeutics

The convergence of immune and neuroendocrine signaling creates a feedback loop in which microbiota-driven inflammation affects neuroendocrine activity, and neuroendocrine hormones reciprocally shape immune responses (Park et al., 2025). This dynamic can significantly impact classes of drugs including antidepressants, antipsychotics, immunotherapies, and chemotherapeutics (Sun et al., 2016). For instance, heightened stress responses may decrease the efficacy of selective serotonin reuptake inhibitors (SSRIs) by altering serotonin metabolism, while immune activation can affect monoclonal antibody clearance (Vaswani et al., 2003).

2.3.4. Nutritional Modulation of Immune–Neuroendocrine Crosstalk

Dietary interventions provide a powerful means to regulate this axis and optimize drug outcomes. Prebiotics such as inulin, galactooligosaccharides, and resistant starch enhance SCFA production, reinforcing Treg activity and reducing pro-inflammatory cytokines (Guarino et al., 2020). Polyphenol-rich foods (e.g., green tea, berries, turmeric) exhibit antioxidant and anti-inflammatory properties, supporting immune balance and mitigating stress-induced HPA activation (Winiarska-Mieczan et al., 2023). Probiotic strains like *Lactobacillus rhamnosus* and *Bifidobacterium longum* have been shown to modulate cortisol levels and improve mood, indirectly stabilizing drug absorption and metabolism (Tette et al., 2022). Omega-3 fatty acids and fermented foods further strengthen gut–brain communication by reducing systemic inflammation and supporting neuronal signaling pathways (Zinkow et al., 2024).

2.3.5. Clinical Implications

Maintaining a balanced gut microbiome through targeted nutrition can help stabilize immune and neuroendocrine responses, reducing variability in drug absorption and metabolism (Wiertsema et al., 2021). Personalized dietary plans incorporating probiotics, prebiotics, and polyphenols may enhance therapeutic outcomes for patients receiving psychotropic medications, immunomodulators, or chronic disease therapies (Bubnov et al., 2015). By leveraging the gut–immune–brain axis, clinicians can use nutritional strategies to fine-tune drug efficacy, minimize adverse effects, and improve overall pharmacotherapy success.

2.4. Interindividual Variability

Interindividual variability in drug response is a critical challenge in clinical pharmacology, and the gut microbiome has emerged as a key determinant of these differences. While host genetics, age, sex, and lifestyle are well-recognized contributors, the composition and metabolic activity of the gut microbiota add an additional, highly dynamic layer of variability that can profoundly influence drug absorption, metabolism, and therapeutic efficacy (El Aidy et al., 2016). Each person harbors a unique microbial "fingerprint," shaped by diet, environment, antibiotic use, and health status, which in turn dictates the production of enzymes, metabolites, and signaling molecules that interact with drugs in distinct ways (Zaidi et al., 2023).

2.4.1. Microbial Composition and Metabolic Capacity

The relative abundance of specific bacterial taxa and their functional genes governs the metabolic transformations that orally administered drugs undergo before reaching systemic circulation (Zimmermann et al., 2019). Certain bacteria, such as *Eggerthella lenta*, *Bacteroides fragilis*, and *Clostridium scindens*, express reductases, hydrolases, or dehydroxylases that can activate, inactivate, or toxify drugs (Martinelli & Thiele, 2024). For example, *E. lenta* can inactivate the cardiac drug digoxin by reducing it to a non-therapeutic form, and the extent of this reaction varies depending on the strain's arginine-dependent operon expression (Haiser et al., 2014). Similarly, interindividual differences in microbial β-glucuronidase activity can influence the enterohepatic recycling of drugs like irinotecan, impacting both efficacy and toxicity (Parvez et al., 2021).

2.4.2. Host–Microbiome Interactions

Microbiome-driven variability does not occur in isolation but interacts with host factors to create complex pharmacokinetic profiles. Microbial metabolites such as SCFAs, secondary bile acids, and tryptophan derivatives can modulate host pathways including cytochrome P450 enzyme activity, transporter expression (e.g., P-glycoprotein), and immune signaling (Liu et al., 2022). These interactions affect drug absorption rates, distribution patterns, and clearance, leading to significant patient-to-patient differences even when identical doses are administered (Teo et al., 2015). For instance, variations in bile acid pools shaped by microbial activity can alter the solubility and bioavailability of lipophilic drugs, while SCFA production may regulate epigenetic

mechanisms that control hepatic enzyme expression (Pavlović et al., 2016).

2.4.3. Impact of Diet and Lifestyle

Dietary patterns strongly influence interindividual variability by shaping microbial composition and metabolic output. A high-fiber, plant-rich diet promotes SCFA-producing bacteria such as *Faecalibacterium prausnitzii*, enhancing gut barrier integrity and potentially improving drug absorption (Meiners et al., 2025). Conversely, high-fat or high-protein diets favor bile-tolerant microbes like *Bilophila wadsworthia*, altering bile acid profiles and drug solubility (Tong et al., 2021). Alcohol consumption, smoking, and circadian rhythm disruptions further modulate the microbiome, contributing to unpredictable drug responses (Forsyth et al., 2015).

2.4.4. Nutritional Strategies to Reduce Variability

Personalized nutrition represents a promising approach to mitigate microbiome-related differences in drug efficacy. Prebiotics, probiotics, and synbiotics can be tailored to increase beneficial microbial taxa and stabilize metabolic outputs relevant to specific drugs (Edwards et al., 2020). For example, targeted probiotic supplementation may reduce β-glucuronidase activity to lower irinotecan toxicity or enhance SCFA production to strengthen gut barrier function for improved oral drug absorption (Yue et al., 2021). Diets enriched in polyphenols, omega-3 fatty acids, or resistant starch may also help harmonize microbial functions and reduce interindividual pharmacokinetic variability.

2.4.5. Clinical Implications:

Understanding the contribution of the gut microbiome to interindividual variability allows for more precise pharmacotherapy. Microbiome profiling, combined with dietary assessment, can guide clinicians in selecting optimal drug dosages, identifying patients at risk for altered drug metabolism, and designing nutritional interventions to enhance therapeutic outcomes (Cammarota et al., 2020). As microbiome sequencing and metabolomic tools become more accessible, integrating microbiome-informed dietary strategies into precision medicine will be essential for reducing variability, improving drug efficacy, and minimizing adverse effects across diverse patient populations (Kashyap et al., 2017).

Table 1. Representative drugs affected by gut microbiome–mediated metabolism, key microbial species/enzymes involved, underlying mechanisms, and resulting clinical outcomes.

Drug	Microbial Species/Enzymes	Mechanism of Interaction	Clinical Outcomes	Reference
Digoxin	Eggerthella lenta (expresses cardiac glycoside reductase, cgr)	Microbial reduction of digoxin to inactive metabolites, decreasing systemic drug concentrations and therapeutic efficacy.	Reduced digoxin efficacy in patients with high E. lenta abundance; potential need for dose adjustment.	(Haiser et al., 2014)
Levodopa	Enterococcus faecalis (tyrosine decarboxylase)	Conversion of levodopa to dopamine in the gut lumen, and limiting systemic absorption	Lower peak plasma levodopa levels (Cmax); potential worsening of motor symptom control in Parkinson's disease patients	(Miyaue et al., 2025)
Metformin	Akkermansia muciniphila (mucin-degrading), SCFA-producing bacteria (e.g., Bifidobacterium, Faecalibacterium)	Alters gut microbiota composition, increases abundance of mucin-degrading and SCFA-producing bacteria, modulating bile acid metabolism and glucose homeostasis	Improved glycemic control, enhanced insulin sensitivity, and potential mitigation of gastrointestinal side effects	(De La Cuesta-Zuluaga et al., 2017)
Clopidogrel	Gut microbiota (specific species not detailed; study focused	Microbiota-related metabolites modulate	Variability in antiplatelet response;	(Amin et al., 2018)

		on microbiome-associated metabolites affecting drug response)	clopidogrel activation and platelet reactivity	identification of patients with high on-treatment platelet reactivity in coronary artery disease	
	Tamoxifen	Staphylococcus epidermidis, and Enterococcus faecalis	Tamoxifen metabolites inhibit growth of these resistant bacteria, potentially affecting gut microbiota composition	Potential modulation of gut microbial composition; antimicrobial effects may influence drug metabolism and host–microbiome interactions	(Miró-Canturri et al., 2021)
	Metformin	Akkermansia muciniphila (mucin-degrading), SCFA-producing bacteria (e.g., Bifidobacterium, Faecalibacterium)	Alters gut microbiota composition, increases abundance of mucin-degrading and SCFA-producing bacteria, modulating bile acid metabolism and glucose homeostasis	Improved glycemic control, enhanced insulin sensitivity, and potential mitigation of gastrointestinal side effects	(De La Cuesta-Zuluaga et al., 2017)
	Warfarin	Enterococcus spp., Escherichia-shigella spp.	Gut microbes influence vitamin K metabolism and modulate warfarin pharmacodynamics	Variability in anticoagulant response; altered International Normalized Ratio levels in heart valve replacement patients, affecting therapeutic efficacy and safety	(L. Wang et al., 2020)
	Cisplatin	Lactobacillus reuteri, Clostridium butyricum	Probiotic administration reconstitutes gut microbiota, enhances butyric acid production, and suppresses renal inflammation	Attenuation of cisplatin-induced renal damage; improved renal function and reduced systemic inflammation	(Hsiao et al., 2021)
n	Acetaminophen (Paracetamol)	Gut microbiota modulated by probiotic administration (Lactobacillus rhamnosus GG, Bifidobacterium longum, and mixed probiotic strains)	Probiotics lowered β-glucuronidase activity, decreasing deconjugation of acetaminophen-glucuronide and reducing enterohepatic recirculation	Lower Cmax and AUC with faster clearance in mice	(J. K. Kim et al., 2018)

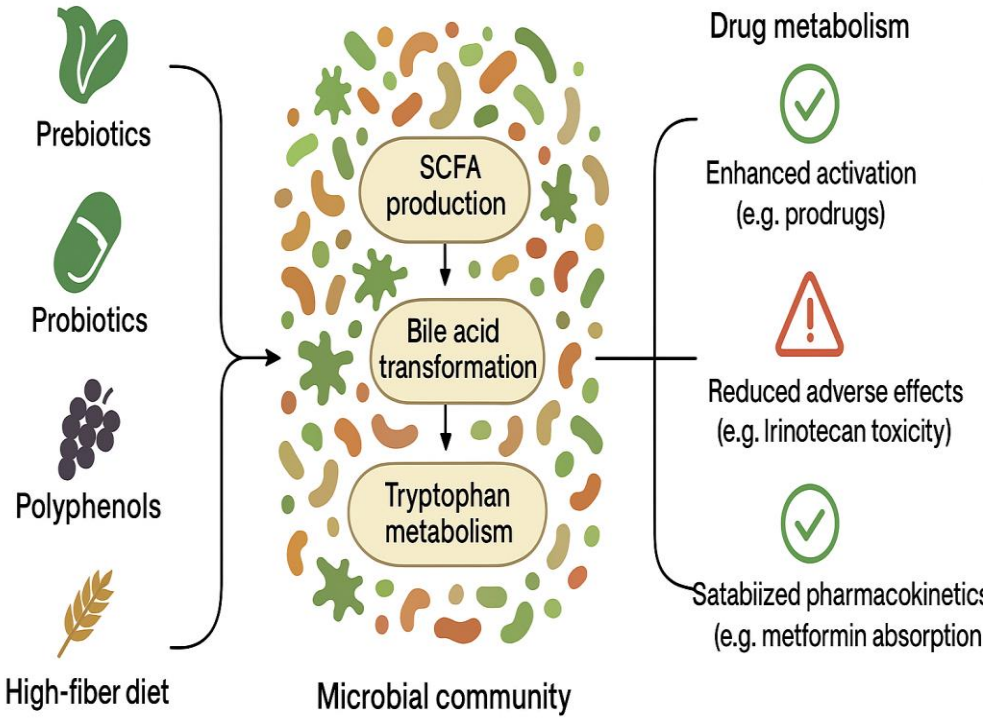

Fig. 2. Mechanistic Pathways of Nutritional Modulation

3. Nutritional Interventions to Modulate Microbiome Drug Interactions

Dietary strategies represent one of the most effective and non-invasive tools for modulating the gut microbiome to improve drug efficacy and safety (Jacobs et al., 2009). Targeted nutritional interventions can reshape microbial composition, enhance the production of beneficial metabolites, and stabilize intestinal functions that influence drug absorption, metabolism, and clearance (Shang et al., 2024). Below are key approaches that harness nutrition to optimize microbiome–drug interactions.

3.1. Prebiotics: Fueling Beneficial Microbes

Prebiotics are non-digestible dietary substrates such as inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), resistant starch, and certain polyphenols that selectively stimulate the growth and metabolic activity of beneficial gut bacteria (Guarino et al., 2020). By serving as fermentation fuel for taxa like Bifidobacterium and Faecalibacterium, prebiotics promote the production of SCFAs, which strengthen gut barrier integrity, lower luminal pH, and regulate host immune responses (Ashaolu et al., 2021). These effects create a more favorable environment for drug solubility and absorption, particularly for weakly basic drugs whose ionization is enhanced in slightly acidic conditions.

Prebiotics can also influence drug metabolism indirectly by modulating hepatic cytochrome P450 enzymes through SCFA-mediated signaling pathways (Pan & Umapathy, 2024). For example, increased butyrate levels have been linked to the suppression of pro-inflammatory cytokines that can upregulate drug-metabolizing enzymes, stabilizing pharmacokinetic profiles (Jourova et al., 2022). Incorporating fiber-rich foods such as chicory root, onions, garlic, and whole grains can thus reduce interindividual variability in drug response and improve therapeutic outcomes (Khalid et al., 2022).

3.2. Probiotics: Live Microbial Therapeutics

Probiotics are live microorganisms that confer health benefits when consumed in adequate amounts. Common strains include *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*, which can restore microbial balance, outcompete pathogenic species, and modulate drug–microbiome interactions (Prajapati et al., 2024). Probiotics produce enzymes and metabolites that can directly or indirectly influence drug metabolism (Abdul Manan, 2025). For example, certain *Lactobacillus* species produce β-glucosidase and bile salt hydrolase, affecting bile acid profiles and enhancing the solubilization of lipophilic drugs (O'Flaherty et al., 2018).

Probiotic supplementation has also been shown to mitigate antibiotic-associated dysbiosis, reducing the risk of altered drug pharmacokinetics and secondary infections (Dahiya & Nigam, 2023). Furthermore, probiotics may reduce intestinal

inflammation and strengthen epithelial tight junctions, promoting predictable drug absorption. Strain-specific formulations tailored to the pharmacological context for instance, *Bifidobacterium breve* for immunomodulatory drugs or *Lactobacillus rhamnosus* for psychotropic agents can improve therapeutic consistency (Bocchio et al., 2024).

3.3. Synbiotics and Postbiotics

Synbiotics combine prebiotics and probiotics to deliver synergistic effects, enhancing the colonization and activity of beneficial microbes while providing substrates for SCFA production (Markowiak & Ślizewska, 2017). This dual approach maximizes the microbiome's ability to regulate drug absorption and metabolism. Clinical studies have demonstrated that synbiotic interventions can reduce β-glucuronidase activity, thereby lowering the risk of drug reactivation and toxicity (e.g., irinotecan-associated gastrointestinal side effects) (Mahdy et al., 2023). Postbiotics, in contrast, refer to non-viable microbial components or metabolites such as SCFAs, bacteriocins, and extracellular polysaccharides that exert health benefits without requiring live bacteria (Aggarwal et al., 2022). Postbiotics can mimic the functional effects of a balanced microbiome, modulating gut pH, tightening epithelial junctions, and interacting with host receptors that influence cytochrome P450 expression (Smolinska et al., 2025). These properties make postbiotics particularly valuable for patients with compromised immunity or those unable to tolerate live probiotics.

3.4. Whole-Diet Approaches

Beyond targeted supplements, whole-diet strategies can induce broad and sustained changes in microbial ecology, thereby influencing drug responses (Tini et al., 2025). Diets rich in plant-based fibers, polyphenols, and fermented foods enhance microbial diversity and SCFA production, supporting stable pharmacokinetic profiles (Vila-Real et al., 2025). The Mediterranean diet, for example, promotes taxa such as *Roseburia* and *Akkermansia*, which reinforce gut barrier function and reduce systemic inflammation factors that can improve the bioavailability of orally administered drugs (Perrone & D'Angelo, 2025). Conversely, Western-style diets high in fat and refined sugars promote bile-tolerant microbes like *Bilophila wadsworthia*, which increase secondary bile acids and may unpredictably alter the solubility of lipophilic drugs (Y. Wu et al., 2019). Transitioning to a fiber-rich, antioxidant-rich diet can help normalize microbial metabolism, reduce inflammatory enzyme activation, and improve drug efficacy across a range of therapeutic classes, from statins to chemotherapeutics (Estarriaga-Navarro et al., 2025).

3.5. Precision Nutrition: Matching Diet to Microbial Genotype

Emerging advances in metagenomics and metabolomics enable the development of precision nutrition strategies tailored to an individual's microbial genotype and metabolic profile (de Toro-Martín et al., 2017). Microbiome sequencing can identify functional genes responsible for specific drug transformations, such as the cardiac glycoside reductase operon in *Eggerthella lenta*, which inactivates the cardiac drug digoxin (Haiser et al., 2013). By identifying individuals with high-risk microbial features, clinicians can design dietary plans to suppress or counteract these metabolic activities for instance, increasing dietary arginine intake to inhibit digoxin reduction. Precision nutrition also considers interindividual differences in SCFA production, bile acid metabolism, and transporter regulation, allowing for the selection of specific fibers, polyphenols, or probiotic strains that align with a patient's microbiome (Bianchetti et al., 2023). This personalized approach holds promise for minimizing adverse drug reactions, optimizing dosing regimens, and improving therapeutic consistency in conditions such as diabetes, cardiovascular disease, and cancer. Nutritional interventions offer a powerful, non-pharmacological means to modulate microbiome–drug interactions. Whether through prebiotics, probiotics, synbiotics, postbiotics, or precision dietary strategies, targeted nutrition can stabilize the gut environment, enhance drug solubility, and regulate host metabolic pathways (H. Y. Li et al., 2021). Integrating microbiome-informed dietary plans into clinical practice represents a critical step toward personalized pharmacotherapy, improving drug efficacy and reducing interindividual variability in therapeutic outcomes (Shukla et al., 2024).

CLINICAL EVIDENCE AND CASE STUDIES

Clinical evidence increasingly demonstrates that the gut microbiome significantly influences drug efficacy across multiple therapeutic areas. In oncology, baseline gut microbial diversity and composition have been linked to responses to immune checkpoint inhibitors (ICIs) (Araji et al., 2022). Responders often harbor taxa that enhance systemic and tumor-specific immune responses (Andrews et al., 2018). Interventional studies using fecal microbiota transplantation (FMT) from ICI responders into non-responders have, in some cases, restored therapeutic sensitivity, accompanied by increases in tumor-infiltrating CD8+ T cells and favorable immune gene expression signatures (Jamal et al., 2023). Mechanistically, microbial modulation of antigen presentation, T-cell priming, and SCFA- and bile-acid-mediated effects on the tumor microenvironment are implicated. These findings suggest microbiome profiling could become a predictive biomarker and guide adjunctive microbiome-targeted strategies in cancer therapy (Tong & Lou, 2025).

4.1. Oncology

Emerging clinical studies demonstrate that gut microbiome composition profoundly influences the efficacy of immune checkpoint inhibitors (ICIs), including PD-1/PD-L1 and CTLA-4 blockade. Patients with higher microbial diversity and enrichment of taxa such as Akkermansia muciniphila, Faecalibacterium prausnitzii, and certain Bifidobacterium species

exhibit improved antitumor responses and longer progression-free survival (Miller & Carson, 2020). Mechanistically, these microbes enhance antigen presentation, promote T-cell priming, and modulate systemic and tumor microenvironment immune activity through metabolites like SCFAs and secondary bile acids (Gomes et al., 2023). Interventional studies using fecal microbiota transplantation (FMT) from ICI responders into non-responders have led to partial restoration of therapeutic responses, including increases in tumor-infiltrating CD8+ T cells and favorable shifts in immune gene expression (Verhoef et al., 2023). These findings suggest that baseline microbiome profiling may serve as a predictive biomarker, and targeted microbiome modulation through diet, prebiotics, probiotics, or FMT represents a potential adjunct strategy to enhance oncology therapeutics.

4.2. Cardiovascular Pharmacotherapy

The microbiome can directly modify drug pharmacokinetics, as exemplified by digoxin inactivation. Eggerthella lenta strains expressing the cardiac glycoside reductase (cgr) operon metabolize digoxin into inactive derivatives, decreasing systemic drug concentrations and therapeutic efficacy (Ganamurali & Sabarathinam, 2025). Clinical studies integrating metagenomics and pharmacokinetic monitoring show that patients harboring high abundance of cgr-positive strains have lower circulating digoxin levels and diminished clinical response (Verdegaal & Goodman, 2024). Diet influences microbial gene expression; arginine-rich diets have been shown to inhibit cgr operon activity, thereby reducing microbial digoxin inactivation (Sharma et al., 2019). These observations underscore the importance of microbiome assessment and dietary modulation in optimizing cardiovascular pharmacotherapy and highlight potential precision nutrition strategies to mitigate microbiome-mediated drug interactions.

4.3. Metabolic Disorders

In type 2 diabetes, the gut microbiome plays a pivotal role in modulating the effects of metformin (Lee et al., 2021). Clinical investigations reveal that metformin alters gut microbial composition, increasing SCFA-producing bacteria such as *Bifidobacterium* and *Akkermansia*, while also affecting bile acid metabolism (Y. Wang et al., 2024). These microbiome shifts contribute to improved glucose homeostasis, enhanced insulin sensitivity, and modulation of gastrointestinal tolerance (Aron-Wisnewsky & Clement, 2014). Interindividual variability in microbial composition correlates with differences in glycemic response and side-effect profiles (Noce et al., 2019). Nutritional interventions such as high-fiber diets, prebiotics, and targeted probiotics can enhance the abundance of beneficial taxa, promoting SCFA production, improving gut barrier function, and potentially optimizing drug absorption and efficacy (Shang et al., 2024).

4.4. Neurological Disorders

Gut microbial metabolism significantly affects central nervous system drug bioavailability. In Parkinson's disease, *Enterococcus faecalis* expresses tyrosine decarboxylase (TyrDC) that converts levodopa into dopamine within the gut lumen, limiting systemic absorption and reducing availability for the brain (Miyaue et al., 2025). Clinical studies demonstrate that higher intestinal abundance of tyrDC genes correlates with lower plasma levodopa concentrations, greater motor fluctuations, and reduced clinical efficacy (Y. Zhang et al., 2022). Interventions aimed at reducing small intestinal bacterial overgrowth (SIBO) or selectively targeting decarboxylating microbes through diet, antibiotics, or probiotics have been proposed to improve pharmacokinetics and clinical outcomes (Mustafa et al., 2025). These findings highlight the need to consider gut microbial composition when optimizing therapy for CNS-active agents.

4.5. Antimicrobial Therapy

Broad-spectrum antibiotics have a profound impact on the gut microbiome, reducing diversity, depleting SCFA-producing taxa, and altering bile acid metabolism (W. Wang et al., 2025). Such disruptions can affect the absorption, metabolism, and systemic availability of concurrently or subsequently administered drugs, including chemotherapeutics, immunomodulators, and central nervous system medications (Donald Harvey & Morgan, 2014). Clinical evidence demonstrates that interventions such as fecal microbiota transplantation (FMT) or administration of defined microbiota-based therapeutics can restore microbial balance, re-establish metabolic functions, and normalize pharmacokinetic profiles (Zikou et al., 2024). Nutritional support through fiber-rich diets, prebiotics, and fermented foods further promotes recovery of microbial diversity and functional capacity, reducing interindividual variability in drug response and improving therapeutic outcomes after antibiotic-induced dysbiosis (Safarchi et al., 2025). Overall, these clinical observations highlight the critical role of the gut microbiome in shaping drug efficacy across diverse therapeutic areas. Understanding microbiome–drug interactions and implementing dietary or microbiome-targeted interventions can improve pharmacotherapy, reduce adverse effects, and minimize interindividual variability, paving the way for precision medicine approaches that integrate host–microbiome dynamics.

CHALLENGES, LIMITATIONS, AND FUTURE DIRECTIONS

Despite compelling mechanistic and clinical evidence, the integration of nutritional microbiome modulation into pharmacotherapy faces significant scientific, regulatory, and logistical challenges. Addressing these barriers is critical to translating proof-of-concept findings into routine clinical practice (Fig. 3).

5.1. Interindividual Variability

One of the primary challenges is the high degree of interindividual variability in microbiome composition and function. Each person harbors a unique microbial ecosystem shaped by genetics, diet, environment, age, medication history, and disease state (Karkman et al., 2017). This variability can lead to markedly different drug responses, even among patients receiving identical therapies. Predicting which individuals will benefit from microbiome-targeted interventions or nutritional modulation remains difficult without precise microbial profiling (De Filippis et al., 2018). Additionally, functional redundancy within the microbiome complicates predictions, as different microbial taxa may perform similar biochemical transformations affecting drug metabolism (Moya & Ferrer, 2016).

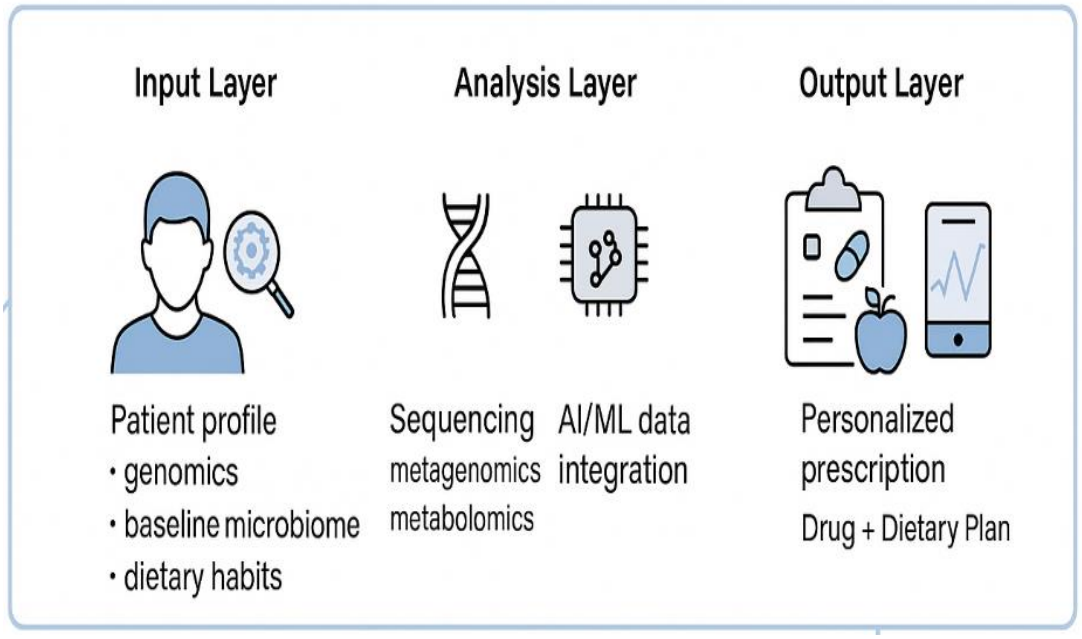

Figure 3. Future Landscape of Precision Nutrition–Pharmacotherapy

5.2. Temporal Instability

The gut microbiome is dynamic and influenced by transient factors such as diet, infection, antibiotic exposure, circadian rhythms, and lifestyle changes (Choi et al., 2021). These temporal fluctuations can alter microbial metabolic capacity and, consequently, drug pharmacokinetics and pharmacodynamics (Nguyen et al., 2021). Short-term interventions may therefore have variable effects depending on the baseline stability of the microbiome and the timing of drug administration relative to dietary or microbial changes (Leeming et al., 2019). Sustaining beneficial microbiome configurations over time presents a significant challenge for designing effective nutritional or microbial adjuncts to pharmacotherapy (Mimee et al., 2016).

5.3. Mechanistic Complexity

The mechanisms through which the microbiome modulates drug efficacy are multifactorial and highly interconnected (Song et al., 2023). Microbial metabolism can directly inactivate, activate, or transform drugs; influence bile acid composition; produce metabolites such as short-chain fatty acids that regulate host enzymes and transporters; and modulate immune and neuroendocrine pathways (S. Wang et al., 2024). Disentangling these overlapping effects to identify causative mechanisms is difficult, particularly given the bidirectional interactions between host and microbiome (Witherden et al., 2017). This complexity complicates the development of targeted interventions and the ability to predict drug outcomes based solely on microbial composition (Lopatkin & Collins, 2020).

5.4. Regulatory and Ethical Considerations

Translating microbiome-targeted interventions into clinical practice involves navigating regulatory and ethical challenges (Lim & Lim, 2025). Interventions such as fecal microbiota transplantation (FMT), live microbial therapeutics, or genetically engineered probiotics raise safety concerns, including the risk of pathogen transmission, unintended metabolic effects, and long-term ecological impacts on the host microbiome (Merrick et al., 2020). Regulatory frameworks for approving microbiome-based or nutrition-driven pharmacotherapy adjuncts are still evolving, and clear standards for safety, quality control, and clinical efficacy are needed (Rodriguez et al., 2025). Ethical considerations also arise regarding donor selection, patient consent, and equitable access to advanced microbiome therapies (Mikail et al., 2020).

5.5. Clinical Trial Design Challenges

Designing robust clinical trials to evaluate microbiome-mediated effects on drug efficacy is complex. Heterogeneity in patient microbiomes, diet, lifestyle, and concomitant medications introduces confounding variables (Schupack et al., 2022). Standardizing nutritional interventions, controlling for baseline microbiome differences, and defining appropriate endpoints (e.g., pharmacokinetic changes, clinical response, metabolite production) are challenging (Gilbert et al., 2025). Additionally, many microbiome-mediated effects are subtle, require large sample sizes to detect, and may vary over time, further complicating trial design and interpretation (Johnson et al., 2020).

5.6. Emerging Technologies and Future Directions

Advances in multi-omics, high-resolution metagenomics, metabolomics, and computational modeling are providing new tools to overcome these challenges. Functional characterization of microbial genes, real-time monitoring of metabolites, and predictive modeling of microbiome–drug interactions can inform precision nutrition and personalized pharmacotherapy strategies. Synthetic biology approaches, engineered probiotics, and microbiome-derived postbiotics offer targeted interventions to modulate drug metabolism safely. Future research should focus on integrating longitudinal microbiome data with host genomics, metabolomics, and clinical phenotyping to develop predictive frameworks. Additionally, establishing standardized guidelines for microbiome-targeted nutritional interventions, optimizing trial design, and addressing regulatory and ethical considerations will be critical to translating these insights into routine clinical practice.

CONCLUSION

The gut microbiome is now recognized as a key determinant of interindividual variability in drug response, influencing pharmacokinetics, pharmacodynamics, and therapeutic efficacy. Nutritional strategies ranging from prebiotic fibers and probiotics to polyphenol-rich diets and targeted dietary patterns offer a practical, non-invasive approach to reshape microbial composition and function, thereby optimizing pharmacotherapy outcomes. Evidence from mechanistic studies and early clinical trials demonstrates that diet can modulate microbial enzymes responsible for drug activation, deactivation, and enterohepatic recycling, ultimately improving the safety and effectiveness of a wide range of therapeutic agents. The successful integration of microbiome-informed nutrition into clinical practice will require key advancements, including personalized profiling through rapid and cost-effective metagenomics and metabolomics to match diets with drug responses. Reliable biomarkers of microbial drug-metabolizing capacity are needed to predict individual treatment outcomes. Clear regulatory frameworks must ensure the quality and consistency of microbiome-targeted foods and supplements, while adaptive clinical trial designs should incorporate flexible dietary interventions alongside standard pharmacotherapy. This holistic approach promises to reduce adverse effects, maximize efficacy, and pave the way for a new era of microbiome-aware, diet-integrated precision medicine.

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Venkatesan Karthick: Writing– original draft, Writing, review & editing, Conceptualization, Supervision. Suresh Sekar: Writing, review & editing, Conceptualization, and Data curation. Rajkumar Thamarai: Writing, review & editing, Data curation, Formal analysis, Investigation, Resources. Singamoorthy Amalraj: Writing, review & editing, Conceptualization, Supervision, Methodology.

Declarations

- Human and Animal Rights and Informed Consent
- This article does not contain any studies with human or animal subjects performed by any of the authors.
- Declaration of competing interest
- The authors declare that they have no competing interests.

Data Availability

This review is based on previously published data, which are cited throughout the manuscript. No new data were generated or analyzed in the course of this study. All data supporting the findings of this review are available from the cited literature.

REFERENCE

1. Abdul Manan, M. (2025). Progress in Probiotic Science: Prospects of Functional Probiotic-Based Foods and Beverages. International Journal of Food Science, 2025(1). https://doi.org/10.1155/ijfo/5567567
2. Aggarwal, S., Sabharwal, V., Kaushik, P., Joshi, A., Aayushi, A., & Suri, M. (2022). Postbiotics: From emerging concept to application. In Frontiers in Sustainable Food Systems (Vol. 6). https://doi.org/10.3389/fsufs.2022.887642

3. Ali, Q., Ma, S., La, S., Guo, Z., Liu, B., Gao, Z., Farooq, U., Wang, Z., Zhu, X., Cui, Y., Li, D., & Shi, Y. (2022). Microbial short-chain fatty acids: a bridge between dietary fibers and poultry gut health — A review. Animal Bioscience, 35(10). https://doi.org/10.5713/ab.21.0562
4. Amin, A. M., Sheau Chin, L., Teh, C. H., Mostafa, H., Mohamed Noor, D. A., Abdul Kader, M. A. S. K., Kah Hay, Y., & Ibrahim, B. (2018). Pharmacometabolomics analysis of plasma to phenotype clopidogrel high on treatment platelets reactivity in coronary artery disease patients. European Journal of Pharmaceutical Sciences, 117. https://doi.org/10.1016/j.ejps.2018.03.011
5. Andrews, M. C., Reuben, A., Gopalakrishnan, V., & Wargo, J. A. (2018). Concepts Collide: Genomic, immune, and microbial influences on the tumor microenvironment and response to cancer therapy. In Frontiers in Immunology (Vol. 9, Issue MAY). https://doi.org/10.3389/fimmu.2018.00946
6. Anwer, E. K. E., Ajagbe, M., Sherif, M., Musaibah, A. S., Mahmoud, S., ElBanbi, A., & Abdelnaser, A. (2025). Gut Microbiota Secondary Metabolites: Key Roles in GI Tract Cancers and Infectious Diseases. Biomedicines, 13(1), 100. https://doi.org/10.3390/biomedicines13010100
7. Araji, G., Maamari, J., Ahmad, F. A., Zareef, R., Chaftari, P., & Yeung, S. C. J. (2022). The Emerging Role of the Gut Microbiome in the Cancer Response to Immune Checkpoint Inhibitors: A Narrative Review. Journal of Immunotherapy and Precision Oncology, 5(1). https://doi.org/10.36401/JIPO-21-10
8. Aron-Wisnewsky, J., & Clement, K. (2014). The Effects of Gastrointestinal Surgery on Gut Microbiota: Potential Contribution to Improved Insulin Sensitivity. In Current Atherosclerosis Reports (Vol. 16, Issue 11). https://doi.org/10.1007/s11883-014-0454-9
9. Ashaolu, T. J., Ashaolu, J. O., & Adeyeye, S. A. O. (2021). Fermentation of prebiotics by human colonic microbiota in vitro and short-chain fatty acids production: a critical review. Journal of Applied Microbiology, 130(3). https://doi.org/10.1111/jam.14843
10. Baky, M. H., Salah, M., Ezzelarab, N., Shao, P., Elshahed, M. S., & Farag, M. A. (2024). Insoluble dietary fibers: structure, metabolism, interactions with human microbiome, and role in gut homeostasis. Critical Reviews in Food Science and Nutrition, 64(7), 1954–1968. https://doi.org/10.1080/10408398.2022.2119931
11. Basińska-Ziobroń, A., Danek, P. J., & Daniel, W. A. (2025). The effect of prolonged treatment with antipsychotic drugs on cytochrome P450 − drug metabolizing enzymes. Mechanisms of action and significance for pharmacotherapy. Expert Opinion on Drug Metabolism & Toxicology, 21(8), 921–937. https://doi.org/10.1080/17425255.2025.2517731
12. Bianchetti, G., De Maio, F., Abeltino, A., Serantoni, C., Riente, A., Santarelli, G., Sanguinetti, M., Delogu, G., Martinoli, R., Barbaresi, S., Spirito, M. De, & Maulucci, G. (2023). Unraveling the Gut Microbiome–Diet Connection: Exploring the Impact of Digital Precision and Personalized Nutrition on Microbiota Composition and Host Physiology. Nutrients, 15(18). https://doi.org/10.3390/nu15183931
13. Bocchio, F., Mancabelli, L., Milani, C., Lugli, G. A., Tarracchini, C., Longhi, G., Conto, F. De, Turroni, F., & Ventura, M. (2024). Compendium of Bifidobacterium -based probiotics: characteristics and therapeutic impact on human diseases. Microbiome Research Reports, 3(4). https://doi.org/10.20517/mrr.2024.52
14. Bosi, A., Banfi, D., Bistoletti, M., Giaroni, C., & Baj, A. (2020). Tryptophan Metabolites Along the Microbiota-Gut-Brain Axis: An Interkingdom Communication System Influencing the Gut in Health and Disease. In International Journal of Tryptophan Research (Vol. 13). https://doi.org/10.1177/1178646920928984
15. Bubnov, R. V., Spivak, M. Y., Lazarenko, L. M., Bomba, A., & Boyko, N. V. (2015). Probiotics and immunity: Provisional role for personalized diets and disease prevention. In EPMA Journal (Vol. 6, Issue 1). https://doi.org/10.1186/s13167-015-0036-0
16. Burke, K., & Li, Y. (2025). Impact of Gut Microbiota on Drug Metabolism and Absorption. Current Pharmacology Reports, 11(1), 49. https://doi.org/10.1007/s40495-025-00429-8
17. Cammarota, G., Ianiro, G., Ahern, A., Carbone, C., Temko, A., Claesson, M. J., Gasbarrini, A., & Tortora, G. (2020). Gut microbiome, big data and machine learning to promote precision medicine for cancer. Nature Reviews Gastroenterology and Hepatology, 17(10). https://doi.org/10.1038/s41575-020-0327-3
18. Chai, J., Jiang, P., Wang, P., Jiang, Y., Li, D., Bao, W., Liu, B., Liu, B., Zhao, L., Norde, W., Yuan, Q., Ren, F., & Li, Y. (2018). The intelligent delivery systems for bioactive compounds in foods: Physicochemical and physiological conditions, absorption mechanisms, obstacles and responsive strategies. In Trends in Food Science and Technology (Vol. 78). https://doi.org/10.1016/j.tifs.2018.06.003
19. Choi, H., Rao, M. C., & Chang, E. B. (2021). Gut microbiota as a transducer of dietary cues to regulate host circadian rhythms and metabolism. In Nature Reviews Gastroenterology and Hepatology (Vol. 18, Issue 10). https://doi.org/10.1038/s41575-021-00452-2
20. Conlon, M. A., & Bird, A. R. (2015). The impact of diet and lifestyle on gut microbiota and human health. In Nutrients (Vol. 7, Issue 1). https://doi.org/10.3390/nu7010017

21. Cullin, N., Azevedo Antunes, C., Straussman, R., Stein-Thoeringer, C. K., & Elinav, E. (2021). Microbiome and cancer. In Cancer Cell (Vol. 39, Issue 10). https://doi.org/10.1016/j.ccell.2021.08.006
22. Currò, D. (2018). The role of gut microbiota in the modulation of drug action: a focus on some clinically significant issues. In Expert Review of Clinical Pharmacology (Vol. 11, Issue 2). https://doi.org/10.1080/17512433.2018.1414598
23. Cusumano, G., Flores, G. A., Venanzoni, R., & Angelini, P. (2025). The Impact of Antibiotic Therapy on Intestinal Microbiota: Dysbiosis, Antibiotic Resistance, and Restoration Strategies. Antibiotics, 14(4), 371. https://doi.org/10.3390/antibiotics14040371
24. Dahiya, D., & Nigam, P. S. (2023). Antibiotic-Therapy-Induced Gut Dysbiosis Affecting Gut Microbiota—Brain Axis and Cognition: Restoration by Intake of Probiotics and Synbiotics. In International Journal of Molecular Sciences (Vol. 24, Issue 4). https://doi.org/10.3390/ijms24043074
25. Dahlgren, D., & Lennernäs, H. (2019). Intestinal permeability and drug absorption: predictive experimental, computational and in vivo approaches. In Pharmaceutics (Vol. 11, Issue 8). https://doi.org/10.3390/pharmaceutics11080411
26. Daoust, L., Pilon, G., & Marette, A. (2021). Perspective: Nutritional Strategies Targeting the Gut Microbiome to Mitigate COVID-19 Outcomes. In Advances in Nutrition (Vol. 12, Issue 4). https://doi.org/10.1093/advances/nmab031
27. Dash, B., Shireen, M., Pushpendra, Mr., Kumar, S., Goel, A., Semwal, P., & Rani, R. (2024). A Comprehensive Review: Pharmacogenomics and Personalized Medicine Customizing Drug Therapy Based on Individual Genetics Profiles. Chinese Journal of Applied Physiology, 40, e20240011. https://doi.org/10.62958/j.cjap.2024.011
28. De Filippis, F., Vitaglione, P., Cuomo, R., Canani, R. B., & Ercolini, D. (2018). Dietary interventions to modulate the gut microbiome-how far away are we from precision medicine. In Inflammatory Bowel Diseases (Vol. 24, Issue 10). https://doi.org/10.1093/ibd/izy080
29. De La Cuesta-Zuluaga, J., Mueller, N. T., Corrales-Agudelo, V., Velásquez-Mejía, E. P., Carmona, J. A., Abad, J. M., & Escobar, J. S. (2017). Metformin is associated with higher relative abundance of mucin-degrading akkermansia muciniphila and several short-chain fatty acid-producing microbiota in the gut. Diabetes Care, 40(1). https://doi.org/10.2337/dc16-1324
30. Den Besten, G., Van Eunen, K., Groen, A. K., Venema, K., Reijngoud, D. J., & Bakker, B. M. (2013). The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. In Journal of Lipid Research (Vol. 54, Issue 9). https://doi.org/10.1194/jlr.R036012
31. de Oliveira, D. P., Todorov, S. D., & Fabi, J. P. (2024). Exploring the Prebiotic Potentials of Hydrolyzed Pectins: Mechanisms of Action and Gut Microbiota Modulation. Nutrients, 16(21), 3689. https://doi.org/10.3390/nu16213689
32. de Toro-Martín, J., Arsenault, B. J., Després, J. P., & Vohl, M. C. (2017). Precision nutrition: A review of personalized nutritional approaches for the prevention and management of metabolic syndrome. In Nutrients (Vol. 9, Issue 8). https://doi.org/10.3390/nu9080913
33. Dima, C., Assadpour, E., Dima, S., & Jafari, S. M. (2020). Bioavailability of nutraceuticals: Role of the food matrix, processing conditions, the gastrointestinal tract, and nanodelivery systems. In Comprehensive Reviews in Food Science and Food Safety (Vol. 19, Issue 3). https://doi.org/10.1111/1541-4337.12547
34. Disca, V., Carrà, F., Stampini, M., Arlorio, M., & Locatelli, M. (2025). Treatments of food and food by-products to enhance gut microbiota short-chain fatty acids production. Food Bioscience, 72, 107435. https://doi.org/10.1016/j.fbio.2025.107435
35. Donald Harvey, R., & Morgan, E. T. (2014). Cancer, inflammation, and therapy: Effects on cytochrome P450-mediated drug metabolism and implications for novel immunotherapeutic agents. Clinical Pharmacology and Therapeutics, 96(4). https://doi.org/10.1038/clpt.2014.143
36. Duan, H., Yu, L., Tian, F., Zhai, Q., Fan, L., & Chen, W. (2022). Antibiotic-induced gut dysbiosis and barrier disruption and the potential protective strategies. In Critical Reviews in Food Science and Nutrition (Vol. 62, Issue 6). https://doi.org/10.1080/10408398.2020.1843396
37. Edwards, P. T., Kashyap, P. C., & Preidis, G. A. (2020). Microbiota on biotics: Probiotics, prebiotics, and synbiotics to optimize growth and metabolism. American Journal of Physiology - Gastrointestinal and Liver Physiology, 319(3). https://doi.org/10.1152/AJPGI.00028.2020
38. El Aidy, S., Stilling, R., Dinan, T. G., & Cryan, J. F. (2016). Microbiome to brain: Unravelling the multidirectional axes of communication. In Advances in Experimental Medicine and Biology (Vol. 874). https://doi.org/10.1007/978-3-319-20215-0_15
39. Enright, E. F., Joyce, S. A., Gahan, C. G. M., & Griffin, B. T. (2017). Impact of gut microbiota-mediated bile acid metabolism on the solubilization capacity of bile salt micelles and drug solubility. Molecular Pharmaceutics, 14(4). https://doi.org/10.1021/acs.molpharmaceut.6b01155
40. Erikainen, S., & Chan, S. (2019). Contested futures: envisioning "Personalized," "Stratified," and "Precision" medicine. New Genetics and Society, 38(3). https://doi.org/10.1080/14636778.2019.1637720

41. Estarriaga-Navarro, S., Valls, T., Plano, D., Sanmartín, C., & Goicoechea, N. (2025). Potential Application of Plant By-Products in Biomedicine: From Current Knowledge to Future Opportunities. Antioxidants, 14(8), 942. https://doi.org/10.3390/antiox14080942
42. Evans, W. E., & Johnson, J. A. (2001). Pharmacogenomics: The inherited basis for interindividual differences in drug response. In Annual Review of Genomics and Human Genetics (Vol. 2). https://doi.org/10.1146/annurev.genom.2.1.9
43. Faustino, C., Serafim, C., Rijo, P., & Reis, C. P. (2016). Bile acids and bile acid derivatives: use in drug delivery systems and as therapeutic agents. In Expert Opinion on Drug Delivery (Vol. 13, Issue 8). https://doi.org/10.1080/17425247.2016.1178233
44. Feng, W., Liu, J., Ao, H., Yue, S., & Peng, C. (2020). Targeting gut microbiota for precision medicine: Focusing on the efficacy and toxicity of drugs. In Theranostics (Vol. 10, Issue 24). https://doi.org/10.7150/thno.47289
45. Forsyth, C. B., Voigt, R. M., Burgess, H. J., Swanson, G. R., & Keshavarzian, A. (2015). Circadian rhythms, alcohol and gut interactions. In Alcohol (Vol. 49, Issue 4). https://doi.org/10.1016/j.alcohol.2014.07.021
46. Ganamurali, N., & Sabarathinam, S. (2025). Microbial modulation of digoxin bioavailability: A pharmacomicrobiome perspective on Eggerthella lenta's role in steroid-like drug metabolism and precision therapeutics. The Journal of Steroid Biochemistry and Molecular Biology, 252, 106792. https://doi.org/10.1016/j.jsbmb.2025.106792
47. Gao, K., Mu, C. L., Farzi, A., & Zhu, W. Y. (2020). Tryptophan Metabolism: A Link between the Gut Microbiota and Brain. In Advances in Nutrition (Vol. 11, Issue 3). https://doi.org/10.1093/advances/nmz127
48. Gao, P., Rinott, E., Dong, D., Mei, Z., Wang, F., Liu, Y., Kamer, O., Yaskolka Meir, A., Tuohy, K. M., Blüher, M., Stumvoll, M., Stampfer, M. J., Shai, I., & Wang, D. D. (2024). Gut microbial metabolism of bile acids modifies the effect of Mediterranean diet interventions on cardiometabolic risk in a randomized controlled trial. Gut Microbes, 16(1). https://doi.org/10.1080/19490976.2024.2426610
49. Gao, S., Sun, R., Singh, R., Yu So, S., Chan, C. T. Y., Savidge, T., & Hu, M. (2022). The role of gut microbial β-glucuronidase in drug disposition and development. Drug Discovery Today, 27(10), 103316. https://doi.org/10.1016/j.drudis.2022.07.001
50. Gasaly, N., de Vos, P., & Hermoso, M. A. (2021). Impact of Bacterial Metabolites on Gut Barrier Function and Host Immunity: A Focus on Bacterial Metabolism and Its Relevance for Intestinal Inflammation. In Frontiers in Immunology (Vol. 12). https://doi.org/10.3389/fimmu.2021.658354
51. Ghosh, S. S., Wang, J., Yannie, P. J., & Ghosh, S. (2020). Intestinal barrier dysfunction, LPS translocation, and disease development. Journal of the Endocrine Society, 4(2). https://doi.org/10.1210/jendso/bvz039
52. Gilbert, J. A., Azad, M. B., Bäckhed, F., Blaser, M. J., Byndloss, M., Chiu, C. Y., Chu, H., Dugas, L. R., Elinav, E., Gibbons, S. M., Gilbert, K. E., Henn, M. R., Ishaq, S. L., Ley, R. E., Lynch, S. V., Segal, E., Spector, T. D., Strandwitz, P., Suez, J., … Knight, R. (2025). Clinical translation of microbiome research. Nature Medicine, 31(4), 1099–1113. https://doi.org/10.1038/s41591-025-03615-9
53. Gomes, S., Rodrigues, A. C., Pazienza, V., & Preto, A. (2023). Modulation of the Tumor Microenvironment by Microbiota-Derived Short-Chain Fatty Acids: Impact in Colorectal Cancer Therapy. In International Journal of Molecular Sciences (Vol. 24, Issue 6). https://doi.org/10.3390/ijms24065069
54. Guarino, M. P. L., Altomare, A., Emerenziani, S., Di Rosa, C., Ribolsi, M., Balestrieri, P., Iovino, P., Rocchi, G., & Cicala, M. (2020). Mechanisms of action of prebiotics and their effects on gastro-intestinal disorders in adults. In Nutrients (Vol. 12, Issue 4). https://doi.org/10.3390/nu12041037
55. Guo, R., Jiang, C., Niu, Y., Niu, C., Chen, B., Yuan, Z., Hua, Y., & Wei, Y. (2025). ShenQiGan Extract Repairs Intestinal Barrier in Weaning-Stressed Piglets by Modulating Inflammatory Factors, Immunoglobulins, and Short-Chain Fatty Acids. Animals, 15(15), 2218. https://doi.org/10.3390/ani15152218
56. Habteweld, H. A., & Asfaw, T. (2023). Novel dietary approach with probiotics, prebiotics, and synbiotics to mitigate antimicrobial resistance and subsequent out marketplace of antimicrobial agents: A review. In Infection and Drug Resistance (Vol. 16). https://doi.org/10.2147/IDR.S413416
57. Haiser, H. J., Gootenberg, D. B., Chatman, K., Sirasani, G., Balskus, E. P., & Turnbaugh, P. J. (2013). Predicting and manipulating cardiac drug inactivation by the human gut bacterium Eggerthella lenta. Science, 341(6143). https://doi.org/10.1126/science.1235872
58. Haiser, H. J., Seim, K. L., Balskus, E. P., & Turnbaugh, P. J. (2014). Mechanistic insight into digoxin inactivation by Eggerthella lenta augments our understanding of its pharmacokinetics. Gut Microbes, 5(2). https://doi.org/10.4161/gmic.27915
59. Hakkola, J., Bernasconi, C., Coecke, S., Richert, L., Andersson, T. B., & Pelkonen, O. (2018). Cytochrome P450 Induction and Xeno-Sensing Receptors Pregnane X Receptor, Constitutive Androstane Receptor, Aryl Hydrocarbon Receptor and Peroxisome Proliferator-Activated Receptor α at the Crossroads of Toxicokinetics and Toxicodynamics. In Basic and Clinical Pharmacology and Toxicology (Vol. 123). https://doi.org/10.1111/bcpt.13004

60. Hernández, M. A. G., Canfora, E. E., Jocken, J. W. E., & Blaak, E. E. (2019). The short-chain fatty acid acetate in body weight control and insulin sensitivity. In Nutrients (Vol. 11, Issue 8). https://doi.org/10.3390/nu11081943
61. Hillman, E. T., Lu, H., Yao, T., & Nakatsu, C. H. (2017). Microbial ecology along the gastrointestinal tract. In Microbes and Environments (Vol. 32, Issue 4). https://doi.org/10.1264/jsme2.ME17017
62. Holscher, H. D. (2017). Dietary fiber and prebiotics and the gastrointestinal microbiota. In Gut Microbes (Vol. 8, Issue 2). https://doi.org/10.1080/19490976.2017.1290756
63. Hsiao, Y. P., Chen, H. L., Tsai, J. N., Lin, M. Y., Liao, J. W., Wei, M. S., Ko, J. L., & Ou, C. C. (2021). Administration of lactobacillus reuteri combined with clostridium butyricum attenuates cisplatin-induced renal damage by gut microbiota reconstitution, increasing butyric acid production, and suppressing renal inflammation. Nutrients, 13(8). https://doi.org/10.3390/nu13082792
64. Jacobs, D., Gaudier, E., Duynhoven, J., & Vaughan, E. (2009). Non-Digestible Food Ingredients, Colonic Microbiota and the Impact on Gut Health and Immunity: A Role for Metabolomics. Current Drug Metabolism, 10(1). https://doi.org/10.2174/138920009787048383
65. Jamal, R., Messaoudene, M., de Figueiredo, M., & Routy, B. (2023). Future indications and clinical management for fecal microbiota transplantation (FMT) in immuno-oncology. In Seminars in Immunology (Vol. 67). https://doi.org/10.1016/j.smim.2023.101754
66. Jamar, G., Ribeiro, D. A., & Pisani, L. P. (2021). High-fat or high-sugar diets as trigger inflammation in the microbiota-gut-brain axis. In Critical Reviews in Food Science and Nutrition (Vol. 61, Issue 5). https://doi.org/10.1080/10408398.2020.1747046
67. Jia, W., Li, H., Zhao, L., & Nicholson, J. K. (2008). Gut microbiota: A potential new territory for drug targeting. Nature Reviews Drug Discovery, 7(2). https://doi.org/10.1038/nrd2505
68. Johnson, A. J., Zheng, J. J., Kang, J. W., Saboe, A., Knights, D., & Zivkovic, A. M. (2020). A Guide to Diet-Microbiome Study Design. In Frontiers in Nutrition (Vol. 7). https://doi.org/10.3389/fnut.2020.00079
69. Jourova, L., Satka, S., Frybortova, V., Zapletalova, I., Anzenbacher, P., Anzenbacherova, E., Hermanova, P. P., Drabonova, B., Srutkova, D., Kozakova, H., & Hudcovic, T. (2022). Butyrate Treatment of DSS-Induced Ulcerative Colitis Affects the Hepatic Drug Metabolism in Mice. Frontiers in Pharmacology, 13. https://doi.org/10.3389/fphar.2022.936013
70. Karkman, A., Lehtimäki, J., & Ruokolainen, L. (2017). The ecology of human microbiota: dynamics and diversity in health and disease. In Annals of the New York Academy of Sciences (Vol. 1399, Issue 1). https://doi.org/10.1111/nyas.13326
71. Kasarello, K., Cudnoch-Jedrzejewska, A., & Czarzasta, K. (2023). Communication of gut microbiota and brain via immune and neuroendocrine signaling. In Frontiers in Microbiology (Vol. 14). https://doi.org/10.3389/fmicb.2023.1118529
72. Kashyap, P. C., Chia, N., Nelson, H., Segal, E., & Elinav, E. (2017). Microbiome at the Frontier of Personalized Medicine. In Mayo Clinic Proceedings (Vol. 92, Issue 12). https://doi.org/10.1016/j.mayocp.2017.10.004
73. Kaulmann, A., & Bohn, T. (2016). Bioactivity of Polyphenols: Preventive and Adjuvant Strategies toward Reducing Inflammatory Bowel Diseases - Promises, Perspectives, and Pitfalls. In Oxidative Medicine and Cellular Longevity (Vol. 2016). https://doi.org/10.1155/2016/9346470
74. Khalid, W., Arshad, M. S., Jabeen, A., Muhammad Anjum, F., Qaisrani, T. B., & Suleria, H. A. R. (2022). Fiber-enriched botanicals: A therapeutic tool against certain metabolic ailments. Food Science and Nutrition, 10(10). https://doi.org/10.1002/fsn3.2920
75. Kim, C. H., Park, J., & Kim, M. (2014). Gut Microbiota-Derived Short-Chain Fatty Acids, T Cells, and Inflammation. Immune Network, 14(6). https://doi.org/10.4110/in.2014.14.6.277
76. Kim, J. K., Choi, M. S., Jeong, J. J., Lim, S. M., Kim, I. S., Yoo, H. H., & Kim, D. H. (2018). Effect of probiotics on pharmacokinetics of orally administered acetaminophen in mice. Drug Metabolism and Disposition, 46(2). https://doi.org/10.1124/dmd.117.077222
77. Knudsen, K. E. B., Lærke, H. N., Hedemann, M. S., Nielsen, T. S., Ingerslev, A. K., Nielsen, D. S. G., Theil, P. K., Purup, S., Hald, S., Schioldan, A. G., Marco, M. L., Gregersen, S., & Hermansen, K. (2018). Impact of diet-modulated butyrate production on intestinal barrier function and inflammation. In Nutrients (Vol. 10, Issue 10). https://doi.org/10.3390/nu10101499
78. König, J., Wells, J., Cani, P. D., García-Ródenas, C. L., MacDonald, T., Mercenier, A., Whyte, J., Troost, F., & Brummer, R. J. (2016). Human intestinal barrier function in health and disease. Clinical and Translational Gastroenterology, 7(10). https://doi.org/10.1038/ctg.2016.54
79. Koppel, N., Rekdal, V. M., & Balskus, E. P. (2017). Chemical transformation of xenobiotics by the human gut microbiota. In Science (Vol. 356, Issue 6344). https://doi.org/10.1126/science.aag2770
80. Krautkramer, K. A., Fan, J., & Bäckhed, F. (2021). Gut microbial metabolites as multi-kingdom intermediates. In Nature Reviews Microbiology (Vol. 19, Issue 2). https://doi.org/10.1038/s41579-020-0438-4
81. Larabi, A. B., Masson, H. L. P., & Bäumler, A. J. (2023). Bile acids as modulators of gut microbiota composition and function. In Gut Microbes (Vol. 15,

Issue 1). https://doi.org/10.1080/19490976.2023.2172671
82. Lee, C. Bin, Chae, S. U., Jo, S. J., Jerng, U. M., & Bae, S. K. (2021). The relationship between the gut microbiome and metformin as a key for treating type 2 diabetes mellitus. In International Journal of Molecular Sciences (Vol. 22, Issue 7). https://doi.org/10.3390/ijms22073566
83. Leeming, E. R., Johnson, A. J., Spector, T. D., & Roy, C. I. L. (2019). Effect of diet on the gut microbiota: Rethinking intervention duration. In Nutrients (Vol. 11, Issue 12). https://doi.org/10.3390/nu11122862
84. Li, H. Y., Zhou, D. D., Gan, R. Y., Huang, S. Y., Zhao, C. N., Shang, A., Xu, X. Y., & Li, H. Bin. (2021). Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: A narrative review. In Nutrients (Vol. 13, Issue 9). https://doi.org/10.3390/nu13093211
85. Lim, E. C. N., & Lim, C. E. D. (2025). Microbiome-Targeted Therapies in Gastrointestinal Diseases: Clinical Evidence and Emerging Innovations. Acta Microbiologica Hellenica, 70(3), 36. https://doi.org/10.3390/amh70030036
86. Lindell, A. E., Zimmermann-Kogadeeva, M., & Patil, K. R. (2022). Multimodal interactions of drugs, natural compounds and pollutants with the gut microbiota. In Nature Reviews Microbiology (Vol. 20, Issue 7). https://doi.org/10.1038/s41579-022-00681-5
87. Liu, J., Chen, Q., & Su, R. (2024). Interplay of human gastrointestinal microbiota metabolites: Short-chain fatty acids and their correlation with Parkinson's disease. Medicine, 103(17), e37960. https://doi.org/10.1097/MD.0000000000037960
88. Liu, J., Tan, Y., Cheng, H., Zhang, D., Feng, W., & Peng, C. (2022). Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives. In Aging and Disease (Vol. 13, Issue 4). https://doi.org/10.14336/AD.2022.0104
89. Liu, J., Tian, R., Sun, C., Guo, Y., Dong, L., Li, Y., & Song, X. (2023). Microbial metabolites are involved in tumorigenesis and development by regulating immune responses. Frontiers in Immunology, 14. https://doi.org/10.3389/fimmu.2023.1290414
90. Li, X., Zhang, S., Guo, G., Han, J., & Yu, J. (2022). Gut microbiome in modulating immune checkpoint inhibitors. In eBioMedicine (Vol. 82). https://doi.org/10.1016/j.ebiom.2022.104163
91. Li, Y., Oosting, M., Deelen, P., Ricaño-Ponce, I., Smeekens, S., Jaeger, M., Matzaraki, V., Swertz, M. A., Xavier, R. J., Franke, L., Wijmenga, C., Joosten, L. A. B., Kumar, V., & Netea, M. G. (2016). Inter-individual variability and genetic influences on cytokine responses to bacteria and fungi. Nature Medicine, 22(8). https://doi.org/10.1038/nm.4139
92. Lopatkin, A. J., & Collins, J. J. (2020). Predictive biology: modelling, understanding and harnessing microbial complexity. In Nature Reviews Microbiology (Vol. 18, Issue 9). https://doi.org/10.1038/s41579-020-0372-5
93. Mahdy, M. S., Azmy, A. F., Dishisha, T., Mohamed, W. R., Ahmed, K. A., Hassan, A., Aidy, S. El, & El-Gendy, A. O. (2023). Irinotecan-gut microbiota interactions and the capability of probiotics to mitigate Irinotecan-associated toxicity. BMC Microbiology, 23(1). https://doi.org/10.1186/s12866-023-02791-3
94. Markowiak, P., & Ślizewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. In Nutrients (Vol. 9, Issue 9). https://doi.org/10.3390/nu9091021
95. Martinelli, F., & Thiele, I. (2024). Microbial metabolism marvels: a comprehensive review of microbial drug transformation capabilities. Gut Microbes, 16(1). https://doi.org/10.1080/19490976.2024.2387400
96. Marwaha, K., Cain, R., Asmis, K., Czaplinski, K., Holland, N., Mayer, D. C. G., & Chacon, J. (2025). Exploring the complex relationship between psychosocial stress and the gut microbiome: implications for inflammation and immune modulation. Journal of Applied Physiology, 138(2), 518–535. https://doi.org/10.1152/japplphysiol.00652.2024
97. Maseda, D., Zackular, J. P., Trindade, B., Kirk, L., Roxas, J. L., Rogers, L. M., Washington, M. K., Du, L., Koyama, T., Viswanathan, V. K., Vedantam, G., Schloss, P. D., Crofford, L. J., Skaar, E. P., & Aronoff, D. M. (2019). Nonsteroidal anti-inflammatory drugs alter the microbiota and exacerbate clostridium difficile colitis while dysregulating the inflammatory response. MBio, 10(1). https://doi.org/10.1128/mBio.02282-18
98. Meiners, F., Ortega-Matienzo, A., Fuellen, G., & Barrantes, I. (2025). Gut microbiome-mediated health effects of fiber and polyphenol-rich dietary interventions. Frontiers in Nutrition, 12. https://doi.org/10.3389/fnut.2025.1647740
99. Merrick, B., Allen, L., Masirah M Zain, N., Forbes, B., Shawcross, D. L., & Goldenberg, S. D. (2020). Regulation, risk and safety of Faecal Microbiota Transplant. In Infection Prevention in Practice (Vol. 2, Issue 3). https://doi.org/10.1016/j.infpip.2020.100069
100. Mikail, M., O'Doherty, K. C., Poutanen, S. M., & Hota, S. S. (2020). Ethical implications of recruiting universal stool donors for faecal microbiota transplantation. In The Lancet Infectious Diseases (Vol. 20, Issue 3). https://doi.org/10.1016/S1473-3099(19)30569-9
101. Miller, P. L., & Carson, T. L. (2020). Mechanisms and microbial influences on CTLA-4 and PD-1-based immunotherapy in the treatment of cancer: A narrative review. Gut Pathogens, 12(1). https://doi.org/10.1186/s13099-020-00381-6
102. Mimee, M., Citorik, R. J., & Lu, T. K. (2016). Microbiome therapeutics — Advances and

challenges. In Advanced Drug Delivery Reviews (Vol. 105). https://doi.org/10.1016/j.addr.2016.04.032

103. Miró-Canturri, A., Vila-Domínguez, A., Caretero-Ledesma, M., Ayerbe-Algaba, R., Pachón, J., Jiménez-Mejías, M. E., & Smani, Y. (2021). Repurposing of the Tamoxifen Metabolites to Treat Methicillin-Resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococcus faecalis Infections. Microbiology Spectrum, 9(2). https://doi.org/10.1128/spectrum.00403-21
104. Miyaue, N., Yamamoto, H., Liu, S., Ito, Y., Yamanishi, Y., Ando, R., Suzuki, Y., Mogi, M., & Nagai, M. (2025). Association of Enterococcus faecalis and tyrosine decarboxylase gene levels with levodopa pharmacokinetics in Parkinson's disease. Npj Parkinson's Disease, 11(1), 49. https://doi.org/10.1038/s41531-025-00903-6
105. Mohammed, T. A., & Zalzala, M. H. (2025). Impact of Nuclear Receptors on the Control of Bile Acid Metabolism and Synthesis: A Comprehensive Review. Current Pharmacology Reports, 11(1), 25. https://doi.org/10.1007/s40495-025-00404-3
106. Mousa, S., Sarfraz, M., & Mousa, W. K. (2023). The Interplay between Gut Microbiota and Oral Medications and Its Impact on Advancing Precision Medicine. In Metabolites (Vol. 13, Issue 5). https://doi.org/10.3390/metabo13050674
107. Moya, A., & Ferrer, M. (2016). Functional Redundancy-Induced Stability of Gut Microbiota Subjected to Disturbance. In Trends in Microbiology (Vol. 24, Issue 5). https://doi.org/10.1016/j.tim.2016.02.002
108. Mustafa, F., Noor, R., Murtaza, A., Kanwal, W., Kanwal, F., Kaleem, T., Munir, F., Binti Umar, R. A., Wan Taib, W. R., Krishnasamy, S., Chopra, S., & Chopra, H. (2025). Small Intestinal Bacterial Overgrowth (SIBO) - Prevention and Therapeutic Role of Nutrition, Prebiotics, Probiotics, and Prokinetics. Current Pharmaceutical Design, 31(42), 3354–3364. https://doi.org/10.2174/0113816128373584250407134451
109. Nguyen, J., Lara-Gutiérrez, J., & Stocker, R. (2021). Environmental fluctuations and their effects on microbial communities, populations and individuals. In FEMS Microbiology Reviews (Vol. 45, Issue 4). https://doi.org/10.1093/femsre/fuaa068
110. Noce, A., Marrone, G., Di Daniele, F., Ottaviani, E., Jones, G. W., Bernini, R., Romani, A., & Rovella, V. (2019). Impact of gut microbiota composition on onset and progression of chronic non-communicable diseases. Nutrients, 11(5). https://doi.org/10.3390/nu11051073
111. O'Flaherty, S., Briner Crawley, A., Theriot, C. M., & Barrangou, R. (2018). The Lactobacillus Bile Salt Hydrolase Repertoire Reveals Niche-Specific Adaptation . MSphere, 3(3). https://doi.org/10.1128/msphere.00140-18
112. Oviedo-Boyso, J., Bravo-Patiño, A., & Baizabal-Aguirre, V. M. (2014). Collaborative action of toll-like and nod-like receptors as modulators of the inflammatory response to pathogenic bacteria. In Mediators of Inflammation (Vol. 2014). https://doi.org/10.1155/2014/432785
113. Pan, I., & Umapathy, S. (2024). Probiotics an emerging therapeutic approach towards gut-brain-axis oriented chronic health issues induced by microplastics: A comprehensive review. Heliyon, 10(11), e32004. https://doi.org/10.1016/j.heliyon.2024.e32004
114. Pant, A., Maiti, T. K., Mahajan, D., & Das, B. (2023). Human Gut Microbiota and Drug Metabolism. In Microbial Ecology (Vol. 86, Issue 1). https://doi.org/10.1007/s00248-022-02081-x
115. Park, J. C., Chang, L., Kwon, H.-K., & Im, S.-H. (2025). Beyond the gut: decoding the gut–immune–brain axis in health and disease. Cellular & Molecular Immunology. https://doi.org/10.1038/s41423-025-01333-3
116. Parvez, M. M., Basit, A., Jariwala, P. B., Gaborik, Z., Kis, E., Heyward, S., Redinbo, M. R., & Prasad, B. (2021). Quantitative investigation of irinotecan metabolism, transport, and gut microbiome activation. Drug Metabolism and Disposition, 49(8). https://doi.org/10.1124/dmd.121.000476
117. Patra, A. K., Amasheh, S., & Aschenbach, J. R. (2019). Modulation of gastrointestinal barrier and nutrient transport function in farm animals by natural plant bioactive compounds–A comprehensive review. In Critical Reviews in Food Science and Nutrition (Vol. 59, Issue 20). https://doi.org/10.1080/10408398.2018.1486284
118. Pavlović, N., Goločorbin-Kon, S., Danić, M., Stanimirov, B., Al-Salami, H., Stankov, K., & Mikov, M. (2018). Bile acids and their derivatives as potential modifiers of drug release and pharmacokinetic profiles. Frontiers in Pharmacology, 9(NOV). https://doi.org/10.3389/fphar.2018.01283
119. Pavlović, N., Stanimirov, B., & Mikov, M. (2016). Bile Acids as Novel Pharmacological Agents: the Interplay between Gene Polymorphisms, Epigenetic Factors and Drug Response. Current Pharmaceutical Design, 22(999). https://doi.org/10.2174/1381612822666161006161409
120. Peng, L., Li, Z. R., Green, R. S., Holzman, I. R., & Lin, J. (2009). Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. Journal of Nutrition, 139(9). https://doi.org/10.3945/jn.109.104638
121. Pereira De Sousa, I., & Bernkop-Schnürch, A. (2014). Pre-systemic metabolism of orally administered drugs and strategies to overcome it. In Journal of Controlled Release (Vol. 192). https://doi.org/10.1016/j.jconrel.2014.08.004

122. Perrone, P., & D'Angelo, S. (2025). Gut Microbiota Modulation Through Mediterranean Diet Foods: Implications for Human Health. Nutrients, 17(6), 948. https://doi.org/10.3390/nu17060948
123. Petersen, A. M. (2022). Gastrointestinal dysbiosis and Escherichia coli pathobionts in inflammatory bowel diseases. APMIS, 130(S144). https://doi.org/10.1111/apm.13256
124. Plamada, D., & Vodnar, D. C. (2022). Polyphenols—gut microbiota interrelationship: A transition to a new generation of prebiotics. In Nutrients (Vol. 14, Issue 1). https://doi.org/10.3390/nu14010137
125. Prajapati, K., Bisani, K., Prajapati, H., Prajapati, S., Agrawal, D., Singh, S., Saraf, M., & Goswami, D. (2024). Advances in probiotics research: mechanisms of action, health benefits, and limitations in applications. Systems Microbiology and Biomanufacturing, 4(2), 386–406. https://doi.org/10.1007/s43393-023-00208-w
126. Ridlon, J. M., Devendran, S., Alves, J. M., Doden, H., Wolf, P. G., Pereira, G. V., Ly, L., Volland, A., Takei, H., Nittono, H., Murai, T., Kurosawa, T., Chlipala, G. E., Green, S. J., Hernandez, A. G., Fields, C. J., Wright, C. L., Kakiyama, G., Cann, I., … Gaskins, H. R. (2020). The 'in vivo lifestyle' of bile acid 7α-dehydroxylating bacteria: comparative genomics, metatranscriptomic, and bile acid metabolomics analysis of a defined microbial community in gnotobiotic mice. Gut Microbes, 11(3). https://doi.org/10.1080/19490976.2019.1618173
127. Ridlon, J. M., Kang, D. J., & Hylemon, P. B. (2006). Bile salt biotransformations by human intestinal bacteria. In Journal of Lipid Research (Vol. 47, Issue 2). https://doi.org/10.1194/jlr.R500013-JLR200
128. Rodriguez, J., Cordaillat-Simmons, M., Pot, B., & Druart, C. (2025). The regulatory framework for microbiome-based therapies: insights into European regulatory developments. Npj Biofilms and Microbiomes, 11(1), 53. https://doi.org/10.1038/s41522-025-00683-0
129. Rowe, J. C., & Winston, J. A. (2024). Collaborative Metabolism: Gut Microbes Play a Key Role in Canine and Feline Bile Acid Metabolism. Veterinary Sciences, 11(2), 94. https://doi.org/10.3390/vetsci11020094
130. Ryan, A. (2017). Azoreductases in drug metabolism. In British Journal of Pharmacology (Vol. 174, Issue 14). https://doi.org/10.1111/bph.13571
131. Ryan, A., Kaplan, E., Laurieri, N., Lowe, E., & Sim, E. (2011). Activation of nitrofurazone by azoreductases: Multiple activities in one enzyme. Scientific Reports, 1. https://doi.org/10.1038/srep00063
132. Safarchi, A., Al-Qadami, G., Tran, C. D., & Conlon, M. (2025). Understanding dysbiosis and resilience in the human gut microbiome: biomarkers, interventions, and challenges. Frontiers in Microbiology, 16. https://doi.org/10.3389/fmicb.2025.1559521
133. Sanz, Y., Nadal, I., & Sanchez, E. (2008). Probiotics as Drugs Against Human Gastrointestinal Infections. Recent Patents on Anti-Infective Drug Discovery, 2(2). https://doi.org/10.2174/157489107780832596
134. Šarenac, T. M., & Mikov, M. (2018). Bile acid synthesis: From nature to the chemical modification and synthesis and their applications as drugs and nutrients. In Frontiers in Pharmacology (Vol. 9, Issue SEP). https://doi.org/10.3389/fphar.2018.00939
135. Schupack, D. A., Mars, R. A. T., Voelker, D. H., Abeykoon, J. P., & Kashyap, P. C. (2022). The promise of the gut microbiome as part of individualized treatment strategies. In Nature Reviews Gastroenterology and Hepatology (Vol. 19, Issue 1). https://doi.org/10.1038/s41575-021-00499-1
136. Shang, Z., Pai, L., & Patil, S. (2024). Unveiling the dynamics of gut microbial interactions: a review of dietary impact and precision nutrition in gastrointestinal health. Frontiers in Nutrition, 11. https://doi.org/10.3389/fnut.2024.1395664
137. Sharma, A., Buschmann, M. M., & Gilbert, J. A. (2019). Pharmacomicrobiomics: The Holy Grail to Variability in Drug Response? In Clinical Pharmacology and Therapeutics (Vol. 106, Issue 2). https://doi.org/10.1002/cpt.1437
138. Shukla, V., Singh, S., Verma, S., Verma, S., Rizvi, A. A., & Abbas, M. (2024). Targeting the microbiome to improve human health with the approach of personalized medicine: Latest aspects and current updates. Clinical Nutrition ESPEN, 63, 813–820. https://doi.org/10.1016/j.clnesp.2024.08.005
139. Simpson, R. C., Shanahan, E. R., Scolyer, R. A., & Long, G. V. (2023). Towards modulating the gut microbiota to enhance the efficacy of immune-checkpoint inhibitors. In Nature Reviews Clinical Oncology (Vol. 20, Issue 10). https://doi.org/10.1038/s41571-023-00803-9
140. Slifer, Z. M., & Blikslager, A. T. (2020). The integral role of tight junction proteins in the repair of injured intestinal epithelium. In International Journal of Molecular Sciences (Vol. 21, Issue 3). https://doi.org/10.3390/ijms21030972
141. Smolinska, S., Popescu, F.-D., & Zemelka-Wiacek, M. (2025). A Review of the Influence of Prebiotics, Probiotics, Synbiotics, and Postbiotics on the Human Gut Microbiome and Intestinal Integrity. Journal of Clinical Medicine, 14(11), 3673. https://doi.org/10.3390/jcm14113673
142. Song, S., Fan, M., Wen, X., Shi, X., Lou, Y., He, Z., Wen, C., & Shao, T. (2023). Integrated network pharmacology and gut microbiome analysis to reveal the mechanism of Qu-Zhuo-Tong-Bi decoction against hyperuricemia and gout. Journal

of Ethnopharmacology, 316. https://doi.org/10.1016/j.jep.2023.116736

143. Sousa, T., Yadav, V., Zann, V., Borde, A., Abrahamsson, B., & Basit, A. W. (2014). On the Colonic Bacterial Metabolism of Azo-Bonded Prodrugsof 5-Aminosalicylic Acid. Journal of Pharmaceutical Sciences, 103(10), 3171–3175. https://doi.org/10.1002/jps.24103
144. Sun, Y., Narayan, V. A., & Wittenberg, G. M. (2016). Side effect profile similarities shared between antidepressants and immune-modulators reveal potential novel targets for treating major depressive disorders. BMC Pharmacology and Toxicology, 17(1). https://doi.org/10.1186/s40360-016-0090-9
145. Szymczak-Pajor, I., Drzewoski, J., Kozłowska, M., Krekora, J., & Śliwińska, A. (2025). The Gut Microbiota-Related Antihyperglycemic Effect of Metformin. Pharmaceuticals, 18(1), 55. https://doi.org/10.3390/ph18010055
146. Tahri, A., Niccolai, E., & Amedei, A. (2025). Neurosteroids, Microbiota, and Neuroinflammation: Mechanistic Insights and Therapeutic Perspectives. International Journal of Molecular Sciences, 26(14), 7023. https://doi.org/10.3390/ijms26147023
147. Tan, J., Fu, B., Zhao, X., & Ye, L. (2024). Novel Techniques and Models for Studying the Role of the Gut Microbiota in Drug Metabolism. In European Journal of Drug Metabolism and Pharmacokinetics (Vol. 49, Issue 2). https://doi.org/10.1007/s13318-023-00874-0
148. Teo, Y. L., Ho, H. K., & Chan, A. (2015). Metabolism-related pharmacokinetic drug-drug interactions with tyrosine kinase inhibitors: Current understanding, challenges and recommendations. British Journal of Clinical Pharmacology, 79(2). https://doi.org/10.1111/bcp.12496
149. Tette, F. M., Kwofie, S. K., & Wilson, M. D. (2022). Therapeutic Anti-Depressant Potential of Microbial GABA Produced by Lactobacillus rhamnosus Strains for GABAergic Signaling Restoration and Inhibition of Addiction-Induced HPA Axis Hyperactivity. In Current Issues in Molecular Biology (Vol. 44, Issue 4). https://doi.org/10.3390/cimb44040096
150. Ticho, A. L., Malhotra, P., Dudeja, P. K., Gill, R. K., & Alrefai, W. A. (2020). Intestinal absorption of bile acids in health and disease. Comprehensive Physiology, 10(1). https://doi.org/10.1002/cphy.c190007
151. Tini, S., Baima, J., Pigni, S., Antoniotti, V., Caputo, M., De Palma, E., Cerbone, L., Grosso, F., La Vecchia, M., Bona, E., & Prodam, F. (2025). The Microbiota–Diet–Immunity Axis in Cancer Care: From Prevention to Treatment Modulation and Survivorship. Nutrients, 17(17), 2898. https://doi.org/10.3390/nu17172898
152. Tong, Y., Gao, H., Qi, Q., Liu, X., Li, J., Gao, J., Li, P., Wang, Y., Du, L., & Wang, C. (2021). High fat diet, gut microbiome and gastrointestinal cancer. In Theranostics (Vol. 11, Issue 12). https://doi.org/10.7150/thno.56157
153. Tong, Y., & Lou, X. (2025). Interplay between bile acids, gut microbiota, and the tumor immune microenvironment: mechanistic insights and therapeutic strategies. Frontiers in Immunology, 16. https://doi.org/10.3389/fimmu.2025.1638352
154. Topping, D. L., & Clifton, P. M. (2001). Short-chain fatty acids and human colonic function: Roles of resistant starch and nonstarch polysaccharides. In Physiological Reviews (Vol. 81, Issue 3). https://doi.org/10.1152/physrev.2001.81.3.1031
155. Torrent Rodríguez, A., Font i Barceló, A., Barrantes González, M., Echeverria Esnal, D., Soy Muner, D., Martínez, J. A., & Tuset Creus, M. (2024). Clinically important pharmacokinetic drug-drug interactions with antibacterial agents. Revista Española de Quimioterapia, 37(4), 299–322. https://doi.org/10.37201/req/037.2024
156. Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. In Nature (Vol. 489, Issue 7415). https://doi.org/10.1038/nature11552
157. Tsunoda, S. M., Gonzales, C., Jarmusch, A. K., Momper, J. D., & Ma, J. D. (2021). Contribution of the Gut Microbiome to Drug Disposition, Pharmacokinetic and Pharmacodynamic Variability. In Clinical Pharmacokinetics (Vol. 60, Issue 8). https://doi.org/10.1007/s40262-021-01032-y
158. Urban-Chmiel, R., Marek, A., Stępień-Pyśniak, D., Wieczorek, K., Dec, M., Nowaczek, A., & Osek, J. (2022). Antibiotic Resistance in Bacteria—A Review. In Antibiotics (Vol. 11, Issue 8). https://doi.org/10.3390/antibiotics11081079
159. van Kessel, S. P., de Jong, H. R., Winkel, S. L., van Leeuwen, S. S., Nelemans, S. A., Permentier, H., Keshavarzian, A., & El Aidy, S. (2020). Gut bacterial deamination of residual levodopa medication for Parkinson's disease. BMC Biology, 18(1). https://doi.org/10.1186/s12915-020-00876-3
160. Vaswani, M., Linda, F. K., & Ramesh, S. (2003). Role of selective serotonin reuptake inhibitors in psychiatric disorders: A comprehensive review. In Progress in Neuro-Psychopharmacology and Biological Psychiatry (Vol. 27, Issue 1). https://doi.org/10.1016/S0278-5846(02)00338-X
161. Venisetty, R., & Ciddi, V. (2005). Application of Microbial Biotransformation for the New Drug Discovery Using Natural Drugs as Substrates. Current Pharmaceutical Biotechnology, 4(3). https://doi.org/10.2174/1389201033489847
162. Verdegaal, A. A., & Goodman, A. L. (2024). Integrating the gut microbiome and pharmacology. Science Translational Medicine, 16(732). https://doi.org/10.1126/scitranslmed.adg8357
163. Verhoef, J. I., Klont, E., van Overveld, F. J., & Rijkers, G. T. (2023). The long and winding road of faecal microbiota transplants to targeted intervention for improvement of immune checkpoint inhibition therapy. In Expert Review of

Anticancer Therapy (Vol. 23, Issue 11). https://doi.org/10.1080/14737140.2023.2262765

164. Vila-Real, C., Costa, C., Pimenta-Martins, A., Mbugua, S., Hagrétou, S.-L., Katina, K., Maina, N. H., Pinto, E., & Gomes, A. M. P. (2025). Novel Fermented Plant-Based Functional Beverage: Biological Potential and Impact on the Human Gut Microbiota. Foods, 14(3), 433. https://doi.org/10.3390/foods14030433
165. Wang, G. Y., Qin, S. L., Zheng, Y. N., Geng, H. J., Chen, L., Yao, J. H., & Deng, L. (2023). Propionate promotes gluconeogenesis by regulating mechanistic target of rapamycin (mTOR) pathway in calf hepatocytes. Animal Nutrition, 15. https://doi.org/10.1016/j.aninu.2023.07.001
166. Wang, J., & Zhou, T. (2025). Unveiling gut microbiota's role: Bidirectional regulation of drug transport for improved safety. Medicinal Research Reviews, 45(1), 311–343. https://doi.org/10.1002/med.22077
167. Wang, L., Liu, L., Liu, X., Xiang, M., Zhou, L., Huang, C., Shen, Z., & Miao, L. (2020). The gut microbes, Enterococcus and Escherichia-Shigella, affect the responses of heart valve replacement patients to the anticoagulant warfarin. Pharmacological Research, 159. https://doi.org/10.1016/j.phrs.2020.104979
168. Wang, R., Fan, X., Lu, Y., Chen, D., Zhao, Y., & Qi, K. (2022). Dietary acetic acid suppress high-fat diet-induced obesity in mice by altering taurine conjugated bile acids metabolism. Current Research in Food Science, 5. https://doi.org/10.1016/j.crfs.2022.10.021
169. Wang, S., Ju, D., & Zeng, X. (2024). Mechanisms and Clinical Implications of Human Gut Microbiota-Drug Interactions in the Precision Medicine Era. In Biomedicines (Vol. 12, Issue 1). https://doi.org/10.3390/biomedicines12010194
170. Wang, W., Dang, G., Hao, W., Li, A., Zhang, H., Guan, S., & Ma, T. (2025). Dietary Supplementation of Compound Probiotics Improves Intestinal Health by Modulated Microbiota and Its SCFA Products as Alternatives to In-Feed Antibiotics. Probiotics and Antimicrobial Proteins, 17(4), 1969–1984. https://doi.org/10.1007/s12602-024-10314-3
171. Wang, X., Tang, Q., Hou, H., Zhang, W., Li, M., Chen, D., Gu, Y., Wang, B., Hou, J., Liu, Y., & Cao, H. (2021). Gut Microbiota in NSAID Enteropathy: New Insights From Inside. In Frontiers in Cellular and Infection Microbiology (Vol. 11). https://doi.org/10.3389/fcimb.2021.679396
172. Wang, Y., Jia, X., & Cong, B. (2024). Advances in the mechanism of metformin with wide-ranging effects on regulation of the intestinal microbiota. Frontiers in Microbiology, 15. https://doi.org/10.3389/fmicb.2024.1396031
173. Wiertsema, S. P., van Bergenhenegouwen, J., Garssen, J., & Knippels, L. M. J. (2021). The interplay between the gut microbiome and the immune system in the context of infectious diseases throughout life and the role of nutrition in optimizing treatment strategies. In Nutrients (Vol. 13, Issue 3). https://doi.org/10.3390/nu13030886
174. Wilkinson, G. R. (1997). The effects of diet, aging and disease-states on presystemic elimination and oral drug bioavailability in humans. In Advanced Drug Delivery Reviews (Vol. 27, Issues 2–3). https://doi.org/10.1016/S0169-409X(97)00040-9
175. Winiarska-Mieczan, A., Kwiecień, M., Jachimowicz-Rogowska, K., Donaldson, J., Tomaszewska, E., & Baranowska-Wójcik, E. (2023). Anti-Inflammatory, Antioxidant, and Neuroprotective Effects of Polyphenols—Polyphenols as an Element of Diet Therapy in Depressive Disorders. In International Journal of Molecular Sciences (Vol. 24, Issue 3). https://doi.org/10.3390/ijms24032258
176. Witherden, E. A., Moyes, D. L., Bruce, K. D., Ehrlich, S. D., & Shoaie, S. (2017). Using systems biology approaches to elucidate cause and effect in host-microbiome interactions. In Current Opinion in Systems Biology (Vol. 3). https://doi.org/10.1016/j.coisb.2017.05.003
177. Wu, K., Kwon, S. H., Zhou, X., Fuller, C., Wang, X., Vadgama, J., & Wu, Y. (2024). Overcoming Challenges in Small-Molecule Drug Bioavailability: A Review of Key Factors and Approaches. International Journal of Molecular Sciences, 25(23), 13121. https://doi.org/10.3390/ijms252313121
178. Wu, Y., Wan, J., Choe, U., Pham, Q., Schoene, N. W., He, Q., Li, B., Yu, L., & Wang, T. T. Y. (2019). Interactions Between Food and Gut Microbiota: Impact on Human Health. Annual Review of Food Science and Technology, 10(1), 389–408. https://doi.org/10.1146/annurev-food-032818-121303
179. Xiao, S., Jiang, S., Qian, D., & Duan, J. (2020). Modulation of microbially derived short-chain fatty acids on intestinal homeostasis, metabolism, and neuropsychiatric disorder. In Applied Microbiology and Biotechnology (Vol. 104, Issue 2). https://doi.org/10.1007/s00253-019-10312-4
180. Yang, Y., Aloysius, H., Inoyama, D., Chen, Y., & Hu, L. (2011). Enzyme-mediated hydrolytic activation of prodrugs. Acta Pharmaceutica Sinica B, 1(3). https://doi.org/10.1016/j.apsb.2011.08.001
181. Yin, C., Zhong, R., Zhang, W., Liu, L., Chen, L., & Zhang, H. (2023). The Potential of Bile Acids as Biomarkers for Metabolic Disorders. In International Journal of Molecular Sciences (Vol. 24, Issue 15). https://doi.org/10.3390/ijms241512123
182. Yue, B., Gao, R., Wang, Z., & Dou, W. (2021). Microbiota-Host-Irinotecan Axis: A New Insight Toward Irinotecan Chemotherapy. In Frontiers in Cellular and Infection Microbiology (Vol. 11). https://doi.org/10.3389/fcimb.2021.710945
183. Zaidi, S., Ali, K., & Khan, A. U. (2023). It's all relative: analyzing microbiome compositions, its significance, pathogenesis and microbiota derived

biofilms: Challenges and opportunities for disease intervention. In Archives of Microbiology (Vol. 205, Issue 7). https://doi.org/10.1007/s00203-023-03589-7

184. Zhang, J., Zhang, J., & Wang, R. (2018). Gut microbiota modulates drug pharmacokinetics. In Drug Metabolism Reviews (Vol. 50, Issue 3). https://doi.org/10.1080/03602532.2018.1497647
185. Zhang, L. S., & Davies, S. S. (2016). Microbial metabolism of dietary components to bioactive metabolites: Opportunities for new therapeutic interventions. In Genome Medicine (Vol. 8, Issue 1). https://doi.org/10.1186/s13073-016-0296-x
186. Zhang, S., Zhao, J., Xie, F., He, H., Johnston, L. J., Dai, X., Wu, C., & Ma, X. (2021). Dietary fiber-derived short-chain fatty acids: A potential therapeutic target to alleviate obesity-related nonalcoholic fatty liver disease. In Obesity Reviews (Vol. 22, Issue 11). https://doi.org/10.1111/obr.13316
187. Zhang, Y., He, X., Mo, C., Liu, X., Li, J., Yan, Z., Qian, Y., Lai, Y., Xu, S., Yang, X., & Xiao, Q. (2022). Association between Microbial Tyrosine Decarboxylase Gene and Levodopa Responsiveness in Patients with Parkinson Disease. Neurology, 99(22). https://doi.org/10.1212/WNL.0000000000201204
188. Zhao, Q., Chen, Y., Huang, W., Zhou, H., & Zhang, W. (2023). Drug-microbiota interactions: an emerging priority for precision medicine. In Signal Transduction and Targeted Therapy (Vol. 8, Issue 1). https://doi.org/10.1038/s41392-023-01619-w
189. Zhao, Y., Chen, J., Qin, Y., Yuan, J., Yu, Z., Ma, R., Liu, F., & Zhao, J. (2025). Linking Short-Chain Fatty Acids to Systemic Homeostasis: Mechanisms, Therapeutic Potential, and Future Directions. Journal of Nutrition and Metabolism, 2025(1). https://doi.org/10.1155/jnme/8870958
190. Zhou, X., Wang, S., Wang, X., Chen, X., Zhou, P., Ma, K., & Zhang, P. (2025). Mechanisms of the effect of gut microbes on depression through the microbiota-gut-brain axis. Frontiers in Nutrition, 12. https://doi.org/10.3389/fnut.2025.1634548
191. Zikou, E., Koliaki, C., & Makrilakis, K. (2024). The Role of Fecal Microbiota Transplantation (FMT) in the Management of Metabolic Diseases in Humans: A Narrative Review. Biomedicines, 12(8), 1871. https://doi.org/10.3390/biomedicines12081871
192. Zimmermann, M., Zimmermann-Kogadeeva, M., Wegmann, R., & Goodman, A. L. (2019). Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature, 570(7762). https://doi.org/10.1038/s41586-019-1291-3
193. Zinkow, A., Grodzicki, W., Czerwińska, M., & Dziendzikowska, K. (2024). Molecular Mechanisms Linking Omega-3 Fatty Acids and the Gut–Brain Axis. Molecules, 30(1), 71. https://doi.org/10.3390/molecules30010071