Review

Gut Feeling: What Gut Microbes Do and Why They Matter

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Abstract: The human gut is home to a bustling city of life. Trillions of bacteria, archaea, fungi, protozoa, and viruses live side by side. These microbial passengers help digest food, train the immune system, and produce molecules that support health far beyond the gut. Many of these species remain unknown, and much of their world is still unexplored. Natural products are chemical treasures from plants, fungi, and other natural sources. These bioactive compounds can shape the microbial community in powerful ways. Some promote helpful microbes and suppress harmful ones. Others are transformed by microbial enzymes into new molecules with stronger effects or for better absorption. This review explores the molecular conversations between gut microbes and natural products. It opens a 21-part series that explores how microbiota and natural product interactions can help prevent disease, restore balance, and guide the future of personalized medicine.

Keywords: gut microbiome; natural products; microbial metabolites; host-microbe interactions; microbiome modulation; natural product biotransformation; precision medicine; microbial diversity; functional metabolites

1. Introduction

The human gut microbiome consists of 10-100 trillion microbial cells, forming a highly dynamic and complex ecosystem. These microorganisms play a vital role in breaking down dietary components and releasing bioactive molecules that are critical for human health. The composition and function of the gut microbiota are influenced by factors such as diet, lifestyle, and medication use. A balanced microbiome supports essential physiological processes, including nutrient digestion, immune regulation, and metabolic homeostasis. In contrast, dysbiosis, an imbalance in microbial communities, can disrupt metabolic pathways and elevate the risk of various diseases [1–4]. Bioactive compounds in foods and natural products can restore microbial balance, improving blood sugar control, reducing harmful lipids, and lowering inflammation. The gut microbiome is now recognised as a central link between diet and health outcomes [5,6].

The microbial world remains largely uncharted. Estimates suggest close to a million prokaryotic species exist on Earth, yet only about 20,000 have been cultured. Genome databases currently list about 48,000 species [6,7]. The missing microbes may hold key roles in human health, especially in understudied regions and communities [8]. Natural products, bioactive compounds from plants, fungi, and other sources, can reshape gut microbiota composition and function. These compounds influence microbial metabolism, immune regulation, and host physiology, making them promising tools for health interventions [9]. Once inside the gut, microbes transform these compounds into new molecules with greater bioactivity or improved absorption. Alkaloids, polyphenols, terpenoids, fibres, and fermented foods yield metabolites that strengthen immunity, regulate metabolism, and maintain barrier integrity [10–12].

Polyphenols provide a model system for understanding these interactions. Gut microbes hydrolyse glycosides, cleave aromatic rings, and generate smaller phenolic acids [10,11]. These microbial metabolites show higher bioavailability and stronger biological activity than their parent compounds [10–12]. The resulting molecules act locally in the gut to reinforce barrier integrity and systemically to reduce oxidative stress and vascular inflammation [11,13]. Controlled studies confirm that polyphenol-derived metabolites improve endothelial function, lower inflammatory markers, and support metabolic balance [12,13]. Figure 1 illustrates this bidirectional relationship between natural products and the gut microbiome.

The interaction between natural products and the gut microbiome is two-way. Microbes convert natural products into active metabolites that influence immunity, metabolism, and barrier function [11,13,14]. In return, host physiology and diet shape microbial composition through bile flow, immune tone, and nutrient supply [15].

Bile acids favour bile-tolerant taxa, immune mediators such as antimicrobial peptides and immunoglobulin A (IgA) promote tolerance to commensals, and dietary inputs determine dominant pathways. Fibre-rich diets enhance short-chain fatty acid production, while high-fat or high-sugar diets promote pro-inflammatory metabolites [15]. These factors define the ecological niches that govern microbial composition and function. This review explains these interactions and sets the stage for the disease-focused instalments in the **Gut Feeling** series, where complex science is presented with clarity and precision.

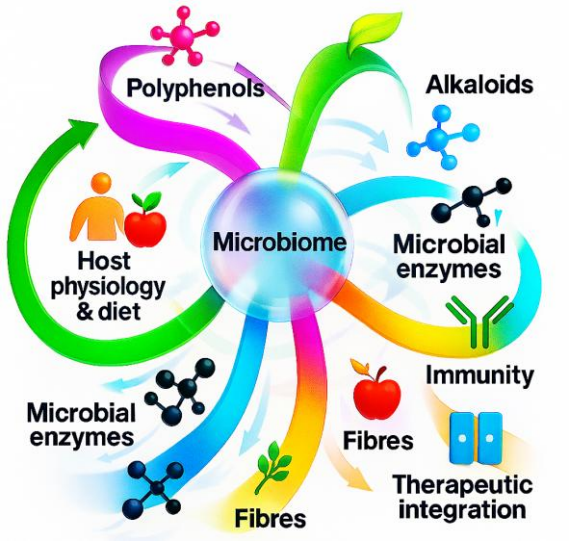

Figure 1. Bidirectional interaction between natural products and the gut microbiome.

2. Core Mechanistic Pathways Linking Gut Microbiota and Host Physiology

The gut microbiota is a dense and diverse community of bacteria, archaea, fungi, and viruses that inhabit the digestive tract [16]. These microorganisms break down dietary components that escape digestion in the upper gut [17]. The resulting metabolites act locally in the intestine and travel through the bloodstream to influence distant organs such as the liver, brain, and immune system [18–20].

Bioactive substrates from plants and fungi provide phenolics and terpenoids that expand the metabolic capacity of the gut microbiota [21,22]. Fermentation-derived fibres further enrich this input, supporting the production of short-chain fatty acids (SCFAs) and other bioactive molecules [23,24]. Once transformed, these compounds modulate microbial activity and generate metabolites that extend their influence beyond the gut, shaping immune control, metabolic adaptation, and barrier function [18,19]. Figure 2 depicts the core mechanistic pathways linking gut microbiota to host physiology.

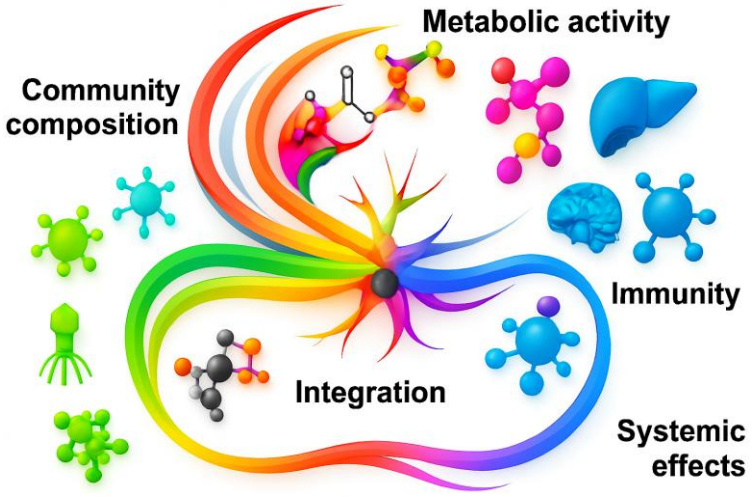

Figure 2. Core mechanistic pathways linking gut microbiota and host physiology.

2.1. Metabolite-Mediated Effects

Gut microbes ferment dietary fibres into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate [25,26]. Acetate enters circulation and regulates appetite through central pathways [27]. Propionate travels to the liver, where it modulates glucose and cholesterol metabolism, while butyrate remains in the colon, fuelling colonocytes and strengthening the epithelial barrier by upregulating tight junction proteins [28].

Amino acids such as tryptophan are converted into indole derivatives that activate the aryl hydrocarbon receptor (AhR), which regulates mucosal immunity and epithelial renewal [29,30]. Microbial enzymes also modify bile acids into secondary forms that signal through the Farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), and regulate lipid absorption, glucose balance, and energy expenditure [31,32]. Figure 3 outlines the metabolite-mediated effects of the gut microbiota.

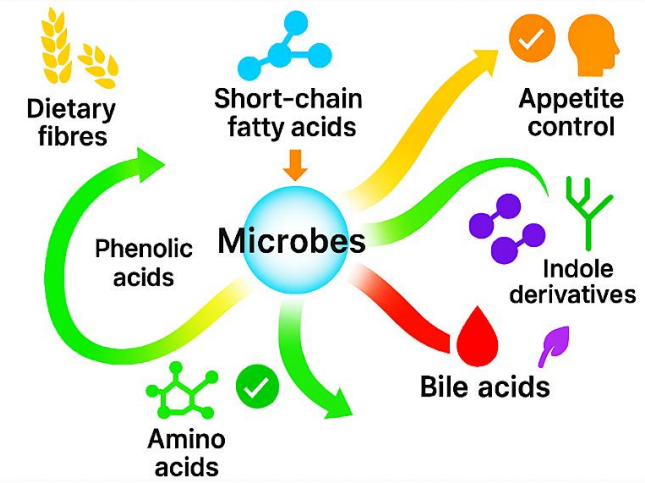

Figure 3. Metabolite-mediated effects of the gut microbiota.

2.2. Immune Modulation

The gut microbiota shapes immune tone by balancing pro-inflammatory and anti-inflammatory signals [16]. Certain bacterial species stimulate regulatory T cells, which suppress excessive immune responses and maintain tolerance [33]. SCFAs promote anti-inflammatory cytokines such as interleukin-10 (IL-10), while excess production of other metabolites can trigger pro-inflammatory cascades [26,34].

Microbial antigens interact with pattern recognition receptors in the gut lining, training the immune system to tolerate commensals while responding to pathogens [35,36]. A disruption of this balance contributes to autoimmune and inflammatory diseases, including inflammatory bowel disease and metabolic syndrome [32,37]. Figure 4 summarises the immune modulation exerted by the gut microbiota.

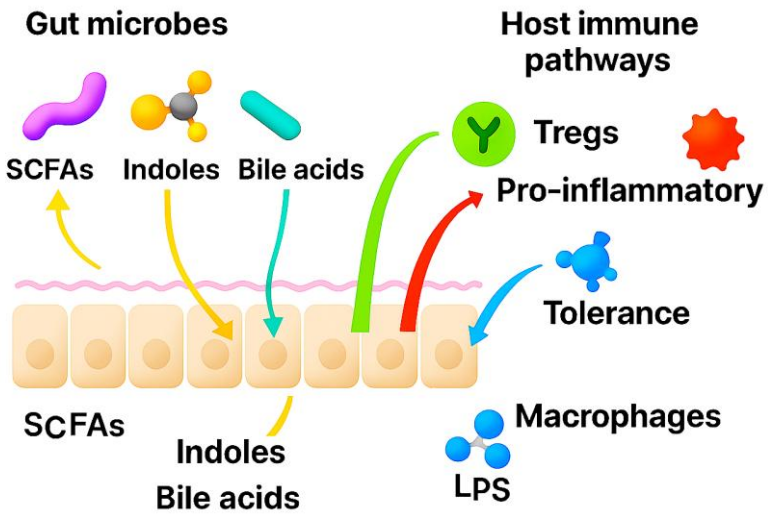

Figure 4. Immune modulation by the gut microbiota.

2.3. Barrier Integrity

The intestinal barrier consists of a mucus layer, epithelial cells, and tight junctions that regulate entry into the bloodstream [38]. The gut microbiota supports barrier function by producing metabolites that nourish epithelial cells and stimulate mucus production [39]. Butyrate is a key energy source for colonocytes and promotes tight junction assembly [28].

Some bacteria degrade mucus or disrupt junction proteins, which increases intestinal permeability [40]. A weakened barrier allows microbial products such as lipopolysaccharides (LPS) to enter circulation, triggering systemic inflammation and metabolic stress [41]. Figure 5 highlights the role of the gut microbiota in maintaining intestinal barrier integrity.

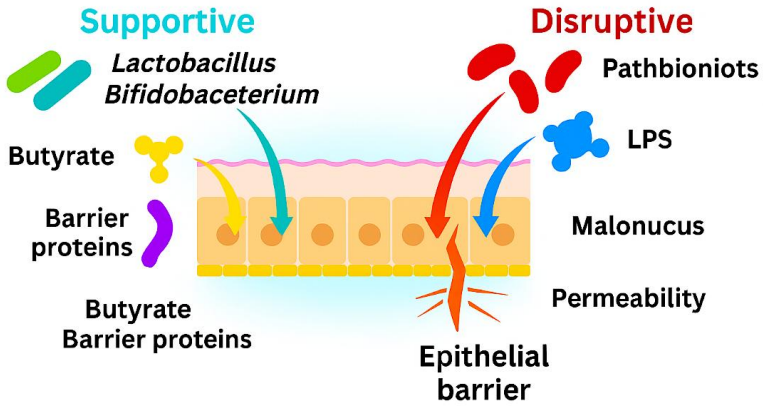

Figure 5. Gut microbiota and intestinal barrier integrity.

2.4. Neural and Endocrine Signalling

The gut microbiota communicates with the brain and endocrine organs through chemical messengers and neural pathways [42]. Microbial metabolites influence the vagus nerve, which links the gut to the brainstem and modulates autonomic responses [18,43]. SCFAs and tryptophan derivatives regulate neurotransmitter production, including serotonin and dopamine, which affect mood and cognition [44,45].

Bile acid signalling interacts with hormonal pathways that control glucose metabolism and stress responses [32,46]. These signals form the gut-brain axis, which influences behaviour, cognition, and emotional state [47,48]. Figure 6 shows the neural and endocrine pathways linking gut microbes to host physiology.

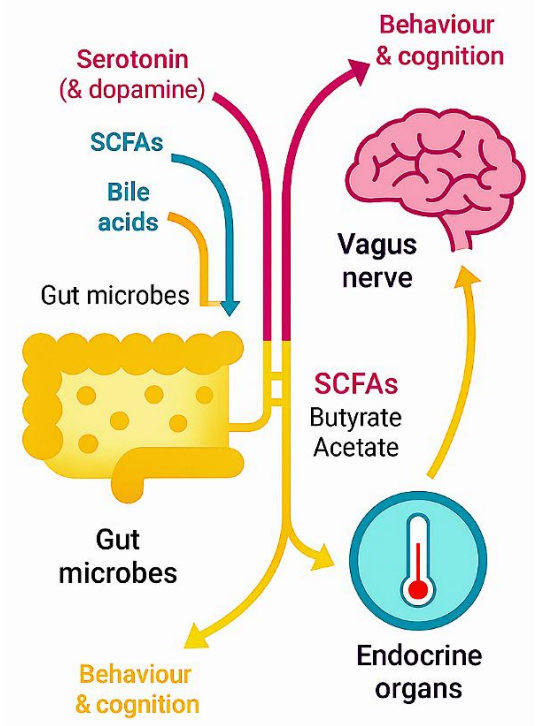

Figure 6. Neural and endocrine signalling in the gut-brain axis.

3. Microbiota-Mediated Effects of Natural Product Classes

Natural products influence the gut microbiota through microbial hydrolysis, demethylation, and ring cleavage reactions that convert parent compounds into smaller, more bioactive metabolites [9,49]. These transformations generate targeted metabolite profiles, including SCFAs, phenolic acids, and alkaloid derivatives, which act locally in the gut and travel through the bloodstream to influence distant organs [10,50]. In parallel, these metabolites engage host signalling pathways, activating GPR41, GPR43, FXR, TGR5, and AhR, thereby modulating immune responses, energy metabolism, and barrier integrity [9,49,50]. These interactions shape immune tone, metabolic balance, and barrier function across multiple organ systems [51,52].

Polyphenols are metabolised by *Bacteroides, Lactobacillus*, and *Eubacterium* through glycoside hydrolysis and urolithin A synthesis. These metabolites reinforce barrier integrity and reduce oxidative stress, with clinical evidence confirming improved metabolic outcomes [12]. Terpenoids such as ginsenosides undergo deglycosylation by *Akkermansia* and *Lactobacillus*, activating FXR and AhR pathways. Preclinical studies demonstrate benefits in colorectal cancer inhibition, inflammatory bowel disease relief, and lipid metabolism [31,53]. Alkaloids such as berberine are transformed by *Blautia* and *Ruminococcus bromii* via oxidation and demethylation, enhancing hypoglycaemic and hypolipidaemic effects. Clinical studies confirm barrier restoration and improved glucose control [54].

Polysaccharides fermented by *Bacteroides* and *Parabacteroides* yield SCFAs and bile acids that regulate immunity and metabolism [55,56]. Clinical and preclinical studies show improvements in type 2 diabetes, obesity, and immune modulation [57]. Amino acids, including branched-chain amino acids (BCAAs) and tryptophan, are metabolised by *Prevotella* and *Clostridium* into SCFAs and indole derivatives, which modulate immunity and neuroprotection. The translational evidence links indole-3-propionic acid to reduced risk of diabetes and neurodegeneration [58]. Clinical and preclinical anchors highlight translational relevance across polyphenols, terpenoids, alkaloids, polysaccharides, and amino acids [12,31,54,55,58,59]. Table 1 summarises the major compound classes, representative microbial taxa, and their biotransformation pathways, linking them to host effects.

Table 1. Microbiota-mediated mechanisms of key natural product classes with clinical/preclinical evidence.

Compound Class	Key Microbes	Main Transformation	Main Host Effects
Polyphenols	*Bacteroides*, *Lactobacillus*, *Eubacterium*	Glycoside hydrolysis yields aglycones, SCFAs, and urolithin A	Anti-inflammatory, antioxidant, strengthening of the gut barrier [50,54,60].
Terpenoids (Ginsenosides)	*Akkermansia*, *Lactobacillus*, *Enterococcus*	Deglycosylation generates FXR, TGR5, and AhR agonists	Reduction of gut inflammation, improvement of lipid metabolism, protection against colorectal cancer [31,53].
Alkaloids (Berberine)	*Blautia*, *Alistipes*, *Ruminococcus bromii*	Oxidation and demethylation enhance bioavailability, inhibit harmful bile acid conversion	Lowering of blood sugar, reduction of blood lipids, restoration of barrier integrity [54,60].
Polysaccharides	*Muribaculaceae, Bacteroides*, *Parabacteroides*	Fermentation produces SCFAs and secondary bile acids	Better glucose control, reduction of obesity, support of immune function [55–58].
Amino acids (BCAAs, Tryptophan)	*Prevotella*, *Clostridium*, *Bifidobacterium*	Microbial conversion yields SCFAs, and indole derivatives	Regulation of immunity, maintenance of metabolic balance, neuroprotection [29,30,58,61].

Polyphenols are abundant in fruits, vegetables, tea, and wine. Gut microbes hydrolyse glycosides into aglycones, which are then cleaved into smaller phenolic acids [50]. *Bacteroides* and *Eubacterium* convert ellagitannins into urolithins, such as urolithin A, which show anti-inflammatory and antioxidant activity [54,55]. These metabolites reinforce intestinal barrier integrity by upregulating tight junction proteins, reducing oxidative stress, and promoting mitochondrial biogenesis [10,11]. Clinical evidence confirms improved metabolic outcomes in humans [12].

Ginsenosides are deglycosylated by *Akkermansia* and *Lactobacillus* [56]. The resulting metabolites activate FXR and TGR5, which regulate bile acid pools, lipid metabolism, and energy expenditure [32]. Tryptophan-derived metabolites from ginsenoside fermentation also engage AhR, modulating mucosal immunity [29,53].

Preclinical evidence demonstrates that ginsenoside-derived metabolites reduce colonic inflammation, improve lipid handling, and suppress colorectal cancer progression [31,56].

Berberine is metabolised by *Blautia* and *Ruminococcus bromii* through oxidation and demethylation [55,60]. These reactions increase berberine bioavailability and enhance its hypoglycaemic and hypolipidaemic effects. Berberine also inhibits microbial conversion of primary bile acids into deoxycholic acid, reducing bile acid-induced barrier disruption [60]. Clinical studies confirm barrier restoration and improved glucose control [54].

Polysaccharides are fermented by Bacteroides and Parabacteroides into SCFAs [25,26]. These SCFAs fuel colonocytes, regulate immune tone, and improve insulin sensitivity [56]. Fermentation also produces secondary bile acids that signal through FXR and TGR5, further modulating lipid and glucose metabolism [57]. Clinical and preclinical studies show that polysaccharide-rich diets reduce obesity, improve type 2 diabetes outcomes, and enhance immune modulation [15,58]. SCFAs also lower colonic pH, suppressing pathogens and favouring beneficial taxa.

Branched-chain amino acids (BCAAs) and tryptophan are metabolised by Prevotella and Clostridium into SCFAs and indole derivatives [29,30]. Indoles activate AhR, which regulates mucosal immunity and barrier function [17]. Translational evidence links indole-3-propionic acid (IPA) to reduced risk of type 2 diabetes and neurodegeneration [61].

3.1. Molecular Action to System-Level Effects

Natural products interact with microbial enzymes in the gut lumen, reshaping the conversion of dietary and endogenous substrates [9,55,62]. These enzymatic shifts alter the production of SCFAs, indoles, and bile acid derivatives, which act locally in the intestine and travel through the bloodstream to influence distant organs [25,26,58,59]. SCFAs provide energy for colonocytes, strengthen tight junctions, and influence liver and brain pathways. Butyrate promotes barrier integrity by assembling junction proteins [28]. Propionate regulates hepatic gluconeogenesis, while acetate enters circulation to modulate appetite [27].

Indole derivatives from tryptophan metabolism activate the aryl hydrocarbon receptor (AhR), which supports mucosal immunity and epithelial renewal [29,30]. Secondary bile acids engage FXR and TGR5, controlling lipid absorption, glucose balance, and energy expenditure [31,32]. Immune cells in the lamina propria respond to these metabolites by adjusting cytokine release and T-cell balance [33].

Once absorbed, microbial metabolites act systemically. They regulate hepatic metabolism, vascular tone, and neural signalling [47,61,63]. Figure 7 presents how microbial enzyme modulation alters SCFA, indole, and bile acid production. These metabolites act locally on colonocytes and immune cells and, once absorbed, signal systemically through AhR, FXR, and TGR5 to regulate metabolism, vascular tone, neural pathways, and energy balance.

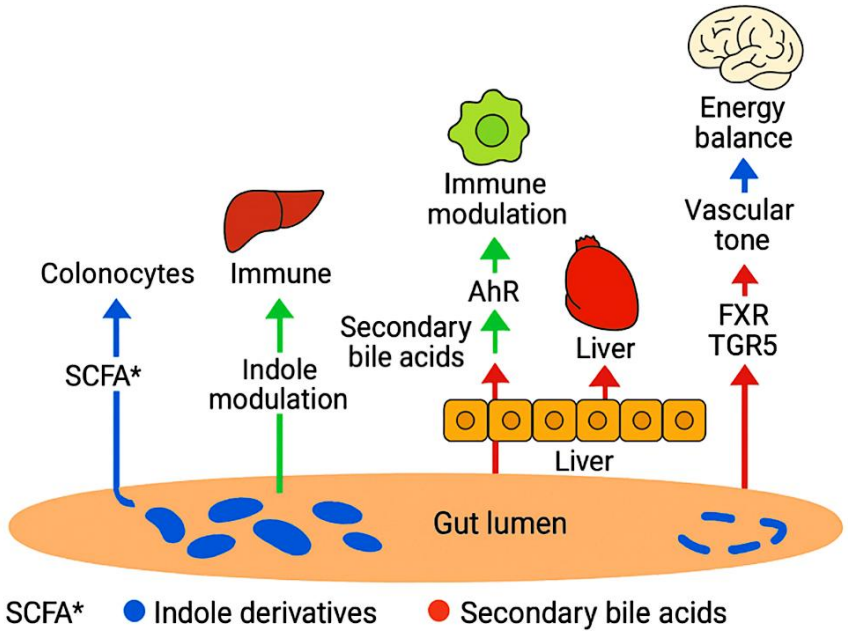

Figure 7. Molecular to systemic effects of natural product-microbiota interactions.

3.2. Multi-Pathway Synergy

Natural products often undergo several enzymatic transformations in the gut. Although these reactions differ, they frequently converge on similar physiological benefits [22,64]. Overlapping pathways can amplify these effects and reduce the risk of single-target resistance [29]. For example, one compound may enhance SCFA production, while another shifts bile acid signalling. In combination, they generate additive or even synergistic outcomes [53,61].

Secondary metabolites from microbial and host co-metabolism also act through multiple receptors at once. SCFAs such as acetate, propionate, and butyrate activate GPR41, GPR43, and GPR109A, influencing energy harvest, inflammatory tone, and epithelial integrity [50,52]. Bile acids produced by microbial deconjugation and transformation bind to FXR and TGR5, regulating lipid metabolism, glucose homeostasis, and enterohepatic signalling [17,50]. Indole derivatives from tryptophan metabolism engage AhR, modulating mucosal immunity, barrier function, and xenobiotic responses [50,52].

When these receptor-mediated pathways converge, they create cross-talk that reinforces immune regulation, stabilises metabolic balance, and preserves barrier integrity [17,50,52]. This synergy explains why complex natural product mixtures often outperform isolated compounds in clinical outcomes. Figure 8 maps the overlapping compound-strain-outcome clusters, highlighting the multi-pathway synergy between secondary metabolites and the gut microbiota.

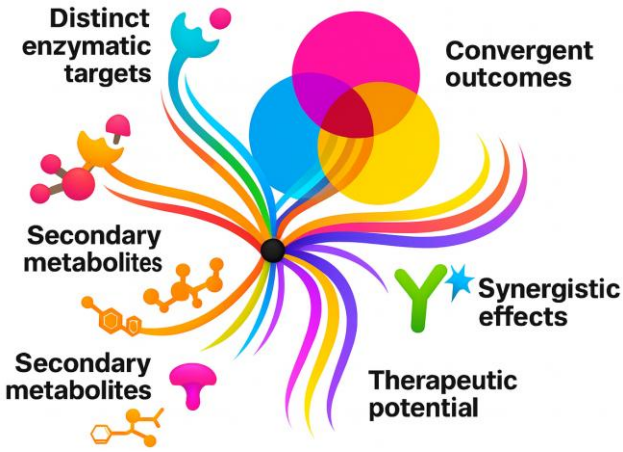

Figure 8. Multi-pathway synergy of natural products and gut microbiota.

3.3. Host-Microbe Co-Regulation in Clinical Contexts

The host shapes its microbial community through bile flow, immune tone, and nutrient supply [65,66]. In turn, microbial metabolites influence host gene expression, metabolic pathways, and immune responses [46,61]. This reciprocal regulation is most evident in metabolic syndrome, inflammatory bowel disease (IBD), and mood disorders [18,20].

In metabolic syndrome, dysbiosis lowers SCFA production and increases pro-inflammatory metabolites such as lipopolysaccharides (LPS) and trimethylamine-N-oxide. Reduced SCFAs weaken the gut barrier and impair insulin sensitivity, while harmful metabolites drive systemic inflammation and lipid accumulation [18,20]. These changes worsen glucose intolerance and elevate cardiovascular risk [18].

In IBD, a loss of microbial diversity reduces butyrate and indole production. Without these protective metabolites, epithelial repair slows, tight junctions loosen, and pro-inflammatory cytokines rise, leading to chronic inflammation and repeated barrier injury [20].

In mood disorders, altered tryptophan metabolism shifts the balance between serotonin and indole-3-propionic acid (IPA). Lower serotonin disrupts neurotransmission, while reduced IPA weakens neuroprotection, impairing gut-brain signalling and contributing to anxiety and depression [46,61].

A combined focus on host and microbial factors produces more durable outcomes. Microbiota-directed nutritional therapies restore SCFA production and improve metabolic tone, while probiotics strengthen the barrier and reduce inflammatory signalling [59]. Bile acid receptor modulators rebalance FXR and TGR5 pathways, improving lipid and glucose metabolism [67]. Figure 9 depicts the host-microbe co-regulation, linking microbial metabolite production to immune, metabolic, and barrier responses.

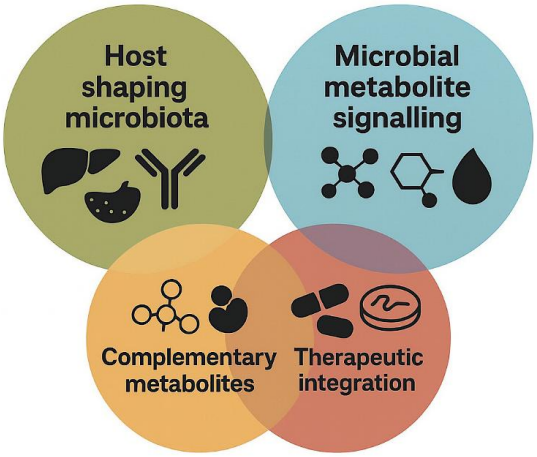

Figure 9. Host-microbe co-regulation in clinical contexts.

3.4. Receptor-Level Interactions

Microbial metabolites bind to host receptors and trigger signalling cascades that connect gut microbial activity to systemic physiology [45,61]. SCFAs such as acetate, propionate, and butyrate activate G protein-coupled receptors GPR41, GPR43, and GPR109A, thereby regulating energy balance, inflammatory tone, and epithelial integrity [25,26,68]. The activation of GPR41 and GPR43 modulates adipose tissue lipolysis and glucose uptake, while the butyrate-mediated activation of GPR109A suppresses nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling, reducing pro-inflammatory cytokine release and supporting colonic epithelial health [28].

Bile acids act as potent signalling molecules. Secondary bile acids generated by microbial enzymes engage the Farnesoid X receptor (FXR) in the ileum and liver, regulating bile acid synthesis, lipid absorption, and glucose metabolism [31]. In parallel, activation of the Takeda G protein-coupled receptor 5 (TGR5) in enteroendocrine cells stimulates glucagon-like peptide-1 (GLP-1) secretion, which enhances insulin sensitivity and energy expenditure [32].

Indole derivatives from tryptophan metabolism bind to the aryl hydrocarbon receptor (AhR) in intestinal epithelial and immune cells [29,30]. AhR activation promotes epithelial renewal, strengthens barrier integrity, and induces regulatory T-cell differentiation [17].

These receptor-level interactions show that microbial metabolites act as molecular messengers. By engaging GPR41, GPR43, GPR109A, FXR, TGR5, and AhR, they connect microbial metabolism to host immunity, energy balance, and barrier function [17,65,68]. Figure 10 outlines these receptor-level interactions, linking microbial metabolites to host signalling pathways.

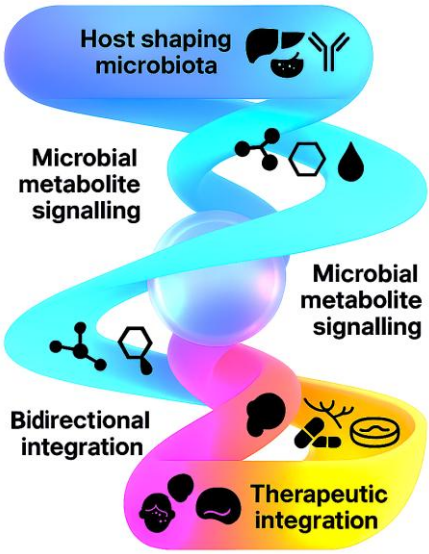

Figure 10. Receptor-level interactions of microbial metabolites with host physiology.

4. Challenges and Future Directions

Current evidence illuminates only fragments of the mechanistic landscape linking natural products to microbiota-mediated health effects [50,51,66]. Most studies focus on isolated pathways or short-term outcomes, leaving the broader host-microbe dialogue unresolved [22,64]. Microbial enzymes clearly transform diverse natural products into bioactive metabolites, yet the full spectrum of enzymatic reactions, metabolite diversity, and receptor cross-talk is still incompletely mapped [50,51,69].

Clinical investigations often provide static snapshots rather than longitudinal trajectories, making it difficult to separate transient fluctuations from stable adaptations. As a result, the field still lacks a predictive framework that integrates biochemical transformations, metabolite signalling, and translational outcomes across compound classes and disease contexts [50,51,64].

Despite rapid advances, several gaps continue to limit reproducibility, predictive accuracy, and translational application. These challenges span multiple levels of investigation, from enzyme mapping to clinical trial design, and require coordinated solutions that integrate discovery-level assays with translational strategies.

Emerging tools are poised to transform the field. Multi-omics profiling (metagenomics, metabolomics, transcriptomics, and proteomics), artificial intelligence (AI)-driven metabolic modelling, organoid and microfluidic systems, and long-term human cohorts will provide the resolution needed to capture dynamic host-microbe interactions [70–73]. Figure 11 illustrates the overarching challenges and future directions in microbiota-mediated therapeutics.

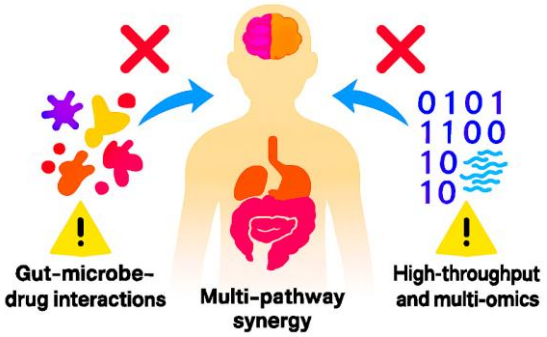

Figure 11. Challenges and future directions in microbiota-mediated therapeutics.

4.1. Enzyme Mapping Gaps

Systematic enzyme-level mapping is essential to predict inter-individual variability in metabolite production and to design targeted interventions [63,73]. Yet, at present, compound-enzyme specificity remains incompletely characterised. Many natural products undergo microbial hydrolysis, oxidation, or demethylation, but the precise enzymes responsible are often unidentified [50,54,69].

Glycosidase-mediated cleavage of polyphenol glycosides by Bacteroides is comparatively well described [54,55]. In contrast, the enzyme spectrum for terpenoid and alkaloid metabolism remains poorly defined [9,50]. Closing this gap will require systematic mapping across taxa and substrates to build predictive frameworks for metabolite production. Figure 12 highlights the incomplete identification of microbial enzymes responsible for natural product transformations.

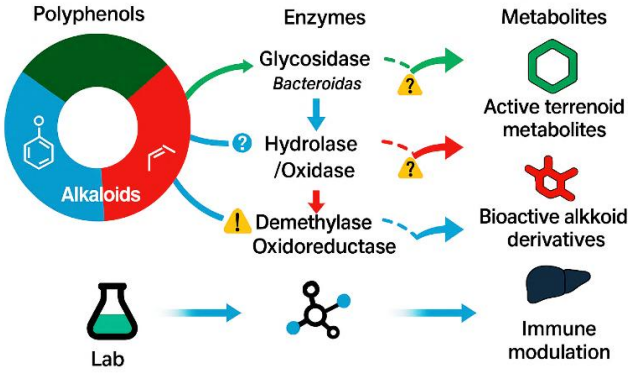

Figure 12. Enzyme mapping gaps in natural product metabolism.

4.2. Lack of Assay Standardisation

Reproducibility in microbiota research is constrained by the absence of standardised microbial enzyme assays. Many studies rely on in-house fermentation models or employ variable substrates that generate non-comparable metabolite profiles, limiting the transferability of mechanistic claims across laboratories [62,73]. Without harmonised protocols, results remain fragmented, and cross-study comparisons are weakened by differences in microbial strains, culture conditions, and analytical platforms.

Validated assays, applied consistently across multiple taxa and substrate classes, are essential to establish reproducible links between microbial transformations and host outcomes [62,73]. Figure 13 provides the variability in microbial assay protocols that undermines reproducibility.

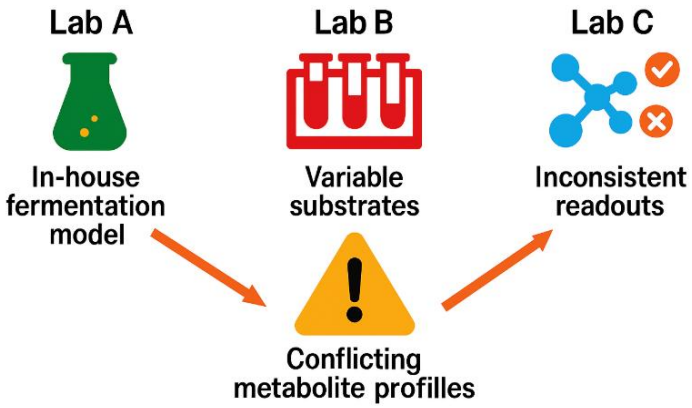

Figure 13. Variability in microbial assay protocols.

4.3. Missing Kinetic Parameters

Even when microbial transformations of natural products are observed, kinetic data for the enzymes involved remain scarce. Most reports provide only qualitative evidence, without constants such as the Michaelis-Menten constant (Km) or the maximum reaction velocity (Vmax), which are essential for quantitative modelling [74,75].

In the absence of kinetic constants, dose-response curves cannot be drawn with precision, and models linking dietary intake to metabolite output remain unstable [74,75]. The lack of kinetic profiling restricts predictive modelling of microbial biotransformation and limits the design of targeted nutritional or therapeutic interventions. Figure 14 shows the lack of kinetic parameters that constrain predictive frameworks in microbiota-mediated metabolism.

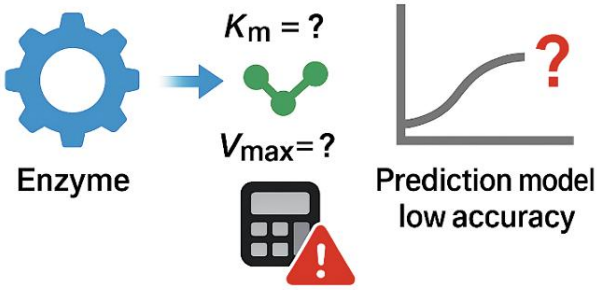

Figure 14. Missing kinetic parameters in microbial biotransformation.

4.4. Gaps in Receptor Cross-Talk Integration

Individual receptor pathways have been described, but their combined action remains poorly understood. SCFAs activate GPR41 and GPR43 to influence energy balance. Bile acids act through the Farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5) to regulate fat and sugar metabolism. Indole compounds from tryptophan activate the aryl hydrocarbon receptor (AhR) to support gut immunity and barrier strength [17,29,68].

The extent to which these signals overlap, compete, or reinforce one another inside the body is still unclear [50,61]. Most studies focus on one receptor-ligand pair at a time, overlooking the layered interactions that occur

when multiple metabolites circulate in combination [9,73]. This narrow view risks oversimplification and may lead to therapies that target single receptors while ignoring compensatory or opposing pathways. Figure 15 shows the missing links between SCFA, bile acid, and indole signalling networks.

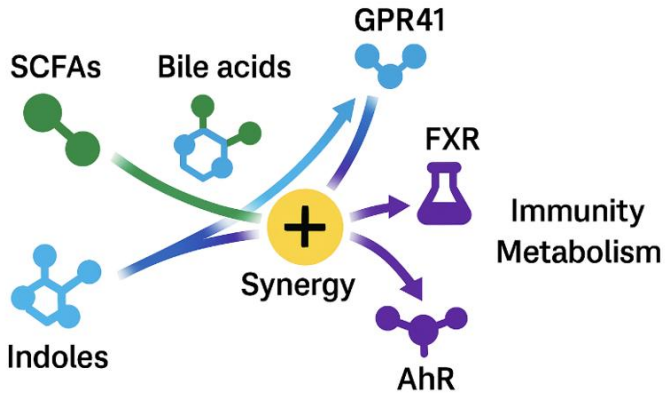

Figure 15. Multi-pathway receptor cross-talk drives host-microbe synergy.

4.5. Insufficient Long-Term Datasets

Most studies of gut microbes and natural products are short, capturing only temporary changes rather than lasting adaptations [50,51,64]. Cross-sectional designs dominate, offering static snapshots that cannot distinguish between brief fluctuations and stable host-microbe states [72,73]. The lack of long-term datasets makes it difficult to trace how microbial transformations of natural products evolve over months or years, or how these changes shape chronic disease [18]. For example, SCFA levels may rise after dietary intervention, but it is not known whether this increase persists [59,61]. Similarly, receptor signalling through FXR, TGR5, and AhR may shift with age, diet, or medication, yet few studies follow these changes over time [9].

Coordinated cohort studies with repeated sampling, harmonised metadata, and integrated multi-omics are needed [72,73]. Such datasets would capture not only immediate responses but also long-term adaptations, feedback loops, and disease-modifying effects. Figure 16 depicts the insufficiency of long-term datasets and the consequences for predictive modelling and clinical translation.

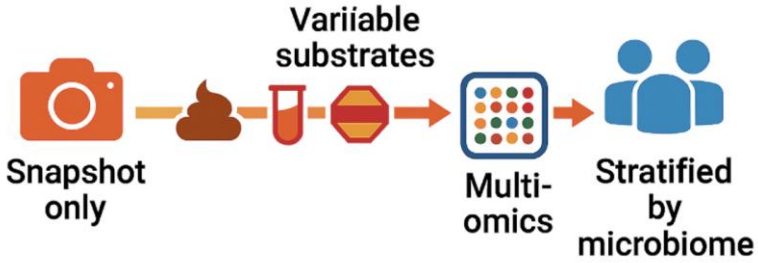

Figure 16. Study design progression to microbiome-stratified cohorts.

4.6. Integrated Strategies for Future Research

Future progress requires strategies that combine enzyme mapping, standardised assays, kinetic profiling, receptor cross-talk, and long-term study design into a single framework [50,51,64]. Multi-omics platforms, integrating metagenomics, metatranscriptomics, metabolomics, and proteomics, can capture the full range of microbial transformations and host responses [70,71]. When paired with artificial intelligence (AI) modelling, these datasets can predict metabolite flow, receptor activity, and health outcomes across diverse populations [72,73].

High-throughput standardised assays are essential to ensure reproducibility across laboratories. For example, glycosidase activity in *Lactobacillus rhamnosus* has been linked to polyphenol metabolism, yet comparable enzyme maps remain incomplete for other taxa [54,55]. Incorporating such examples into systematic enzyme catalogues will help close the specificity gap.

Organoid and microfluidic systems provide controlled environments to test natural product-microbiota interactions at cellular and tissue levels, bridging the gap between laboratory assays and real-world biology [69].

Long-term human cohort studies, aligned across research centres, are essential to confirm these findings and to capture resilience, relapse, and adaptation over time [18,61]. Crucially, future clinical trials should incorporate microbiome stratification to account for inter-individual variability, ensuring that therapeutic precision is achieved across diverse populations.

Clear pipelines are also needed to connect laboratory discoveries with patient care. Diet-based interventions, probiotics, and receptor-targeted drugs should be tested in adaptive clinical trials that account for differences in microbiota composition and metabolite production [9]. Figure 17 demonstrates the integrated strategies for future research, linking discovery-level assays, computational modelling, and translational frameworks.

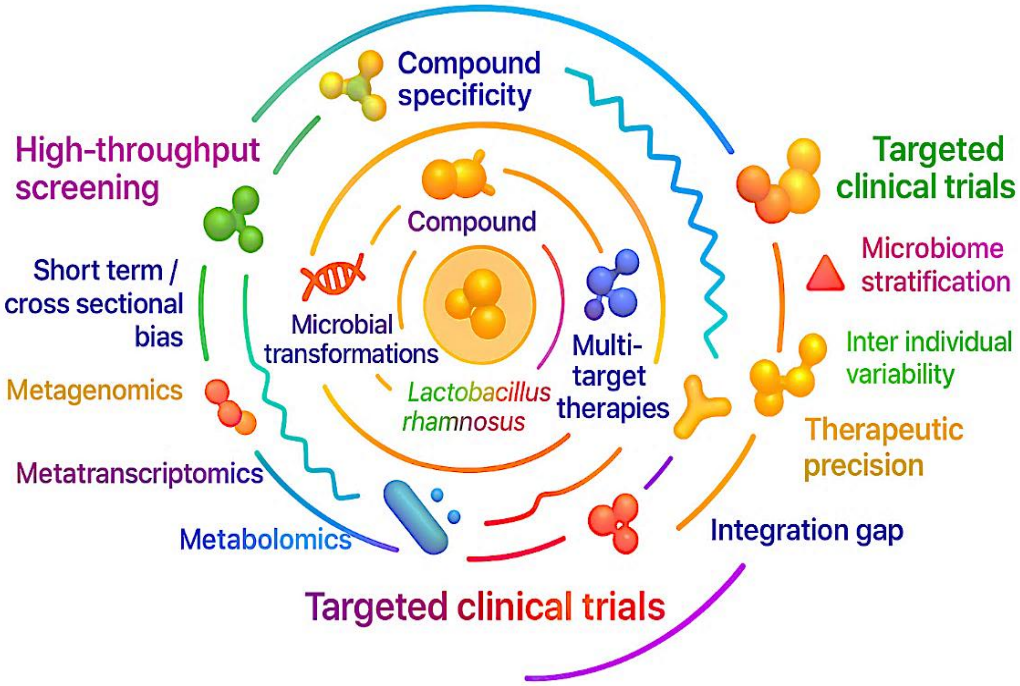

Figure 17. Integrated strategies for future research.

5. Conclusions

This review highlights how natural products shape host physiology through microbiota-mediated mechanisms. Once inside the gut, these compounds interact with microbial enzymes and produce metabolites that influence immunity, metabolism, barrier integrity, and neural signalling. The relationship is two-way: host physiology also shapes microbial composition and activity. Clinical and experimental evidence shows that natural products can restore microbial balance and improve health outcomes across many conditions. Yet current knowledge captures only fragments of the mechanistic network. The enzyme mapping is incomplete, the kinetic data are scarce, and the multi-pathway interactions are only partly described, which limits predictive accuracy. These gaps can be addressed through standardised assays, integrated multi-omics approaches, and carefully designed clinical trials. The gut is a coordinated framework where laboratory discoveries meet patient-focused applications, turning mechanistic insights into targeted, multi-component strategies capable of fine-tuning the system and sustaining long-term health. Within this hidden universe of trillions of microbiomes, each metabolite becomes a verse, each microbial pathway a stanza, and together they compose a living world of resilience, balance, and renewal for humanity.

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Use of AI and AI-Assisted Technologies: Copilot was utilised for infographics.

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