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Dietary modulation of microbial metabolic networks: How gut-derived metabolites shape host immunity and metabolism

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Abstract
Diet is a dominant ecological force shaping gut microbial metabolism and, in turn, host immunity and metabolic homeostasis. While short-chain fatty acids (SCFAs) are well-established mediators of host–microbiome interactions, recent studies have revealed a broader and more complex metabolic landscape involving bile acids, indoles, phenolic compounds, and host-modified microbial metabolites. Dietary interventions—particularly fiber supplementation—can unmask previously uncharacterized metabolic pathways, often referred to as *microbial dark matter*, with profound immunological and metabolic consequences. Notably, bile acid–driven immune activation, fiber-dependent exacerbation of intestinal inflammation, and host conjugation of microbial bile acids into bile acid–methylcysteamine (BA-MCY) highlight bidirectional host–microbe regulatory mechanisms. This review synthesizes emerging evidence on how dietary inputs restructure microbial metabolic networks, how these metabolites modulate immune and metabolic pathways, and the implications for precision nutrition and microbiome-based therapeutics.

Keywords: Gut microbiome, microbial metabolites, dietary fiber, bile acids, immunity, metabolism, precision nutrition

Introduction
The gut microbiome functions as a metabolically active organ whose chemical outputs exert systemic effects on host physiology. Early hypotheses linking intestinal microbes to health, proposed over a century ago, have now been substantiated by advances in metagenomics, metabolomics, and gnotobiotic models. These approaches reveal that microbial metabolites act as signaling molecules influencing immune development, epithelial integrity, and energy homeostasis [1, 2].

Despite extensive cataloguing of microbial taxa, a substantial fraction of microbiome-derived metabolites remains chemically and functionally uncharacterized. This unexplored metabolic space—often termed *microbial dark matter*—is increasingly recognized as a key determinant of host phenotypes [5]. Diet represents a primary, modifiable driver of microbial metabolism; however, dietary interventions yield heterogeneous outcomes across individuals and disease contexts [3, 4]. Understanding how diet uncovers specific microbial metabolic pathways is therefore central to translating microbiome research into clinical practice.

Diet–Microbiome–Host Metabolic Axes
Short-Chain Fatty Acids: Canonical Metabolite Pathways
SCFAs, including acetate, propionate, and butyrate, are produced through microbial fermentation of microbiota-accessible carbohydrates. These metabolites reinforce epithelial barrier function, promote regulatory T-cell differentiation via histone deacetylase inhibition, and exert systemic anti-inflammatory effects [16, 17]. Their protective role in metabolic syndrome, insulin resistance, and colitis is supported by both animal and human studies [2, 18].

Bile Acids as Immune-Active Metabolites
Beyond lipid absorption, bile acids function as potent signaling molecules at the host–microbiome interface. Primary bile acids synthesized in the liver are chemically modified by microbial bile salt hydrolases and dehydroxylation pathways, generating a diverse secondary bile acid pool [10].

Dietary fiber profoundly alters this metabolic axis. Inulin-rich diets increase microbial bile acid metabolites that activate farnesoid X receptor (FXR) signaling in stromal cells, inducing IL-33 production and downstream activation of type 2 immune pathways via ILC2s and eosinophils [10]. Importantly, this immune activation contrasts with the anti-inflammatory effects typically attributed to SCFAs and can exacerbate colitis in susceptible hosts [12], underscoring the context-dependent effects of dietary fiber.

Indoles and Phenolic Compounds
Indole derivatives produced from dietary tryptophan and phenolic metabolites derived from polyphenols represent additional layers of metabolic regulation. These compounds activate aryl hydrocarbon receptor (AhR) signaling, enhancing mucosal barrier integrity and modulating oxidative stress and immune tone [19, 21]. Although less extensively characterized than SCFAs or bile acids, indoles are increasingly recognized as central mediators of host–microbiome communication.

Host Counter-Regulation: BA-MCY Conjugates
A major conceptual advance is the discovery that hosts actively modify microbial metabolites. Host-derived conjugation of bile acids with methylcysteamine (BA-MCY), mediated by vanin-1, generates FXR antagonists that counterbalance microbial FXR agonists [11]. This host-driven mechanism restores bile acid synthesis and improves

cholesterol and lipid homeostasis, illustrating an adaptive feedback loop that constrains excessive microbial signaling.

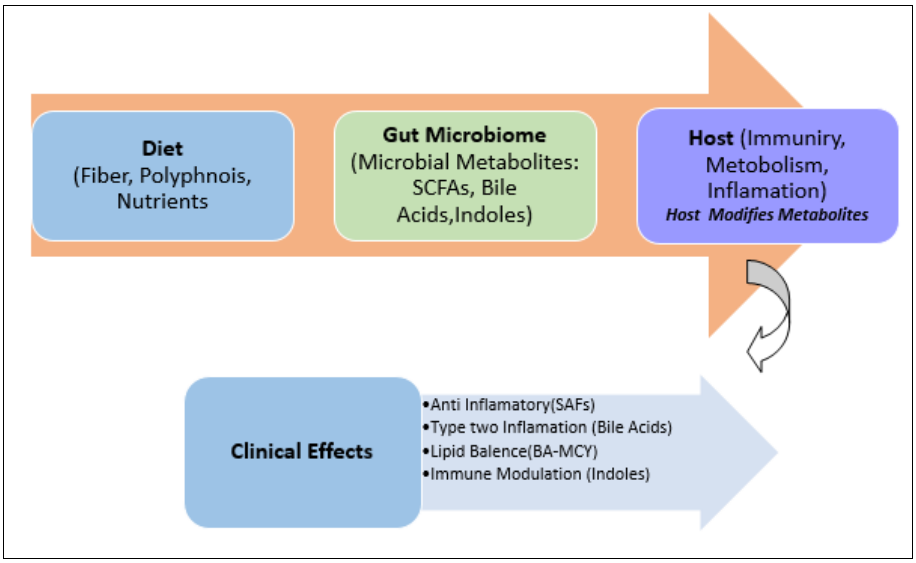
Clinical and Nutritional Implications

Precision Nutrition

Distinct dietary fibers generate unique metabolite profiles depending on microbial composition. Consequently, uniform dietary recommendations may produce divergent outcomes, particularly in inflammatory bowel disease and metabolic disorders [14]. Microbiome-informed fiber selection represents a rational strategy for personalized nutrition.

Inflammatory and Metabolic Diseases

While SCFAs generally confer protection against inflammation and metabolic dysfunction, bile acid metabolites may amplify immune activation and tissue pathology under specific conditions [12, 23]. Similarly, microbial production of trimethylamine-N-oxide (TMAO) links dietary inputs to cardio metabolic risk [8, 28].



Microbiome-Based Therapeutics

Targeted manipulation of microbial metabolic pathways using genetically engineered strains or enzyme-specific interventions has demonstrated causal links between metabolites and host phenotypes [13]. Such approaches lay the foundation for next-generation probiotics and metabolite-centric therapies.

Limitations and Challenges

The limitations include substantial inter-individual variability, partial metabolite annotation, many metabolites remain unidentified and reliance on murine models for mechanistic insights. Most mechanistic studies are in mice. Translation of these findings to humans requires integrated multi-omics profiling and stratified clinical trials.

Future Emphasis

The Expansion of untargeted metabolomics pipelines, integration with transcriptomic and genomic datasets, and development of precision nutrition trials will be essential to fully illuminate microbial metabolic dark matter [15]. Therapeutic exploitation of host-modified metabolites such as BA-MCY represents a promising frontier.

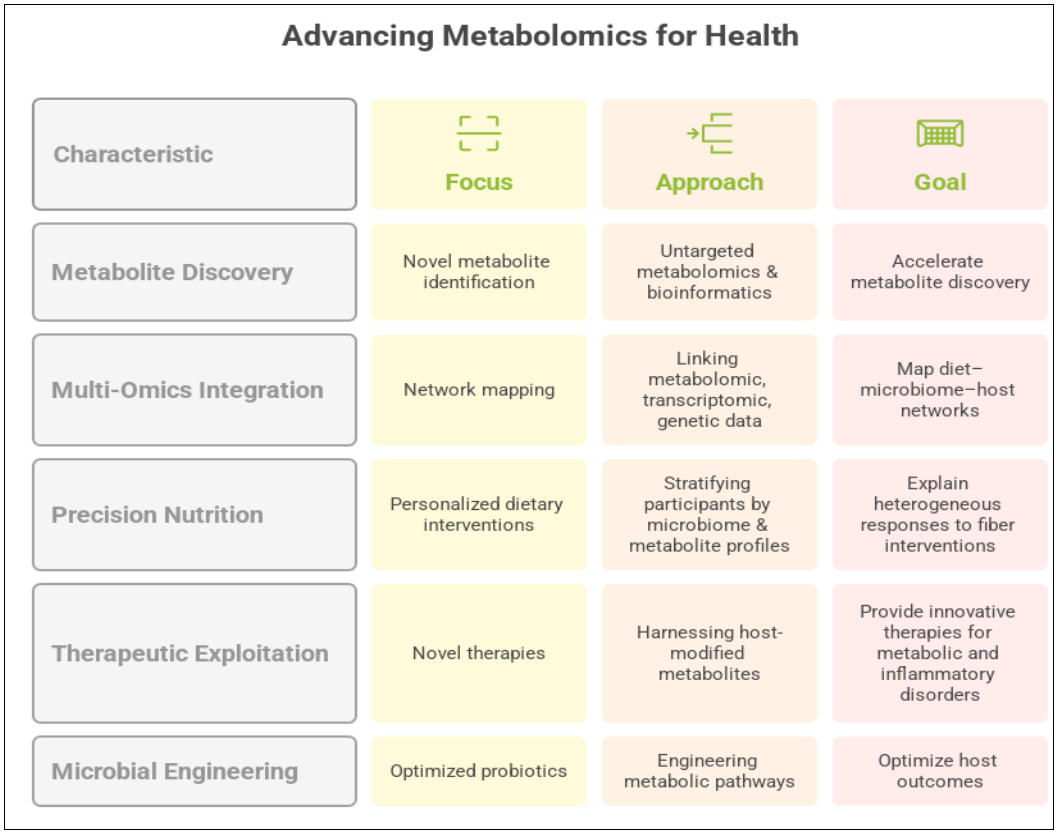
Table 1: Microbial Metabolites and Their Physiological Effects

Metabolite Class	Source	Key Pathways	Physiological Effects	References
Short-chain fatty acids (SCFAs)	Fermentation of dietary fibers (e.g., inulin, resistant starch)	Acetate, propionate, butyrate production	Anti-inflammatory, promotes Treg cells, improves insulin sensitivity, enhances gut barrier function	2, 16, 17
Bile acids (secondary)	Microbial conversion of liver-derived bile salts (via BSH enzymes)	Deconjugation, transformation into secondary bile acids	Activate FXR, regulate IL-33/ILC2 axis, modulate cholesterol metabolism, may drive inflammation in IBD	10, 11, 12, 13
Indoles	Microbial metabolism of tryptophan	Indole-3-acetate, indole-3-propionate	Activate AhR, improve mucosal barrier, regulate oxidative stress	19, 21
Phenolic compounds	Microbial metabolism of polyphenols and aromatic amino acids	Phenylpropionate, ferulic acid, phenylacetic acid	Antioxidant, anti-inflammatory, cardiometabolic benefits	18, 24
Trimethylamine (TMA) / TMAO	Choline, L-carnitine metabolism	Conversion of TMA → TMAO in liver	Promotes atherosclerosis and CVD risk	8, 28

Table 2: Dietary fiber intervention outcomes and variability

Type of Fiber	Microbial Response	Metabolites Produced	Clinical Outcome	Notes
Inulin	Enrichment of Bacteroides and Bifidobacteria	SCFAs, bile acid metabolites	Anti-inflammatory in some; worsens colitis in others	Heterogeneous response in IBD
Resistant starch	Growth of Ruminococcus bromii, Eubacterium rectale	Butyrate, acetate	Improved insulin sensitivity, reduced gut permeability	Consistently beneficial in metabolic studies

Arabinoxylans	Fermentation by Prevotella spp.	SCFAs, phenolic acids	Modulation of lipid metabolism, improved satiety	Population-dependent effects (Western vs non-Western diets)
Mixed fibers (dietary interventions)	Diverse microbial shifts	Mixed SCFA and secondary metabolites	Variable effects on gut inflammation and weight regulation	Highlights need for precision nutrition



Conclusion

The discovery of host–microbiome co-regulatory mechanisms, such as BA-MCY conjugates, underscores the evolutionary sophistication of this partnership. The challenge for nutrition science is to harness these insights to deliver precision interventions that improve immune balance and metabolic health [25, 27].

Dietary modulation of the gut microbiome reveals a complex metabolic network that extends far beyond SCFAs. Bile acids, indoles, phenolic, and host-modified metabolites collectively shape immune and metabolic outcomes in a context-dependent manner [25, 27]. Recognizing diet as a metabolic perturbation rather than a uniformly beneficial intervention is critical for developing microbiome-informed nutritional and therapeutic strategies. The interplay between diet, microbial metabolism, and host physiology is more complex than viewed earlier [29]. While SCFAs remain central to our understanding of microbiome-driven benefits, bile acids, indoles, and host-modified metabolites reveal a multidimensional regulatory network [25, 29, 30].

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Ethical Statement

This review article is based exclusively on the previously published literature and does not involve any new studies with human participants or animals conducted by the author. Ethical approval and informed consent were therefore not required. Proper credit and citations have been provided to the original authors.

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