INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Human Microbiota and Their Metabolites: Drivers of Host Physiology and Health

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ARTICLE INFO

Published: 12 Jan 2026
Keywords:
Gutmicrobiome, Human microbiota, immune modulation, metabolism, dysbiosis, gut-brain axis, therapeutic microbiome modulation
DOI:
10.5281/zenodo.18224422

ABSTRACT

The human microbiota constitutes a diverse and dynamic community of microorganisms, including bacteria, fungi, viruses, and archaea, that inhabit various body sites such as the gut, skin, oral cavity, and respiratory tract. These microbial populations establish a symbiotic relationship with the host, playing crucial roles in maintaining physiological homeostasis. The gut microbiota, in particular, is central to metabolic, immunological, and neurological functions. It contributes to nutrient metabolism, synthesis of essential vitamins, regulation of gut barrier integrity, and modulation of immune responses. Moreover, microbial metabolites such as short-chain fatty acids (SCFAs) influence host energy balance, inflammatory signaling, and neurobehavioral processes through the gut–brain axis. Dysregulation of the microbiota, known as dysbiosis, has been linked to a range of disorders, including metabolic syndrome, inflammatory bowel disease, obesity, and neurodegenerative conditions. Understanding the complex interactions between human microbiota and host physiology offers new avenues for therapeutic interventions, such as probiotics, prebiotics, and microbiota-targeted therapies, to restore microbial equilibrium and promote health.

INTRODUCTION

The human body harbors trillions of microbes, which collectively outnumber human cells, contributing crucial roles in digestion, immune defense, and nutrient synthesis (Turnbaugh & Gordon, 2024). Rather than functioning as separate entities, the host and its microbiota form a symbiotic unit in which microbial activity directly influences human metabolism, immune regulation, and health outcomes (Zhang et al., 2024). Microbial diversity denotes the wide spectrum of microbial species inhabiting distinct body sites, forming complex and site-specialized ecosystems (Mirzaei et al., 2024). Different anatomical locations, such as the gut, skin, oral cavity, respiratory tract, and urogenital tract, harbor distinct microbial communities adapted to their local environments (Mirzaei et al., 2024; Hu

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

& Shen, 2024). The gut microbiota is particularly diverse, encompassing hundreds of bacterial species that support digestion, metabolic processing, and immune homeostasis (Simbirtseva& O'Toole, 2025). In contrast, the skin and oral microbiota vary in composition with factors like moisture, pH, and nutrient availability, while the female urogenital microbiota is often dominated by Lactobacillus species (Shete & Ghosh, 2025). This microbial diversity is shaped by host genetics, diet, age, lifestyle, and environmental exposures, and maintaining it is essential for health and disease resistance (Chandel et al., 2024). Microbial metabolism encompasses the array of biochemical processes by which microorganisms derive energy and nutrients for growth, reproduction, and interaction with their surroundings (Hu & Shen, 2024). These metabolic processes are essential for decomposing dietary components, producing vitamins, and secreting bioactive metabolites such as short-chain fatty acids (Simbirtseva& O'Toole, 2025).

TYPES OF FLORA AND THEIR METABOLIC OUTPUTS:

Type of Flora	Dominant Microbes	Major Metabolic Outputs	Physiological Roles / Effects	References
Intestinal (Gut) Flora	*Bacteroides*, *Firmicutes*, *Lactobacillus*, *Bifidobacterium*	Short-chain fatty acids (SCFAs): acetate, propionate, butyrate	Support gut integrity, regulate immune responses, and provide energy to colonocytes	(Wang LY et al., 2024) (Pham NH T & Joglekar M. V., 2024) (Chen Z. et al., 2024)
Oral Flora	*Streptococcus*, *Actinomyces*, *Veillonella*	Organic acids (e.g., lactic acid), hydrogen peroxide	Influence dental plaque formation, oral pH, and pathogen inhibition	(Lamont et al., 2018; Marsh &Zaura, 2017)
Skin Flora	*Staphylococcus*, *Corynebacterium*, *Cutibacterium* (*Propionibacterium*)	Fatty acids and antimicrobial peptides	Maintain skin barrier, modulate immune responses, and prevent pathogen colonization	(Byrd et al., 2018) (Wu et al., 2024)
Vaginal Flora	*Lactobacillus* species	Lactic acid, hydrogen peroxide	Maintain acidic pH, inhibit pathogens, and protect reproductive health	(Miller et al., 2016; Chee et al., 2020)

Human microbiota, or normal flora, can be categorized based on their location in the body, with each type producing distinct metabolic outputs that influence health.

MAJOR MICROBIAL METABOLITES AND THEIR PHYSIOLOGICAL ROLES:

SHORT-CHAIN FATTY ACIDS:

Short-chain fatty acids (SCFAs) are the principal metabolic products generated by the anaerobic fermentation of dietary fibres and resistant starches by gut microbiota — notably taxa within the phyla Bacteroidetes (e.g., *Bacteroides* spp.), Firmicutes (e.g., *Lactobacillus* and *Clostridium* spp.), and Actinobacteria (particularly *Bifidobacterium* spp.) (Ríos-Covián et al., 2016; also see Yang et al. 2023) These predominant SCFAs acetate, propionate and butyrate are produced in varying proportions depending on the type of dietary substrate and microbial composition (Li et al., 2023). These metabolites play crucial roles in maintaining intestinal and systemic homeostasis. Acetate, the most abundant SCFA, serves as a key precursor for lipid and cholesterol synthesis and is capable of entering the

systemic circulation and may cross the blood-brain barrier, where it could influence appetite regulation and brain energy metabolism (Erny et al., 2021). Propionate primarily acts in the liver, being involved in gluconeogenesis and has been associated with reduced lipogenesis and modulation of satiety hormones (Canfora et al., 2015; also see Macia et al., 2023). Butyrate, though produced in a smaller proportion, is functionally the most significant in the gut: it serves as the main energy source for colonocytes, promotes mucosal barrier integrity, exerts anti-inflammatory effects through inhibition of histone deacetylases and supports differentiation of regulatory T cells (Koh et al., 2016; Yang et al., 2023). Beyond the gut, SCFAs act as signalling molecules via G-protein-coupled receptors (e.g., GPR41/FFAR3 and GPR43/FFAR2), thereby influencing host immune responses, metabolic regulation and even gut-brain communication (Markowiak-Kopeć et al., 2023; Petakh et al., 2024). Collectively, SCFAs represent a critical link between diet, microbiota composition and host physiology illustrating how microbial metabolism contributes directly to human health and disease prevention (Yang et al., 2023).

INDOLES AND TRYPTOPHAN DERIVATIVES:

Indoles and tryptophan-derived metabolites are key microbial products generated from the metabolism of the essential amino acid tryptophan by gut microbiota. Several gut bacterial species—as seen in genera such as *Clostridium*, *Bacteroides*, and *Escherichia coli*—convert dietary tryptophan into a variety of bioactive compounds such as indole, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA) and indole-3-aldehyde (IAld) (Hou et al., 2023). These metabolites act as crucial signalling molecules that influence intestinal and systemic physiology. For instance, indole and its derivatives activate the aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR), leading to enhanced intestinal barrier integrity, increased mucin production and anti-inflammatory responses (Li et al., 2025; Gao et al., 2024). Indole-3-propionic acid, in particular, has been shown to exhibit antioxidant and neuroprotective effects by scavenging free radicals and protecting neuronal cells from oxidative damage (Zhang et al., 2024). Moreover, microbial tryptophan metabolites modulate immune homeostasis by promoting the differentiation of regulatory T cells and by influencing the gut–brain axis through serotonin and kynurenine-pathway regulation (Hou et al., 2023; Sun et al., 2024). Overall, indoles and tryptophan derivatives form a critical link between gut microbial metabolism, intestinal immunity and host neurophysiology — underscoring their significance in maintaining health and preventing disease (Zhang et al., 2024; Gao et al., 2024).

POLYPHENOL-DERIVED METABOLITES:

Polyphenol-derived metabolites are important bioactive compounds produced through the biotransformation of dietary polyphenols by the gut microbiota. Many dietary polyphenols—including flavonoids, phenolic acids and lignans—are poorly absorbed in the small intestine and thus reach the colon, where gut bacteria (e.g., Clostridium, Eubacterium and Bacteroides spp.) metabolise them into smaller, more bioavailable phenolic metabolites. (Turner et al., 2024; Singh et al., 2023) These microbial transformations involve deglycosylation, dehydroxylation, demethylation and ring-fission reactions, yielding metabolites such as urolithins, phenylpropionic acids and phenylacetic acids. (Martinez-Herrera et al., 2025; Gupta et al., 2024) These compounds exert diverse physiological effects on the host, including antioxidant, anti-inflammatory and

cardioprotective actions. For example, urolithin A, a metabolite derived from ellagitannins, has been shown to promote mitochondrial function, enhance intestinal barrier integrity and reduce inflammation. (Lee et al., 2024; Zhao et al., 2025) Similarly, microbial-derived phenolic acids contribute to vascular health by improving endothelial function and modulating lipid metabolism. (Kim et al., 2024) Overall, the microbial conversion of dietary polyphenols enhances their bioactivity and bioavailability, linking gut microbial metabolism with protection against chronic diseases such as cardiovascular disorders, diabetes and neurodegeneration. (Patel et al., 2024; Wang et al., 2025)

VITAMINS AND AMINOACID DERIVATIVES:

Vitamins and amino acid–derived metabolites are key bioactive compounds produced by the gut microbiota that play essential roles in maintaining host metabolism, immunity, and overall health. Several gut bacterial species, including Bacteroides, Bifidobacterium, and Lactobacillus, can synthesise and supply important vitamins such as vitamin K (menaquinones) and various B vitamins—including B_{12} (cobalamin), B_9 (folate), B_2 (riboflavin) and B_6 (pyridoxine) (Tarracchini et al., 2024; Chang et al., 2024). These microbially-synthesised vitamins act as essential cofactors in host enzymatic reactions, supporting energy metabolism, red blood cell formation and DNA synthesis (Dai et al., 2023). In addition to vitamins, microbial metabolism of amino acids generates numerous bioactive metabolites. For instance, the breakdown of tryptophan produces indole derivatives that modulate immune and intestinal functions (Li et al., 2025), while lysine and arginine fermentation yield compounds like cadaverine and agmatine, which can influence cellular signalling and gut motility (Lu et al., 2024; Lillie et ., 2024). Furthermore, microbial-derived γ-aminobutyric acid (GABA), produced from glutamate, acts as a neurotransmitter that participates in gut–brain communication and may affect mood and stress responses (Nakhal et al., 2024). Collectively, vitamins and amino acid–derived microbial metabolites represent a crucial biochemical link between gut microbial activity and host metabolic and neurological health (Gou et al., 2024).

GAS AND VOLATILE METABOLITES:

Gases and volatile metabolites are important microbial products generated during the fermentation and metabolic activities of the gut microbiota. Gases such as hydrogen (H_2), carbon dioxide (CO_2), methane (CH_4), hydrogen sulfide (H_2S), and ammonia (NH_3) — as well as volatile organic compounds (VOCs) including short-chain alcohols, aldehydes and ketones — arise primarily from the microbial breakdown of carbohydrates, proteins and sulfur-containing compounds by diverse taxa (e.g., members of the genera Clostridium, Bacteroides, Methanobrevibacter, and Desulfovibrio) (Smith et al., 2022; Johnson & Lee, 2023). These microbial gases and volatiles play dual physiological roles for the host. For example, H_2 and CH_4 contribute to redox balance in the gut and can influence intestinal motility — with elevated methane production being linked to constipation-predominant irritable bowel-syndrome (IBS-C) (Garcia et al., 2024). H_2S, while toxic at high concentrations, also functions at low concentrations as a signalling molecule: it regulates inflammation, mucosal defence, and vascular tone (Buret& Wallace, 2023). Moreover, microbial VOCs play roles in inter-microbial communication within the gut ecosystem and show promise as biomarkers for gastrointestinal and metabolic disorders (Yang et al., 2025). Overall, gas and volatile metabolites represent a

dynamic interface between microbial metabolism and host physiology, influencing gut function, immune-signalling and disease states (Nguyen et al., 2023).

THE MICROBIOTA-METABOLITE-HOST INTERACTION:

The microbiota–metabolite–host interaction network operates through multiple communication pathways, notably the gut–brain, gut–liver and gut–skin axes, which integrate microbial metabolic activity with host physiology. In the gut–brain axis, microbial metabolites such as short-chain fatty acids (SCFAs), tryptophan-derived compounds and γ-aminobutyric acid (GABA) influence neurochemical signalling, stress responses and behaviour by modulating vagal nerve activity, neurotransmitter production and blood–brain-barrier integrity (Zhang et al., 2025; Lee et al., 2024). The gut–liver axis involves bidirectional communication mediated by microbial metabolites like bile acids, ethanol and lipopolysaccharides (LPS), which can enter the portal circulation and regulate hepatic lipid metabolism, glucose homeostasis and inflammation via the farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5) signalling pathways (Chen et al., 2024; Wang et l., 2024). Disruption of this axis contributes to liver diseases such as non-alcoholic fatty liver disease (NAFLD) and cirrhosis (Zhou et al., 2024). The gut–skin axis represents another critical interface, where microbial metabolites including SCFAs and indole derivatives modulate systemic immunity, oxidative stress and skin barrier function, thereby influencing conditions such as acne, psoriasis and atopic dermatitis (Smith et al., 2025; Brown et al., 2023). Collectively, these interconnected axes demonstrate that microbial metabolites act as signalling mediators linking the gut microbiota with distant organs, coordinating metabolic, immune and neuroendocrine homeostasis throughout the body (Garcia-Mena et al., 2024).

Microbial metabolites play a central role in regulating host immune responses, forming a key component of the microbiota–metabolite–host interaction network. Short-chain fatty acids (SCFAs) — notably acetate, propionate and butyrate — produced by gut microbial fermentation of dietary fibres, act as potent immunomodulatory molecules. SCFAs stimulate the differentiation and expansion of regulatory T cells (Tregs) in the colon by inhibiting histone deacetylases (HDACs) and enhancing the expression of Foxp3, the master transcription factor for Treg development (Huang et al., 2023). This supports mucosal tolerance and suppresses excessive inflammatory responses. Additionally, SCFAs influence dendritic cell maturation and cytokine production, promoting an anti-inflammatory milieu within the gut (Wang et al., 2024). In parallel, indole derivatives — metabolites of the amino acid tryptophan produced by gut bacteria such as Lactobacillus and Clostridium species — modulate mucosal immunity through activation of the aryl hydrocarbon receptor (AhR) pathway in intestinal epithelial and immune cells (Kim et al., 2024). AhR activation by indole-3-aldehyde and related compounds enhances the production of interleukin-22 (IL-22), which strengthens epithelial barrier integrity, promotes antimicrobial peptide expression and supports mucosal homeostasis (Liu et al., 2025). Together, SCFAs and indole derivatives exemplify how microbial metabolites integrate into host immune signalling networks, maintaining intestinal immune balance and protecting against inflammatory and autoimmune disorders (Zhao et al., 2023).

Microbial metabolites have emerged as potent endocrine-like signals that integrate gut microbial

activity with host hormonal and metabolic control. For instance, short-chain fatty acids (SCFAs) — notably acetate, propionate and butyrate — can act on enteroendocrine L cells in the gut via receptors such as GPR41 (FFAR3) and GPR43 (FFAR2), thereby promoting secretion of GLP-1 (glucagon-like peptide-1) and PYY (peptide YY) (Tolhurst et al., 2012). Through these pathways, GLP-1 augments insulin secretion and improves glucose tolerance, while PYY suppresses appetite and slows gastrointestinal transit, thereby linking microbial metabolism to host energy balance and satiety (Canfora et al., 2015; Ribeiro et al., 2024). Beyond SCFAs, microbial metabolites also influence leptin dynamics: for example, acetate has been implicated in up-regulating leptin production via activation of the parasympathetic nervous system (Perry et al., 2016). More broadly, microbiota–host crosstalk extends to the hypothalamic–pituitary–adrenal (HPA) axis: changes in microbial composition or metabolite output may alter cortisol (or corticosterone in rodent models) levels, thereby modulating stress reactivity and systemic metabolic regulation (Rusch et al., 2023). Collectively, these lines of evidence underscore how the microbiota–metabolite–host interaction network positions microbial metabolites as endocrine mediators that integrate gut microbial activity with systemic hormonal homeostasis and metabolic regulation (see also Clemente-Suárez et al., 2024).

Metabolite crosstalk among microbial communities represents a fundamental aspect of the microbiota–metabolite–host interaction network, driving both microbial ecology and host physiology. Within the gut ecosystem, different microbial taxa engage in metabolic cooperation and competition through the exchange of metabolites, a process known as cross-feeding (Flint et al., 2015). For example, Bifidobacterium species ferment complex carbohydrates to produce acetate and lactate, which are subsequently utilized by Faecalibacteriumprausnitzii and Eubacterium rectale to generate butyrate — a key short-chain fatty acid that supports intestinal epithelial health (Ríos-Covían et al., 2016). Similarly, sulfur-reducing bacteria such as Desulfovibrio can utilize hydrogen and lactate produced by fermentative bacteria, regulating redox balance in the gut (Rey et al., 2010). Beyond energy metabolism, microbial crosstalk extends to amino acid and bile acid transformations, influencing the overall composition and function of the gut microbiome. This intricate metabolic interdependence not only enhances microbial diversity and ecosystem resilience, but also shapes the repertoire of metabolites available to the host, ultimately modulating immune, metabolic, and neurological functions (Dodd et al., 2017).

DYSBIOSIS AND ITS PATHOPHYSIOLOGICAL IMPLICATIONS:

Type/ Feature of Dysbiosis	Microbial/ Metabolic Alteration	Pathophysiological Consequences	Associated Disorders	References
Loss of beneficial microbes	Decrease in *Bifidobacterium* and *Lactobacillus* species; reduced production of short-chain fatty acids (SCFAs)	Impaired epithelial barrier, reduced mucosal immunity, increased intestinal permeability	Inflammatory bowel disease (IBD), allergies, autoimmune disorders	Petersen & Round, 2014; Levy et al., 2017
Overgrowth of pathogenic species	Expansion of *Enterobacteriaceae*, *Clostridium difficile*, and sulfate-reducing bacteria;	Chronic inflammation, oxidative stress, endotoxemia	IBD, sepsis, metabolic syndrome	Levy et al., 2017; Thaiss et al., 2016

	increased production of LPS and hydrogen sulfide			
Reduced microbial diversity	Decreased species richness and functional redundancy	Disrupted microbial resilience, loss of cross-feeding, and unstable metabolite networks	Obesity, diabetes, NAFLD	Zhao, 2013; Gilbert et al., 2018
Altered metabolite profiles	Decreased SCFAs; increased harmful metabolites such as secondary bile acids and LPS	Immune dysregulation, insulin resistance, hepatic inflammation	Type 2 diabetes, NAFLD, cardiovascular disease	Levy et al., 2017; Thaiss et al., 2016
Gut–brain axis disruption	Imbalance in microbial neurotransmitter and metabolite signaling (e.g., serotonin, GABA)	Neuroinflammation, altered stress responses, behavioral changes	Depression, autism spectrum disorders	Gilbert et al., 2018

The human microbiota and its metabolites have opened promising translational and therapeutic avenues for improving human health. Microbial communities and their metabolic products—such as short-chain fatty acids (SCFAs), bile-acid derivatives and tryptophan metabolites—play key roles in regulating host immunity, metabolism and neurological function (Nicholson et al., 2012). Therapeutic modulation of the microbiota aims to restore microbial balance and functional diversity through strategies such as probiotics, prebiotics, synbiotics and postbiotics, which enhance beneficial microbial activity and metabolite production (Markowiak&Śliżewska, 2017). Faecal microbiota transplantation (FMT) has emerged as a powerful clinical intervention, particularly for recurrent Clostridioides difficile infection (rCDI) and other dysbiosis-associated disorders (Khoruts& Sadowsky, 2016). Moreover, advances in metabolomics and precision medicine are enabling the development of targeted microbial therapies, including engineered bacterial strains and small-molecule mimetics designed to modulate specific host signalling pathways (Zhao et al., 2021). These translational approaches hold potential not only for gastrointestinal diseases but also for systemic conditions such as obesity, diabetes and neuropsychiatric disorders by re-establishing a healthy microbiota–metabolite–host interaction network (Fan & Pedersen, 2021).

Future research on the human microbial flora and its metabolites is expected to advance toward a more integrated and personalized understanding of the microbiota–metabolite–host axis. The next frontier involves the application of multi-omics technologies—including metagenomics, metabolomics, transcriptomics, and proteomics—to map dynamic interactions between microbes and host physiology at a systems level (Lloyd-Price et al., 2017). Integration of these datasets with artificial intelligence (AI) and machine learning will enable predictive modeling of microbiome-associated disease risks and therapeutic outcomes (Johnson et al., 2019). In addition, the development of engineered probiotics and synthetic microbial consortia offers potential for precisely modulating metabolic outputs to restore host homeostasis (Sheth et al., 2016). Future directions also include expanding microbiome-targeted drug discovery, identifying novel bioactive metabolites that could serve as biomarkers or therapeutic agents (Fan & Pedersen, 2021). Furthermore, longitudinal and personalized microbiome interventions tailored to individual genetic, dietary, and environmental factors—will

likely shape the next generation of preventive and therapeutic strategies. Ultimately, translating microbiome science into clinical practice will depend on establishing causal mechanisms, standardized methodologies, and ethical frameworks for manipulating the human microbiota.

CONCLUSION:

The human microbiota is a complex and dynamic ecosystem that functions in close partnership with its host, forming an integrated superorganism vital for maintaining health and homeostasis. Spread across body sites such as the gut, skin, oral cavity, and urogenital tract, these microbial communities perform essential metabolic roles including nutrient breakdown, vitamin synthesis, and immune regulation. Through the production of metabolites like short-chain fatty acids, bile acid derivatives, indoles, and polyphenol metabolites, the microbiota influences metabolism, immunity, and neuroendocrine signaling. However, disruptions in microbial composition or function—known as dysbiosis—can lead to various disorders such as obesity, diabetes, inflammatory bowel disease, and depression (Khan et al., 2024; Vicchio, 2024). The microbiota's communication with distant organs through the gut–brain, gut–liver, and gut–skin axes highlights its systemic importance, and therapies like probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation aim to restore this ecological balance (Vicchio, 2024; Adom et al., 2025).

Emerging technologies such as multi-omics, artificial intelligence, and synthetic biology are transforming microbiome research, paving the way for precision medicine. Integrating metagenomics, metabolomics, transcriptomics, and proteomics allows scientists to map host–microbe interactions at a systems level (Wu et al., 2024). When combined with AI and machine learning, these approaches can predict disease risks and therapeutic responses (Zhou et al., 2025). Moreover, engineered probiotics and synthetic microbial consortia show promise for fine-tuning microbial metabolism and restoring host homeostasis (Shahid et al., 2025). Future research will focus on microbiome-based drug discovery, identifying novel bioactive metabolites as biomarkers or therapeutic agents (Pammi et al., 2022), and developing personalized interventions based on genetic, dietary, and environmental factors. Translating microbiome science into clinical practice will ultimately rely on uncovering causal mechanisms, standardizing methodologies, and ensuring ethical management of human microbiota.

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HOW TO CITE: Dehima SK, Sian Lawrence, R Hymavathi V, Swathi Putta, Human Microbiota and Their Metabolites: Drivers of Host Physiology and Health, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 1, 1160-1172. https://doi.org/10.5281/zenodo.18224422