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Brief Report

Gut Microbes: Nature's Hidden Chemists with the Potential to Synthesize Therapeutics

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ABSTRACT

The human gut microbiome, once considered a passive collection of commensal organisms, is now recognized as a dynamic biochemical factory. Among its many functions, one of the most remarkable is its capacity to synthesize complex bioactive compounds, including metabolites with pharmacological activity. This article reviews recent discoveries highlighting the drug-like molecules produced by gut microbes, explores the implications for drug discovery and personalized medicine, and proposes a framework for leveraging microbial biosynthesis as a novel therapeutic frontier.

Keywords: Gut microbiome, Biosynthetic gene clusters, Natural products, Microbial metabolism, Drug discovery, Metabolomics, Synthetic biology.

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INTRODUCTION

The human gut is home to trillions of microbes that collectively form a dynamic and highly specialized metabolic ecosystem. Long considered passive passengers within the body, these microbes are now understood to be active biochemical agents, producing, transforming, and regulating compounds with profound pharmacological effects on host physiology.[1-4] In recent years, one of the most exciting revelations in microbiome science has been the recognition that gut bacteria act as "hidden chemists," synthesizing drug-like molecules that impact human health and disease. Their metabolic outputs, including bioactive lipids, peptides, and hormone analogues, have the potential not only to influence existing therapeutic pathways but also to define entirely new ones including disease modifying capabilities.[2,5-11] A particularly promising frontier in this field involves microbiota-derived Bile Acids (BAs). Traditionally viewed as host-synthesized agents critical for fat digestion, BAs are now appreciated as complex signalling molecules that participate in immune regulation, metabolic control, and even tumour dynamics (Figure 1). A recent integrative study combining bile acid metabolomics, microbial genetics, and bioinformatics has revealed that the biosynthetic capabilities of gut microbes in this domain are far more extensive than previously thought.[12] By functionally profiling over 200 putative microbial genes involved in BA metabolism, researchers identified 56 previously uncharacterized bile acids, many of which are detectable in both humans and other mammals. Most strikingly, a subset of these newly identified bile acids was observed to be potent antagonists of the human Androgen Receptor (hAR), a nuclear receptor that regulates gene expression related to development, metabolism, and cancer progression. These microbial BAs were shown to suppress AR-mediated transcriptional activity and inhibit androgen-driven gene expression in human cells.[12] In a compelling proof-of-concept experiment, one of these BAs was demonstrated to suppress tumour growth and enhance the efficacy of anti-programmed death-1 immunotherapy in an AR-dependent manner, providing evidence of a previously unrecognized gut microbiome–cancer axis. This discovery not only expands the catalogue of microbiota-derived molecules with drug-like activity but also establishes a causal and mechanistic link between microbial metabolism and host endocrine signalling.

Beyond bile acids, the gut microbiome is known to produce a range of bioactive compounds including indoles, short-chain fatty acids, and small-molecule peptides that modulate the immune system and affect neurological and metabolic processes (Figure 1). What distinguishes microbial biosynthesis in the gut from classical pharmaceutical chemistry is its adaptability and personalization. The metabolic profiles of individual microbiomes vary with diet, genetics, and environment, resulting in a personalized pharmacological fingerprint that could explain differential drug responses among patients.[2,13,14] Understanding and harnessing this microbial biosynthetic potential presents a new paradigm for drug discovery.[15,16] Instead of synthesizing drugs from scratch through traditional chemical methods, a paradigm shift is emerging in the field of drug discovery, one

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that centres on mining microbial metabolites, particularly those produced by the human gut microbiome.[17,18] This innovative approach leverages the natural biosynthetic capacity of microbes, enabling researchers to identify novel bioactive compounds with therapeutic potential. The gut microbiome functions as a vast chemical factory, continuously generating a wide array of small molecules, peptides, and secondary metabolites that interact with host cells, signalling pathways, and receptors.[2,19-21] By studying the biosynthetic gene clusters encoded in microbial genomes, researchers can uncover new classes of compounds that were previously overlooked using classical pharmaceutical pipelines.[22,23] This microbial-based approach offers several advantages that could significantly improve the current therapeutic development process. First, it introduces a new level of efficiency and sustainability. Traditional drug development often involves labour-intensive screening of large compound libraries or complex multi-step synthesis of novel molecules. In contrast, microbial biosynthesis enables the natural production of complex molecules in a cost-effective and scalable manner, reducing time and resource investment. Moreover, advances in synthetic biology allow researchers to engineer gut microbes to enhance the yield, specificity, and therapeutic action of these compounds *in vivo*.[24] This opens the door for "living therapeutics," where engineered microbial strains are administered to continuously produce therapeutic molecules within the human body, thus eliminating the need for repeated dosing and improving patient compliance. Second, this strategy supports a more personalized approach to medicine. Because the composition of each individual's gut microbiome is shaped by their genetics, diet, environment, and lifestyle, and hence the metabolites produced can vary from person to person.[25-28] This unique metabolic fingerprint may help explain why individuals respond differently to the same drug. By incorporating microbiome profiling into drug development and treatment planning, researchers can predict and account for variations in drug metabolism, efficacy, and toxicity, thereby improving safety and therapeutic outcomes. This can be particularly useful for managing chronic diseases such as diabetes, cancer, or neurodegenerative disorders, where conventional therapies often suffer from variable responses and significant side effects. Additionally, mining microbial metabolites for drug discovery expands the chemical diversity of drug candidates. Microbes produce compounds with structures and mechanisms of action that are distinct from those typically synthesized in pharmaceutical labs. This diversity can help overcome limitations in targeting "undruggable" proteins or pathways that resist conventional small molecule approaches. Some microbial metabolites also function as agonists or antagonists of human receptors, mimicking natural ligands with high specificity and low toxicity.[29-34] Integrating microbial metabolite mining into the drug development process provides a powerful complement to existing pharmaceutical strategies. It enhances drug discovery efficiency, supports personalized treatment, broadens the chemical landscape of therapeutic candidates, and enables the development of microbiome-based therapies that work synergistically with the human host. This represents a transformative shift in therapeutics development, moving from synthetic, one-size-fits-all drugs to tailored microbiome-informed therapeutics that leverage nature's own medicinal chemists.

Emerging evidence underscores the profound influence of gut microbiota-derived metabolites on host physiology, with significant implications for disease development, progression, and therapeutic intervention. Microbial metabolites such as Trimethylamine N-Oxide (TMAO), Phenylacetylglutamine (PAGln), Indoxyl Sulfate (IS), Trimethyllysine (TML), Deoxycholic Acid (DCA), and Trimethylamine (TMA) have been strongly associated with increased risk of Major Adverse Cardiovascular Events (MACEs), stroke, Parkinson's disease, and Type 2 Diabetes Mellitus (T2DM).[15,35,36] Notably, TMAO not only promotes cardiovascular dysfunction but also exacerbates neurological disorders like Parkinson's and stroke through pro-inflammatory and metabolic dysregulation.[37-41] PAGln, by interacting with adrenergic receptors, promotes platelet thrombosis,[42,43] while IS and TML contribute to endothelial dysfunction.[8,44] In metabolic disease, tryptamine and phenethylamine-producing gut microbes drive insulin resistance,[45,46] with molecular mechanisms pointing to altered hepatic and systemic signalling. Moreover, metabolites such as 3-dehydrocarnitine, leucine, and epiandrosterone sulfate have emerged as potential biomarkers in obstructive sleep apnea,[47,48] and indole derivatives (IPA, IAA, and ILA) activate protective pathways (GPR30/AMPK/SIRT1), alleviating neurodegeneration associated with aging.[49,50] In acute and chronic inflammatory diseases, compounds such as Nicotinamide Mononucleotide (NMN) and glutamine reduce organ injury (e.g., in liver ischemia/reperfusion or pancreatitis) via SIRT3-PRDX5 and macrophage metabolic reprogramming, respectively.[51,52] Other anti-inflammatory microbial metabolites, such as 12-ketolithocholic acid, inhibit IL-17A to suppress ulcerative colitis exacerbation,[53-55] while urolithins derived from ellagitannins exhibit potent anti-inflammatory and anticancer activity, especially when paired with standard therapies like 5-fluorouracil.[56-58]

Furthermore, gut microbiota influences a variety of immune, metabolic, and oncological pathways via the production of Short-Chain Fatty Acids (SCFAs) like butyrate, acetate, and propionate. These SCFAs regulate mucosal immunity by promoting IL-22 production, enhancing $CD4^+$ T cells and innate Lymphoid Cells (ILCs) function, and maintaining intestinal homeostasis.[59-61] Butyrate activates the macrophage/WNT/ERK signalling axis to support gut barrier repair[62] and regulates gluconeogenesis in pregnancy via cAMP-PKA-GCN5 pathway.[63] Intriguingly, SCFAs can both support health by enhancing cardiac adaptation to pressure overload[64] and preventing precocious puberty[65] and facilitate disease progression, such

as by promoting prostate cancer growth through Insulin like Growth Factor-1 (IGF-1) signalling.[66] Such counterintuitive and context-dependent effects may explain the contrasting pharmacological profiles observed among different SCFAs. These complex interactions underscore the need for network pharmacology approaches,[67-69] which can model the multifaceted molecular targets and signalling pathways influenced by SCFAs across tissues, thereby enabling a systems-level understanding of their beneficial versus pathological roles. Indole metabolites interact with the aryl hydrocarbon receptor (AhR) to reinforce mucosal immunity and phagocytic activity, even protecting against radiation toxicity and septic injury.[70,71] Metabolites such as inositol-1,4,5-trisphosphate (InsP3) promote epithelial repair,[72] and D-serine confers protection against acute kidney injury.[73] In the context of microbial signalling, autoinducer-2 (AI-2) modulates lung inflammation,[20] while bioactive peptides influence human immunity, even in Inflammatory Bowel Disease (IBD).[74] These findings not only highlight the gut microbiota as a master regulator of immune and metabolic health but also establish a foundation for targeted microbiota-based interventions such as dietary modulation, microbial metabolite supplementation, and microbiome engineering as promising strategies for combating a wide range of diseases, including neurodegeneration, cardiovascular disease, inflammatory disorders, infections, and cancer.

While many microbial metabolites offer therapeutic potential, it is important to acknowledge that not all of them are beneficial. Several gut microbiota-derived compounds have been implicated in the development and progression of pathological conditions. For instance, TMA, produced from dietary choline and carnitine by gut microbes, is converted in the liver to TMAO, a metabolite strongly associated with cardiovascular diseases, including atherosclerosis and stroke.[75-77] Similarly, metabolites such as IS and p-cresyl sulfate have been linked to chronic kidney disease and systemic inflammation.[15,76,78,79] Certain microbial metabolites, like 4-EPS, have even been shown to influence brain function and behaviour in animal models, suggesting a role in neurodevelopmental disorders.[10] These findings underscore the dual nature of the gut microbiome's metabolic output, while some metabolites support host health, others contribute to disease. This opens a promising avenue for therapeutic intervention focused on reshaping the microbiota composition to favour beneficial metabolic profiles. Strategies such as precision probiotics, prebiotic supplementation, dietary modulation, or even microbiome transplantation can be employed to suppress the production of harmful metabolites and promote the synthesis of protective ones. By improving the quality of the gut microbiome, we can potentially prevent or mitigate the impact of harmful microbial metabolism, making microbiota-targeted therapy a vital component of personalized and preventive medicine.

Gut microbiota-derived metabolites activate a broad spectrum of host receptors, eliciting diverse pharmacological effects across physiological systems. SCFAs such as acetate, propionate, and butyrate primarily signal through G-Protein-Coupled Receptors (GPCRs) like GPR41, GPR43, and GPR109A,[11,80,81] where they regulate immune responses, energy homeostasis, and epithelial integrity. Tryptophan-derived metabolites, including Indole-3-Acetic Acid (IAA), Indole-3-Propionic Acid (IPA), and Indole-3-Aldehyde (IAld) engage the AhR,[82,83] influencing mucosal immunity, inflammatory tone, and neuroprotection. Microbial-modified bile acids activate nuclear receptors such as Farnesoid X Receptor (FXR)[84] and Pregnane X Receptor (PXR),[85,86] governing bile acid metabolism, xenobiotic detoxification, and innate immunity. Meanwhile, phenolic metabolites like p-cresol and PAGln interact with adrenergic receptors,[43,87] heightening platelet reactivity and cardiovascular risk. Neuroactive metabolites such as Gamma-Aminobutyric Acid (GABA) produced by specific microbes affect GABAergic signalling,[88,89] potentially influencing behaviour, anxiety, and gut motility. Other microbial products, including butyrate, function as Histone Deacetylase (HDAC) inhibitors,[90,91] thereby modulating host gene expression and epigenetic landscapes. However, not all receptor-mediated effects are beneficial, some contribute to disease pathology. For example, TMAO, a metabolite that indirectly signals through vascular and inflammatory pathways, is associated with heightened cardiovascular risk.[36,38,92] Similarly, excessive activation of certain receptors by microbial toxins can lead to chronic inflammation or metabolic imbalance. These challenges highlight the need for targeted strategies to shift the microbial metabolite profile toward health-promoting compounds. One solution involves the use of next-generation probiotics and engineered bacterial strains designed to produce specific beneficial metabolites while suppressing harmful ones. Dietary modulation through prebiotic fibers, polyphenols, and low-choline diets can also alter microbial composition and function to favour desirable receptor-ligand interactions. Additionally, precision interventions such as microbial gene editing or selective small-molecule inhibitors may allow us to modulate receptor signalling pathways directly. By understanding the receptor-specific actions of gut-derived metabolites, we can develop novel therapies that either amplify protective signals or block deleterious ones, transforming the gut microbiome from a passive player into a programmable pharmacological platform.

Nonetheless, major challenges remain. The complexity of microbial ecosystems and their dependence on host and environmental context complicates the functional mapping of microbial metabolites. Many biosynthetic pathways remain cryptic, and a substantial fraction of gut microbes are not readily culturable using standard techniques. Tools such as gnotobiotic animal models, organoid systems, high-resolution metabolomics, and machine learning-driven genome mining are becoming indispensable in overcoming these hurdles. If

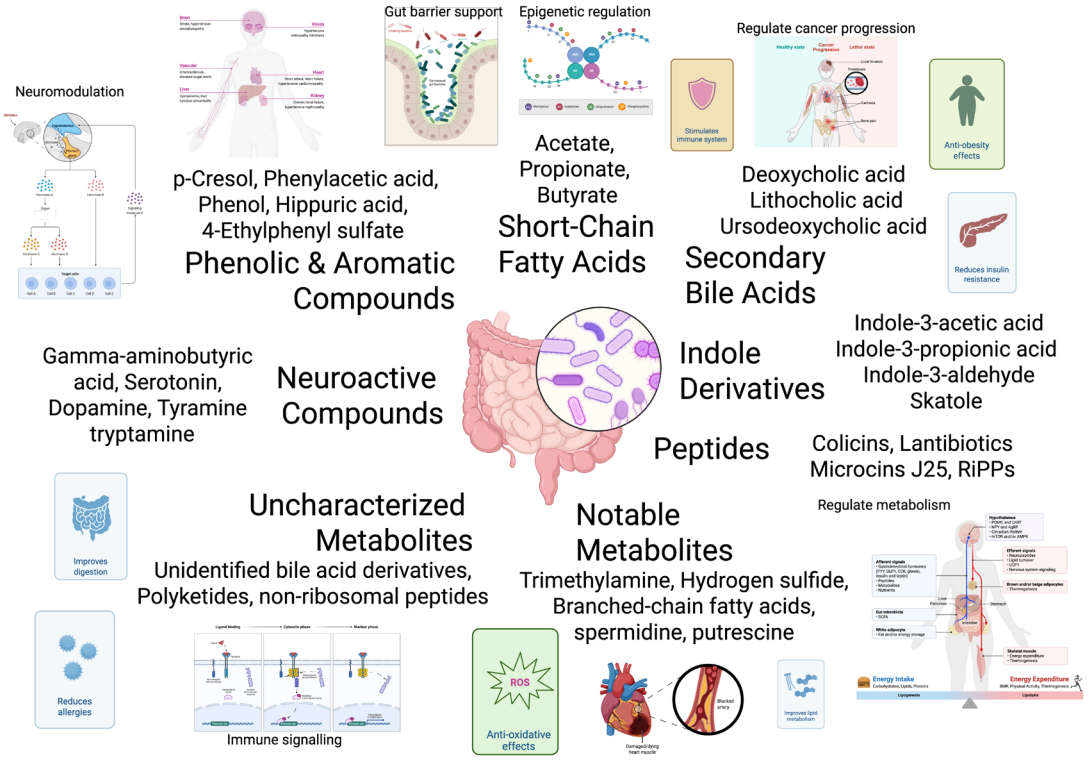

Figure 1: Systematic effects of gut microbiota derived metabolites. The figure shows a few examples of gut microbiota derived metabolites and the diversified effects (beneficial and pathological) on systemic physiology. RiPPs: Ribosomally synthesized and post-translationally modified peptides.

microbes can manufacture compounds that modulate nuclear receptors like hAR, could they also be coaxed to generate analogues of known drugs or entirely new therapeutic classes? With advances in synthetic biology, microbiome editing, and precision metabolomics, we may soon be designing microbial consortia not just for gut health, but as live, programmable drug factories, producing anti-inflammatories, anticancer agents, neuromodulators, and more. Genetically modified microbes are rapidly transforming the landscape of chemical synthesis by serving as programmable platforms to produce complex, high-value compounds. Through advances in synthetic biology and metabolic engineering, scientists can rewire microbial genomes to enhance or introduce new biosynthetic pathways, enabling the precise production of pharmaceuticals. For example, engineered strains of Escherichia coli and Saccharomyces cerevisiae have been developed to produce artemisinin (an antimalarial drug),[93] opioids,[94] and even chemotherapy agents like Taxol precursors.[95,96] In the context of the gut microbiome, researchers are now exploring how genetically modified commensal bacteria can be tailored to synthesize therapeutic molecules directly in the human body, offering targeted treatment for diseases such as metabolic disorders, cancer, and inflammatory bowel disease.[97,98] These engineered microbes not only offer sustainable and scalable alternatives to traditional chemical synthesis but also open new avenues for *in situ* drug delivery, microbiome-based therapeutics, and precision medicine. This vision demands a shift in how we approach drug discovery. Rather than synthesizing every compound *in vitro*, perhaps the future lies in mining and directing the metabolic genius of our microbial partners. The gut microbiome may yet prove to be the most versatile chemist we've ever known. In short, your next medicine may already be living inside you.

CONCLUSION

In conclusion, the gut microbiota functions as a powerful, underexplored source of natural product biosynthesis. Microbes are not merely metabolically bio-transforming drugs, they are also actively synthesizing bioactive chemicals that influence host physiology. Microbes independently produce a vast array of bioactive metabolites from dietary components, host-derived substrates, and their own metabolic processes. These include SCFAs, indole derivatives, secondary bile acids, neurotransmitters (e.g., GABA, serotonin precursors), phenolic compounds, polyamines, and peptides like microcins and lantibiotics. Many of these metabolites interact directly with host receptors (e.g., GPCRs, nuclear receptors, AhR), modulate immune and nervous system activity, influence metabolism, and even impact epigenetic regulation via HDAC inhibition. The microbial biosynthesis of such compounds is increasingly viewed as a form of *in vivo* drug production, with applications in designing living therapeutics, engineered microbes that synthesize specific beneficial molecules

within the host. This opens a powerful new frontier in drug discovery, rather than creating new drugs from scratch, scientists can mine the microbial genome for biosynthetic gene clusters and harness the microbiota's natural metabolic machinery to produce novel therapeutics. As our ability to decode and manipulate these microbial pathways improves, we are entering an era where future therapeutics may originate not in a laboratory beaker, but from the living chemistry lab within our own bodies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

4-EPS: 4-ethylphenyl sulfate; **AhR:** Aryl hydrocarbon receptor; **AI-2:** Autoinducer-2; **BAs:** Bile acids; **DCA:** Deoxycholic acid; **FXR:** Farnesoid X receptor; **GABA:** Gamma-aminobutyric acid; **GPCRs:** G-protein-coupled receptors; **hAR:** Human androgen receptor; **HDAC:** Histone deacetylase; **IAA:** Indole-3-acetic acid; **IAld:** Indole-3-aldehyde; **IBD:** Inflammatory bowel disease; **IGF-1:** Insulin like growth factor-1; **ILA:** Indole-3-lactic acid; **ILCs:** Innate lymphoid cells; **InsP3:** Inositol-1,4,5-trisphosphate; **IPA:** Indole-3-propionic acid; **IS:** Indoxyl Sulfate; **MACEs:** Major adverse cardiovascular events; **NMN:** Nicotinamide mononucleotide; **PAGln:** Phenylacetylglutamine; **PXR:** Pregnane X receptor; **SCFAs:** Short-chain fatty acids; **T2DM:** Type 2 diabetes mellitus; **TMA:** Trimethylamine; **TMAO:** Trimethylamine N-oxide; **TML:** Trimethy-l-lysine.

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