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*Review*

# Microbiome-Derived Effectors and Convergent Host Pathways in Organ Injury and Fibrosis

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**Abstract**

The human microbiome functions as an endocrine-like biochemical network that generates metabolites, structural ligands, and peptides capable of shaping host physiology. Under physiological conditions, these microbiome-derived effectors contribute to epithelial integrity, immune homeostasis, metabolic regulation, and tissue resilience. During dysbiosis, however, the composition and systemic distribution of these effectors are altered, shifting host responses toward injury. Despite their chemical diversity, microbiome-derived signals converge on a limited set of host pathways, including pattern-recognition receptor activation, mitochondrial dysfunction, apoptosis and senescence, inflammatory amplification, and fibrosis, which collectively determine tissue vulnerability across organ systems. This framework links gut imbalance to disorders such as pulmonary fibrosis, acute lung injury, chronic kidney disease, and hepatobiliary inflammation. Microbial peptides represent an emerging layer of regulation. Among these peptides, corisin exemplifies how discrete microbial effectors can directly engage intracellular targets and amplify tissue injury. Together, these observations reframe microbiome-associated disease as a disorder of microbial chemistry and host pathway activation, thereby providing a foundation for mechanism-based biomarkers and targeted therapeutic strategies.

**Keywords:** microbiome; dysbiosis; microbial metabolites; peptides; host-microbe interactions; corisin; inflammation; fibrosis; coagulopathy; bile acids; short-chain fatty acids; tryptophan metabolism

## 1. Introduction

All multicellular organisms coexist with complex, dynamic microbial communities, collectively referred to as the microbiota. The term microbiome encompasses not only the genomes of these microorganisms but also their collective functional capacity and metabolic output [1]. Among all anatomical sites, the gastrointestinal tract harbors the greatest microbial density and diversity, serving as a central hub of host–microbe interaction [2]. In health, the microbiome supports nutrient metabolism, vitamin synthesis, immune maturation, and resistance to pathogen colonization [3,4,5,6,7,8]. Increasingly, however, it is recognized not merely as a passive commensal ecosystem but as a metabolically active, endocrine-like organ that continuously generates bioactive molecules capable of shaping host physiology locally and systemically [9,10].

Traditionally, microbiome research has emphasized compositional changes, alterations in bacterial diversity, and taxonomic abundance as correlates of disease. However, although reduced diversity and shifts in specific genera are frequently associated with pathological states, taxonomic profiles alone provide limited insights into disease pathogenesis. In addition, there is substantial individual variability in microbial communities, which may be influenced by age, genetics, diet, medications, and environmental exposures [11]. Therefore, recent research has shifted toward functional characterization of the microbiome, focusing on microbial enzymatic activities, metabolite production, and secreted molecular effectors [12,13]. This transition from descriptive ecology to mechanistic biochemistry reframes the microbiome as a dynamic source of chemical mediators that interact with host cells and tissues. Molecules released from the microbial communities includ short-chain fatty acids, secondary bile acids, trypto-

phan metabolites, trimethylamine N-oxide, bioactive peptides, and structural components such as lipopolysaccharide and peptidoglycan fragments.

Under physiological conditions, microbiota-derived effectors contribute to maintaining epithelial barrier integrity, immune tone, metabolic homeostasis, and vascular function [14,15]. In contrast, during dysbiosis or epithelial barrier disruption, microbial metabolites and peptides can translocate into the circulation and reach distant organs, where they may promote disease by modulating multiple host signaling pathways [3,16]. Although these signals are chemically diverse, they often converge on common host stress responses, including reactive oxygen species (ROS) generation, apoptosis, senescence, procoagulant activity, proinflammatory cytokine production, and excessive extracellular matrix deposition, thereby driving organ injury and fibrosis.

Rather than providing an exhaustive catalog of microbiome-associated diseases, this review adopts a mechanism-centered approach. We focus on pulmonary fibrosis, acute lung injury, acute cholangitis, and chronic kidney disease as representative barrier-organ disorders in which microbiome-derived metabolites and peptides converge on shared host pathways, mitochondrial stress, apoptosis, senescence, inflammation, and fibrosis. By integrating insights from microbial ecology, metabolomics, and experimental models, we propose that these conditions exemplify a broader principle: the microbiome acts as a systemic biochemical network whose products can either preserve homeostasis or drive multi-organ pathology. Understanding these effector-level mechanisms not only refines our conceptualization of dysbiosis but also identifies actionable therapeutic nodes, including metabolite modulation, receptor-targeted strategies, and neutralization of pathogenic microbial peptides.

## 2. The Microbiome as a Source of Systemic Bioactive Molecules

The microbiome produces a vast, chemically diverse repertoire of bioactive molecules that extends its influence well beyond local ecological interactions. These microbial products act as signaling mediators between microorganisms and host tissues, regulating epithelial integrity, immune homeostasis, metabolic function, and vascular biology. Under physiological conditions, many of these compounds contribute to host protection and resilience. However, during dysbiosis and barrier disruption, the qualitative and quantitative balance of microbial metabolites and peptides shifts, enabling the systemic dissemination of metabolites and peptides that can promote inflammation, mitochondrial dysfunction, cellular stress, and tissue injury. This section summarizes major classes of microbiome-derived bioactive molecules with demonstrated relevance to host pathology.

### *2.1 Small-Molecule Metabolites*

#### 2.1.1 Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs), principally acetate, propionate, and butyrate, are generated by bacterial fermentation of dietary fibers and are among the most abundant microbiome-derived metabolites. SCFAs play central roles in maintaining epithelial barrier integrity, regulating immune tolerance, and preserving metabolic homeostasis [17,18,19]. Mechanistically, they signal through G protein–coupled receptors (GPR41, GPR43, and GPR109A) and function as histone deacetylase (HDAC) inhibitors, thereby shaping transcriptional programs in epithelial and immune cells [20,21,22]. In experimental models of lung, kidney, and intestinal injury, SCFAs attenuate oxidative stress, suppress proinflammatory cytokine production, and reduce epithelial apoptosis [23,24,25,26]. Conversely, depletion of SCFA-producing bacteria correlates with heightened inflammation and increased susceptibility to tissue injury and fibrosis, underscoring the protective dimension of this metabolite class [27]. However, the effects of SCFAs are not uniformly protective, as they can also promote inflammatory responses or pathological remodeling under specific conditions, depending on their concentration, the target cell type, and the local tissue environment [28].

#### 2.1.2 Bile Acids

Primary bile acids synthesized in the liver undergo extensive microbial modification in the intestine, including deconjugation and 7α-dehydroxylation, generating a complex pool of secondary bile acids. These metabolites function as signaling molecules through the nuclear receptor farnesoid X receptor (FXR) and the G protein–coupled bile acid receptor TGR5. Under physiological conditions, balanced bile acid signaling through FXR and TGR5 contributes to epithelial barrier integrity, immune homeostasis, antimicrobial defense, and metabolic regulation [29,30]. However, the effects of bile acids are also context-dependent, and dysregulated bile acid composition, particularly enrichment of specific secondary bile acids, can promote epithelial injury, inflammasome activation, inflammation, and fibrotic remodeling in both intestinal and extraintestinal tissues [31]. Dysbiosis-associated alterations in bile-acid composition disrupt these signaling pathways and have been linked to enhanced inflammatory and fibrotic responses in the lung, liver, biliary tract, and kidney [29]. Thus, microbial control of bile-acid metabolism represents a major conduit through which intestinal ecology shapes systemic inflammatory tone.

#### 2.1.3 Tryptophan Metabolites

The microbiome extensively metabolizes dietary tryptophan into indole derivatives, kynurenines, and other bioactive compounds [32]. Many of these metabolites activate the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that regulates mucosal im-

munity, oxidative balance, and epithelial differentiation [33]. Under physiological conditions, AhR activation by microbial tryptophan metabolites supports epithelial barrier integrity, promotes immune tolerance, and contributes to the maintenance of mucosal homeostasis [34]. However, the biological effects of tryptophan-derived metabolites are highly context-dependent, as excessive or sustained AhR activation, or activation by distinct ligand classes, can promote proinflammatory signaling, epithelial stress responses, fibroblast activation, and cellular senescence in various disease settings [35,36,37].

#### 2.1.4 Trimethylamine-N-Oxide

Trimethylamine N-oxide (TMAO) is produced through microbial conversion of dietary choline and carnitine to trimethylamine (TMA), followed by hepatic oxidation [38]. Under physiological conditions, TMAO contributes to cellular homeostasis by functioning as an osmolyte and stabilizing protein structure, thereby supporting proper protein folding and cellular stress responses [39]. However, under conditions of metabolic imbalance or dysbiosis, elevated circulating TMAO levels have been implicated in endothelial dysfunction, platelet hyperreactivity, and inflammatory signaling [40]. Increased TMAO concentrations are associated with adverse cardiovascular and renal outcomes and have been linked to thromboinflammatory complications in systemic diseases [41]. Mechanistically, TMAO promotes vascular inflammation, enhances platelet responsiveness, and contributes to prothrombotic states, thereby linking microbiome-derived metabolism to vascular and coagulation pathology [42]. Collectively, these observations indicate that the biological effects of TMAO are context-dependent, reflecting a balance between its physiological roles in maintaining cellular stability and its potential to drive vascular dysfunction and inflammation under pathological conditions.

### *2.2 Microbial Structural Products*

Beyond small-molecule metabolites, bacterial structural components exert potent immunomodulatory effects. Under physiological conditions, controlled exposure to microbial structural products contributes to immune homeostasis by promoting basal innate immune signaling, maintaining epithelial barrier integrity, and supporting host–microbe mutualism [43]. Lipopolysaccharide (LPS), derived from Gram-negative bacteria, and peptidoglycan fragments from bacterial cell walls can engage pattern-recognition receptors, including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) proteins, thereby shaping antimicrobial defense, epithelial renewal, and immune tolerance [44].

However, under conditions of dysbiosis or barrier disruption, increased translocation and sustained exposure to these structural ligands can drive pathological responses. Chronic or excessive activation of TLR and NOD signaling pathways promotes NF-κB activation, inflammasome signaling, oxidative stress, and the production of proinflammatory cytokines, leading to epithelial injury, apoptosis, and fibroblast activation [45]. This shift from regulated signaling to persistent inflammatory activation provides a mechanistic link between microbial imbalance, systemic inflammation, and progressive tissue remodeling in multiple organs.

Collectively, these observations indicate that microbial structural products function as conditional regulators of host responses, contributing to immune homeostasis under controlled conditions but promoting inflammatory and fibrotic pathology when their exposure is excessive or dysregulated.

### *2.3 Microbial Peptides as Emerging Host-Interacting Effectors*

In addition to metabolites and structural motifs, the microbiome produces a diverse array of peptides with biological activity, including bacteriocins and quorum-sensing peptides that function in microbial competition and interspecies communication [46,47,48]. Under physiological conditions, these peptides play essential roles in maintaining microbial ecosystem stability by regulating population dynamics, coordinating gene expression, and limiting the expansion of competing or pathogenic organisms [49]. In parallel, microbial peptides can influence host–microbe interactions by modulating epithelial barrier function and immune responses, thereby contributing to mucosal homeostasis and host defense [50].

However, under conditions of dysbiosis or barrier disruption, microbial peptides can exert deleterious effects on host tissues. Increased production, altered composition, or systemic dissemination of these peptides may lead to inappropriate activation of host signaling pathways, promoting inflammation, epithelial injury, and disease progression. For example, certain quorum-sensing peptides and bacterially derived peptides have been shown to directly interact with host cells, disrupt immune signaling, and contribute to inflammatory or degenerative processes [51,52,53].

Mechanistically, microbial peptides differ from other microbiome-derived signals in several important respects. Small-molecule metabolites, including short-chain fatty acids, bile acids, and tryptophan-derived indoles, primarily act through receptor-mediated signaling or epigenetic modulation, whereas structural components such as lipopolysaccharide and peptidoglycan activate pattern-recognition receptors and downstream inflammatory transcriptional programs [54,,55]. In contrast, microbial peptides may directly interact with cellular membranes or intracellular targets, enabling more immediate perturbation of cellular homeostasis compared with receptor-restricted ligands [18,55,56,57]. In this context, certain peptides may function as proximal triggers of mitochondrial stress, apoptosis, and inflammatory amplification.

Corisin represents one example of such microbiome-derived peptides with pathogenic potential. Experimental studies suggest that it can enter host cells through both direct membrane interaction and carrier-mediated uptake via the serum albumin–cubilin pathway, thereby allowing access to intracellular compartments and mitochondrial targets [57]. Once internalized, it induces mitochondrial dysfunction, reactive oxygen species generation, and apoptosis [57]. Importantly, these properties are not unique to corisin, and the extent to which microbial peptides broadly share the capacity for intracellular penetration and direct engagement of host pathways remains incompletely defined.

Taken together, microbial peptides constitute a functionally diverse class of host-interacting molecules that support microbial ecology and host homeostasis under physiological conditions but, when dysregulated, can act as direct effectors of cellular injury and amplifiers of inflammatory responses.

## 3. Convergent Host Pathways Activated by Microbiome-Derived Signals

As described above, microbiome-derived molecules span chemically distinct classes, including small metabolites (e.g., SCFAs, bile acids, tryptophan catabolites, and TMAO), structural products (e.g., LPS and peptidoglycan fragments), and emerging peptide effectors [58]. Despite this diversity, many of these inputs converge on a limited set of host pathways that regulate barrier integrity, inflammatory amplification, cell fate, tissue remodeling, and thrombo-inflammation [59]. However, this convergence should not be interpreted as implying identical mechanisms in all organs. Rather, shared pathways are engaged through organ-specific sensing and regulatory mechanisms, so that the same microbial signal may produce distinct outcomes depending on tissue exposure, receptor and transporter expression, local stromal and immune cell composition, and the pre-existing injury state of the target organ [60,61,62].

Under conditions of dysbiosis and barrier disruption, heightened systemic exposure to microbial products can redirect these host responses toward mitochondrial stress, epithelial and endothelial dysfunction, apoptosis, senescence, and profibrotic remodeling [59]. Importantly, the path from gut imbalance to organ injury is not linear: microbial products are first filtered by intestinal permeability, hepatic biotransformation, plasma protein binding, and organ-specific uptake systems, which together determine which signals reach a given tissue and at what effective concentration [63] (Fig. 1).

### *3.1 Pattern-Recognition Receptor Signaling as an Upstream Gateway*

Microbial structural products represent canonical triggers of innate immune activation. LPS stimulates Toll-like receptor 4 (TLR4) signaling and drives transcriptional programs that amplify cytokine production and inflammatory cell recruitment [64]. In parallel, peptidoglycan-derived motifs are sensed intracellularly by NOD1 and NOD2, which activate NF-κB and MAPK pathways and shape inflammatory responses in different tissue compartments [65]. These pattern-recognition receptor (PRR)-driven signals do not act in isolation but interact with metabolic signaling pathways, potentially tuning the magnitude and persistence of inflammation [66].

At the same time, PRR signaling is strongly shaped by tissue context. In the lung, microbial and gut-derived signals are interpreted largely through alveolar epithelial cells and alveolar macrophages, where SCFA-sensitive GPCR signaling and innate immune programs can modulate the inflammatory threshold of the distal airspace [67]. In the kidney, by contrast, circulating microbial metabolites and structural signals are superimposed on a transport-dependent epithelial system in which proximal tubular cells are selectively exposed to solutes through basolateral transporters, creating a distinct inflammatory and metabolic landscape [68]. Thus, PRR activation should be viewed as a shared upstream framework rather than a uniform molecular program: although core inflammatory modules may be shared, the sensing cell types, regulatory cofactors, and downstream pathological consequences may differ in each organ [69,70,71] (Fig. 1).

### *3.2 Mitochondrial Dysfunction and Oxidative Stress as a Central Integration Node*

A recurring downstream consequence of inflammatory and metabolic perturbation is mitochondrial dysfunction, characterized by altered bioenergetics and increased ROS generation [72]. Mitochondrial stress can directly impair epithelial barrier function and promote maladaptive cell-fate decisions, including apoptosis and senescence, which are increasingly recognized as relevant to fibrotic remodeling [73]. In fibrotic diseases, mitochondria serve as an integration point where inflammatory cues, oxidant burden, and profibrotic signaling intersect [72,74].

However, the mechanistic pathway of mitochondrial stress is not identical in all organs. For example, in pulmonary fibrosis, mitochondrial dysfunction is tightly linked to the vulnerability of alveolar epithelial cells, especially the bronchoalveolar epithelium, and is coupled to epithelial reprogramming, ER stress, defective repair, and fibroblast-activating signals [75]. In kidney fibrosis, mitochondrial injury is centered more prominently in tubular epithelial cells, where high metabolic demand, toxin uptake, and persistent TGF-β/Smad signaling promote oxidative stress, senescence, and maladaptive tubulointerstitial crosstalk [76].

This distinction helps explain why a common hub such as mitochondrial ROS can still yield organ-specific pathology: in the lung, it primarily destabilizes epithelial regeneration in a mechanically dynamic gas-exchange surface, whereas in the kidney, it is superimposed on a solute-handling epithelium specialized for vectorial trans-

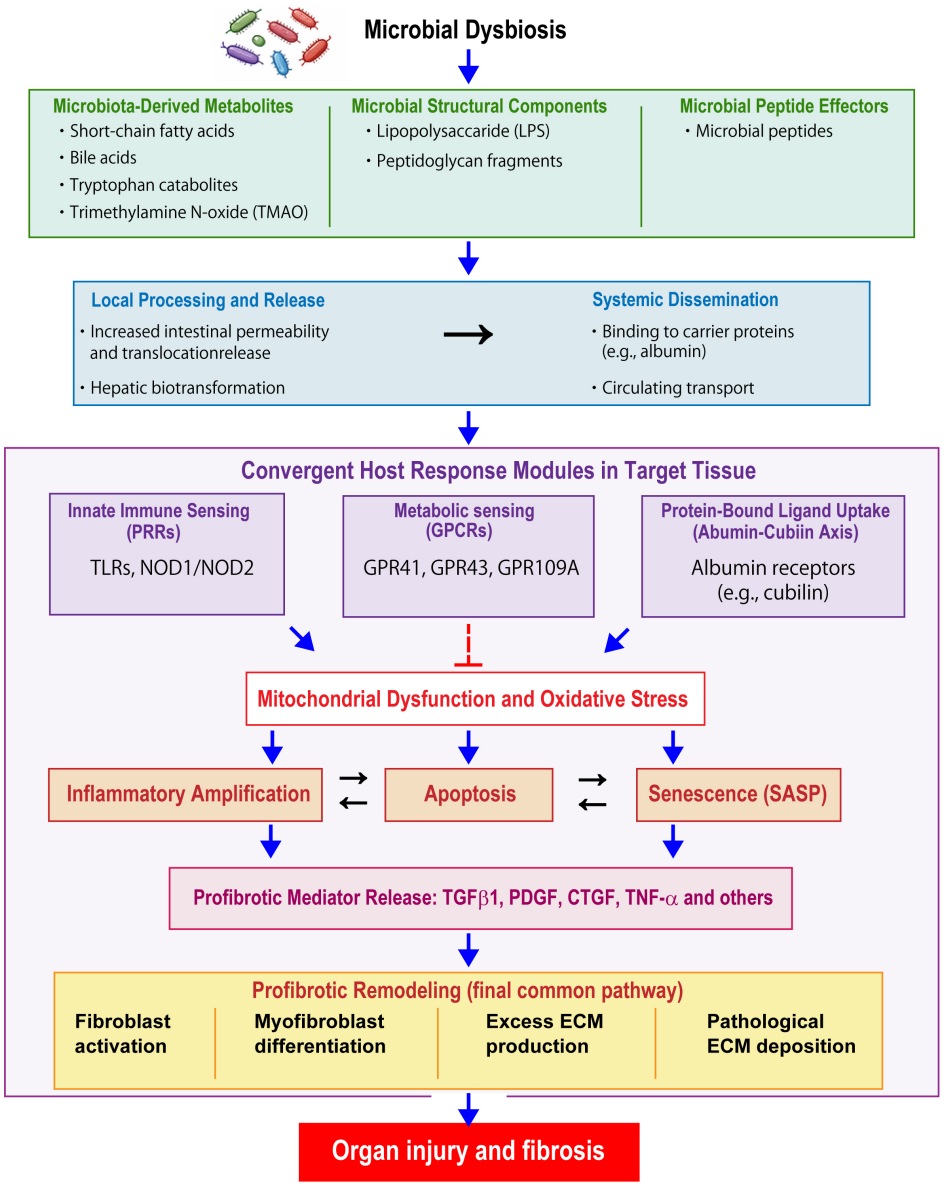


**Fig. 1. Convergent host pathways initiated by microbiota-derived molecules driving organ injury and fibrosis**. Microbial dysbiosis leads to the generation of diverse microbiota-derived molecules, including metabolites (e.g., short-chain fatty acids, bile acids, tryptophan catabolites, and trimethylamine N-oxide [TMAO]), structural components (e.g., lipopolysaccharide [LPS] and peptidoglycan fragments), and microbial peptide effectors. These molecules undergo local processing and release, facilitated by increased intestinal permeability and hepatic biotransformation, and subsequently enter the systemic circulation, where they are transported, often bound to carrier proteins such as albumin, to distant organs. In target tissues, these signals engage distinct but convergent host response modules, including innate immune sensing via pattern-recognition receptors (PRRs; e.g., Toll-like receptors and NOD1/NOD2), metabolic sensing through G protein–coupled receptors (GPCRs; e.g., GPR41, GPR43, and GPR109A), and protein-bound ligand uptake pathways mediated by albumin receptors (e.g., cubilin). Notably, metabolic sensing pathways may exert modulatory or inhibitory effects on downstream signaling cascades. Despite their diverse origins and sensing mechanisms, these inputs converge on shared intracellular pathways characterized by mitochondrial dysfunction and oxidative stress. This central node promotes key pathological processes, including inflammatory amplification, apoptosis, and cellular senescence associated with a senescence-associated secretory phenotype (SASP), which are interconnected and mutually reinforcing. These processes drive the release of profibrotic mediators, including transforming growth factor-β1 (TGFβ1), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), tumor necrosis factor-α (TNF-α), and other factors, culminating in a final common pathway of profibrotic remodeling. This remodeling is characterized by fibroblast activation, myofibroblast differentiation, excessive extracellular matrix (ECM) production, and pathological ECM deposition, ultimately leading to progressive organ injury and fibrosis. The figure was prepared and created by the authors using Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

port and highly susceptible to intracellular toxin accumulation [61,68,75] (Fig. 1).

### *3.3 Apoptosis and Cellular Senescence: Two Linked Cell-Fate Programs Driving Injury and Remodeling*

When mitochondrial stress exceeds adaptive thresholds, apoptosis becomes a prominent outcome, particularly in barrier epithelia [72]. Epithelial loss can trigger aberrant wound healing and contribute to fibroblast activation and extracellular matrix accumulation [77]. In parallel, persistent stress can drive cells into cellular senescence, commonly characterized by induction of p21/p16 and a senescence-associated secretory phenotype (SASP) [78]. Senescent cells can actively shape tissue microenvironments by secreting proinflammatory and profibrotic mediators, thereby promoting immune cell recruitment, matrix remodeling, and fibrosis progression [78]. Together, apoptosis and senescence can be viewed as complementary outcomes of sustained exposure to microbial products and inflammatory-metabolic stress: apoptosis drives barrier failure and acute injury, whereas senescence sustains chronic low-grade inflammation and fibrotic remodeling via SASP-driven feedback loops.

Here again, organ context matters. In the lung, apoptosis and senescence are particularly harmful because loss of alveolar epithelial integrity impairs re-epithelialization and promotes fibroblast persistence within the confined alveolar niche [75]. In the kidney, by contrast, senescent proximal tubular epithelial cells can influence a wider tissue compartment by releasing paracrine mediators that activate interstitial fibroblasts, recruit inflammatory cells, and promote microvascular loss. These effects accelerate tubulointerstitial fibrosis, even when the initiating injury is metabolic rather than directly infectious [57,76] (Fig. 1).

### *3.4 Profibrotic Remodeling as a Final Common Pathway*

In all organs, fibrosis represents a stereotyped response to chronic injury in which fibroblast activation and excessive extracellular matrix deposition compromise tissue architecture and function [79]. TGF-β1 is widely regarded as a master regulator of fibrogenesis, but its mode of activation, dominant target cells, and regulatory circuitry are not identical across organs [80]. In the lung, TGF-β activity is closely linked to epithelial injury and to the local activation of latent TGF-β by epithelial integrins, particularly αvβ6, within a mechanically stressed alveolar environment [81]. This creates a spatially restricted profibrotic program in which injured epithelial cells, activated fibroblasts, and matrix stiffening reinforce one another. In the kidney, by contrast, TGF-β1-driven fibrosis is organized more prominently around tubular epithelial injury, pericyte/fibroblast activation, and sustained Smad signaling modulated by post-translational control [76,82]. In addition, recent work emphasizes that renal fibrosis is shaped not only by canonical TGF-β/Smad activity but also by the origin and heterogeneity of myofibroblasts, including important contributions from interstitial mesenchymal cells and pericyte-like populations [83].

These differences in tissue- and organ-specific responses are highly relevant to the pathogenesis of microbiome-associated diseases. For example, kidney-selective accumulation of gut-derived uremic toxins is facilitated by proximal tubular transport systems such as OAT1/OAT3, providing a plausible mechanism by which dysbiosis can preferentially intensify tubular stress, senescence, and TGF-β-linked interstitial fibrosis [68,76]. In the lung, organ specificity is more likely to arise from immune and epithelial priming through the gut–lung axis, including SCFA-sensitive regulation of alveolar macrophages and epithelial injury programs that determine whether a profibrotic response is triggered [84]. Therefore, it is more accurate to regard fibrosis as a shared endpoint reached through different organ-specific routes: the same broad pathways recur, but the initiating sensors, intermediate cell states, and feedback loops are tailored to the biology of each tissue (Fig. 1).

### *3.5 Determinants of Organ Specificity in Microbiome-Linked Injury*

A key unresolved question is how gut-derived signals generate selective disease phenotypes in particular organs. Current evidence suggests that organ specificity reflects the combined action of at least four filters: (1) differential systemic delivery determined by intestinal permeability, hepatic transformation, and plasma carrier binding; (2) tissue-specific expression of receptors and transporters; (3) the intrinsic vulnerability of local parenchymal cells; and (4) organ-specific stromal and immune feedback circuits [3,63,85,86,87,88].

This framework helps reconcile convergence with specificity. Shared microbial signals do not act on a biologically uniform host; instead, they enter tissues that differ profoundly in vascular architecture, epithelial function, matrix mechanics, and cellular composition. As a result, similar upstream perturbations can be translated into distinct disease outcomes such as alveolar fibrosis, tubulointerstitial scarring, vascular dysfunction, or thrombo-inflammation.

## 4. Microbial Peptides in Disease: Corisin as an Illustrative Example

While small-molecule metabolites and structural microbial components have long been studied as modulators of host physiology and inflammation, microbiome-derived peptides are emerging as a functionally distinct class of effectors capable of directly influencing host cell biology [89,90]. Among these, corisin has been investigated as one example of a bacterial peptide with potential pathogenic activity [91]. Its study provides insight into how microbial peptides may act as circulating mediators linking dysbiosis to tissue injury, although its role should be inter-

preted within the broader, still-evolving landscape of host–microbiome interactions.

### *4.1 Origin, Biochemical Features, and Circulatory Presence*

Corisin was identified as a 19–amino-acid peptide fragment derived from bacterial transglycosylases produced by *Staphylococcus nepalensis* and related species. The peptide is generated through proteolytic processing, likely mediated by serine proteases, and exhibits physicochemical properties compatible with interaction with circulating proteins, particularly serum albumin, which may facilitate systemic distribution following barrier disruption [91]. Corisin has been detected in experimental models and in selected human samples, including bronchoalveolar lavage fluid and plasma from patients with idiopathic pulmonary fibrosis and other inflammatory conditions [57]. However, current evidence regarding its prevalence, concentration range, and stability in human circulation remains limited, and standardized detection methods and independent validation across cohorts are still needed.

### *4.2 Cellular Effects: Mitochondrial Stress, Apoptosis, and Inflammation*

Experimental studies suggest that corisin can induce mitochondrial dysfunction, increase reactive oxygen species generation, and activate apoptosis pathways in epithelial and parenchymal cells [48]. These processes are consistent with broader models of mitochondrial stress–driven tissue injury [92]. Corisin has also been reported to enhance the expression of proinflammatory mediators, including MCP-1, thereby potentially amplifying local inflammatory responses [93]. However, it should be noted that most mechanistic evidence has been generated *in vitro* or in animal models using synthetic peptides, and it remains unclear to what extent these observations recapitulate physiological exposure levels, native peptide conformations, and *in vivo* biological effects.

### *4.3 Profibrotic Signaling and Tissue Remodeling*

Corisin has been shown to enhance expression of TGF-β1 and other profibrotic mediators in experimental systems, suggesting a potential role in fibroblast activation and extracellular matrix remodeling [57,91]. In preclinical models of lung injury, exogenous corisin exposure has been associated with increased collagen deposition, whereas neutralization strategies attenuate fibrosis-related readouts [91]. Nevertheless, fibrosis is a multifactorial process involving numerous overlapping pathways, and the relative contribution of corisin compared with other microbial and host-derived mediators has not yet been established.

### *4.4 Coagulation Activation and Thrombo-Inflammation*

Corisin has also been implicated in coagulation-related pathways, including the induction of tissue factor expression and the modulation of anticoagulant systems *in vitro* [94]. In experimental models, targeting corisin has been associated with reduced markers of thrombo-inflammation [94]. However, these findings remain largely preclinical, and the causal role of corisin in human thrombo-inflammatory disorders has yet to be demonstrated.

### *4.5 Translational Considerations and Current Limitations*

The identification of microbiome-derived peptides such as corisin raises the possibility of targeting discrete microbial effectors as a therapeutic strategy. Preclinical studies suggest that neutralization of corisin can attenuate epithelial injury, inflammation, and fibrosis-related outcomes [93,95]. At present, however, several key challenges limit translational application, including incomplete understanding of peptide biogenesis and regulation, variability in microbial sources, uncertainty regarding systemic exposure levels in humans, and the need for robust biomarkers to identify relevant patient populations. In addition, potential redundancy among microbial effectors suggests that targeting a single peptide may not be sufficient to achieve sustained therapeutic benefit.

### *4.6 Comparison With Other Microbiome-Derived Effectors*

While classical microbiome-derived metabolites, such as bile acids, and structural components, such as LPS, primarily signal through host receptors, corisin may engage host cells through distinct and complementary mechanisms [96,97]. In addition to direct cellular penetration, corisin may associate with circulating proteins such as albumin, potentially facilitating receptor-mediated uptake through albumin-handling pathways [57]. Despite these differences in cellular entry and sensing mechanisms, these diverse microbial signals converge on a limited set of host responses, including mitochondrial stress, inflammatory amplification, and tissue remodeling [98].

Corisin should therefore be viewed not as a singular defining mediator but as an illustrative example of a broader class of microbiome-derived peptides that influence host biology. Its study highlights both the potential importance of peptide effectors in disease and the need for further investigation to establish their physiological relevance, specificity, and therapeutic tractability in human systems.

## 5. Disease Case Studies

To examine this framework in representative host–environment interface diseases, we highlight four disorders, pulmonary fibrosis, acute lung injury/ARDS, acute cholangitis, and chronic kidney disease, in which microbiome-derived metabolites, structural ligands, and peptide effectors converge on shared host pathways, including mitochondrial stress, apoptosis and senescence, inflammatory

amplification, fibrosis, and thrombo-inflammation. Importantly, although these pathways are shared, their activation is shaped by organ-specific exposure, cellular targets, and microenvironmental context, leading to distinct clinical phenotypes [75].

### *5.1 Pulmonary Fibrosis*

Idiopathic pulmonary fibrosis (IPF) is characterized by repetitive epithelial injury and aberrant wound healing [99]. Increased bacterial burden in BALF correlates with worse outcomes, supporting a contributory role for microbiome perturbation [100,101]. Beyond local airway microbiota, the gut–lung axis contributes to fibrogenesis. Germ-free conditions and microbial exposure modulate fibrosis severity in bleomycin models, and intestinal dysbiosis (e.g., *Candida albicans* overgrowth) exacerbates fibrosis via IL-17A–dependent pathways [102,103,104].

Mechanistically, microbial signals converge on mitochondrial dysfunction and epithelial apoptosis in alveolar epithelial cells, which are central drivers of fibrotic remodeling [105]. Mitochondrial ROS and epithelial injury amplify TGF-β activation, particularly through integrin-mediated activation of latent TGF-β in the alveolar niche [105]. Corisin provides one example of a microbial peptide that may contribute to epithelial injury, as neutralization attenuates fibrosis in experimental models [93].

Thus, pulmonary fibrosis exemplifies how microbiome-derived signals converge on epithelial mitochondrial stress, apoptosis, and TGF-β–driven remodeling within a lung-specific epithelial–mesenchymal microenvironment.

### *5.2 Acute Lung Injury and ARDS*

ALI/ARDS is characterized by diffuse epithelial and endothelial injury with intense inflammation [106,107]. LPSinduced models highlight the central role of PRR signaling in driving neutrophilic inflammation [108]. Microbial metabolites modulate disease severity. For example, SCFAs such as butyrate attenuate inflammation through epigenetic and GPCR-mediated mechanisms [109]. At the mechanistic level, severe viral lung injury reflects the convergence of innate sensing pathways, mitochondria-centered immunometabolic stress, dysregulated inflammatory signaling, and epithelial barrier failure [110]. These interconnected processes promote the rapid amplification of cytokine signaling, oxidative stress, and coagulation activation [110]. Effector-level amplification may also occur via microbiota-derived peptides, as suggested by studies demonstrating attenuation of LPS-induced lung injury following corisin neutralization [95].

In this context, ARDS illustrates how convergent pathways, PRR signaling, mitochondrial stress, and thrombo-inflammation are rapidly activated in a highly vascularized and immune-reactive organ, leading to acute organ failure rather than chronic remodeling.

### *5.3 Acute Cholangitis*

Acute cholangitis arises from biliary obstruction and bacterial infection, leading to systemic inflammation and organ dysfunction [111]. Microbiome profiling shows that bile harbors a distinct microbial community influenced by duodenal reflux and local conditions [112,113,114]. Mechanistically, cholangiocytes are highly responsive to microbial signals through TLR4 and other PRRs, leading to NF-κB activation, cytokine production, and epithelial injury [115,116]. In addition, bile acids themselves modulate inflammatory signaling and epithelial stress responses, linking metabolic and microbial pathways [117]. Importantly, cholangitis represents a setting in which microbial signals converge on epithelial inflammation, mitochondrial stress, and systemic inflammatory amplification in a biliary-specific environment characterized by bile acid exposure and obstructive pressure [118]. These features create a unique context in which local infection rapidly translates into systemic inflammatory and thrombotic complications. Corisin has been reported to be elevated in bile and plasma in cholangitis [110]. However, its mechanistic contribution remains to be defined relative to established inflammatory pathways.

### *5.4 Chronic Kidney Disease*

CKD involves bidirectional gut–kidney communication, in which dysbiosis increases systemic exposure to microbial metabolites and toxins [119,120]. Key mediators include indoxyl sulfate and p-cresyl sulfate, which promote inflammation and fibrosis [121,122]. Organ specificity in CKD is strongly influenced by renal transport systems. Gut-derived solutes are selectively taken up by proximal tubular cells via transporters such as OAT1 and OAT3, leading to intracellular accumulation and mitochondrial stress [61]. These signals converge on mitochondrial dysfunction, cellular senescence, and TGF-β/Smad–driven fibrotic remodeling within the tubulointerstitial compartment, distinguishing renal fibrosis from lung fibrosis despite shared pathway activation [76]. Thus, CKD illustrates how microbiome-derived signals converge on shared pathways but are shaped by kidney-specific transport, metabolic, and cellular mechanisms to drive progressive fibrosis.

## 6. Therapeutic Implications

The emerging view of the microbiome as a systemic biochemical network that produces both protective and pathogenic mediators has important therapeutic implications. Rather than focusing solely on eradicating microbes, future interventions will likely need to restore functional microbial homeostasis, rebalance metabolite profiles, and selectively neutralize injurious microbial effectors. However, the development of such approaches is challenging because microbiome–host interactions are highly context-dependent, vary across individuals, and involve complex

biological networks that are only partially understood. In this context, interventions can be organized into three complementary levels: ecological restoration, metabolite modulation, and effector-targeted therapies, each with distinct opportunities and limitations.

### *6.1 Ecological Restoration: Rebalancing Microbial Communities*

Ecological interventions aim to reshape microbial community structure and function toward a state that favors the production of protective metabolites and limits the generation of harmful ligands. Dietary modification is the most accessible approach, as fiber-rich diets increase the abundance of SCFA-producing taxa and enhance butyrate availability, supporting epithelial barrier integrity and dampening inflammation [123]. Probiotics and prebiotics have demonstrated the capacity to modulate microbial composition and metabolic output, although responses are heterogeneous and strain-specific [124].

However, a major challenge for ecological interventions is the substantial interindividual variability in microbiome composition and functional responses, which limits the reproducibility and predictability of therapeutic outcomes across patient populations [125,126].

More advanced ecological strategies include fecal microbiota transplantation (FMT), rationally designed microbial consortia, and bacteriophage-based approaches targeting pathogenic taxa [127]. While FMT has shown clear efficacy in recurrent *Clostridioides difficile* infection, its application to complex chronic diseases has yielded variable results, reflecting challenges related to donor selection, engraftment stability, and long-term safety [128,129,130]. Similarly, next-generation approaches such as defined microbial consortia and phage therapy are promising but remain at early translational stages, with unresolved issues including ecological stability, off-target effects, and regulatory standardization [131,132,133].

### *6.2 Metabolite Modulation: Correcting Host–Microbe Biochemical Imbalance*

A second therapeutic layer involves direct modulation of microbiome-derived metabolites and their host receptors. SCFA supplementation or stimulation of endogenous SCFA production can attenuate inflammatory signaling, reduce epithelial apoptosis, and preserve barrier function through activation of G protein–coupled receptors and epigenetic mechanisms [134]. Nevertheless, clinical translation of SCFA-based therapies is complicated by pharmacokinetic limitations, including rapid absorption, short half-life, and difficulties in achieving tissue-specific concentrations without off-target effects [135].

Similarly, targeting bile-acid signaling pathways through agonists or antagonists of FXR and TGR5 offers a means to restrain inflammatory and fibrotic programs in the lung, liver, biliary epithelium, and kidney [136]. Although FXR agonists such as obeticholic acid have entered clinical use, adverse effects, including pruritus and dyslipidemia, as well as context-dependent efficacy, highlight the complexity of manipulating bile acid signaling pathways [137].

Manipulation of tryptophan metabolism and aryl hydrocarbon receptor (AhR) signaling represents another promising avenue. However, the pleiotropic and ligand-specific nature of AhR signaling introduces significant challenges, as different ligands can elicit divergent, and sometimes opposing, biological responses depending on cell type and disease context [138]. In parallel, inhibition of microbial enzymes responsible for harmful metabolites could reduce systemic exposure to profibrotic and prothrombotic signals [139]. Despite encouraging preclinical data, selective targeting of microbial metabolic pathways *in vivo* remains technically challenging due to redundancy within microbial communities and the risk of unintended metabolic compensation [140].

### *6.3 Effector-Targeted Therapies: Neutralization of Pathogenic Microbial Peptides*

The identification of microbiome-derived peptides with direct pathogenic activity introduces a third therapeutic dimension: selective neutralization of injurious effectors. Corisin exemplifies this paradigm. Preclinical studies demonstrate that monoclonal antibody-mediated neutralization of corisin reduces epithelial apoptosis, dampens inflammatory cytokine production, attenuates profibrotic remodeling, and limits coagulation activation in models of pulmonary fibrosis, acute lung injury, SARS-CoV-2–associated disease, and diabetic kidney injury [57,93,94,95]. A key challenge for this therapeutic approach is identifying and validating pathogenic microbial peptides in humans and establishing their causal contribution to disease in many heterogeneous clinical settings [141]. In addition, therapeutic targeting of circulating peptides also requires careful consideration of pharmacodynamics, tissue penetration, and potential interactions with carrier proteins such as serum albumin, which may influence both efficacy and biodistribution [142].

Effector-targeted strategies offer several conceptual advantages. First, they provide specificity, sparing beneficial microbial metabolites and commensal organisms. Second, they can be deployed even when dysbiosis is established, functioning downstream of ecological disturbance. Third, they are readily combinable with ecological and metabolite-modulating approaches. However, unlike host-derived targets, pathogenic microbial peptides may exhibit interindividual and interstrain variability, posing challenges for patient stratification and biomarker development [143].

### *6.4 Integrated and Personalized Approaches*

Given the complexity and interindividual variability of the microbiome, optimal therapy will likely require a combination and personalization. Profiling of microbial composition, circulating metabolites, and effector peptides

could guide patient stratification. Recent advances in multi-omics integration, including metagenomics, metabolomics, and proteomics, are beginning to enable such precision approaches, although standardization, cost, and data interpretation remain major barriers to clinical implementation [144,145]. Moreover, longitudinal studies are needed to determine whether microbiome-targeted interventions can produce durable clinical benefits, as many current approaches show transient effects without sustained ecological or metabolic reprogramming [146].

## 7. Methodological Challenges and Current Limitations in Microbiome–Host Interaction Research

A major challenge in microbiome–host interaction research is that mechanistic interpretation often outpaces methodological standardization. In particular, the detection and quantification of microbiome-derived metabolites remain highly sensitive to sample collection, storage conditions, extraction protocols, analytical platform, and matrix effects, making cross-study comparison difficult and sometimes limiting reproducibility [147]. Reviews of microbiome metabolite quantification emphasize that pre-analytical handling and analytical heterogeneity remain major sources of variability, especially for low-abundance and chemically unstable metabolites [147].

A second limitation is that functional metagenomics and genome-based inference do not always translate into *in vivo* biochemical activity. Metagenomic data can predict genetic potential, but they often cannot determine whether a pathway is expressed, whether the encoded product is generated at biologically relevant levels, or which host compartment is exposed to it. Recent reviews, therefore, stress the need to complement metagenomics with transcriptomics, proteomics, metabolomics, cultivation, and experimental validation [148,149].

Establishing causality remains another major pain point. Associations between microbial features and disease can be distorted by confounding factors such as diet, medication use, bowel preparation, geography, host genetics, disease stage, and differences in absolute microbial load. Consensus and methodological papers increasingly recommend longitudinal designs, quantitative profiling, standardized reporting, and interventional or mechanistic follow-up studies to move beyond correlation [150].

Finally, integration of host and microbiome datasets remains analytically challenging. Multi-omic studies are powerful, but linking taxa, genes, metabolites, and host phenotypes into a coherent mechanistic chain requires careful statistical modeling and remains vulnerable to overfitting, sparse data structures, and inconsistent feature annotation [151]. For this reason, current conclusions about microbiome-derived effectors should often be interpreted as biologically plausible but still provisional until supported by orthogonal validation.

## 8. Future Directions

Future microbiome research must continue the transition from descriptive compositional analyses toward a mechanistic and translational framework centered on microbiome-derived bioactive molecules and their systemic effects. A key priority will be to define, with chemical and biological precision, the mediators that link microbial ecology to host stress pathways, including activation of pattern-recognition receptors, mitochondrial dysfunction, apoptosis, senescence, inflammation, and fibrosis.

Advancing this goal will require detailed characterization of the biosynthetic origins, enzymatic processing, and regulatory networks governing the production of major microbial effectors, including short-chain fatty acids, bile acids, tryptophan metabolites, trimethylamine-derived products, and microbial peptides. Equally important is understanding their pharmacokinetics within the host, including stability, carrier interactions, tissue distribution, receptor engagement, and clearance, to establish physiologically relevant exposure–response relationships.

Emerging technologies such as single-cell and spatial multi-omics, combined with metabolomics and imaging approaches, will be critical for identifying the cellular targets and transcriptional programs engaged by microbial signals across tissues. Integration of these approaches with gnotobiotic models, organoids, and longitudinal human studies will help distinguish causal mechanisms from associative findings and clarify how dysbiosis reshapes host biology over time.

Another major challenge is to understand how environmental, dietary, and pharmacologic factors reshape microbial function and influence the balance between protective and pathogenic signals. Addressing this variability will be essential for developing predictive models of disease susceptibility and therapeutic response.

Ultimately, these advances will enable the development of precision microbiome medicine, including targeted modulation of microbial metabolism, selective inhibition of harmful pathways, and effector-directed interventions. The integration of microbial, metabolic, and host-derived biomarkers will further support early detection, patient stratification, and dynamic monitoring of treatment responses.

Together, these efforts will redefine the microbiome as a dynamic biochemical network that shapes organ homeostasis and disease, providing new opportunities for therapeutic intervention across diverse inflammatory and fibrotic disorders.

## 9. Conclusion

Accumulating evidence supports a unifying view in which the microbiome functions as a distributed, endocrine-like biochemical network whose metabolites, structural ligands, and peptide effectors shape host stress biology at a systemic level. These diverse signals converge on a lim-

ited set of host pathways, including pattern-recognition receptor activation, mitochondrial dysfunction, apoptosis and senescence, inflammatory amplification, and fibrosis, that determine tissue vulnerability and disease trajectory across organ systems. Together, these insights suggest that dysbiosis should be understood not only as a taxonomic imbalance but also as a disturbance of microbial chemistry and effector signaling, with important implications for mechanism-based therapeutic intervention. Deciphering and targeting this host–microbe interface offers new opportunities for treating inflammatory and fibrotic diseases.

## Abbreviations

AhR, Aryl hydrocarbon receptor; ALI, Acute lung injury; ARDS, Acute respiratory distress syndrome; BALF, Bronchoalveolar lavage fluid; CKD, Chronic kidney disease; FMT, Fecal microbiota transplantation; FXR, Farnesoid X receptor; GPR, G protein–coupled receptor; HDAC, Histone deacetylase; IPF, Idiopathic pulmonary fibrosis; LPS, Lipopolysaccharide; MCP-1, Monocyte chemoattractant protein-1; NOD, Nucleotide-binding oligomerization domain; PRR, Pattern-recognition receptor; ROS, Reactive oxygen species; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SCFAs, Short-chain fatty acids; TF, Tissue factor; TGFβ1, Transforming growth factor beta 1; TGR5, Takeda G protein–coupled receptor 5; TMA, Trimethylamine; TMAO, Trimethylamine N-oxide; TLRs, Toll-like receptors.

## Author Contributions

Project administration and conceptualization of the manuscript: ECG and VFD; literature search: VFD, HF, RS, CNDG, MT, KN, OH, ECG, IC, TK, and TY; writing-original draft: VFD and ECG; preparation of the figures: VFD, DL, CNDG, and ECG; writing-review & editing: VFD, HF, CNDG, MT, KN, OH, ECG, IC, DL, TK, and TY. All authors contributed to revising the manuscript, reviewed and approved the final version. All authors have participated sufficiently in the work. All authors agree to take responsibility for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

There is an invention disclosure by CNDG, ECG, and IC on the corisin peptide and anticorisin mAb developed for the treatment of organ fibrosis described in this review. Given his role as the Editorial Board member, Esteban C. Gabazza had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Amedeo Amedei. The other authors declare no conflicts of interest regarding the preparation of this review manuscript.

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