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Review

Microbiota-Derived Metabolites Mediate Immune Regulatory Networks in the Gut-Skin Axis of Psoriasis

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Abstract

Psoriasis is a chronic immune-mediated inflammatory disease affecting 2–3% people globally. Current biologic therapies targeting interleukin-23 and interleukin-17 pathways achieve only partial responses in most patients, highlighting the need for understanding upstream triggers. Emerging evidence implicates gut microbiome dysbiosis as a notable contributor to psoriasis pathogenesis through metabolite-mediated immune regulation. Psoriasis patients exhibit characteristic gut microbial alterations, including depletion of beneficial commensals such as *Faecalibacterium prausnitzii* and expansion of proinflammatory taxa. These compositional changes are associated with altered profiles of immunomodulatory metabolites, including short-chain fatty acids, tryptophan-derived indole compounds, and secondary bile acids, which promote regulatory T-cell differentiation, enhance immune tolerance through aryl hydrocarbon receptor activation, and modulate metabolic-immunological pathways. Such metabolic alterations may impair regulatory T cell function, promote T helper 17 (Th17) differentiation, compromise intestinal barrier integrity, and influence tissue-resident memory T cells that perpetuate disease chronicity. This process facilitates bacterial product translocation that amplifies inflammation, thereby amplifing relationship is bidirectional; psoriatic skin inflammation reciprocally affects gut homeostasis through circulating inflammatory mediators, systemic immune cell activation, and neuroendocrine stress pathways. Recent clinical evidence demonstrates that biologic therapies normalize gut microbiome composition and reduce trimethylamine N-oxide levels, supporting bidirectional gut-skin communication. These interactions create self-perpetuating cycles, suggesting that therapeutic strategies interrupting this feedback loop may offer novel treatment approaches. This review synthesizes current evidence on metabolite-mediated immune regulatory networks linking gut microbiome dysbiosis to psoriatic inflammation, evaluates clinical trials of microbiome-targeted interventions, and discusses methodological challenges, regulatory considerations, and future research directions for clinical translation. Understanding these mechanisms may inform the development of microbiome-targeted therapeutic approaches.

Keywords: psoriasis; gastrointestinal microbiome; short-chain fatty acid; immunomodulation; dysbiosis

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory disease affecting approximately 2–3% of the global population [1]. It is characterized by well-demarcated erythematous plaques with silvery scales, most commonly on extensor surfaces, scalp, and trunk [2,3]. Beyond visible cutaneous features, psoriasis significantly reduces quality of life through associated comorbidities, including psoriatic arthritis, cardiovascular conditions, metabolic syndrome, and psychological distress [4,5,6]. Psoriasis arises from interactions between genetic susceptibility and environmental triggers, culminating in dysregulated immune responses dominated by the interleukin (IL)-23 and IL-17 pathways. Hyperactivated T helper 17 (Th17) cells produce proinflammatory cytokines that drive keratinocyte hyperproliferation, recruit neutrophils, and perpetuate inflammatory cascades [7]. While biologic agents targeting tumor necrosis factor-alpha (TNF-α), IL-17, or IL-23 have transformed management, most patients achieve only partial responses or experience relapse upon treatment cessation [8]. These therapies address downstream inflammatory mediators rather than upstream triggers, highlighting the need for understanding mechanisms that initiate and sustain psoriatic inflammation.

Emerging evidence implicates the gut microbiome as an environmental factor influencing immune homeostasis and inflammatory susceptibility [9]. The human gastrointestinal tract harbors trillions of microorganisms engaging in continuous bidirectional communication with the host immune system, shaping immune development, tolerance

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mechanisms, and inflammatory tone [10]. This dialog operates through direct microbial-immune cell interactions, bacterial structural components engaging pattern recognition receptors, and diverse metabolites generated through microbial metabolism. The gut-skin axis has emerged as a relevant framework for understanding dermatological disorders. Multiple investigations employing culture-independent molecular techniques have identified characteristic dysbiosis patterns in psoriasis patients, marked by reduced diversity and altered bacterial taxa representation compared to healthy individuals [11,12,13]. However, uncertainties persist regarding the causal relationship between gut dysbiosis and cutaneous inflammation.

The link between gut microbial compositional changes and cutaneous inflammation lies in altered production of bioactive microbial metabolites that serve as molecular mediators of host-microbe communication [14]. The gut microbiome functions as a metabolic organ, transforming dietary components and host molecules into thousands of small-molecule metabolites that enter circulation and interact with host receptors across diverse tissues. Short-chain fatty acids (SCFAs) generated through bacterial fermentation of dietary fibers, tryptophan derivatives produced through microbial amino acid metabolism, and secondary bile acids modified by bacterial enzymes have emerged as important immunomodulatory signals [15]. These metabolites engage receptors on immune cells, modulate epigenetic landscapes, influence barrier function, and shape the balance between proinflammatory and regulatory immune responses. The documented depletion of metabolite-producing bacteria and reduced metabolite concentrations in psoriasis patients suggest that functional deficits in microbial metabolite production, rather than compositional changes alone, represent the relevant mechanistic consequence of gut dysbiosis [16,17].

The relationship between gut dysbiosis and cutaneous inflammation is bidirectional. Gut-derived metabolites and microbial products influence inflammatory responses manifesting in the skin, while inflammatory mediators generated in psoriatic lesions enter circulation and reciprocally influence intestinal homeostasis and gut microbiome composition through effects on epithelial barrier function, immune cell populations, and neuroendocrine stress pathways [18]. This bidirectional communication creates self-perpetuating pathological cycles wherein initial perturbations become amplified through positive feedback loops, elucidating the chronic relapsing nature of psoriasis and the difficulty in achieving durable remission [19]. Host genetic factors modulate multiple nodes within these cycles, influencing immune responsiveness to microbial signals and gut microbiome composition, thereby determining individual susceptibility and phenotypic expression [20].

This review synthesizes current evidence on gut microbiome-derived metabolites in psoriasis pathogenesis, emphasizing immune regulatory networks through which these molecules influence the development and perpetuation of psoriasis. We examine characteristic dysbiosis patterns and their functional metabolic consequences. Additionally, we analyze how metabolite classes modulate immune cell differentiation and function, focusing on the regulatory T (Treg) cell versus Th17 balance. Furthermore, we assess the reverse influence of cutaneous inflammation on gut homeostasis and how bidirectional interactions establish self-perpetuating cycles modulated by genetic factors. We also reviewed clinical evidence regarding microbiome-targeted interventions and their translational potential. This review provides a framework for understanding the gut-skin axis in psoriasis and identifies knowledge gaps requiring resolution to translate mechanistic insights into therapeutic advances.

2. Characteristics of Gut Microbiota Dysbiosis in Psoriasis Patients

2.1 Alterations in Microbial Composition and Diversity

Multiple studies employing 16S ribosomal RNA gene sequencing and metagenomic analyses have documented distinct microbial signatures in psoriasis patients compared to healthy individuals [21,22,23]. Investigations across geographically diverse cohorts from Europe, Asia, and South America reveal reproducible dysbiosis patterns, although consistency varies across studies [24,25,26]. These patterns suggest a restructuring of the gut microbial community's metabolic potential and functional orientation. However, most evidence derives from cross-sectional studies, which cannot definitively establish whether dysbiosis represents a cause, consequence, or epiphenomenon of psoriatic inflammation.

Compositional analyses reveal shifts across multiple taxonomic levels. At the phylum level, the Firmicutes to Bacteroidetes ratio shows elevation in psoriasis patients. Finer taxonomic resolution reveals characteristic alterations. *Faecalibacterium prausnitzii*, a butyrate-producing bacterium with anti-inflammatory properties, shows consistent depletion across cohorts, representing one of the more robust microbial signatures of psoriasis [27]. *Akkermansia muciniphila*, which maintains intestinal barrier integrity through interactions with the mucus layer and epithelial cells, demonstrates a reduction [28]. Other beneficial SCFA-producing genera within Firmicutes, including *Ruminococcus*, *Lachnospira*, and *Blautia*, also show reduced representation [29]. This selective depletion within Firmicutes appears paradoxical given the overall phylum-level expansion but reflects metabolic and functional heterogeneity within this diverse taxonomic group. The expanding Firmicutes clades may lack the capacity for generating beneficial metabolites, while those producing anti-inflammatory compounds undergo selective depletion. Conversely, certain taxa demonstrate increased abundance. *Prevotella copri* shows elevated levels despite overall Bacteroidetes contraction, consistent with its association with

various immune-mediated disorders, including rheumatoid arthritis [30]. The Dialister genus, frequently enriched in psoriasis, produces metabolic byproducts including hydrogen sulfide. Whether these enriched taxa directly contribute to inflammation or expand secondarily due to ecological changes remains unresolved. The expansion of potentially proinflammatory taxa combined with the depletion of anti-inflammatory commensals creates an overall shift toward a proinflammatory state.

Psoriasis patients exhibit altered microbial diversity patterns, reflecting broader ecological perturbations. Alpha diversity, which quantifies species richness and evenness within individual samples, tends to be reduced across multiple metrics, including the Shannon index, Simpson index, and observed species richness. This diversity loss suggests a less complex and potentially less resilient microbial ecosystem. Diverse communities typically demonstrate greater functional redundancy and stability, whereas communities with reduced diversity may be more susceptible to further disruption and less capable of maintaining the full metabolic functions associated with a healthy microbiome. Beta diversity analyses consistently demonstrate that psoriasis patients form distinct clusters separate from healthy individuals in principal coordinate analysis, indicating a characteristic microbial community structure distinguishable from the healthy baseline state [31].

Gut microbiome alterations have been associated with the clinical activity of psoriasis. In plaque psoriasis, greater disease severity has been linked to differences in gut microbial richness, taxonomic composition, and functional potential [21,32]. At the genus level, univariate analyses in a small study associated higher abundances of *Faecalibacterium* and *Parabacteroides* with higher Psoriasis Area and Severity Index (PASI) scores and greater body surface area involvement [33]. Microbial associations with disease activity have also been reported in psoriatic arthritis, where a bacterial network centered on *Bacteroides* correlated positively with Disease Activity in Psoriatic Arthritis (DAPSA) scores [34]. However, another metagenomic study detected no significant differences in overall gut microbial composition across PASI categories or between patients with cutaneous psoriasis and those with psoriatic arthritis [25]. Together, these observations suggest that associations between microbial features and disease activity vary across study populations and do not establish a causal relationship.

The compositional and diversity changes establish a clear dysbiosis pattern characterized by selective depletion of beneficial organisms with anti-inflammatory and barrier-protective properties, coupled with the expansion of taxa associated with proinflammatory potential. Fig. 1 summarizes the major taxonomic alterations observed in psoriasis patients at phylum and genus levels, illustrating how shifts across these hierarchical taxonomic ranks correspond to distinct metabolic functional profiles. At the phylum level, alterations affect the relative abundance of major bacterial groups, including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, while genus-level analysis reveals specific organisms showing increased or decreased representation within each phylum. These taxonomic alterations raise questions about their functional consequences.

2.2 Functional Alterations in Metabolic Pathways

Understanding the functional consequences of compositional changes requires examining the metabolic pathways encoded by the gut microbiome and its bioactive products. Microbial communities with similar taxonomic profiles can exhibit different functional capacities, and taxonomically distinct communities may converge on similar metabolic outputs. Metagenomic sequencing, which captures the complete genetic repertoire of the microbiome, and metabolomic profiling, which directly measures small-molecule metabolites in fecal samples and circulation, provide complementary insights into how the dysbiotic microbiome in psoriasis differs functionally from the healthy state.

Among the most consistently altered pathways are those involved in SCFA biosynthesis. SCFAs, particularly acetate, propionate, and butyrate, represent primary fermentation products generated when gut bacteria metabolize dietary fibers and resistant starches that escape digestion in the upper gastrointestinal tract. Metagenomic analyses reveal alterations in gene abundance encoding key enzymes in SCFA production pathways. The butyryl-CoA transferase pathway, representing the dominant route for butyrate synthesis in human gut bacteria, shows reduced gene abundance in psoriasis patients, consistent with the observed depletion of butyrate-producing species such as *Faecalibacterium prausnitzii* and various Clostridium cluster IV and XIVa members [35]. Similarly, genes encoding enzymes in propionate biosynthesis pathways, including the succinate and acrylate pathways, exhibit altered abundance patterns. Metabolomic measurements demonstrate that fecal SCFA concentrations, particularly butyrate, are reduced in psoriasis patients compared to healthy controls [36]. This reduction in genetic capacity to produce SCFAs and actual metabolite concentrations suggests a meaningful functional deficit in the psoriatic gut microbiome. These metabolites enter circulation and reach distant organs, including the skin, where they exert immunomodulatory effects through receptor-mediated and epigenetic mechanisms.

Tryptophan metabolism represents another metabolic axis profoundly affected by gut microbiome dysbiosis in psoriasis. Tryptophan, an essential amino acid obtained through diet, can be metabolized through multiple pathways, including the kynurenine pathway in host tissues, the serotonin pathway in enterochromaffin cells and neurons, and various bacterial transformation pathways in the gut [37]. Gut bacteria convert tryptophan into numerous bioactive metabolites, including indole, indole-3-acetic acid, indole-3-propionic acid, indole-3-aldehyde,

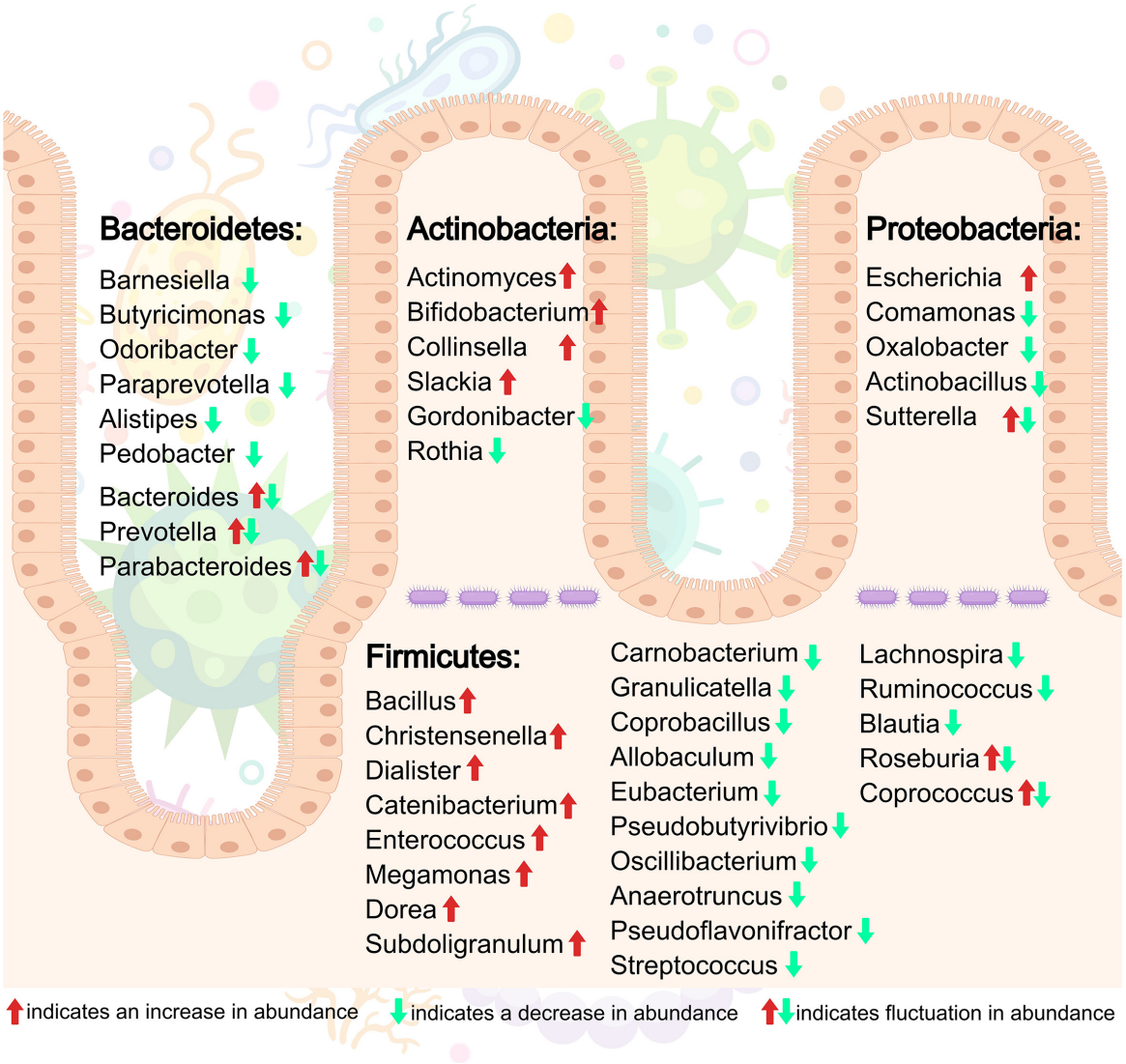


Fig. 1. Taxonomic alterations of gut microbiota at phylum and genus levels in psoriasis patients. This figure illustrates characteristic gut microbial composition changes in psoriasis patients compared to healthy controls, based on a systematic review of published studies. Bacterial taxa are organized by four major phyla (Bacteroidetes, Actinobacteria, Proteobacteria, Firmicutes) and presented at the genus level. The figure shows complex alterations with depletion of multiple beneficial genera, including butyrate-producing taxa such as Butyricimonas, Coprobacillus, and Pseudobutyrivibrio, alongside the expansion of potentially proinflammatory genera. The figure was created with MedPeer (https://image.medpeer.cn/).

and tryptamine, each with distinct biological activities and receptor targets [38]. Metagenomic studies identify alterations in bacterial genes encoding tryptophan-metabolizing enzymes in psoriasis patients [39]. The tryptophanase enzyme, which catalyzes the conversion of tryptophan to indole, and subsequent enzymes modifying indole into various derivatives show altered gene abundance patterns consistent with observed taxonomic shifts. Certain Clostridium species and Lactobacillus strains capable of producing beneficial indole derivatives are depleted in psoriasis, potentially reducing the generation of metabolites that activate aryl hydrocarbon receptor (AhR) and promote immune tolerance [40]. Metabolomic analyses detect differences in tryptophan-derived metabolite profiles between psoriasis patients and controls, with some studies reporting reduced levels of protective indole derivatives, though findings show variability across investigations [41]. The balance between host and microbial tryptophan metabolism appears disrupted in psoriasis, potentially influencing local intestinal immune regulation and inflammatory tone throughout the body. Many tryptophan-derived bacterial metabolites serve as ligands for AhR, a transcription factor with important roles in immune cell differentiation and skin barrier function, suggesting that alterations in this metabolic pathway may have direct relevance to psoriasis pathogenesis [42].

Beyond SCFAs and tryptophan metabolites, the psoriatic gut microbiome exhibits alterations in several other metabolic pathways with potential immunological significance. Bile acid metabolism represents a notable example, as gut bacteria extensively modify primary bile acids secreted by the liver into diverse secondary bile acids through deconjugation, dehydroxylation, and other transformations [43]. These secondary bile acids function as signaling molecules activating receptors, including farnesoid X receptor (FXR) and takeda G protein-coupled receptor 5 (TGR5), influencing glucose metabolism, lipid homeostasis, and immune responses [44]. Metagenomic studies identify alterations in bacterial bile salt hydrolase genes and other bile acid-modifying enzymes in psoriasis, potentially affecting the spectrum of bile acids present in the intestine and circulation [45]. Trimethylamine metabolism represents another altered pathway, as certain gut bacteria convert dietary choline, carnitine, and betaine into trimethylamine, which is subsequently oxidized by host hepatic enzymes to trimethylamine N-oxide (TMAO) [46]. Studies have reported elevated TMAO levels in psoriasis patients, potentially reflecting gut microbiome alterations and metabolic comorbidities common in this population [47].

Functional alterations documented through metagenomic and metabolomic approaches show that compositional changes in the psoriatic gut microbiome translate into meaningful shifts in metabolic pathway activities and metabolite production profiles. Convergent evidence from gene abundance patterns and actual metabolite measurements supports a model in which selective depletion of beneficial commensal organisms and expansion of proinflammatory taxa result in a metabolically distinct microbial community. This altered community exhibits reduced capacity to generate anti-inflammatory metabolites while potentially producing elevated levels of proinflammatory compounds. Understanding how these metabolite deficiencies influence host immune responses requires a detailed examination of the molecular mechanisms through which specific microbial metabolites interact with immune cells to shape inflammatory tone and regulate the balance between pathogenic and protective immune responses. Table 1 (Ref. [16,35,36,37,39,40,41,43,44,45,46,47,48,49,50,51,52]) presents the key functional alterations in microbial metabolic pathways documented in psoriasis.

3. Immuno-Metabolic Regulation by Microbiota-Derived Metabolites

3.1 Short-Chain Fatty Acids and T Cell Differentiation

SCFAs are the most abundantly produced and extensively studied class of gut microbiota-derived metabolites, serving as crucial molecular links between intestinal microbial communities and host immune regulation [53]. The documented reduction in SCFA-producing bacteria and diminished fecal concentrations of these metabolites in patients with psoriasis raise important mechanistic questions regarding how this deficit influences immune cell function and contributes to inflammatory dysregulation. SCFAs, particularly acetate, propionate, and butyrate, exert biological effects through multiple complementary mechanisms, including activation of G protein-coupled receptors and inhibition of histone deacetylase (HDAC) enzymes. These mechanisms ultimately influence the differentiation, activation, and effector functions of various immune cell populations, particularly concerning the pathophysiology of psoriasis.

The receptor-mediated actions of SCFAs primarily involve three G protein-coupled receptors (GPRs) designated GPR41, GPR43, and GPR109A. These receptors exhibit distinct tissue expression patterns, ligand preferences, and downstream signaling characteristics [48]. GPR43, also designated FFAR2, shows broad expression across immune cell types, including neutrophils, eosinophils, monocytes, macrophages, and T lymphocytes. The receptor binds acetate and propionate with relatively high affinity while showing weaker interactions with butyrate. Its activation triggers multiple intracellular signaling cascades depending on the cellular context. In myeloid cells such as neutrophils and macrophages, GPR43 activation by SCFAs suppresses the production of proinflammatory cytokines, including TNF-α and IL-6, although it can enhance chemotaxis and antimicrobial functions in certain contexts. GPR41, or FFAR3, exhibits different ligand preferences and tissue distribution, with notable expression in peripheral tissues and enteroendocrine cells [54]. GPR109A shows preferential binding to butyrate and related compounds. Its activation in immune cells, particularly macrophages and dendritic cells, promotes anti-inflammatory responses, including increased IL-10 production and suppression of proinflammatory mediators. Within T lymphocytes, these receptors mediate crucial effects on cell differentiation and function. GPR43 activation on T cells influences the balance between effector and regulatory populations, with SCFA signaling through this receptor enhancing T regulatory (Treg) cell generation while suppressing differentiation of proinflammatory Th cell subsets.

Complementing receptor-mediated actions, SCFAs function as inhibitors of HDAC enzymes, directly influencing the epigenetic landscape and gene expression patterns in immune cells. HDACs remove acetyl groups from lysine residues on histone proteins, generally resulting in chromatin condensation and transcriptional repression. By inhibiting these enzymes, SCFAs promote histone acetylation, leading to a more open chromatin configuration and enhanced accessibility of transcription factors to regulatory DNA elements [55]. This epigenetic mechanism operates in a concentration-dependent manner, with butyrate showing the most potent HDAC inhibitory activity, followed by propionate and acetate [49]. In naïve T cells encountering antigenic stimulation, the epigenetic environment profoundly influences lineage commitment decisions. SCFAs,

Table 1. Functional alterations in microbial metabolic pathways in psoriasis.

Metabolic pathway	Metabolite products	Alteration type	Immune regulatory effects	Ref.
SCFA biosynthesis	Butyrate	Decreased production; Reduced gene abundance	Promotes Treg cell differentiation and Foxp3 expression; Inhibits HDAC enzymes; Suppresses Th17 responses	[35,36]
SCFA biosynthesis	Propionate, Acetate	Decreased fecal concentration	Activates GPR43 on immune cells; Enhances Treg function; Reduces proinflammatory cytokine production	[48,49]
Tryptophan metabolism	Indole derivatives (indole-3-propionic acid, indole-3-aldehyde)	Reduced metabolite levels; Altered bacterial gene abundance	Activates AhR to enhance immune tolerance; Promotes Treg cell development; Suppresses Th17 differentiation	[40,41]
Tryptophan metabolism	Kynurenine pathway metabolites	Altered metabolic profile	Modulates immune cell activation and differentiation; Influences inflammatory balance	[37,50]
Secondary bile acid metabolism	Deoxycholic acid, Lithocholic acid	Altered microbial bile acid metabolism; secondary bile acid profiles vary across individual metabolites and study contexts	Activates FXR and TGR5 receptors; Suppresses proinflammatory responses in macrophages; Modulates metabolic homeostasis	[43,45,51]
Secondary bile acid metabolism	Conjugated and unconjugated bile acids	Altered metabolic profile; Changes in bile salt hydrolase gene abundance	Influences intestinal barrier function; Regulates antimicrobial peptide production; Modulates immune cell function	[44,52]
TMAO metabolism	Trimethylamine N-oxide (TMAO)	Elevated serum levels	Associated with systemic inflammation and metabolic comorbidities; Potentially contributes to cardiovascular risk	[46,47]
Amino acid metabolism	Short-chain fatty acids and amino acid derivatives	Decreased production capacity	Supports intestinal barrier integrity; Regulates immune cell metabolism and function	[16,39]

Abbreviations: AhR, aryl hydrocarbon receptor; Foxp3, forkhead box P3; FXR, farnesoid X receptor; GPR43, G protein-coupled receptor 43; HDAC, histone deacetylase; SCFA, short-chain fatty acid; TGR5, Takeda G protein-coupled receptor 5; Th17, T helper 17 cell; TMAO, trimethylamine N-oxide; Treg, regulatory T cell.

through HDAC inhibitory activity, modulate the expression of lineage-defining transcription factors and cytokine genes determining whether T cells differentiate into regulatory, helper, or cytotoxic phenotypes. The *Foxp3* gene, encoding the master transcription factor for Treg cell identity and function, contains multiple regulatory regions sensitive to histone acetylation status. Butyrate treatment enhances histone acetylation at the *Foxp3* promoter and conserved noncoding sequence regions, facilitating increased *Foxp3* expression and promoting Treg cell differentiation from naïve precursors [56]. This enhancement occurs *in vitro* and *in vivo*, where SCFA supplementation or administration of butyrate-producing bacterial strains increases the frequency and suppressive capacity of Treg cells in intestinal tissues and peripheral lymphoid organs. Beyond direct effects on *Foxp3* expression, HDAC inhibition by SCFAs influences the acetylation status of the Foxp3 protein itself, enhancing its stability and transcriptional activity. The integration of receptor-mediated signaling and HDAC inhibition raises questions about how these mechanisms coordinate within immune cells. Current evidence suggests that both mechanisms can occur within individual T cells, although their relative contributions may vary depending on SCFA concentrations, cellular metabolic state, and differentiation stage [57]. Receptor signaling through GPR43 and GPR109A likely provides rapid responses to acute changes in metabolite availability, while HDAC inhibition, requiring higher metabolite concentrations, may exert more durable effects on cell fate decisions. Beyond their effects on circulating immune cells, SCFAs influence tissue-resident memory T cell populations that play critical roles in the persistence and recurrence of chronic inflammatory diseases. These specialized lymphocytes residing in peripheral tissues, including the skin, rely heavily on fatty acid oxidation for energy generation. Butyrate serves as a metabolic substrate and as an epigenetic modulator through HDAC inhibition, affecting chromatin accessibility at genes encoding effector cytokines and tissue residency factors. Evidence demonstrating that microbial metabolites can influence distant organ systems, including skeletal muscle function, supports

the concept that metabolite deficiency resulting from gut dysbiosis may affect immune cell populations residing in cutaneous tissue [58].

SCFAs exert differential effects on Treg cells versus proinflammatory Th subsets, particularly IL-17-producing Th17 cells. Substantial evidence demonstrates that SCFAs potently promote Treg cell differentiation and function, expanding this immunosuppressive population and enhancing its capacity to restrain inflammatory responses [59]. Conversely, SCFAs suppress differentiation and effector functions of Th17 cells through several interconnected mechanisms [60]. Butyrate inhibits the expression of key Th17-associated transcription factors, including RORγt, the master regulator of Th17 lineage commitment, through HDAC-dependent and independent pathways. Additionally, SCFAs suppress the production of IL-17A, IL-17F, and IL-22, the signature cytokines produced by Th17 cells that drive keratinocyte hyperproliferation, neutrophil recruitment, and inflammatory amplification characteristic of psoriatic plaques. In psoriasis, the documented reduction in SCFA production capacity and metabolite concentrations suggests that patients experience a relative deficit in these regulatory signals. This deficit could shift the balance away from Treg cells and toward Th17 cells, aligning with the immunological imbalance observed in psoriatic lesions where Th17 cells are markedly expanded and Treg cell function appears compromised [61]. The functional consequences extend beyond simple changes in cell numbers to affect the stability of T cell phenotypes. SCFAs stabilize the Treg cell phenotype and prevent its conversion to proinflammatory effector cells under inflammatory conditions. This phenomenon holds particular relevance given T cell plasticity and the tendency of Treg cells to lose Foxp3 expression and acquire effector functions in inflammatory microenvironments. The capacity of SCFAs to preserve Treg cell stability even under inflammatory challenge suggests that metabolite deficiency in psoriasis may contribute not only to impaired generation of Treg cells but also to their functional instability [62]. The relevance of SCFA-mediated T cell regulation to psoriasis pathophysiology has been substantiated through multiple experimental approaches in animal models. In the imiquimod-induced psoriasis model, where topical application of the Toll-like receptor agonist imiquimod generates skin lesions resembling psoriatic plaques with epidermal hyperplasia, immune cell infiltration, and elevated IL-17 production, administration of butyrate or other SCFAs markedly attenuates severity. Treated animals exhibit reduced skin thickness, decreased scaling, lower inflammatory cell infiltration, and diminished expression of psoriasis-associated cytokines including IL-17A, IL-22, and TNF-α. Mechanistic analyses reveal that this therapeutic effect correlates with increased Treg cell frequencies in skin-draining lymph nodes and reduced Th17 cell numbers [63]. Importantly, the protective effects of SCFAs are abrogated in mice lacking GPR43 or when Treg cells are depleted, confirming that beneficial actions depend on receptor-mediated enhancement of Treg cell responses [64]. These experimental observations are consistent with clinical findings showing reduced fecal abundance of the SCFA-producing bacterium *Faecalibacterium prausnitzii* in patients with psoriasis compared with healthy controls [65]. Convergent evidence from mechanistic studies, animal models, and clinical correlations supports SCFAs as important mediators linking gut dysbiosis to psoriasis pathogenesis. However, several questions remain unresolved. The extent to which circulating SCFA concentrations, as opposed to local intestinal levels, influence immune responses in distant tissues such as the skin requires further investigation. The relative contributions of the three major SCFAs and whether deficiency of specific metabolites drives particular aspects of immune dysregulation also merit additional study.

3.2 Tryptophan Metabolites and Aryl Hydrocarbon Receptor Signaling

Tryptophan metabolism represents a second major axis through which gut microbiota-derived metabolites influence immune regulation, with direct relevance to psoriasis pathophysiology [66]. Unlike SCFAs, which are produced exclusively through microbial fermentation of dietary carbohydrates, tryptophan metabolites arise from a more complex metabolic landscape involving competition and cooperation between host and microbial enzymatic pathways. Tryptophan, an essential amino acid obtained through dietary sources, serves as a substrate for multiple transformation routes. The host kynurenine pathway, operating primarily in the liver and immune cells, converts tryptophan into metabolites including kynurenine and kynurenic acid [50]. The serotonin biosynthetic pathway, active in enterochromaffin cells and neurons, transforms tryptophan into serotonin and downstream products. Gut bacteria contribute a third major metabolic route, converting tryptophan into diverse indole-containing compounds through distinct enzymatic mechanisms [67]. The balance between these competing pathways determines the spectrum of tryptophan-derived molecules available to interact with host receptors. In the context of gut dysbiosis, alterations in microbial community composition shift this balance, potentially depleting beneficial bacterial metabolites while skewing tryptophan flux toward alternative pathways with differing immunological consequences.

AhR, initially characterized for its role in xenobiotic metabolism and toxicity responses to environmental pollutants, has emerged as a crucial sensor of microbial metabolic activity through its ability to bind bacterially derived tryptophan metabolites [68]. This receptor exhibits widespread expression across immune cell types and barrier tissues, including substantial presence in intestinal epithelial cells, dendritic cells, T lymphocytes, and keratinocytes in the skin [69,70,71]. Upon ligand binding, AhR un-

dergoes conformational changes facilitating its translocation from the cytoplasm to the nucleus, where it dimerizes with aryl hydrocarbon receptor nuclear translocator protein and binds to specific DNA sequences termed xenobiotic response elements in the promoter regions of target genes. In dendritic cells, which serve as critical antigen-presenting cells shaping T cell responses, AhR activation modulates maturation status, cytokine production, and capacity to induce different T cell fates. Ligand-activated dendritic cells exhibit reduced expression of co-stimulatory molecules and decreased production of proinflammatory cytokines, including IL-12 and IL-23, while maintaining or enhancing IL-10 production [72]. This altered activation state renders dendritic cells more tolerogenic, favoring the induction of regulatory rather than effector T cell responses. AhR also directly influences T cell differentiation and function through cell-intrinsic mechanisms. In Treg cells, receptor activation enhances Foxp3 expression and promotes the development of regulatory phenotypes with potent suppressive capacity, operating through transcriptional mechanisms distinct from those engaged by SCFAs [73,74].

The effects of AhR activation on Th17 cells appear more complex and context-dependent. Certain high-affinity synthetic ligands, such as 6-Formylindolo[3,2-b] carbazole, can promote Th17 differentiation under specific *in vitro* conditions. However, physiological ligands derived from microbial tryptophan metabolism, particularly indole derivatives, generally suppress Th17 responses or promote regulatory phenotypes [75]. Ligand structure and binding affinity may influence the duration and intensity of receptor activation, potentially engaging different subsets of target genes. The cytokine milieu present during T cell activation profoundly shapes differentiation outcomes, and AhR signaling may interact differently with distinct cytokine-driven pathways. Oxygen availability and the associated metabolic context may also influence T-cell differentiation in response to AhR activation [76]. Beyond direct effects on immune cell differentiation and function, AhR signaling influences intestinal and cutaneous barrier integrity, processes with clear relevance to gut homeostasis and skin pathology in psoriasis [77]. In intestinal epithelial cells, AhR activation enhances the expression of antimicrobial peptides and promotes IL-22 production, a cytokine that stimulates epithelial proliferation and barrier reinforcement. The receptor also regulates tight junction protein expression and epithelial cell turnover rates, contributing to the maintenance of intestinal barrier function that prevents the inappropriate translocation of bacterial products [78]. Mice lacking functional AhR expression exhibit increased intestinal permeability and heightened susceptibility to inflammatory challenges [79].

The relevance of AhR signaling to skin biology has become increasingly appreciated. Keratinocytes express functional AhR, and its activation influences their proliferation, differentiation, and production of barrier proteins and antimicrobial peptides [80]. In psoriasis, where keratinocyte hyperproliferation and abnormal differentiation represent cardinal features, AhR signaling may exert regulatory effects that counterbalance pathological processes. Topical application of AhR agonists in experimental models of psoriasiform dermatitis reduces inflammation and epidermal thickening, effects attributed to direct actions on keratinocytes and modulation of immune cell function in the skin [81,82]. The recent clinical development of tapinarof, a topical AhR-modulating agent demonstrating efficacy in psoriasis treatment, provides compelling translational evidence for the therapeutic potential of engaging this pathway [83,84,85]. However, genetic polymorphisms in *AHR* itself or in downstream signaling components may further influence individual susceptibility to the consequences of reduced ligand availability.

Animal studies support the functional relevance of tryptophan metabolite deficiency to psoriasis-like inflammation. Administration of indole-3-aldehyde or indole-3-propionic acid to mice with imiquimod-induced dermatitis attenuates severity through AhR-dependent mechanisms, with effects including reduced skin inflammation, decreased Th17 cell accumulation, and enhanced Treg cell function. Conversely, mice lacking AhR or treated with receptor antagonists show exacerbated psoriasiform inflammation, confirming the protective role of this signaling pathway. The convergence of evidence from microbiome alterations, metabolite measurements, genetic associations where available, and experimental models establishes tryptophan metabolism and AhR signaling as a second major axis of metabolite-mediated immune regulation relevant to psoriasis, operating through mechanisms distinct from but complementary to SCFA signaling.

3.3 Secondary Bile Acids and Metabolic-Immune Crosstalk

Bile acids represent a third major class of gut microbiota-modified molecules that bridge metabolic and immunological regulation with potential implications for psoriasis pathophysiology [86]. Unlike SCFAs and tryptophan metabolites, which are synthesized de novo or extensively modified by bacteria, bile acids originate from host hepatic cholesterol metabolism and undergo structural modifications during enterohepatic circulation through gut microbial enzyme actions. Primary bile acids, specifically cholic acid and chenodeoxycholic acid in humans, are synthesized in hepatocytes through complex enzymatic pathways involving cytochrome P450 enzymes. These molecules are conjugated with glycine or taurine, secreted into bile, and released into the duodenum following meals to facilitate lipid emulsification and absorption. Most bile acids are efficiently reabsorbed in the terminal ileum through active transport mechanisms and returned to the liver via portal circulation, completing the enterohepatic cycle. However, a fraction escapes ileal absorption and

enters the colon, where resident bacteria extensively modify these molecules through deconjugation, dehydroxylation, and other transformations. Bacterial bile salt hydrolase (BSH) enzymes catalyze the removal of conjugating groups, generating unconjugated primary bile acids. Subsequently, specific bacterial species possessing appropriate enzymatic machinery perform dehydroxylation reactions that remove hydroxyl groups from the steroid nucleus, converting primary bile acids into secondary bile acids, including deoxycholic acid and lithocholic acid [87]. The efficiency and specificity of these transformations depend critically on the composition and metabolic activities of the gut microbiome. The alterations in gut microbiome composition observed in patients with psoriasis are likely to influence bile acid metabolism, potentially affecting the spectrum and concentrations of secondary bile acids generated in the intestine and subsequently entering systemic circulation [51].

The biological significance of secondary bile acids extends beyond their classical role as detergents facilitating lipid digestion. These molecules function as signaling mediators that activate specific nuclear and membrane receptors, influencing diverse physiological processes, including glucose and lipid metabolism, energy expenditure, and immune responses [88]. FXR, a nuclear hormone receptor highly expressed in the liver, intestine, and other metabolically active tissues, serves as the primary intracellular sensor for bile acids. This receptor binds bile acids with varying affinities, with chenodeoxycholic acid and certain semi-synthetic derivatives showing particularly potent activation, while secondary bile acids exhibit more modest agonist activity. Upon ligand binding, FXR heterodimerizes with Retinoid X Receptor and regulates the transcription of genes involved in bile acid synthesis, transport, and metabolism, creating negative feedback loops that maintain bile acid homeostasis [89]. Beyond this metabolic regulatory role, FXR activation influences immune function. In macrophages and other myeloid cells, receptor activation suppresses the production of proinflammatory cytokines and reduces the expression of genes involved in inflammatory responses [90]. In intestinal epithelial cells, FXR signaling enhances barrier function and regulates antimicrobial peptide production [91]. The second major bile acid receptor, TGR5, also known as G Protein-Coupled Bile Acid Receptor 1 (GPBAR1), represents a membrane-bound receptor responding to bile acids with a preference profile distinct from FXR. Lithocholic acid and certain other secondary bile acids activate this receptor with high potency [92]. The receptor exhibit broad tissue distribution, including the liver, intestine, adipose tissue, muscle, and immune cells. In metabolic tissues, TGR5 activation stimulates energy expenditure and improves glucose homeostasis through mechanisms involving increased Glucagon-Like Peptide-1 secretion and enhanced insulin sensitivity [93]. In immune cells, particularly macrophages, receptor activation exerts anti-inflammatory effects, suppressing the production of TNF-α and other proinflammatory mediators while promoting alternatively activated phenotypes [94].

Studies examining bile acid profiles in patients with psoriasis have yielded initial evidence of alterations, although this area remains less extensively investigated compared to SCFAs and tryptophan metabolites. Metagenomic analyses identify changes in the abundance of bacterial genes encoding bile acid-modifying enzymes, particularly BSH, in psoriatic gut microbiomes compared to healthy controls [95]. Metabolomic measurements detect differences in concentrations of specific primary and secondary bile acids in fecal samples and serum, although precise patterns show some variability across studies. Some studies report elevated ratios of primary to secondary bile acids, suggesting reduced microbial transformation efficiency, while others report more complex alterations, with increases in certain secondary bile acids and decreases in others [52]. Nevertheless, the functional consequences of these changes for psoriasis pathogenesis remain to be fully elucidated. The established roles of bile acids in immune regulation and metabolic homeostasis, combined with documented microbiome alterations affecting bile acid metabolism, support the hypothesis that this pathway contributes to metabolite-mediated dysregulation characteristic of psoriasis. However, the relative importance of bile acid alterations compared to SCFA and tryptophan metabolite deficiencies requires further investigation.

Trimethylamine N-oxide represents another gut microbiota-derived metabolite with important implications for systemic inflammation and cardiovascular risk in psoriasis [96]. Intestinal bacteria metabolize dietary choline, carnitine, and betaine to generate trimethylamine, which undergoes hepatic oxidation to form TMAO. This process depends on specific gut microbial taxa, particularly members of the Proteobacteria and Firmicutes phyla. Elevated TMAO levels are associated with oxidative stress, endothelial dysfunction, and atherosclerosis. Recent clinical investigations reveal that patients with psoriasis exhibit increased circulating TMAO concentrations. Treatment with IL-17 or IL-23 inhibitors significantly reduces TMAO levels in parallel with improvements in skin manifestations [97]. This reduction suggests that controlling skin inflammation improves gut microbial metabolic function, providing evidence for bidirectional gut-skin communication. The decrease in TMAO is particularly notably given the elevated cardiovascular disease risk in psoriasis populations. As a biomarker of gut microbiome metabolic function, TMAO may serve as an indicator of dysbiosis severity and treatment response.

4. Bidirectional Gut-Skin Regulation and Pathological Loops

4.1 Reverse Impact of Cutaneous Inflammation on Intestinal Homeostasis

The previous sections established how gut microbiome dysbiosis and resulting metabolite deficiencies contribute to immune dysregulation and inflammatory processes that can manifest in cutaneous pathology. However, the relationship between intestinal and cutaneous inflammation does not operate as a simple unidirectional pathway from gut to skin. Growing evidence supports bidirectional communication, wherein inflammatory processes occurring in psoriatic skin lesions exert reciprocal effects on intestinal homeostasis and gut microbiome composition [98]. This reverse influence involves multiple immune cell populations, including neutrophils, macrophages, dendritic cells, Th cell subsets, and, importantly, skin-resident memory T cells, which perpetuate disease chronicity. The cutaneous inflammation characteristic of psoriasis generates substantial quantities of proinflammatory mediators that enter systemic circulation, and these circulating factors can influence distant tissues, including the intestinal mucosa. Additionally, the chronic inflammatory state associated with psoriasis engages neuroendocrine stress response pathways that modulate gastrointestinal function through neural and hormonal mechanisms. Clinical observations of gut microbiome changes following effective treatment of skin manifestations provide compelling indirect evidence for the impact of cutaneous inflammation on intestinal ecology [99].

Psoriatic skin lesions represent sites of intense inflammatory activity characterized by the production of numerous cytokines and chemokines that extend beyond local tissue effects to generate systemic consequences. In the intestinal mucosa, circulating TNF-α activates nuclear factor kappa B signaling pathways in epithelial cells, leading to decreased expression of occludin, claudin-1, and zonula occludens-1 proteins that form tight junctions. This molecular disruption increases paracellular permeability and compromises the epithelial barrier [100]. Chronic IL-17A exposure modifies the glycosylation patterns of mucin proteins secreted by goblet cells, changing the biochemical composition of the mucus layer that serves as habitat for mucosa-associated bacteria. These alterations affect which bacterial species can successfully colonize this niche. In experimental models, IL-22 promotes intestinal transit-amplifying cell proliferation while reducing $Lgr5^{+}$ stem cell numbers and impairing enterocyte maturation, indicating a disturbance of epithelial homeostasis [101]. Studies involving various inflammatory models demonstrate that systemic exposure to these cytokines increases intestinal permeability and compromises barrier integrity through the disruption of cytoskeletal organization [102]. Beyond direct effects, systemic inflammatory mediators influence the intestinal microbiome indirectly through alterations in intestinal pH, mucus composition, antimicrobial peptide profiles, and oxygen tension, all of which shift the ecological landscape and promote dysbiotic community structures.

Multiple immune cell populations actively participate in this reverse communication. Neutrophils accumulating in psoriatic plaques release reactive oxygen species, neutrophil elastase, and myeloperoxidase into circulation, which, upon reaching the intestinal mucosa, directly damage epithelial cells and activate resident immune populations [103]. Macrophages in psoriatic skin lesions adopt M1 proinflammatory phenotypes, and their secreted cytokines reach intestinal tissues, influencing gut-resident macrophages to shift toward M1 polarization [104]. This altered macrophage phenotype contributes to chronic intestinal inflammation that disrupts epithelial homeostasis and selects dysbiotic microbial communities. Dendritic cells activated in psoriatic lesions produce high levels of IL-23 and related mediators that enter circulation and influence dendritic cell populations in gut-associated lymphoid tissues [105]. Gut dendritic cells exposed to this systemic inflammatory milieu undergo functional reprogramming, losing their normal capacity to induce oral tolerance and adopting a more immunogenic phenotype that promotes effector T cell rather than Treg cell differentiation [106]. These systemic influences disrupt the balance between Th17 and Treg cells in intestinal tissues. Circulating inflammatory signals from cutaneous sources promote Th17 differentiation in gut-associated lymphoid tissues while impairing Treg cell function. Intestinal Treg cells exhibit decreased Foxp3 stability, diminished suppressive capacity, and increased susceptibility to conversion into inflammatory effector cells. This systemic skewing creates an intestinal immune environment hostile to commensal bacteria, contributing to dysbiosis through immune-mediated selection pressures.

Skin-resident memory T cells are essential as they link cutaneous inflammation to disease chronicity [107]. These specialized T lymphocytes take up permanent residence in cutaneous tissues after initial activation, expressing tissue retention markers including CD69 and CD103. In psoriasis, these resident memory populations are enriched for Th17 and Th1 phenotypes capable of rapidly producing inflammatory cytokines upon restimulation, explaining why psoriasis tends to recur in previously affected sites. The function and stability of these cells are influenced by systemic metabolic signals, including microbiota-derived metabolites. Unlike naïve T cells relying on glycolysis, tissue-resident memory T cells depend on fatty acid oxidation [108]. SCFAs serve as metabolic substrates while also functioning as epigenetic modulators through HDAC inhibition, modulating the expression of genes involved in tissue residency programming and influencing chromatin accessibility at effector cytokine loci. In SCFA deficiency resulting from gut dysbiosis, these cells may maintain more accessible chromatin at inflammatory gene loci, allowing for vigorous responses to restimulation. Tryptophan-derived

indole metabolites influence these cells through AhR activation, which modulates their cytokine production and responsiveness to inflammatory stimuli. The documented depletion of indole-producing bacterial species in psoriasis results in reduced AhR ligand availability, and skin-resident memory T cells in this metabolite-deficient environment lack restraining signals that would normally limit their inflammatory output. The simultaneous depletion of SCFAs and indole derivatives creates a systemic metabolic environment favoring the development and persistence of highly reactive tissue-resident memory T cells [109]. These cells, lacking metabolic brake signals normally provided by a healthy microbiome, maintain proinflammatory phenotypes, facilitating disease chronicity and recurrence, thus linking gut microbial ecology to tissue-level cellular memory underlying the relapsing nature of psoriasis.

The chronic inflammatory state engages neuroendocrine stress response pathways that exert notably effects on gastrointestinal function and gut microbiome composition. Chronic inflammation activates the hypothalamic-pituitary-adrenal axis as IL-1β, IL-6, and TNF-α cross the blood-brain barrier and stimulate corticotropin-releasing hormone secretion, which promotes cortisol release [110]. Prolonged cortisol exposure suppresses secretory immunoglobulin A production, alters mucin glycosylation patterns, modulates tight junction assembly, and paradoxically promotes Th17 responses in gut-associated lymphoid tissues despite acute anti-inflammatory effects. Sympathetic activation increases catecholamine release, affecting intestinal motility, blood flow, and mucosal oxygen tension. Altered motility changes bacterial interactions with epithelial surfaces, while changes in blood flow can introduce oxygen into the typically anaerobic colonic lumen, favoring facultative anaerobes over obligate anaerobes. Recent studies reveal that biologic therapy also corrects metabolic dysfunction, with IL-17 and IL-23 inhibitors reducing circulating trimethylamine N-oxide levels [111]. Reduction in TMAO following successful treatment suggests that controlling skin disease ameliorates gut microbial metabolic dysfunction, demonstrating that the inflammatory burden influences not only gut microbiome composition but also functional metabolic output. This finding is crucial given the elevated cardiovascular risk in psoriasis populations. Patients who achieve better clinical responses show more pronounced microbiome normalization, supporting a correlation between skin inflammation control and gut improvement. The reverse influence of cutaneous inflammation on intestinal homeostasis carries important implications for understanding psoriasis chronicity. This reciprocal relationship creates self-reinforcing cycles wherein gut dysbiosis promotes cutaneous inflammation through metabolite-mediated mechanisms, while cutaneous inflammation exacerbates gut dysbiosis through circulating cytokines, immune cell reprogramming, skin-resident memory maintenance, and neuroendocrine activation. This bidirectional amplification explains the chronic relapsing nature of psoriasis and suggests that interventions targeting either gut microbiome or cutaneous inflammation might exert beneficial effects extending beyond their direct targets by interrupting pathological cycles.

4.2 Self-Perpetuating Pathological Cycle and Genetic Modulation

The preceding discussions established individual components of a complex pathological process linking gut microbiome alterations to cutaneous inflammation in psoriasis. The characterization of dysbiosis patterns revealed depletion of beneficial commensals and corresponding functional metabolic deficits. The examination of metabolite-immune interactions detailed how deficiencies in SCFAs, tryptophan derivatives, and bile acids influence Treg cell and Th17 cell differentiation. The analysis of reverse cutaneous-to-intestinal signaling demonstrated how skin inflammation reciprocally affects gut homeostasis. These components interconnect to form a self-perpetuating cycle. Gut microbiome dysbiosis depletes beneficial organisms, including *Faecalibacterium prausnitzii* and butyrate-producing species, reducing the production of immunomodulatory metabolites. These metabolite deficiencies impair immune homeostasis through diminished GPR43 signaling, decreased histone acetylation at immune regulatory loci, reduced AhR activation, and disrupted bile acid receptor signaling. The resulting immune dysregulation manifests as expanded Th17 populations and compromised Treg function. In genetically susceptible individuals, these immunological perturbations trigger cutaneous inflammation, with hyperactivated Th17 cells driving keratinocyte hyperproliferation and neutrophil recruitment. This cutaneous inflammation generates systemic consequences that exacerbate the initiating gut dysbiosis through circulating cytokines, immune cell reprogramming, skin-resident memory T cell maintenance, and neuroendocrine activation. These reverse effects amplify the original dysbiosis, creating a positive feedback loop wherein each component reinforces the others.

Understanding the evidence base supporting each component of this cycle is crucial for interpreting its validity and identifying knowledge gaps. The observational evidence documenting gut microbiome alterations in psoriasis is robust, with multiple independent studies consistently identifying similar dysbiosis patterns, particularly *Faecalibacterium prausnitzii* depletion [112]. Metabolomic analyses corroborate these findings, demonstrating reduced SCFA concentrations [113]. These observational findings establish a strong foundation for the proposed model. The mechanisms linking metabolite deficiencies to immune dysregulation rest on substantial experimental evidence, predominantly from *in vitro* studies and animal models. However, direct demonstration of these mecha-

nisms operating in human psoriasis patients remains limited, representing a notably evidence gap. The causal relationship between gut dysbiosis and psoriasis is supported by gnotobiotic animal experiments and metabolite transplantation studies. In humans, the strongest causal evidence comes from longitudinal observations showing that successful treatment of cutaneous inflammation leads to gut microbiome normalization over subsequent weeks to months. The temporal sequence supports causality, although randomized controlled trials directly testing whether microbiome modification prevents or treats psoriasis remain limited. The bidirectional nature of the relationship, while mechanistically plausible, relies partly on extrapolation from other disease models. The influence of metabolite deficiency on skin-resident memory T cells represents an emerging concept requiring further validation through human studies combining microbiome profiling, metabolite measurements, immune phenotyping, and clinical outcomes.

Host genetic factors profoundly modulate the initiation and perpetuation of this pathological cycle, determining individual susceptibility and clinical phenotype [114]. The major histocompatibility complex (MHC) region on chromosome 6p21 exerts the strongest effect, with *HLA-C*06:02* significantly increasing risk and occurring in most early-onset patients [115]. This allele encodes a class I MHC molecule presenting peptide antigens to CD8-positive T cells. Individuals carrying *HLA-C*06:02* may mount more vigorous inflammatory responses to bacterial peptides that translocate across compromised intestinal barriers, with the allele's peptide-binding preferences determining which microbial antigens elicit strong responses. Beyond the MHC, variants in *IL23R* influence T cell responsiveness to IL-23 signaling, directly modulating susceptibility to dysregulated immune responses promoted by metabolite deficiencies [116]. An individual carrying risk variants that enhance IL-23 receptor signaling may develop pathogenic Th17 responses even with relatively mild metabolite deficiency, whereas someone with protective variants may tolerate more substantial depletion without developing overt psoriasis. Genetic variants also influence gut microbiome composition through effects on immune function, mucus production, and antimicrobial peptide secretion. In psoriasis, genetic variants associated with altered immune responses or epithelial barrier function may render individuals more susceptible to developing dysbiosis following perturbations. The interplay between genetic susceptibility and environmental factors, with the gut microbiome serving as a crucial, partially genetics-influenced environmental component, determines whether the pathological cycle becomes established. Genetic factors set the thresholds and responsiveness of various cycle nodes, while environmental factors, including diet, infections, and stress, influence microbiome and modulate metabolite production. Psoriasis emerges when the combination of genetic susceptibility and environmental perturbations crosses a critical threshold, initiating the self-reinforcing cycle.

The recognition of this self-perpetuating cycle has important implications for developing therapeutic strategies. Since psoriasis results from a self-reinforcing bidirectional cycle, interventions targeting single components may provide only temporary benefit unless feedback mechanisms are durably disrupted. Several potential intervention points exist, each with distinct advantages and limitations. At the microbiome and metabolite levels, interventions could include probiotic supplementation, prebiotic administration, or direct metabolite supplementation. These upstream interventions address metabolic deficits that drive immune dysregulation. However, probiotic colonization faces challenges from colonization resistance mechanisms, and metabolite supplementation faces bioavailability issues. In established disease, restoring metabolite levels alone may be insufficient if downstream immune dysregulation has become self-sustaining through resident memory populations. At the immune regulation level, current biologic therapies targeting IL-23, IL-17, or TNF-α effectively interrupt the cycle at the inflammatory amplification stage, and successful control of skin inflammation leads to improvements in gut microbiome composition and metabolic function. However, biologics do not correct original metabolite deficiencies or restore normal microbiome composition to healthy baselines. Upon treatment cessation, the underlying metabolic environment potentially allows for cycle re-establishment, explaining disease recurrence after discontinuing therapy. At the tissue memory level, skin-resident memory T cells perpetuate chronicity, yet no therapies currently specifically target these populations. Topical AhR agonists may influence their function through local application. Systemic metabolite restoration might affect these cells by altering the epigenetic landscape maintaining their proinflammatory phenotype. Combination strategies integrating interventions at multiple cycle nodes offer theoretical advantages. Initiating biologic therapy to suppress inflammation while implementing microbiome-directed interventions to restore metabolite production may achieve synergistic effects, with biologics creating permissive environments for microbiota recovery while microbiome restoration provides metabolic signals needed to re-establish immune homeostasis and prevent resident memory reactivation. Timing matters, as early intervention before cycle establishment may be more effective than treating chronic disease. For high genetic risk individuals, maintaining gut microbiome health may delay or prevent disease onset, although testing this requires long-term prospective studies.

5. Clinical Evidence and Therapeutic Exploration

5.1 Current Evidence and Implementation Challenges

Multiple clinical investigations have explored microbiome-targeted interventions for psoriasis, employing strategies ranging from probiotic and prebiotic supplementation to fecal microbiota transplantation and dietary modifications. These studies provide preliminary evidence that modulating the gut microbiome may influence psoriatic inflammation; however, results have been inconsistent, and the quality of evidence varies substantially. Probiotic trials represent the most extensively studied approach, utilizing various single-strain or multi-strain formulations of *Lactobacillus* and *Bifidobacterium* species, administered over 8 to 24 weeks. Prebiotic interventions show promise in promoting beneficial commensal growth but have received comparatively less investigation. Fecal microbiota transplantation remains limited to small studies with mixed outcomes. Dietary interventions, particularly calorie restriction, have demonstrated clinical benefits that may partly operate through microbiome modulation. An emerging area examines how established psoriasis therapies, particularly biologic agents, influence gut microbiome composition and metabolic function, providing indirect evidence for bidirectional gut-skin interactions. Table 2 (Ref. [97,117,118,119,120,121,122,123,124,125,126,127,128]) systematically summarizes clinical trials and interventional studies in this field.

The inconsistent results across microbiome intervention trials reflect substantial methodological limitations. Most published trials had inadequate statistical power as they enroll fewer than 50 participants per group when 100 to 200 participants per group are typically required. Many studies lack rigorous placebo controls or employ open-label designs, particularly problematic given that placebo response rates of 20% to 30% commonly occur in dermatology trials. Marked heterogeneity in bacterial strains, doses (varying across three orders of magnitude), treatment duration (8 to 24 weeks), and outcome measures prevents meaningful meta-analysis. Most critically, most trials measured only clinical outcomes without microbiome compositional analysis, metabolite measurements, or immune phenotyping. When trials report positive results without mechanistic validation, it is impossible to determine whether benefits arise from hypothesized gut microbiome mechanisms or from different pathways. The few studies including mechanistic endpoints demonstrate that interventions can modify gut microbiome composition, reduce circulating lipopolysaccharide, and alter inflammatory cytokine profiles; however, whether mechanistic changes predict clinical response in individual patients remains unclear.

Dietary interventions represent an important but understudied dimension of microbiome-targeted therapy. Mediterranean dietary patterns, characterized by high consumption of vegetables, fruits, whole grains, legumes, and olive oil, have been associated with increased gut microbiome diversity and enhanced SCFA production. Recent evidence supports the Mediterranean diet as a key non-pharmacological intervention for psoriasis management, with adherence reducing clinical severity while improving metabolic and cardiovascular risk profiles through the antioxidant and anti-inflammatory properties of plant-based foods [129]. Clinical trials examining calorie restriction in overweight or obese psoriasis patients demonstrate substantial disease improvements correlating with weight reduction and metabolic changes. Obesity exacerbates inflammation and metabolic dysfunction in psoriasis through multiple mechanisms, including increased adipose tissue production of proinflammatory adipokines, thereby creating a bidirectional pathogenic relationship [130]. Collaboration between dermatologists and nutritionists could provide patients with evidence-based dietary guidance aimed at increasing fermentable fiber intake, promoting polyphenol-rich foods, and reducing proinflammatory dietary components.

Patient-level heterogeneity likely contributes substantially to variable responses. Psoriasis encompasses considerable clinical heterogeneity, including distinct morphological subtypes, disease severity, and duration. Baseline gut microbiome composition shows substantial inter-individual variation, with dysbiosis severity and patterns differing considerably among individuals. Concurrent treatments, dietary habits, lifestyle factors (stress, sleep quality, physical activity), and host genetic background likely modulate treatment responses. These multiple sources of heterogeneity suggest that future research should focus on identifying which patient subgroups derive benefit from which interventions under specific conditions. Developing predictive biomarkers that integrate baseline microbiome features, host genetic markers, metabolic phenotypes, and clinical characteristics into algorithms guiding personalized treatment selection represents a critical priority.

5.2 Translational Challenges and Future Directions

Advancing this field from preliminary findings to validated clinical applications requires establishing causal relationships through well-designed human mechanistic studies. Such investigations should integrate microbiome interventions with comprehensive phenotyping that systematically tracks gut microbial composition, metabolite concentrations in fecal samples and circulation, immune cell populations, gene expression profiles, and clinical outcomes over time. Multi-compartment metabolomic approaches tracking metabolite changes across fecal, serum, and tissue samples can reveal alterations in microbiome-host interactions [131]. Dose-response and cessation studies will strengthen causal inference if clear relationships emerge between intervention intensity, mechanistic biomarker changes, and clinical improvement.

Combination strategies that integrate microbiome-targeted interventions with conventional therapies represent

Table 2. Clinical trials and interventional studies of microbiome-targeted therapies in psoriasis.

Type	Study & Design	Intervention & Sample size	Control & Duration	Main results	Mechanism verified	Ref.
Probiotic Interventions	RCT, double-blind	*B. longum* CECT 7347, *B. lactis* CECT 8145, *L. rhamnosus* CECT 8361; 10^9 CFU/day, 12 weeks; n = 90 (46 vs 44)	Placebo, 12 weeks	PASI-75: 66.7% vs 41.9% ($p < 0.05$); PGA clear/almost clear: 48.9% vs 30.2%; 6-month relapse: 20% vs 41.9% ($p = 0.027$)	Yes (microbiome composition changes; decreased Micromonospora and Rhodococcus; increased Collinsella and Lactobacillus)	[117]
	RCT	*L. acidophilus, B. bifidum, B. lactis, B. longum*; 1.8×10^9 CFU twice daily, 8 weeks; n = 50 (25 vs 25)	Placebo, 8 weeks	PASI reduction: 5.26 vs 0.48 ($p = 0.049$); PASI-50: 40% vs 16%; PASI-75: 24% vs 8%; DLQI improved ($p = 0.045$)	Yes (hs-CRP, IL-6, oxidative stress markers measured)	[118]
	RCT	*L. acidophilus, B. bifidum, B. lactis, B. longum*; $\geq 1.6 \times 10^9$ CFU/g twice daily, 8 weeks; n = 46 (23 vs 23)	Placebo, 8 weeks	PASI reduction: –5.06 vs 0.30 ($p = 0.049$); PASI-50: 52% vs 5%; Serum LPS decreased 7.21 vs 2.74 mmol/L ($p = 0.010$)	Yes (LPS, hs-CRP, IL-1β measured)	[119]
	RCT	Lactocare® (7 strains) + fructooligosaccharide; 10^9 CFU twice daily, 12 weeks; n = 38 completed (24 vs 14)	Placebo, 12 weeks	Serum trace elements improved: Zn 91.90→101.86 µg/dL ($p = 0.033$); Ca 9.14→9.67 mg/dL ($p < 0.001$)	Partial (serum electrolytes and trace elements only)	[120]
	RCT	*L. rhamnosus* ATCC 7469; 5 mL daily (6×10^9 CFU/mL), 6 months; n = 80 completed (41 vs 39)	Placebo, 6 months	PASI reduction: –1.58 vs –1.90 ($p = 0.620$, NS); DLQI: + 0.05 vs −3.33 (between-group $p = 0.107$, NS)	No	[121]
Probiotic + Prebiotic Combination	Open-label	Bacillus mixture (5 strains); 2×10^9 CFU/day, 12 weeks + Precision prebiotics 5 g/day (last 8 weeks); n = 63 (42 vs 21)	Standard topical care, 12 weeks	PASI: 10.0→8.1 vs 8.6→8.7 ($p < 0.001$); DLQI: 7.2→5.8 vs 7.7→8.4 ($p < 0.001$)	Yes (microbiome analysis in subset; increased diversity, Firmicutes/Bacteroidetes ratio, acetate/propionate; decreased LPS bacteria; improved cytokine profile)	[122]
Fecal Microbiota Transplantation	RCT	Single FMT (50 g donor stool in 250 mL saline, duodenal delivery); n = 31 (15 vs 16). All on methotrexate 15–25 mg/week	Sham (saline), 26 weeks	Treatment failure: 60% vs 19% (RR 3.20, $p = 0.018$); HAQ-DI worsened in FMT group; ACR20: 47% vs 50% (NS)	Partial (microbiome samples collected but not reported)	[123]
	RCT, proteomic analysis	Same FMT protocol; n = 31 (15 vs 16) with 31 healthy controls	Sham, 26 weeks; plasma at baseline, weeks 4, 12, 26	92 inflammation proteins analyzed; 5 proteins differed significantly (TNF $p = 0.002$, IFN-γ $p = 0.011$, SCF, MMP-1, SLAMF1); FMT increased IFN-γ, decreased CCL19 and IL-6	Yes (comprehensive Olink inflammation panel via proximity extension assay)	[124]

Table 2. Continued.

Type	Study & Design	Intervention & Sample size	Control & Duration	Main results	Mechanism verified	Ref.
Dietary Interventions	RCT	Low-calorie diet ≤1000 kcal/d, 8 weeks + biologics; n = 262 (131 vs 131)	Normal diet + biologics, 24 weeks	Weight loss 12.9 vs gain 1.5 kg; PASI improvement 84% vs 69%; PASI-75: 85.9% vs 59.3% ($p < 0.001$)	Partial (lipid profiles; BMI-PASI correlation)	[125]
	RCT	Calorie restriction (0.8−1.0 × RMR) + aerobic exercise 40 min 3 × /week, 20 weeks; n = 303 (151 vs 152)	Informative counseling, 20 weeks	PASI reduction: 48% vs 25.5% ($p = 0.02$); PASI-50: 49.7% vs 34.2% ($p = 0.006$); Weight loss ≥5%: 29.8% vs 14.5%	Partial (clinical and anthropometric measures only)	[126]
	Single-arm	Phase 1: VLCKD <500 kcal/d, 4 weeks; Phase 2: Mediterranean diet, 6 weeks; n = 37	No control, 10 weeks	Weight loss 12.0% (10.6 kg); PASI reduction 10.6 points ($p < 0.001$); PASI-50: 97.3%; PASI-75: 64.9%	Yes (TNF-α, IFN-γ, IL-1β, IL-2 reduced ∼50% at week 4; AMFT measured)	[127]
Biologic Therapy-Microbiome Studies	Phase 3b RCT substudy	Ustekinumab (anti-IL-12/23) 45–90 mg standard dosing; n = 114 (478 total trial)	Response-based vs fixed dosing, up to 112 weeks	Microbiome diversity and composition changed with treatment; lesional/nonlesional skin diverged; body-site dispersion increased	Yes (16S rRNA sequencing at 6 body sites)	[128]
	Prospective pilot	Anti-IL-17 (secukinumab, ixekizumab, bimekizumab) or anti-IL-23 (guselkumab, risankizumab, tildrakizumab); n = 33	Before-after design, 16 weeks	PASI reduction 90.61% (18.49→1.70, $p < 0.001$); PASI-100: 66.7%; DLQI: 15.51→5.51 ($p < 0.001$)	Yes (TMAO decreased 4.92→3.07 µmol/L, $p = 0.02$; d-ROMs: 421.24→333.58 UCARR, oxLDL reduced, all $p < 0.001$)	[97]

Abbreviations: ACR20, American College of Rheumatology 20% improvement; AMFT, aorto-mesenteric fat thickness; B., Bifidobacterium; CFU, colony-forming units; DLQI, Dermatology Life Quality Index; d-ROMs, derived reactive oxygen metabolites; FMT, fecal microbiota transplantation; HAQ-DI, Health Assessment Questionnaire Disability Index; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; L., Lactobacillus; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NS, not significant; oxLDL, oxidized low-density lipoprotein; PASI, Psoriasis Area and Severity Index; PASI-50/75/90/100, 50%/75%/90%/100% improvement in PASI score; PGA, Physician Global Assessment; RCT, randomized controlled trial; RMR, resting metabolic rate; RR, relative risk; SCF, stem cell factor; TMAO, trimethylamine-N-oxide; TNF, tumor necrosis factor; VLCKD, very low-calorie ketogenic diet. →, change from baseline to endpoint.

a rational but underexplored approach. Concurrent administration of probiotics or prebiotics alongside biologic therapies might achieve effects by simultaneously interrupting inflammatory amplification while restoring metabolic signals that support immune homeostasis. Alternatively, microbiome modulation might serve as maintenance therapy, allowing a reduction in biologic exposure once remission is achieved. Multi-modal microbiome interventions, combining probiotics with prebiotics and dietary counseling, may prove more effective than single-component strategies by addressing different aspects of microbiome restoration.

Developing predictive biomarkers represents a critical priority for precision medicine approaches. Baseline gut microbiome features (alpha diversity metrics, abundance of specific taxa such as *Faecalibacterium prausnitzii*, functional gene repertoires), baseline metabolite measurements (fecal SCFAs, circulating tryptophan metabolites), and host genetic markers (variants in immune signaling genes such as *IL23R*) may predict responsiveness to interventions. Early-response biomarkers that change within weeks could enable adaptive treatment strategies. Developing such biomarker panels requires large prospective studies with comprehensive baseline profiling and longitudinal sampling, potentially employing machine learning approaches.

Regulatory frameworks governing microbiome-based therapeutics remain in evolution. Probiotics are classified as dietary supplements in most jurisdictions, subjecting them to less stringent oversight than medications. Developing specific strains as approved therapeutics would require pharmaceutical development pathways, including preclinical studies and phase I through III clinical trials. Fecal microbiota transplantation faces distinct challenges regarding donor screening standards, pathogen exclusion protocols, and product classification. Metabolite-based therapeutics align more closely with traditional small-molecule drug development, offering the advantages of chemical standardization but requiring solutions to bioavailability and targeted delivery challenges.

Future investigations should prioritize patients with mild to moderate psoriasis, individuals showing inadequate responses to or intolerance of biologic therapies, and patients with psoriatic arthritis, given emerging connections between gut inflammation and joint disease. Research priorities include adequately powered randomized controlled trials with appropriate blinding and mechanistic validation, biomarker development studies, comparative effectiveness research examining different intervention strategies, and long-term safety and efficacy assessments. The field must balance enthusiasm for this therapeutic avenue with a realistic acknowledgment of substantial evidence gaps and implementation challenges.

6. Conclusion

Accumulated evidence establishes gut microbiome dysbiosis as an important contributor to psoriasis pathogenesis through metabolite-mediated immune regulatory networks. Alterations in beneficial commensals and associated metabolite profiles, including SCFAs, tryptophan derivatives, and bile acids, may impair Treg cell function while promoting Th17 differentiation and compromising intestinal barrier integrity. Critically, this relationship is bidirectional, with cutaneous inflammation reciprocally influencing gut homeostasis through systemic cytokine responses and neuroendocrine activation, creating self-perpetuating pathological cycles modulated by host genetic factors that determine individual susceptibility and phenotype in psoriasis. While current evidence has established mechanistic connections between gut dysbiosis and psoriatic inflammation, notably knowledge gaps remain regarding temporal relationships, causal directionality, inter-individual variability, and optimal therapeutic strategies. Translating these insights into clinical benefit will require rigorous investigation through well-designed trials to determine whether microbiome-targeted interventions can serve as adjunctive therapies complementing conventional treatments. The gut microbiome thus represents a potentially modifiable factor in psoriasis pathogenesis offering new perspectives on the mechanisms underlying the condition and therapeutic possibilities, although realizing this potential demands continued multidisciplinary research and careful evidence-based clinical translation that balances therapeutic promise against the need for robust scientific validation.

Author Contributions

HZ, DL, XY, and YZ conceptualized the review. HZ and HY conducted the investigation. HZ, HY, and LZ contributed to writing the original draft. HZ, DL, LZ, HY, XY, and YZ were involved in review and editing. DL performed validation. LZ carried out visualization. HY was responsible for data curation. XY and YZ secured funding acquisition. HZ, XY, and YZ supervised the review. YZ managed resources and project administration. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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