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Hydrogen Sulfide-Producing Gut Bacteria as a Trigger for Seborrheic Dermatitis in Ulcerative Colitis

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Abstract

Background and Objectives: The gut-skin axis is a critical pathway linking gut microbiota composition and skin health. Evidence suggests that dysbiosis in inflammatory bowel disease (IBD) may exacerbate seborrheic dermatitis (SD), a chronic inflammatory skin condition. This review investigates the role of hydrogen sulfide (H_2S)-producing bacteria, particularly *Desulfovibrio* species, in disrupting cutaneous lipid homeostasis and contributing to SD in IBD patients. Elevated H_2S production by these bacteria is hypothesized to drive systemic inflammation and cutaneous lipid dysregulation, providing new insights into the pathophysiology of SD in IBD populations. **Methods:** A comprehensive literature review was conducted, synthesizing findings from microbiome studies, H_2S biochemistry, and skin barrier research. Advanced techniques such as 16S rRNA sequencing, lipidomics, and H_2S quantification were analyzed to elucidate the connections between gut-derived H_2S and skin inflammation. Inclusion criteria focused on studies involving IBD patients with concurrent SD or elevated H_2S-producing bacterial populations. **Results:** IBD-associated gut dysbiosis is characterized by increased *Desulfovibrio* species and elevated H_2S levels, which impair epithelial integrity and contribute to systemic inflammation. H_2S dysregulation disrupts lipid metabolism in sebum, weakening the skin barrier and promoting overgrowth of *Malassezia*

species, a key factor in SD pathogenesis. Pro-inflammatory cytokines, such as TNF-α and IL-17, are upregulated, exacerbating skin inflammation. Despite these insights, critical knowledge gaps remain regarding H_2S concentration thresholds and specific pathways linking gut and skin inflammation. **Conclusions:** Targeting H_2S-producing bacteria and gut dysbiosis holds promise for managing SD in IBD patients. Integrated therapeutic strategies, such as probiotics, prebiotics, and dietary modifications, may address the dual burden of gut and skin inflammation. Longitudinal studies and standardized methodologies are needed to advance understanding and improve outcomes in this population.

Keywords

Gut-Skin Axis, Seborrheic Dermatitis, Inflammatory Bowel Disease, Hydrogen Sulfide, *Desulfovibrio*, Dysbiosis, Lipid Metabolism, Cutaneous Inflammation, Microbiome Therapy, Pro-Inflammatory Cytokines

1. Introduction

Both the skin and the gut, two of the largest barrier function organs, are connected by a complex bidirectional communication system involving microbial metabolite interactions and modulation of the immune system [1]. This tightly coupled interplay in the gut-skin axis is evident when investigating the key molecular and cellular responses to microbial dysbiosis, and its role in the manifestation of cutaneous disorders. The gut and skin host extensive microbiomes composed of bacteria, fungi, and viruses, which thrive in symbiotic relationships with their human host [1]. Microbial dysbiosis, an alteration in the symbiotic balance, can disrupt the endothelial barrier, eliciting responses from both the innate and adaptive immune systems [1]. When these responses persist in the gut, a heightened level of pro-inflammatory cytokines can influence the conditions of the skin microbiome [1]. For example, the overgrowth of pathogenic bacteria or a reduction in symbiotic microbial diversity can stimulate cytokines IL-17 and TNF-α, key players in inflammatory skin conditions such as seborrheic dermatitis and psoriasis [1]. In addition to IL-17 and TNF-α causing systemic inflammation, gut microbiome-derived metabolites may influence skin systemic inflammation and skin health in disease states. An excess of neurotransmitters such as GABA, dopamine, serotonin, and acetylcholine produced by the microbiome of the intestines may cross into the blood and spread to other organs, manifesting as systemic effects [1]. Other metabolites, such as hydrogen sulfide (H_2S), short-chain fatty acids, and tryptophan-derived, interact with systemic pathways to alter skin barrier function and inflammation. SCFAs, such as butyrate and acetate, work to enhance the epithelial barrier, but failure of adequate absorption in the intestines can alter the integrity of the skin barrier [1]. The disbalance of pro-inflammatory and anti-inflammatory effects of cytokines, neurotransmitters, and other metabolites are the

key pathways that mediate the gut-skin axis.

Gut microbiota dysbiosis has been shown to specifically contribute to the pathophysiology of co-existing inflammatory bowel disease (IBD) and seborrheic dermatitis (SD) SD is a pruritic and flaking skin condition mostly causing inflammation of the skin of the scalp that is prevalent in up to 50% of the world's population [1]. Due to a disruption in the skin-gut axis, SD is more common in the patient population with IBD. A hallmark of IBD is impaired gut endothelial barrier integrity that promotes chronic immune system dysregulation, displaying a heightened systemic inflammatory state [2]. Alterations in gut microbiota leading to systemic inflammation can lead to a feedback loop that exacerbates symptoms in coexisting IBD and SD [3]. For example, the microbial metabolite hydrogen sulfide (H_2S) that is a common byproduct of many bacteria, including *Desulfovibrio*, can raise H_2S levels above a beneficial physiological level, resulting in a heightened inflammatory state through the aforementioned TH17 and cytokine mechanisms interconnected within the gut-skin axis [1]. Without suppressing the systemic inflammation as a result of gut dysbiosis, patients with IBD may struggle to control symptoms of SD, a cutaneous disease that is often chronic.

Current therapeutic strategies are effective in managing the resultant inflammatory state of the skin and gut individually through solely SD and IBD targeted treatments. In spite of effective individual treatments for SD and IBD, more directed treatment may surface through attentive assessment of the gut microbiome and manipulation of imbalances affecting the gut-skin axis. For example, dietary intake of lipids, glucose, and acetate influence sebaceous gland activity of the skin, leading to high sebum levels associated with seborrheic dermatitis [1]. By altering the diet to restrict calories and high levels of sugar, fats and acetate, a patient may experience reduced sebum production, potentially improving cutaneous SD [4]. To better manage treatment of co-existing SD and IBD, therapeutic strategies should address both gut and skin inflammatory processes simultaneously, such as identifying gut microbiome changes in IBD directly influential in the inflammatory state of the skin during SD. By addressing these conditions simultaneously, a patient's treatment may be more targeted and effective in addressing both gastrointestinal and cutaneous manifestations of IBD.

This review aims to evaluate and synthesize existing evidence linking H_2S-producing bacteria, such as *Desulfovibrio*, to gut and skin inflammatory conditions. This will be done by synthesizing evidence from microbiome studies, H_2S biochemistry, and skin barrier research to elucidate the connection between gut dysbiosis and cutaneous manifestations. Previously advanced analytical approaches, including 16s rRNA sequencing, H_2S measurement techniques, and lipidomics, have studied mechanisms by which H_2S bacteria in the gut disrupt the barrier and inflammatory homeostasis of the skin [5] [6]. Despite this, significant knowledge gaps remain concerning the threshold levels of H_2S, the precise molecular mechanisms involved, and its interactions with other microbial metabolites contributing to skin inflammation. Furthermore, this review aims to analyze the thera-

peutic potential of targeting gut dysbiosis and microbial metabolites to better manage cutaneous SD in the setting of IBD. Exploring these mechanisms could pave the way for innovative therapies to treat SD and IBD concomitantly. This emerging field offers the potential for developing personalized treatment approaches to effectively target the sources of gut microbial dysbiosis and systemic inflammation in IBD patients with SD.

2. Literature Review Methodology

To investigate the interplay between the gut-skin axis, IBD, SD, and H_2S-producing bacteria, a systematic literature search was conducted across four major biomedical databases: PubMed, Scopus, Web of Science, and the Cochrane Library. These platforms were selected for their comprehensive indexing of peer-reviewed studies in clinical medicine, microbiome science, and dermatology. The search encompassed publications from 2012 to 2024, providing a broad and up-to-date view of research in this evolving field.

Filters were applied to restrict results to English-language, peer-reviewed articles, and to exclude conference abstracts, editorials, and gray literature. Systematic reviews and randomized controlled trials were specifically prioritized within the Cochrane Library to ensure inclusion of high-quality evidence. Studies were included if they 1) involved human or animal subjects, 2) reported on microbiome composition, H_2S quantification, or skin/gut clinical outcomes, and 3) employed quantitative or mixed-methods approaches with well-described methodology.

Standardized frameworks for extracting data in microbiome research, including microbiome composition, H_2S levels, and skin outcomes, are essential for ensuring consistency and reproducibility across studies. For microbiome composition, tools like the Microbiome Standards Initiative and the use of QIIME 2 (Quantitative Insights into Microbial Ecology) and DADA2 pipelines provide structured methods for processing 16S rRNA sequencing data. These frameworks enable taxonomic classification, diversity analyses, and functional profiling, ensuring comparability across studies. Quantification of H_2S levels often utilizes standardized biochemical assays, such as colorimetric detection methods or gas chromatography-mass spectrometry (GC-MS), which provide reliable measurements of H_2S concentration in biological samples. For skin outcomes, validated scoring systems such as the Psoriasis Area and Severity Index (PASI), Eczema Area and Severity Index (EASI), and dermatology-specific quality-of-life indices like the Dermatology Life Quality Index (DLQI) are commonly used to quantify disease severity and patient-reported outcomes.

Given the heterogeneity across microbiome and dermatological studies, a narrative synthesis approach was used to integrate findings. Heterogeneity has the potential to complicate studies such as this by leading to varying results regarding the evidence and conclusions being drawn about H_2S producing bacteria and their metabolic activity. As such this ultimately would limit the reliability of the potential associations drawn from this study. Quantitative data were pooled where fea-

sible using meta-analytical techniques, and thematic analysis was applied. Key outcomes were stratified by microbiome-host interaction mechanisms, the role of H_2S in skin and gut inflammation, and implications for disease pathophysiology.

3. Current Understanding of Pathophysiology

3.1. Mechanisms of Seborrheic Dermatitis Development in Inflammatory Bowel Disease

The development of SD in patients with IBD is intricately linked to gut microbiota dysbiosis, which disrupts both systemic and localized inflammatory responses. The gut microbiota, a complex ecosystem influenced by genetics, diet, and environmental factors, plays a critical role in immune modulation, vitamin production, and lipid metabolism [3]. Dysbiosis, which results in an imbalance in microbial diversity and functionality, alters the production of essential metabolites like short-chain fatty acids (SCFAs) and free fatty acids (FFAs), which are crucial for inflammation regulation and skin health. To briefly explain the role of SCFAs and their role in this mechanism, SCFAs exhibit anti-inflammatory and barrier protective effects, ultimately providing a protective nature and counterbalancing the proinflammatory impact of elevated H_2S [3]. Elevated levels of proinflammatory cytokines, such as interleukin-6 (IL-6), are commonly observed in IBD and exacerbate systemic inflammation, worsening SD symptoms [3]. Specific microbial strains, including Akkermansia and Lactobacillus, play significant roles in the gut-skin axis and SD pathogenesis. A reduction in Akkermansia correlates with disrupted FFA profiles and elevated IL-6 levels, pointing to impaired lipid metabolism [3] [7]. This dysfunction negatively impacts the skin barrier, creating a conducive environment for Malassezia species overgrowth, a hallmark of SD [8]. Additionally, gut dysbiosis impairs the gut microbiota's ability to process dietary fibers into anti-inflammatory SCFAs like butyrate, acetate, and propionate, essential for immune regulation and skin health. These imbalances contribute to oxidative stress, disrupt the skin barrier, and exacerbate SD symptoms [6]. Gut microbial fermentation of undigested proteins and amino acids produces toxic metabolites, including indoxyl sulfate and trimethylamine N-oxide (TMAO), which exacerbate systemic inflammation and disrupt lipid metabolism, further compromising the skin barrier. This impaired barrier increases susceptibility to microbial colonization and inflammation, reinforcing the vicious cycle of SD pathogenesis. The interplay between gut dysbiosis, systemic inflammation, and lipid metabolism highlights the necessity for a holistic approach to treating SD in IBD patients [6]. Addressing gut health and microbial diversity may offer more effective management strategies.

3.2. H_2S Biology and Disease

Hydrogen sulfide (H_2S) plays a dual role in human health, acting both as a protective molecule and a potential contributor to IBD. At lower concentrations (below 1 mM), H_2S has protective effects, including preventing apoptosis, reducing

leukocyte adhesion to blood vessels, increasing cyclooxygenase-2 (COX-2) expression, and promoting neutrophil clearance through apoptosis. These functions collectively reduce inflammation. However, at higher concentrations, H_2S exhibits genotoxic and cytotoxic effects, interfering with cellular processes like DNA repair, cell cycle progression, and mitochondrial respiration by inhibiting cytochrome c oxidase. This inhibition disrupts energy production and cellular function, potentially leading to abnormal growth in the colonic mucosa. Additionally, H_2S facilitates the conversion of nitrite to nitric oxide, a compound that can damage intestinal cells [7]. In the gastrointestinal tract, H_2S is produced by the gut microbiota through two main pathways: the reduction of sulfate by sulfate-reducing bacteria (SRB) during anaerobic respiration and the fermentation of sulfur-containing amino acids by other bacterial species. Key SRBs, such as *Desulfovibrio piger* and *D. desulfuricans*, along with *Fusobacterium nucleatum* and *Prevotella spp.,* are responsible for H_2S production. Elevated levels of H_2S-producing bacteria are observed in individuals with IBD, including ulcerative colitis (UC) and Crohn's disease (CD). In UC, both SRB activity and H_2S production are significantly elevated, along with increased mucin sulphatase activity that releases sulfate for H_2S synthesis. Similar findings are observed in CD, especially in children with severe disease [7] [9]. These findings underscore the role of microbial dysbiosis in exacerbating IBD through overproduction of H_2S. Furthermore, intestinal cells themselves produce H_2S via enzymes like cystathionine β-synthase, cystathionine γ-lyase, and 3-mercaptopyruvate sulfurtransferase [10]. The colon has a detoxification system that regulates H_2S levels to protect against its harmful effects. However, dysfunction in this system can contribute to IBD development. For instance, reduced activity of detoxification enzymes like rhodanese has been linked to colitis in animal models, while compensatory increases in activity have been observed in red blood cells of IBD patients. The diet also influences H_2S production, with high-protein diets rich in sulfur-containing amino acids contributing to increased H_2S levels and exacerbating IBD symptoms. These dietary and metabolic interactions highlight the importance of maintaining balanced H_2S levels for intestinal health.

3.3. Current Treatment Approaches

Current treatment strategies for managing SD in patients with IBD focus on alleviating skin symptoms and addressing underlying systemic factors, including gut dysbiosis and nutrient deficiencies. Topical antifungal agents such as ketoconazole or ciclopirox effectively manage fungal overgrowth by *Malassezia* species, commonly implicated in SD pathogenesis [11]. Corticosteroids and calcineurin inhibitors like tacrolimus help reduce inflammation and redness, though their long-term use can cause side effects like skin thinning and an increased risk of infection. In IBD patients, malabsorption of key nutrients, such as zinc, vitamin E, and biotin, can worsen SD, making targeted supplementation essential for improving skin integrity [12]. However, these treatments provide mainly sympto-

matic relief and may not address the root causes, leading to recurring SD. Emerging integrated therapies that target gut microbiota composition are gaining attention. Probiotic and prebiotic interventions show promise in restoring gut flora balance, reducing systemic inflammation, and indirectly improving skin health. Dietary modifications, such as anti-inflammatory or low-FODMAP diets, have also shown benefits in minimizing gut-related triggers that exacerbate both IBD and SD. The low-FODMAP diet specifically reduces the intake of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are poorly absorbed in the gut and contribute to bloating and inflammation [13]. By limiting high-FODMAP foods like onions, garlic, certain fruits, and dairy products, this diet helps reduce gastrointestinal symptoms, which can, in turn, alleviate skin conditions like SD [12]. While promising, further research is needed to standardize and optimize these integrated approaches to benefit patients managing both SD and IBD.

4. The Role of *Desulfovibrio* in IBD and SD

Desulfovibrio, a genus of sulfate-reducing bacteria, has gained significant attention for its potential role in inflammatory diseases such as IBD [14]. Studies indicate a heightened prevalence and activity of H_2S-producing bacteria, including *Desulfovibrio*, in individuals with IBD. This association highlights the possible contribution of these bacteria to the inflammatory processes underlying the disease [14]. Notably, the gut microbiomes of IBD patients show an increased abundance of H_2S-producing bacteria compared to healthy controls [15]. Additionally, elevated activity of *Desulfovibrio* often correlates with more severe disease pathology [15].

Desulfovibrio exhibits unique metabolic capabilities, particularly in producing hydrogen sulfide (H_2S) via sulfate reduction [16]. While H_2S is essential for physiological functions in regulated amounts, its overproduction can become cytotoxic and promote inflammation [16]. This dual role positions *Desulfovibrio* as a significant contributor to gut dysbiosis and IBD pathogenesis. While there are numerous amounts of microbes that produce H_2S within the gut microbiota, all via various pathways, *Desulfovibrio* is the major producer of H_2S [14]-[16]. It is evident that a shift in microbes that produce H_2S such as *clostridium* and *fusobacterium* exists, however the increase number of *Desulfovibrio* microbes present indicates that this particular microbe produces H_2S in a different manner that directly impacts not only the gut but also the skin [14]-[16]. *Desulfovibrio* utilizes a sulfate reduction mechanism to produce H_2S which ultimately leads to gut dysbiosis and IBD pathogenesis.

Excess H_2S disrupts the physiological balance within the gut, compromising mucosal integrity through multiple mechanisms [16]. One primary mechanism is mitochondrial impairment. H_2S inhibits cytochrome c oxidase, a critical enzyme in the electron transport chain, leading to reduced ATP production. This disruption forces cells to rely on anaerobic metabolism, resulting in the accumulation of

metabolic byproducts like lactate, which exacerbates oxidative stress and inflammation [16]. Mitochondrial dysfunction also promotes the generation of reactive oxygen species (ROS), causing oxidative damage to lipids, proteins, and DNA. This damage compromises the integrity of gut epithelial cells, increasing their susceptibility to injury and allowing opportunistic pathogens and other proinflammatory organisms to invade [16]. When evaluating how H_2S plays a role in the development of skin pathologies, one can look towards how H_2S disrupts skin homeostasis by interfering with lipid metabolism through the inhibition of mitochondrial function and the development of ROS, and the modulation of the peroxisome proliferator-activated receptors (PPARs) [16]. This pathway ultimately regulates sebum production, with alteration in such pathways can in turn drive the development of skin pathologies such as SD by promoting a preferable environment for organisms to grow [16].

The resulting epithelial damage triggers the release of proinflammatory cytokines, including TNF-alpha and IL-1β, further amplifying inflammation [16]. These cytokines not only exacerbate local gut pathology but can also induce systemic inflammation. Systemic cytokine release enables inflammation to reach other tissues, such as the skin, potentially contributing to dermatologic conditions like SD.

5. H_2S as a Mediator of Systemic and Dermatologic Inflammation

Emerging evidence underscores the role of H_2S as a critical mediator linking gut-derived inflammation to systemic conditions such as SD. While proinflammatory cytokines drive inflammatory responses, H_2S itself exerts direct effects on skin health [17]. It disrupts lipid metabolism, as observed by Coavoy-Sánchez *et al.*, altering the production and composition of sebum—a vital component of the skin's protective barrier [17]. These alterations compromise skin homeostasis, creating conditions conducive to disease development [17].

In this compromised environment, *Malassezia*, a yeast implicated in SD pathogenesis, thrives. This organism exacerbates SD through its ability to trigger immune responses and release inflammatory byproducts [18]. The combined impact of ROS production, epithelial damage, and H_2S dysregulation intensifies the characteristic symptoms of SD, such as erythema, scaling, and itching [17].

The connections between *Desulfovibrio*, H_2S, and systemic inflammation reveal a multifaceted relationship influencing both gut and skin health. The pro-inflammatory effects of H_2S, mediated through oxidative stress, mitochondrial dysfunction, and immune modulation, highlight its pivotal role in IBD and SD pathogenesis.

While there are still gaps in understanding the full extent of H_2S's impact, current research provides valuable insights into the intricate interplay between *Desulfovibrio*, gut dysbiosis, and systemic inflammatory pathways. These findings pave the way for further exploration into targeted therapeutic strategies aimed at miti-

gating the effects of H_2S overproduction. A deeper understanding of these mechanisms could lead to improved interventions for conditions like IBD and SD, underscoring the broader implications of gut microbiome research.

6. Gut Microbiome Dysbiosis and Its Link to Inflammatory Conditions: Insights into IBD and SD

The gut microbiome composition in patients with IBD differs significantly from that in healthy individuals. Dysbiosis, an imbalance in the microbial community, may either trigger the disease or result from its progression. Studies consistently show reduced microbial diversity and enrichment of less diverse phyla in the gut microbiota of IBD patients compared to healthy controls [19]. Recent research should prioritize examining the microbiome composition in IBD patients with concurrent skin conditions, such as SD. Evidence suggests that *Malassezia* species are more prevalent in IBD patients, potentially correlating with heightened inflammatory processes that may trigger SD outbreaks, as *Malassezia* is the primary organism implicated in SD pathogenesis [20].

The altered gut microbiome in IBD patients increases the risk of other inflammatory conditions. The gut microbiota is essential for breaking down food and facilitating nutrient absorption in the small intestine. Dysbiosis disrupts this process, leading to deficiencies in critical nutrients such as vitamin K, vitamin B12, butyrate, and propionate—compounds vital for maintaining epithelial barrier integrity [1]. Compromised epithelial integrity in the gut can extend to the skin, increasing the risk of inflammatory conditions like SD. Furthermore, IBD-associated dysbiosis facilitates the proliferation of H_2S-producing bacteria, such as *Desulfovibrio*, elevating H_2S levels systemically. H_2S regulates cell proliferation and influences T cell function, both of which may impact psoriasis development [21]. Similarly, H_2S dysregulation may impair the body's ability to control SD or exacerbate existing SD, resulting in prolonged treatment durations and increased reliance on antifungals or steroids, which carry additional side effects.

7. Limitations in Current Research on Gut-Skin Connections

A common limitation in studies exploring the gut-skin axis is the variability in assessing the gut microbiome across different severity levels of IBD with concurrent SD. Severe forms of IBD are often associated with more pronounced gut dysbiosis, which could exacerbate SD. Further research should stratify microbiome data based on disease severity to better understand its impact on patient outcomes. Additionally, differences in microbiome analysis methods—such as sequencing technologies, targeted genomic regions (e.g., 16S rRNA vs. metagenomics), and sampling sites—pose challenges in comparing results across studies. Such methodological variability limits the ability to draw definitive conclusions about the gut-skin connection.

H_2S measurement methods also vary widely, including breath analysis, tissue sampling, and fluid assays using techniques such as the methylene blue method,

gas chromatography, fluorescent probes, and spectrophotometry [22]. Each method has distinct advantages and limitations, resulting in inconsistencies in sensitivity and specificity across studies. For instance, a study utilizing spectrophotometry to quantify H_2S levels highlighted challenges in comparing findings due to methodological discrepancies [9]. Developing a universal, standardized method for H_2S measurement would strengthen the reliability of conclusions and enable more robust comparisons of H_2S levels in IBD and SD patients. Consistency in measurement techniques is crucial for understanding how H_2S impacts inflammatory pathways and its downstream effects on diseases like SD.

H_2S: A Double-Edged Sword in Inflammation

H_2S plays a complex role in inflammation, exhibiting both proinflammatory and anti-inflammatory effects. While high levels of H_2S contribute to oxidative stress, cytokine release, and epithelial damage, low levels of H_2S may have protective effects. As a reducing agent, H_2S can neutralize circulating oxidant species and support neutrophil function by forming sulfites [23]. This duality suggests that the impact of H_2S depends on its concentration. Quantifying H_2S levels in IBD and SD patients could clarify its role in disease progression and identify therapeutic thresholds. If low H_2S levels are found to mitigate inflammatory processes, treatments targeting H_2S reduction might help manage these comorbid conditions and reduce exacerbation frequency.

Factors Influencing Gut Dysbiosis and Future Directions

The gut microbiome is influenced by various factors, including geographic region, dietary habits, and genetic predispositions. Regional differences in microbiota composition may contribute to dysbiosis, increasing the likelihood of a "leaky gut" and impairing the intestinal mucosal barrier [1]. Further research is needed to investigate how these factors interact with gut dysbiosis to affect systemic inflammation and skin conditions. Additionally, the mechanistic link between *Desulfovibrio*-induced H_2S production in IBD and its inflammatory effects on the skin remains unclear. More studies are needed to establish a direct causal relationship and explore the immunological functions of the gut-skin axis, including epithelial barriers, T cells, and IgA antibodies [24]. Immunotherapy targeting these pathways may offer a promising approach for managing IBD and SD concurrently. Rather than treating these conditions in isolation, integrated therapies could improve patient compliance, reduce treatment complexity, and prevent exacerbations.

The gut-skin axis represents a critical area of investigation, particularly in understanding the role of H_2S in inflammatory pathways. Current research highlights its dual nature, with both harmful and potentially protective effects depending on concentration. Addressing gaps in knowledge—such as standardizing H_2S measurement techniques, classifying microbiome profiles by disease severity, and exploring immunological connections—could provide a more comprehensive understanding of the interplay between gut dysbiosis and systemic inflammation. These insights may pave the way for innovative, targeted treatments that improve

outcomes for patients with IBD and SD.

8. Future Directions and Clinical Implications

Longitudinal studies are essential to elucidate the causal relationships between gut microbiota dysbiosis, H_2S production, and SD in patients with IBD. These studies could monitor microbial composition, levels of H_2S, and skin health over time to uncover mechanisms by which gut dysbiosis influences systemic and localized inflammation. By following cohorts of IBD patients with varying severities of SD, researchers can determine whether specific sulfate-reducing bacteria, such as *Desulfovibrio* species, directly exacerbate SD or merely correlate with its severity. Advanced statistical models could also identify thresholds of H_2S concentrations that transition from physiological signaling to pathological inflammation. Kushkevych *et al.*'s study used principal component analysis to evaluate the parameters of *Desulfovibrio* species' growth by isolating the strain from the feces of healthy control patients and individuals with ulcerative colitis, demonstrating that greater kinetics of H_2S production contribute to IBD development [25]. To ensure consistency, standardized methodologies for microbiome analysis, such as 16S rRNA sequencing and shotgun metagenomics, must be established. Likewise, harmonizing H_2S quantification techniques, including gas chromatography and mass spectrometry, could reduce variability in findings across studies, as reliable detection of H_2S in biological samples is complicated by its volatility and redox lability [26]. This standardization would enable the pooling of data from multiple research efforts, improving our understanding of the gut-skin axis. Such longitudinal studies can also uncover whether changes in the microbiome precede or follow shifts in H_2S production, clarifying causality. Establishing these methods will lay the groundwork for identifying actionable biomarkers and designing therapeutic interventions.

Investigating the gut microbiota for novel therapeutic targets offers a promising pathway for managing systemic and localized inflammation in IBD and SD. Sulfate-reducing bacteria, such as *Desulfovibrio* species, represent a potential therapeutic target, as they are significant contributors to H_2S production in the gut. Strategies such as using probiotics and prebiotics like glycomacropeptide could reduce these bacteria while promoting beneficial microbial metabolites like short-chain fatty acids, which enhance intestinal barrier function and reduce pH, as well as exhibit anti-inflammatory properties [27]. Glycomacropeptide, which is derived from casein, is a bioactive peptide that is capable of inhibiting the growth of various pathogenic bacteria while also promoting the beneficial taxa, which play a key role in maintaining the mucosal barrier. It was demonstrated that glycomacropeptide is able to reduce the adhesion of bacteria to their target cells, including the pathological EHEC O157. Additionally, prebiotics like inulin and fructooligosaccharides can selectively stimulate the growth of short-chain fatty acid producing bacteria, which further supports intestinal homeostasis.

Therapeutic agents that modulate H_2S production or inhibit its pro-inflamma-

tory effects could mitigate systemic inflammation linked to both IBD and SD. Biomarkers that reflect microbial dysbiosis, elevated H_2S levels, or lipid metabolism disruptions in the skin could help clinicians predict therapeutic responses and personalize treatments. This can include up-regulated oxidative stress biomarkers, such as nitric oxide (NO), malondialdehyde (MDA), and 8-hydroxydeoxyguanosine (8-OHdG), which are elevated in patients with IBD and inflammatory skin diseases [28]. Monitoring such biomarkers could allow clinicians to assess treatment efficacy and adjust interventions in real-time. Additionally, microbial signatures identified through metagenomics or metabolomics could distinguish patients likely to benefit from specific therapies [29]. For example, metabolomic profiling revealing reduced butyrate levels or increased H_2S concentrations could inform the selection of short chain fatty acid enhancing or H_2S targeting interventions. This approach ensures that treatments are not only targeted but also minimize adverse effects, improving overall outcomes. Combining microbial and metabolic biomarkers with clinical features could further enhance the precision of these therapeutic strategies.

Integrating microbiome and metabolite analysis into diagnostic protocols could transform the management of IBD patients with skin manifestations like SD. Diagnostic approaches that combine 16S rRNA sequencing, lipidomics, and H_2S quantification could provide a comprehensive picture of the gut-skin axis, as these tools may help identify patients at risk for severe skin conditions, enabling earlier and more effective intervention. Moreover, since skin manifestations often precede the onset of IBD, they can serve as clinical indicators for early intervention and diagnosis of IBD [30]. Personalized treatment strategies informed by such diagnostic insights have the potential to improve outcomes. For example, while anti-TNF therapy is the first line for IBD, it's been shown that the altered skin microbiota profile in IBD patients can predispose them to manifestations of skin side effects following anti-TNF treatment, which could exacerbate SD [31]. Precision medicine could guide the selection of anti-inflammatory agents that target shared pathways between IBD and SD, enhancing their efficacy and minimizing side effects. Additional tailored approaches may include dietary modifications, probiotics, or systemic therapies designed to restore gut microbial balance and reduce inflammation [1]. By addressing both gastrointestinal and dermatological symptoms simultaneously, personalized treatments can improve patients' quality of life. In the future, integrating advanced diagnostic and therapeutic tools into routine clinical practice will help address the dual burden of IBD and SD effectively. A multidisciplinary approach will ensure that patients receive comprehensive care tailored to their unique microbial and metabolic profiles.

9. Conclusion

In summary, emerging evidence highlights significant associations between gut microbiota dysbiosis, hydrogen sulfide (H_2S), and SD in IBD patients. H_2S, a common byproduct of *Desulfovibrio* species, drives mucosal damage and oxidative

stress, contributing to intestinal inflammation. IBD patients commonly experience dysbiosis as there is a reduction in beneficial microbes and a surge in pro-inflammatory species. H_2S and dysbiosis may potentially influence skin conditions like SD through the gut-skin axis. Although many studies support the gut-skin axis, it is important to note that there are limitations as there is a lack of longitudinal studies and inconsistent methodologies. In particular, there remain gaps in the understanding of the mechanisms governing dysbiosis and inflammatory skin conditions. Future studies should address these gaps by elucidating specific biological pathways in gut and skin dysbiosis, conducting longitudinal studies, and incorporating diverse patient populations. Translating findings into clinical practice can be achieved by personalizing each patient's care, integrating diagnostic tools, and implementing interdisciplinary care models. Emerging therapies like fecal microbiota transplantation (FMT), probiotics, prebiotics, and small-molecule microbiome modulators show promise in targeting gut microbiota; however, regulatory hurdles, scalability, and patient adherence may pose a challenge.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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