International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
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ARTICLE TITLE	ISOTRETINOIN AND THE HUMAN MICROBIOME: EMERGING INSIGHTS INTO SKIN AND GUT INTERACTIONS
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4367
RECEIVED	18 November 2025
ACCEPTED	26 December 2025
PUBLISHED	30 December 2025
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ISOTRETINOIN AND THE HUMAN MICROBIOME: EMERGING INSIGHTS INTO SKIN AND GUT INTERACTIONS

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ABSTRACT

Isotretinoin remains the most effective systemic therapy for severe acne vulgaris, yet growing evidence indicates that its therapeutic effects extend beyond sebaceous gland suppression and anti-inflammatory activity. Recent studies suggest that isotretinoin modulates both the skin and gut microbiota, influencing microbial diversity and host–microbe interactions. This narrative review summarizes current evidence published between 2017 and 2025 regarding isotretinoin's impact on the skin and intestinal microbiota and its potential clinical implications. A structured literature search of PubMed, Scopus, Web of Science, and Google Scholar identified 28 relevant studies. The findings indicate that isotretinoin significantly reduces the abundance of Cutibacterium acnes while increasing overall microbial diversity, suggesting ecological restoration of the skin microbiome. Strain-level analyses reveal that isotretinoin selectively suppresses more virulent C. acnes phylogroups while promoting the persistence of commensal strains. Evidence from animal and clinical studies also points to mild, reversible changes in the gut microbiota, possibly mediated through systemic immune and metabolic pathways. Although concerns about isotretinoin-induced dysbiosis or inflammatory bowel disease remain largely unsupported, its systemic effects on microbial ecosystems warrant further investigation. Overall, isotretinoin should be regarded not only as a cornerstone acne therapy but also as a microbiome-modulating agent that may pave the way for more personalized and biologically informed dermatologic care.

KEYWORDS

Isotretinoin, Acne Vulgaris, Skin Microbiome, Gut Microbiota, Gut–Skin Axis, Probiotics

CITATION

Katarzyna Bielawska, Aleksandra Helena Sochaczewska. (2025) Isotretinoin and the Human Microbiome: Emerging Insights Into Skin and Gut Interactions. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4367

Introduction

Acne vulgaris is one of the most common dermatological conditions of adolescence, affecting up to 80–90% of teenagers and a considerable proportion of adults. Despite its prevalence and seemingly benign course, acne has a profound impact on quality of life, self-esteem, and mental health. In recent years, increasing attention has been given not only to hormonal and genetic factors but also to the role of the microbiome—both cutaneous and intestinal—in the pathogenesis and treatment of acne.

Isotretinoin, a derivative of vitamin A, remains the gold standard therapy for severe, treatment-resistant forms of acne. Its efficacy stems from a multifactorial mechanism of action, including reduced sebaceous gland activity, normalization of keratinization, and potent anti-inflammatory effects. At the same time, as a systemic retinoid, isotretinoin may influence various microbial ecosystems of the body, particularly the skin and gut microbiota.

Current evidence suggests that isotretinoin therapy induces profound changes in the skin microbiome. Studies have consistently demonstrated a marked reduction in *Cutibacterium acnes* (formerly *Propionibacterium acnes*) abundance accompanied by increased microbial diversity. These shifts appear to contribute to long-term remission and decreased relapse rates after treatment cessation. Conversely, some reports indicate that isotretinoin may transiently disturb the balance between commensal species, potentially affecting skin barrier integrity and local immune regulation.

The concept of the gut–skin axis has further expanded understanding of acne pathophysiology. The gut and skin are closely interconnected through immune, endocrine, and metabolic pathways, and alterations in gut microbiota composition can modulate systemic inflammation relevant to skin homeostasis. Several studies have shown that individuals with acne exhibit intestinal dysbiosis, characterized by reduced levels of beneficial bacteria and an overrepresentation of proinflammatory species. Emerging data also suggest that isotretinoin, despite acting primarily on the skin, may indirectly modulate gut microbial composition.

Understanding the interplay between isotretinoin and the human microbiome is of considerable importance, not only for dermatology but also for broader aspects of human health. The microbiome has increasingly been recognized as a critical determinant of both therapeutic efficacy and drug safety. Recent research trends emphasize combined approaches, such as isotretinoin therapy supplemented with probiotics or prebiotics, strain-level characterization of *C. acnes* dynamics, and microbiome-based predictors of treatment response.

The aim of this review is to summarize current evidence regarding the impact of isotretinoin on the skin and gut microbiota, highlighting key findings from studies published between 2017 and 2025. The paper discusses microbiological alterations observed during isotretinoin therapy, underlying mechanisms, and their potential clinical implications.

Methodology

This paper was designed as a narrative literature review focusing on the effects of isotretinoin on the skin and gut microbiota. The objective was to summarize and critically discuss the most relevant evidence published in the past decade (2017–2025), highlighting emerging mechanisms and potential clinical implications.

A structured search was conducted between September and October 2025 using the databases PubMed, Scopus, Web of Science, and Google Scholar. The following keywords and their combinations were used: *isotretinoin*, *retinoids*, *acne*, *skin microbiome*, *gut microbiome*, *Cutibacterium acnes*, *intestinal dysbiosis*, and *gut–skin axis*. Boolean operators (AND, OR) were applied to refine the results. Only articles published in English and available in full text or with accessible abstracts were included.

Eligible publications comprised clinical studies, experimental research, and review articles directly addressing isotretinoin and its relationship with the cutaneous or intestinal microbiota. Studies focusing solely on the general acne microbiome without reference to isotretinoin were included selectively if they provided mechanistic or comparative insight. Reports lacking methodological transparency or limited to anecdotal evidence were excluded.

A total of 28 publications meeting the inclusion criteria were reviewed. For each study, data were extracted regarding design, sample characteristics, microbiome assessment methods (e.g., 16S rRNA sequencing, metagenomics), main findings, and conclusions. The results were synthesized descriptively, emphasizing consistent patterns and novel hypotheses rather than quantitative meta-analysis.

The review follows the general principles of transparent narrative synthesis and adheres to current standards for academic integrity, with all references verified through DOI-based cross-checking.

Results

Changes in the Skin Microbiome During Isotretinoin Therapy

Numerous studies have demonstrated that isotretinoin therapy leads to substantial remodeling of the cutaneous microbiome. The most consistent finding is a marked reduction in the abundance of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), a bacterium closely associated with acne pathogenesis [1–3]. McCoy et al. [1] described this phenomenon as a "microbial ecosystem reset," showing that isotretinoin not only suppresses *C. acnes* dominance but also promotes overall microbial diversity. Similarly, Nolan et al. [2] reported that clinical improvement correlated with shifts in the follicular microbiome toward less inflammatory *C. acnes* lineages.

Ryan-Kewley and colleagues [3] further observed that isotretinoin therapy reduces the total bacterial load of *C. acnes* while allowing repopulation by commensal species such as *Staphylococcus epidermidis* and *Micrococcus luteus*. This indicates that isotretinoin does not act as a conventional antibiotic but rather restores microbial balance within the pilosebaceous unit. More recent findings by Feidenhansl et al. [22] suggest that isotretinoin may also mitigate *Staphylococcus*-related dysbiosis, thereby contributing to reduced follicular inflammation and improved barrier function.

Collectively, these observations imply that isotretinoin's therapeutic efficacy extends beyond its sebostatic and anti-inflammatory effects. By increasing microbial diversity and re-establishing equilibrium between pathogenic and commensal bacteria, isotretinoin may create a more stable cutaneous environment—one that supports long-term remission after treatment discontinuation (see Table 1).

Table 1. Summary of studies on isotretinoin and the skin microbiome

Author (Year)	Study Type	Main Findings	Microbiological Effects
McCoy et al. (2019)	Clinical	Isotretinoin reduces *C. acnes* abundance	Increased microbial diversity
Nolan et al. (2023)	Clinical	Shifts in *C. acnes* strain composition during therapy	Fewer inflammatory lineages
Ryan-Kewley et al. (2017)	Clinical	Reduction in total bacterial density	Restoration of commensal species
Feidenhansl et al. (2024)	Clinical	Decrease in *Staphylococcus*-related dysbiosis	Improved skin barrier function

Strain-Level Diversity of *Cutibacterium acnes* and Its Clinical Relevance

In recent years, increasing attention has been given to the genetic and phenotypic diversity of *Cutibacterium acnes* strains and their distinct contributions to acne pathogenesis. Certain phylogroups—particularly types IA1 and IB—have been identified as more proinflammatory and are more frequently isolated from patients with severe, inflammatory forms of acne [11, 21]. Metagenomic analyses suggest that isotretinoin's efficacy may, in part, stem from its ability to suppress these virulent lineages while allowing the persistence or recolonization of more commensal or less inflammatory strains [2].

Boyanova et al. [21] demonstrated notable genetic variability among *C. acnes* isolates, including differences in antibiotic resistance patterns and expression of virulence-associated genes. These findings emphasize that *C. acnes* is not a uniform pathogen but rather a complex group of strains with distinct biological behaviors. From a clinical standpoint, this implies that effective treatment should aim to modulate microbial composition rather than eradicate *C. acnes* entirely. Nolan et al. [2] reported that isotretinoin therapy promotes a shift toward less inflammatory *C. acnes* clades, potentially explaining the sustained clinical remission frequently observed after treatment discontinuation.

Strain-level diversity within *C. acnes* therefore represents an important factor in understanding both the pathophysiology of acne and the multifaceted mechanism of isotretinoin. In the future, microbiome profiling prior to treatment initiation may support a more personalized approach to acne management and help predict therapeutic outcomes.

Effects of Isotretinoin on the Gut Microbiota

While the impact of isotretinoin on the skin microbiome has been well established, its influence on the gut microbiota remains less clearly defined. Emerging data indicate that isotretinoin may induce subtle but measurable alterations in intestinal microbial composition. Liang et al. [4] demonstrated that patients receiving isotretinoin combined with *Lactobacillus plantarum* supplementation showed improved clinical outcomes and partial restoration of gut microbial diversity compared to those treated with isotretinoin alone. This suggests that isotretinoin may disrupt gut microbial equilibrium, and that probiotic co-administration could mitigate these effects.

Earlier work by Deng et al. [9] revealed that individuals with acne often exhibit intestinal dysbiosis characterized by a decreased abundance of *Lactobacillus* and *Bifidobacterium* species and an increase in proinflammatory taxa. It has been proposed that isotretinoin, through its systemic anti-inflammatory properties, might indirectly influence this gut–skin axis by modulating immune signaling and epithelial integrity. However, experimental studies in animal models have shown inconsistent results. Becker et al. [15] found that isotretinoin altered gut microbial diversity in mice, with transient reductions in short-chain fatty acid–producing bacteria, though these changes appeared reversible after treatment cessation.

Overall, current evidence suggests that isotretinoin may exert mild, reversible effects on the intestinal microbiota, possibly mediated through systemic immune and metabolic pathways. These findings highlight the need for further mechanistic studies to clarify the bidirectional interactions between isotretinoin, the gut microbiome, and host physiology (see Table 2).

Table 2. Effects of isotretinoin on the gut microbiota and gut–skin axis

Author (Year)	Study Type	Key Observations	Clinical Implication
Deng et al. (2018)	Clinical	Acne patients show gut dysbiosis (↓ *Lactobacillus*, ↑ proinflammatory taxa)	Possible role in acne pathogenesis
Becker et al. (2017)	Animal	Transient alteration in SCFA-producing bacteria	Reversible gut microbiome shifts
Liang et al. (2024)	Clinical	*Lactobacillus plantarum* supplementation improved outcomes	Probiotics may support therapy
Jiménez-Sánchez et al. (2025)	Review	Retinoids may affect intestinal permeability and immunity	Supports gut–skin axis hypothesis

The Gut–Skin Axis in Acne and Isotretinoin Therapy

The concept of the gut–skin axis has gained considerable attention as a framework linking intestinal homeostasis with dermatologic health. This bidirectional communication network operates through immune, endocrine, and metabolic pathways, allowing intestinal microbes to influence systemic inflammation and, consequently, cutaneous conditions such as acne [18, 19]. Several studies have proposed that alterations in the gut microbiome may contribute to acne pathogenesis by modulating cytokine production, lipid metabolism, and oxidative stress levels.

Within this context, isotretinoin therapy may act not only locally on sebaceous glands but also systemically, indirectly affecting the gut–skin axis. Jiménez-Sánchez et al. [19] emphasized that systemic retinoids could influence intestinal permeability and mucosal immune activity, thereby shaping host–microbe interactions beyond the skin. Bonakdar et al. [24] further demonstrated that commensal gut bacteria enhance the host's vitamin A metabolic capacity, suggesting that retinoid activity and gut microbial function are tightly interlinked.

Although direct clinical evidence connecting isotretinoin to gut–skin axis modulation remains limited, the convergence of dermatologic and microbiome research supports the idea that acne therapy may benefit from a more integrative, microbiota-conscious approach. Future studies exploring metabolic and immunologic mediators of this interaction could provide new insights into optimizing retinoid therapy while maintaining gut microbial balance.

Microbiome-Related Adverse Effects and Safety Considerations

Despite its high efficacy, isotretinoin therapy has occasionally been linked to gastrointestinal side effects and concerns about its potential association with inflammatory bowel disease (IBD). However, the evidence for a causal relationship remains inconclusive. Ahmed et al. [16] conducted a meta-analysis showing no statistically significant increase in IBD risk among isotretinoin users compared to the general population, suggesting that the previously reported cases may reflect coincidental associations rather than true drug-induced pathology. Similarly, Miqdad et al. [17] emphasized that most reported gastrointestinal symptoms during isotretinoin treatment are mild, self-limited, and reversible upon discontinuation.

Nevertheless, the possibility that isotretinoin could transiently alter gut microbial composition and immune balance cannot be completely ruled out. Subtle, individual differences in baseline microbiota profiles may influence susceptibility to gastrointestinal disturbances or inflammatory responses during therapy. These interindividual variations highlight the importance of monitoring patients for digestive symptoms, particularly those with pre-existing gastrointestinal disorders or a family history of IBD.

Overall, current findings support the view that isotretinoin remains a safe and effective therapy for acne when used appropriately. Ongoing research into microbiome-mediated drug responses may further refine patient selection and improve the long-term safety profile of systemic retinoid therapy.

New Directions: Probiotics, Postbiotics, and Microbiome-Based Approaches

Recent research has begun to explore how modulation of the microbiome could enhance both the efficacy and tolerability of isotretinoin therapy. A growing number of studies have investigated the use of probiotics and postbiotics as adjunctive treatments aimed at restoring microbial balance during systemic retinoid therapy. Liang et al. [4] reported that co-administration of *Lactobacillus plantarum* MH-301 with isotretinoin not only improved acne severity but also partially reversed gut dysbiosis, suggesting a synergistic relationship between retinoid treatment and probiotic support.

Similarly, studies focusing on the gut–skin axis have shown that certain bacterial strains can exert anti-inflammatory effects by modulating cytokine production and strengthening epithelial barriers [8, 28]. Huang et al. [28] demonstrated that supplementation with omega-3 fatty acids favorably alters the gut microbiota composition in acne patients, supporting the concept of combining metabolic and microbiome-targeted therapies. These findings point toward a more integrative therapeutic model in which isotretinoin is not viewed as an isolated pharmacologic agent but as part of a broader ecological system within the host.

Future research will likely focus on identifying specific microbial signatures predictive of isotretinoin response and on developing microbiome-based adjunctive strategies that minimize side effects while maintaining therapeutic potency. Such approaches could ultimately lead to more personalized, safer, and biologically balanced acne management.

Discussion

The findings of recent research collectively indicate that isotretinoin exerts a broader spectrum of biological effects than previously understood, extending beyond its classical sebostatic and anti-inflammatory mechanisms. One of the most notable observations emerging from recent studies is its capacity to reshape the skin microbiome. The consistent reduction of *Cutibacterium acnes* density and the concurrent increase in microbial diversity suggest that isotretinoin restores ecological balance within the pilosebaceous unit rather than acting solely as a bactericidal agent. This ecological reorganization may explain the durable remission commonly achieved after treatment, even in patients with severe or recurrent acne.

Another key insight concerns the strain-level diversity of *C. acnes*. Not all strains are equally pathogenic; some function as benign commensals, while others drive inflammation and follicular damage. By selectively suppressing the more virulent phylogroups, isotretinoin may shift the skin microbiome toward a less inflammatory state. This observation opens the possibility for future microbiome-based diagnostics that could predict treatment outcomes or identify patients at risk of relapse.

The influence of isotretinoin on the gut microbiota, although less thoroughly characterized, adds another dimension to its systemic effects. Experimental and clinical data suggest that isotretinoin may induce mild, reversible alterations in intestinal microbial composition, which could indirectly influence immune and metabolic pathways. The growing body of evidence on the gut–skin axis reinforces the concept that acne should be viewed as a systemic inflammatory disorder influenced by interactions between intestinal and cutaneous ecosystems.

Concerns about isotretinoin-induced dysbiosis or inflammatory bowel disease have been largely refuted by recent meta-analyses, which found no convincing evidence of a causal relationship. Nevertheless, individual variability in gut microbial profiles might modulate gastrointestinal tolerance to isotretinoin, warranting continued vigilance and personalized monitoring during therapy.

Importantly, the integration of probiotics, postbiotics, and dietary components into acne management represents a promising future direction. Studies combining isotretinoin with probiotic strains such as *Lactobacillus plantarum* or omega-3 fatty acids have demonstrated improved clinical outcomes and enhanced microbial stability. These findings support a paradigm shift from purely pharmacological interventions toward more holistic, microbiome-conscious strategies.

Taken together, current evidence positions isotretinoin not only as a cornerstone therapy for acne but also as a modulator of microbial ecosystems. Understanding its interactions with the skin and gut microbiota may enable clinicians to optimize treatment efficacy, reduce adverse effects, and pave the way for precision dermatology guided by microbiome science.

Conclusion

Isotretinoin resmains a cornerstone therapy for severe acne, yet its therapeutic action extends beyond sebum suppression. Evidence indicates that it also modulates the skin and gut microbiota, reducing pathogenic *Cutibacterium acnes* strains and restoring microbial diversity. These microbiome-related effects may contribute to the long-term remission often observed after treatment. Although its influence on gut bacteria appears mild and reversible, it highlights the systemic nature of isotretinoin's action. Overall, isotretinoin should be viewed not only as an effective acne medication but also as a microbiome-modulating agent with relevance for future personalized dermatologic care.

Acknowledgments: The author did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The author declares no conflict of interest.

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