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# Clinical Efficacy and Safety of Topical Microbiome Modulation for Acne Vulgaris: A Systematic Review of Clinical Studies Published Between 2020 and 2025

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**Abstract.** Acne vulgaris is a common chronic inflammatory disorder in which effective treatment should control lesions while preserving skin barrier function and microbial homeostasis. In clinical practice, standard topical therapies may cause irritation, while prolonged antibiotic exposure raises antimicrobial resistance concerns. Topical microbiome modulation has therefore emerged as a targeted strategy using postbiotics, probiotic-derived products, and bacteriophages. This systematic review evaluated the clinical efficacy and safety of these interventions. Following PRISMA 2020, PubMed, ScienceDirect, and Google Scholar were searched for primary human studies published from 2020 to 2025. Five studies met the eligibility criteria. LactoSporin reduced sebum from 106.74 ± 9.78 to 61.41 ± 7.91 µg/cm² after 21 days, a 42.4% reduction. A Lactiplantibacillus plantarum ferment lysate improved acne lesions in 59.1% of participants and reduced sebum in 72.7% by week 4. A Lactobacillus paracasei-derived lotion produced inflammatory-lesion improvement comparable with 2.5% benzoyl peroxide and fewer treatment-associated adverse effects, 7.69% versus 26.92%. Bacteriophage BX001 reduced facial Cutibacterium acnes burden, although standardized clinical lesion endpoints were limited. Overall risk of bias was low to moderate, mainly because of small samples, open-label designs, and incomplete blinding. Topical microbiome modulation is promising as an adjunct or alternative, but current evidence does not establish superiority over standard therapy.

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## 1. Introduction

Acne vulgaris remains a substantial dermatological burden during adolescence and early adulthood. In 2021, the global age-standardized prevalence among people aged 10-24 years was approximately 9,790.5 per 100,000 population, or 9.79%, with the highest age-specific burden occurring at 15-19 years [1]. Beyond visible lesions, acne can impair quality of life, self-image, and psychosocial well-being, which makes durable and tolerable management clinically important [2-3].

Current evidence describes acne as an inflammatory disorder shaped by follicular hyperkeratinization, sebum production, host immunity, and microbial ecology rather than by Cutibacterium acnes abundance alone. Strain-level differences in C. acnes and interactions with other commensals can influence inflammatory signaling [4–6]. Changes in microbial function can further shape disease expression [7]. Recent reviews therefore emphasize microbial balance, barrier integrity, and host-microbe interactions as relevant therapeutic targets [8–10].

Mechanistically, acne-associated dysbiosis is best understood as a shift in strain composition and microbial function rather than a simple increase in total Cutibacterium acnes. Dysbiotic communities can amplify innate immune signaling, follicular inflammation, sebum-associated ecological change, and barrier disturbance, which together promote comedonal and inflammatory lesions [5],[6],[8]. Microbiome-directed therapy is therefore intended to interrupt this cycle through selective suppression of acne-associated strains, delivery of microbial metabolites or lysates with anti-inflammatory activity, reinforcement of barrier function, and preservation of commensal ecology [9],[10].

Guidelines continue to support benzoyl peroxide, topical retinoids, topical antibiotics, and selected systemic agents for acne management [11]. These treatments are effective, but local dryness, irritation, erythema, dermatitis, and application-site discomfort can occur with benzoyl peroxide [12-13]. Repeated antibiotic exposure also contributes to antimicrobial stewardship concerns [14–16]. This treatment gap has increased interest in approaches that suppress pathogenic activity without indiscriminately disrupting the resident skin microbiota.

Topical microbiome modulation includes postbiotics, probiotic-derived products, and bacteriophages that act locally through antimicrobial, anti-inflammatory, barrier-supporting, or strain-selective mechanisms. However, clinical evidence remains scattered across small studies with different formulations, follow-up periods, and endpoints [17–19]. This review therefore synthesizes recent human evidence on clinical lesion response, sebum and barrier outcomes, microbiological effects, safety, risk of bias, and comparative performance against established topical therapy.

Previous reviews have generally examined probiotics across oral and topical routes, summarized the broader acne microbiome, or mapped heterogeneous probiotic evidence without integrating clinical and microbiological endpoints in a single topical framework [20–22]. In contrast, this review jointly evaluates topical postbiotics, probiotic-derived products, and bacteriophages, while comparing lesion efficacy, sebum and barrier outcomes, microbiome changes, safety, and performance against conventional topical therapy. This integrated product-to-outcome comparison constitutes the principal novelty of the review.

The review question was structured using PICO. The population comprised adolescents or adults with acne vulgaris. The intervention comprised topical microbiome-directed products, including postbiotics, probiotic-derived preparations, and targeted bacteriophages. Comparators included placebo, vehicle, benzoyl peroxide, another topical acne treatment, or baseline when a controlled comparison was unavailable. Outcomes included inflammatory and non-inflammatory lesion response, sebum, transepidermal water loss and other barrier measures, microbiome composition or C. acnes burden, adverse events, and tolerability.

## 2. Method

This systematic review followed the PRISMA 2020 reporting framework [23]. The review question focused on whether topical microbiome-modulating interventions improve clinical or biophysical acne outcomes and remain tolerable in human participants. Eligibility criteria were defined before study selection, and the review was organized into initial, implementation, and final evaluation stages to make the procedure transparent and reproducible.

PubMed, ScienceDirect, and Google Scholar were searched for English-language primary human studies published from 2020 to 2025. A reproducible Boolean string based on the reported search concepts was: ("acne vulgaris" OR acne) AND (microbiome OR microbiota OR probiotic OR postbiotic OR bacteriophage) AND (topical OR cream OR lotion OR gel). Database-specific syntax was adjusted when required, while the concepts and publication limits were retained.

Operational definitions were applied before screening. A topical probiotic was defined as a formulation intended to deliver viable microorganisms to the skin, although no eligible study ultimately evaluated a strictly viable topical probiotic. A postbiotic was defined as a preparation of inanimate microorganisms, microbial components, or their metabolites that conferred a local biological effect; accordingly, ferment lysates and cell-free probiotic-derived preparations were included as postbiotic or probiotic-derived interventions. Products with nonspecific antimicrobial activity alone were excluded unless the study explicitly targeted an acne-associated microbial component or measured a microbiome-related outcome. Bacteriophages were categorized as targeted microbiome modulation because they selectively reduce defined C. acnes populations, while also being acknowledged as precision antimicrobial therapy [17,24,25]. These definitions restricted the review to interventions with an explicit microbiome-directed rationale rather than all topical anti-acne antimicrobials.

The database search identified 142 records. After 32 duplicates were removed, 110 titles and abstracts were screened and 78 records were excluded because they were unrelated to acne or the skin microbiome, focused only on oral interventions, or were reviews, editorials, or opinion papers. Thirty-two full texts were assessed, 27 were excluded for ineligible intervention, non-clinical design, incomplete data, or unclear clinical outcomes, and five studies entered the qualitative synthesis.

Eligible studies were randomized controlled trials, clinical trials, exploratory studies, or pilot studies involving human participants with acne and a topical probiotic, postbiotic, probiotic-derived, or bacteriophage intervention. Studies were excluded when they were non-clinical, oral-only, case reports, reviews, editorials, or unavailable in full text. Data extraction covered design, sample, intervention, duration, lesion outcomes, sebum, transepidermal water loss, microbiome measures, adverse events, and statistical results.

Two reviewers independently screened eligible reports and extracted data using a standardized form developed for this review. The form captured study design, participant characteristics, sample size, intervention and comparator, treatment duration, lesion outcomes, sebum, transepidermal water loss, microbiome measures, adverse events, and statistical results. The reviewers compared completed forms, resolved discrepancies through discussion and consensus, and checked the final entries against the full-text articles before synthesis.

Methodological quality was evaluated using the Cochrane Risk of Bias tool, version 1, commonly designated RoB 1. The assessment covered random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was rated as low, high, or unclear risk, and an overall qualitative judgment was assigned. RoB 1 was selected because the included evidence comprised randomized trials alongside pilot and exploratory clinical studies for which the original domain-based framework could be applied consistently. Two reviewers completed the assessments independently and resolved disagreements by consensus.

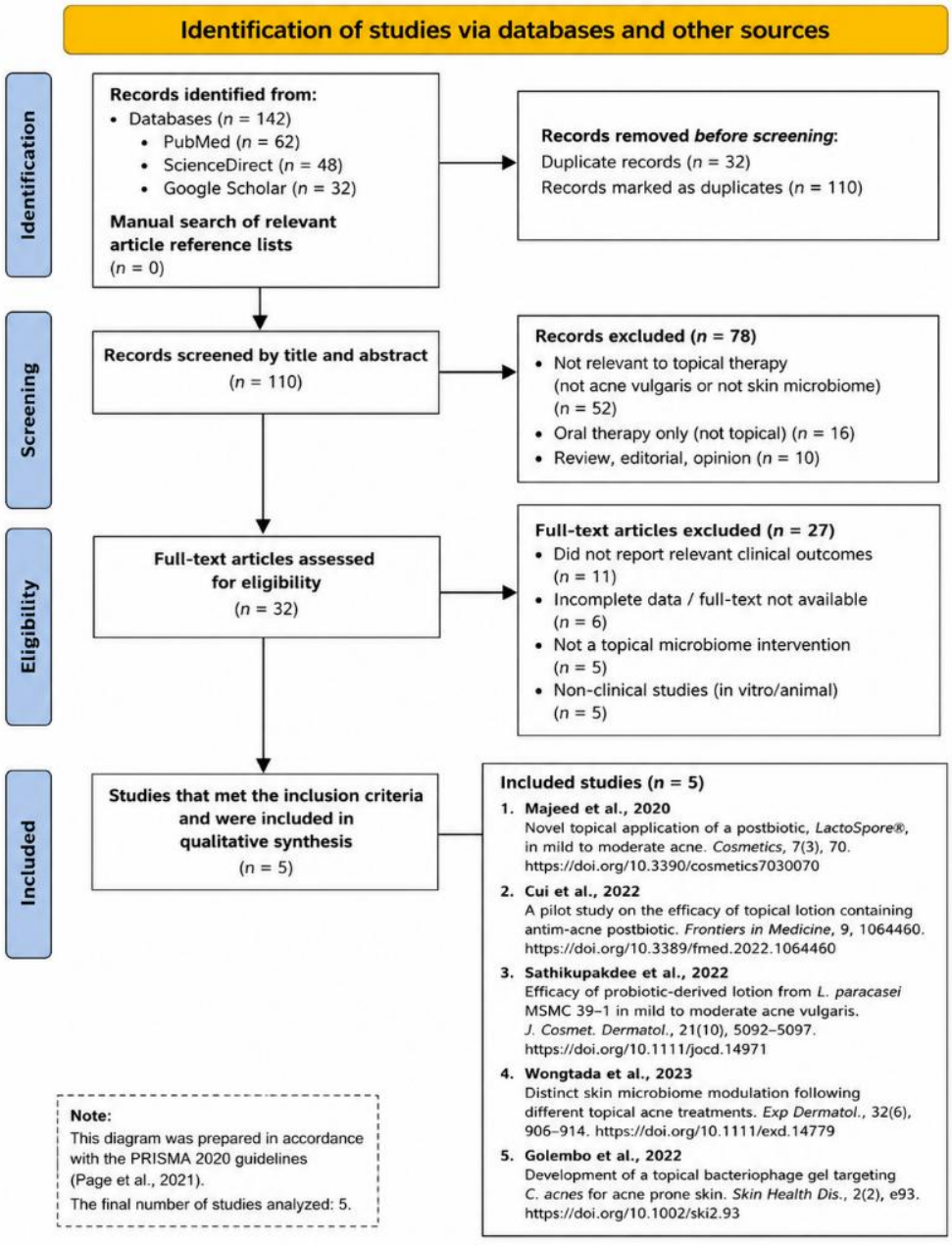


**Figure 1.** PRISMA 2020 Flow Diagram of Study Selection

## 3. Results and Discussion

### 3.1. Characteristics of Included Studies

The studies included in this review consisted of primary clinical investigations employing various designs, including randomized controlled trials, pilot studies, exploratory studies, and early-phase clinical trials. Overall, the interventions focused on topical microbiome modulation through postbiotics (e.g., LactoSporin®), probiotic-derived formulations, and bacteriophage-based therapies targeting *Cutibacterium acnes*. The intervention periods ranged from three to four weeks, with sample sizes varying from small to moderate cohorts.

**Table 1.** Characteristics of Clinical Studies on Topical Microbiome Modulation in Acne Vulgaris

| Author (Year) | Study Design / Sample | Intervention | Main Outcomes | Assessment Methods | Clinical Findings | Statistical Significance |
|---|---|---|---|---|---|---|
| Majeed et al. [25] | Open-label randomized monocentric study; n = 64 | LactoSporin® 2% w/w cream vs. benzoyl peroxide for 3 weeks | Sebum secretion, oiliness, pimples, acne spots, redness | Sebumeter; clinical assessment; Antera | Significant reductions in sebum secretion, oiliness, pimples, acne spots, and redness; no irritation reported | $p < 0.0001$ for sebum reduction; clinically significant improvement |
| Cui et al. [26] | Pilot study; 4 weeks | Topical anti-acne lotion containing *Lactiplantibacillus plantarum* VHProbi® E15 ferment lysate | Acne lesions, TEWL, sebum, pore/AOI, hydration, pH | Visia®-CR and CK-MPA® systems | Acne lesions improved from week 2 onward; reductions in TEWL and sebum levels | Lesions: $p < 0.01$; TEWL: $p < 0.05$; Sebum: $p < 0.05$ |
| Sathikulpakdee et al. [27] | Randomized controlled trial; n = 104; 4 weeks | Probiotic-derived lotion from *Lactobacillus paracasei* MSMC 39-1 vs. 2.5% benzoyl peroxide | Inflammatory lesion count, erythema index, adverse effects | Lesion count, erythema index, side-effect assessment | Comparable efficacy to benzoyl peroxide with fewer adverse effects | Significant improvement in both groups; no significant between-group difference |
| Wongtada et al. [28] | Randomized investigator-blinded exploratory study; n = 45 | Comparison of topical acne treatments with microbiome analysis | Skin microbiota diversity, acne severity, sebum, tolerability | Skin swabs; 16S rRNA sequencing; QIIME2 | Measurable microbiome alterations following treatment | Alpha diversity decreased significantly ($p = 0.010$; $p = 0.004$); beta diversity changed significantly ($p = 0.001$) |
| Golembo et al. [29] | Phase 1 randomized clinical trial | BX001 topical bacteriophage gel targeting *C. acnes* | *C. acnes* burden, safety, tolerability | Clinical trial assessment and ex vivo model | Safe and well tolerated; reduced *C. acnes* burden | Significant reduction in *C. acnes* load ($p = 0.0078$; $p = 0.0413$) |

The quantitative pattern is more informative than a simple statement of significant improvement. The largest lesion reductions were reported in the open-label postbiotic study [25], but its lack of blinding increases expectancy and assessment bias. The controlled probiotic-derived lotion study [27]

provides stronger comparative evidence because inflammatory improvement was similar to benzoyl peroxide, while the single-arm pilot [26] supports feasibility rather than comparative efficacy. This distinction is essential because promising within-group changes do not establish treatment superiority.

**Table 2.** Risk of Bias Assessment of Included Studies (Cochrane Framework)

| Study | Random Sequence Generation | Allocation Concealment | Blinding (Participants & Personnel) | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting | Overall Risk |
|---|---|---|---|---|---|---|---|
| Majeed et al. [25] | Unclear | Unclear | High (open-label) | Moderate | Low | Unclear | Moderate |
| Cui et al. [26] | Unclear | Unclear | High (pilot study) | Moderate | Low | Unclear | Moderate |
| Sathikulpakdee et al. [27] | Low | Low | Moderate | Low | Low | Low | Low |
| Wongtada et al. [28] | Low | Unclear | Low (investigator-blinded) | Low | Low | Unclear | Low–Moderate |
| Golembo et al. [29] | Low | Unclear | Moderate | Moderate | Low | Unclear | Moderate |

Risk-of-bias findings ranged from low to moderate overall, but the sources of uncertainty differed across studies. Open-label and pilot designs were most vulnerable to performance and detection bias [25-26]. Some randomized trials incompletely described allocation concealment or selective reporting [27–29]. Consequently, the evidence base is stronger for short-term signals of efficacy and tolerability than for definitive comparative effectiveness or long-term safety.

### 3.2. Clinical Efficacy of Topical Microbiome Modulation on Acne Lesions

Topical microbiome modulation produced consistent signals of improvement in inflammatory acne, but the strength of evidence differed by design. The probiotic-derived randomized trial showed significant reductions in inflammatory lesions and erythema in both treatment arms, with no between-group difference [27]. This finding supports non-inferior short-term potential against benzoyl peroxide, but it also contradicts any claim that microbiome modulation is already more effective than established therapy.

The open-label postbiotic study reported reductions of 63.11% in open comedones, 50.02% in closed comedones, 69.96% in papules, and 83.02% in pustules after 21 days [25]. A separate pilot study found lesion improvement in 59.1% of participants by week 4 [26]. These results are clinically encouraging, yet the absence of blinding or a concurrent comparator in the weaker designs means regression to the mean, natural fluctuation, and expectation effects cannot be excluded.

Recent microbiome literature provides a biological rationale for these findings because acne severity is linked to strain-level C. acnes ecology, host inflammatory signaling, and interactions among resident microorganisms [5],[6],[8]. However, the present clinical studies did not consistently measure strain replacement and lesion response in the same causal framework. The most defensible interpretation is therefore that topical microbiome modulation can improve inflammatory outcomes in the short term, while superiority and durable remission remain unproven.

### 3.3. Sebum, Barrier Function, and Plausible Mechanisms

Biophysical outcomes suggest that some microbiome-directed formulations may influence the local skin environment. LactoSporin reduced sebum by 42.4%, from 106.74 ± 9.78 to 61.41 ± 7.91 μg/cm², while benzoyl peroxide produced a similar 43.4% reduction [25]. The L. plantarum ferment-lysate study reported reduced sebum in 72.7% of participants and improved transepidermal water loss in 68.2% after four weeks [26]. These changes support a combined sebum and barrier effect rather than a lesion-only response.

Mechanistic interpretation should remain cautious. LactoSporin has shown in vitro inhibition of 5-alpha-reductase, which offers a plausible route through androgen-related sebaceous activity, but the clinical trial did not establish that this pathway caused the observed sebum reduction [25]. The L. paracasei-derived supernatant has antimicrobial activity against C. acnes and can suppress inflammatory signaling such as tumor necrosis factor alpha, which more directly supports an anti-inflammatory mechanism [27]. For L. plantarum lysate, the precise sebocyte pathway remains unresolved despite favorable sebum and barrier outcomes [26].

This uncertainty is important because microbiome products are chemically and biologically heterogeneous. Reviews published from 2023 to 2025 describe potential actions involving microbial competition, bacteriocin-like activity, barrier reinforcement, immune modulation, and metabolite signaling [8],[24],[30]. The reviewed trials support clinical plausibility for several of these pathways, but they do not yet allow one shared biochemical mechanism to be assigned across postbiotics, probiotic derivatives, and bacteriophages.

Figure 2 summarizes how the four intervention classes differ in composition, microbiological selectivity, host effects, and observed clinical relevance. Postbiotics and probiotic-derived products primarily deliver nonviable microbial components or metabolites [25–27]. BX001 directly edits the microbial population through strain-selective phage activity [29].

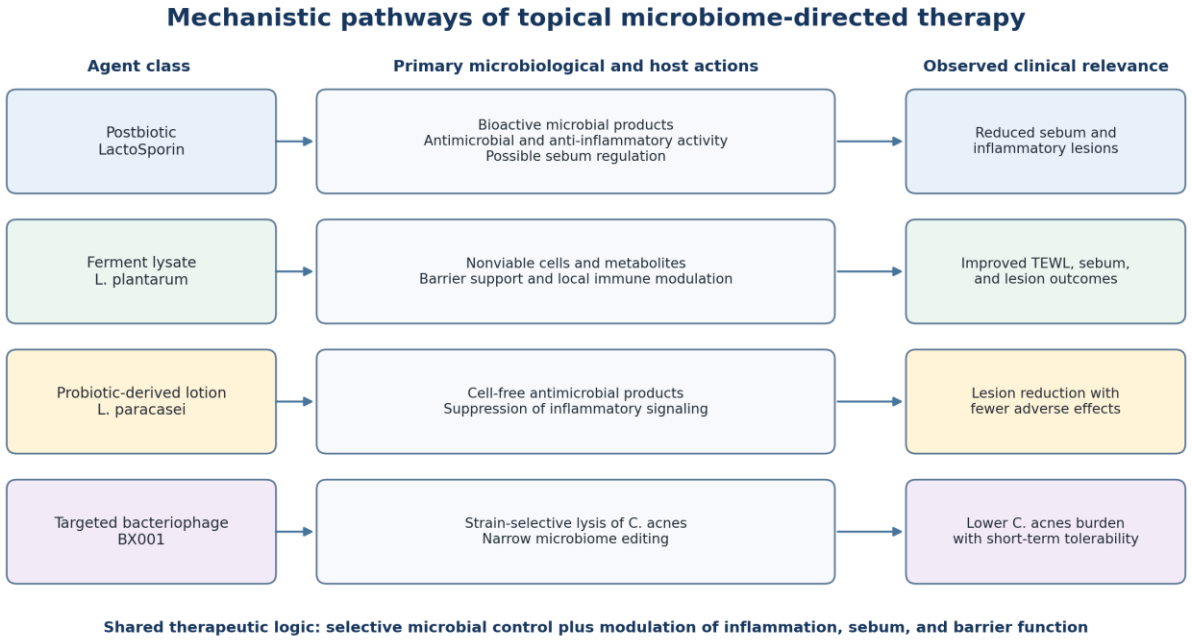


**Figure 2.** Mechanistic Comparison of Topical Microbiome-Directed Interventions Evaluated in The Included Clinical Studies

### 3.4. Microbiome Remodeling and Bacteriophage Therapy

Microbiological outcomes showed that topical treatment can alter the acne-associated ecosystem, but not every microbiome change is necessarily beneficial. In the exploratory comparison study, alpha diversity decreased after retinoic acid and benzoyl peroxide at month 1, while beta diversity changed significantly across all treatment groups [28]. These findings demonstrate treatment-specific remodeling, yet lower diversity cannot automatically be equated with clinical improvement because skin microbial function and strain composition may matter more than diversity alone [5],[9],[31].

Bacteriophage BX001 represents a more selective approach because it targets C. acnes rather than broadly suppressing resident bacteria. The phase 1 trial showed a significant reduction in facial C. acnes burden with high-dose BX001 while maintaining an acceptable short-term safety profile [29]. This direction is consistent with recent phage research that positions bacteriophages as precision antimicrobials with potential value when antibiotic resistance is a concern [17]. However, the trial was not designed to establish robust lesion-count superiority, so microbiological target engagement should not be presented as proven clinical efficacy.

### 3.5. Safety, Tolerability, and Comparison with Conventional Therapy

Safety findings favor microbiome-directed approaches, but the evidence is uneven. The strongest comparative signal came from the randomized probiotic-derived lotion trial, where treatment-associated adverse effects occurred in 7.69% of participants compared with 26.92% in the benzoyl peroxide group [27]. The LactoSporin study reported one withdrawal after worsening inflammatory lesions but no serious adverse events or local intolerance, while the BX001 trial reported only mild or moderate adverse events and no serious events or adverse-event-related discontinuations [25],[29].

The reviewed studies did not consistently itemize every symptom, so claims about specific events such as dryness, burning, or erythema should not be generalized beyond what each trial reported. Outside these five studies, benzoyl peroxide commonly produces local dryness, irritation, dermatitis, erythema, pain, or pruritus [13]. Acne guidelines emphasize balancing efficacy with tolerability [11]. Separate stewardship evidence warns against unnecessary antibiotic exposure [14–16]. Thus, lower aggregate adverse-event rates are promising, but incomplete symptom-level reporting prevents a definitive safety ranking across formulations.

Conventional therapy therefore remains the clinical benchmark. The included evidence shows comparable short-term inflammatory efficacy for one probiotic-derived lotion and substantial within-group improvement for several microbiome-directed products [25–27], but no study establishes broad superiority across acne phenotypes. The most realistic role at present is as an adjunct or alternative for selected patients, particularly when irritation or prolonged antibiotic exposure is a concern, rather than as a universal replacement for guideline-supported treatment.

### 3.6. Limitations and Clinical Interpretation

This evidence base is limited by only five eligible studies, small to moderate samples, heterogeneous formulations, and inconsistent endpoints. Most interventions were assessed for only three to four weeks, although one study extended to three months. Differences in lesion definitions, microbiome sequencing, sebum measurement, and adverse-event reporting prevented meta-analysis and limited direct comparison. Publication bias is also possible because small early-phase studies with favorable signals may be more likely to appear in the literature.

The review itself also has limitations. Google Scholar increases search breadth but has less reproducible indexing than bibliographic databases, and the final evidence set was too small for subgroup or sensitivity analysis. Future trials should use larger multicenter samples, blinded outcome assessment, standardized inflammatory and non-inflammatory lesion counts, validated patient-reported outcomes, predefined safety categories, strain-level microbiome measures, and longer follow-

up. These improvements are necessary to determine which microbiome strategy works, for whom, and for how long.

## 4. Conclusion

Across five clinical studies, topical microbiome modulation produced measurable short-term benefits for acne-related outcomes. LactoSporin reduced sebum by 42.4% and reduced open comedones, closed comedones, papules, and pustules by 63.11%, 50.02%, 69.96%, and 83.02%, respectively. A L. plantarum ferment lysate improved lesion counts in 59.1% of participants and reduced sebum in 72.7%. A L. paracasei-derived lotion achieved inflammatory improvement comparable with 2.5% benzoyl peroxide while showing fewer treatment-associated adverse effects, 7.69% versus 26.92%. BX001 also demonstrated targeted reduction of facial C. acnes burden, although standardized clinical lesion efficacy remained limited.

Overall methodological quality was low to moderate in risk of bias, and interpretation is constrained by small samples, short follow-up, incomplete blinding, and heterogeneous outcomes. The available evidence supports topical postbiotics, probiotic derivatives, and bacteriophages as promising adjunctive or alternative strategies, not established replacements for conventional acne therapy. Larger blinded randomized trials with standardized efficacy, microbiome, and symptom-level safety endpoints are required before routine clinical recommendations can be strengthened.

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