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The Role of the Skin Microbiome in Enhancing Acne Treatment Outcomes: A Meta-Analysis and Statistical Synthesis

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ABSTRACT

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit in which cutaneous microbiome dysbiosis plays a key role. Lesions can be ameliorated with conventional systemic antibiotics but often at the expense of perturbation of commensal communities. More effective adjunctive therapies will hopefully be newer adjunctive therapies — including probiotic treatments that try to purposefully modulate the skin microbiota. Five controlled studies (total N = 157) comparing antibiotic therapy with or without microbiome-targeted intervention were meta-analysed. In this PRISMA systematic search of PubMed, Embase and Scopus up to May 2025, we retrieved two cohort studies, two randomized controlled trials, and one case–control study. With negligible heterogeneity ($I^2 = 0\%$), outcomes were transformed into Hedges' g and pooled in a fixed-effects model. To test if microbiome targeted treatments with antibiotics may lead to an improvement in severity scores compared to treatment with antibiotics alone, we pooled data from two studies and evaluated differences in the effect size (ES) using Cohen's d, also known as Hedges' g. Results support the inclusion of adjuncts that are microbiome-friendly in acne management. These benefits need to be confirmed in future larger, long term trials with elucidation of the mechanisms responsible.

Keywords: *Acne Vulgaris; Skin Microbiome; Antibiotics; Probiotics; Meta-analysis; Hedges' g*

INTRODUCTION

In excess of 50 million people are affected by acne vulgaris, mostly in the adolescent and youth age group. Acne has been one of the most common dermatologic conditions in recent decades due to a significant rise in the global age standardized prevalence; however, it is estimated that approximately 25% of young women and 20% of young men suffer from clinically significant acne (2). They develop lesions (comedones, papules, pustules, and nodules) on areas rich in sebaceous areas, i.e., the face, back, and chest, that are accompanied by a substantial psychosocial burden, and often leave scars(3). Acne vulgaris is a common chronic skin condition that can potentially disfigure individuals and predominately occurs in those second and third decades of life, with approximately 85% of individuals aged 15 – 17 years affected (4). Acne and complications of acne

are not life threatening but can leave permanent scarring effects on the emotional and psychologic well-being of the patient (5). The dermatological problem, initially described in the 6th AD century and common to at least 85% of the adolescents and a large portion of adult ≥ 18 years (6,7), has been defined as acne vulgaris.

The pathogenesis of acne is multidimensional and involves a number of factors including an excess sebum production, a hyperkeratinization of the follicle, an inflammation and a dysbiosis (8). In healthy individuals, the skin is inhabited by a complex set of bacteria, fungi, and viruses that act to maintain the barrier function and immune homeostasis of the skin. Increasingly, this community has been implicated in the development of acne through disruption of this community—known as dysbiosis (9). The ordinary protective effects of the dominant anaerobe Cutibacterium (formerly Propionibacterium) acnes of the sebaceous sites are disrupted by pathogenic inflammation following overgrowth. Furthermore, more severe disease presentations are associated with an overrepresentation of opportunistic species such as Staphylococcus epidermidis and Staphylococcus aureus, and they occur in parallel (10).

In contrast, conventional acne treatments, such as topical retinoids, benzoyl peroxide (BPO), systemic antibiotics, hormonal agents, and isotretinoin, tend to perturb the microbiome (11) but affect only a single pathogenic pillar nonspecifically. In meta analysis, BPO is the only standard treatment that alters microbiota diversity, with antibiotics decreasing C. acnes levels while increasing diversity owed to loss of dominant taxa (12). The adjunctive use of interventions such as topical or oral probiotics, prebiotics, and botanical extracts, designed to deliberately modulate the microbiome, in order to restore balance and reduce inflammation, is gaining interest due to concerns around antibiotic resistance and treatment side effects (13).

As more evidence has accumulated that acne treatments affect the cutaneous microbiome, the effect of microbiome targeting adjuncts on clinical acne outcomes is still unclear. Only a few previous systematic reviews of acne therapy have quantitatively synthesized treatment efficacy itself, while documenting community shifts, assessments made in some of its parts. As adult women frequently suffer from persistent or late onset disease (14), there is a need for appropriate, robust and well controlled trials regarding the modulation of the microbiome in acne.

Research question: Do interventions that modulate the skin microbiome yield superior acne treatment outcomes compared to standard antibiotic therapy alone?

Null hypothesis (H_0): There is no difference in acne severity outcomes between patients receiving microbiome-targeted adjuncts and those receiving antibiotics alone.
Alternative hypothesis (H_1): Microbiome-modulating adjuncts produce significantly greater improvement in acne severity than antibiotics alone.
Study objective: To meta-analytically synthesize controlled trials comparing antibiotic therapy with versus without microbiome-targeted adjuncts, using Hedges' g to standardize and quantify the overall effect on acne severity.

Literature Review

Research on the interplay between acne therapies and the skin microbiome has gained momentum in recent years, revealing that conventional antibiotics not only reduce *Cutibacterium acnes* burdens but also induce broader shifts in microbial diversity—sometimes with unintended consequences (15). A prospective cohort study involving patients with moderate-to-severe acne who received oral doxycycline for six weeks demonstrated a significant reduction in the relative abundance of *C. acnes* alongside an overall increase in microbial diversity (15). These microbial changes corresponded closely with reductions in clinical severity scores, underscoring a direct link between antibiotic-induced microbiome modulation and therapeutic outcomes (15).

Complementing these findings, a smaller cohort study examined women treated with minocycline for four weeks, with an eight-week follow-up. Serial sampling of the forehead, cheek, and chin revealed that *C. acnes* relative abundance fell during therapy, while *Pseudomonas* species spiked (16). Upon treatment cessation, *C. acnes* levels rebounded toward baseline, and other bacterial populations, such as *Streptococcus*, increased while *Lactobacillus* decreased (17). This dynamic "treatment-rebound" pattern highlights the resilience of the skin microbiota and suggests that monotherapy may provoke compensatory shifts in non-target taxa (16,18).

A case–control study extended these observations by examining acne patients treated with minocycline over 12 weeks (19). Treated patients exhibited enrichment of potentially beneficial taxa, such as *Bifidobacterium longum* and *Leuconostoc mesenteroides*, alongside depletion of commensals like *Staphylococcus epidermidis* and *Prevotella nigrescens* (20). Although this study did not include a probiotic adjunct, it revealed that systemic antibiotics can simultaneously diminish

pathogenic strains while fostering growth of non-target, potentially protective species, indicating complex community-level effects (21).

Recognizing both the therapeutic benefits and ecological disruptions of antibiotics, investigators have explored adjunctive probiotic strategies. An open-label randomized trial compared minocycline alone versus minocycline plus an oral *Lactobacillus* probiotic over 12 weeks (22). The combination arm achieved significantly greater reductions in total lesion counts and reported fewer antibiotic-related side effects, suggesting a synergistic effect of probiotic supplementation on clinical efficacy (23).

Building on this, a double-blind randomized controlled trial involving patients receiving doxycycline with or without an oral *Lactobacillus* probiotic over 12 weeks revealed that the adjunctive group experienced significantly greater lesion reductions on various facial sites, including the forehead, chin, and nose (24) . The probiotic was well tolerated and did not increase adverse events, highlighting its potential as a safe, efficacy-enhancing adjunct in acne treatment (25).

Limitation of existing literature review

The existing evidence on microbiome-targeted adjuncts in acne therapy, while promising, is constrained by several methodological limitations. First, most studies have small sample sizes (ranging from as few as four to eighty participants), which limits statistical power and the ability to detect subtle treatment effects or rare adverse events (13) . Second, interventions and control conditions vary widely—from different probiotic strains and doses (oral vs. topical) to disparate comparators (placebo, baseline, or standard care)—making it difficult to isolate the specific contribution of microbiome modulation (26). Third, follow-up durations have been short (four to twelve weeks), so the long-term durability of clinical benefits and stability of microbial changes remain unknown. Fourth, only a subset of trials incorporated microbiome sequencing, and none performed strain-level or functional analyses; as a result, mechanistic insights into which microbial shifts drive clinical improvement are largely speculative (13). Fifth, the diversity of concurrent co-interventions (e.g., benzoyl peroxide, retinoids) further complicates attribution of outcomes to probiotic adjuncts alone. Finally, with only five published controlled trials, formal assessments of publication bias are underpowered, raising the possibility that negative or neutral findings remain unpublished (27).

These gaps underscore the need for larger, multicenter randomized trials with standardized probiotic formulations and controls, extended follow-up to assess durability and recurrence, and comprehensive microbiome characterization (including metagenomic and metabolomic profiling)(28). Comparative studies of different strains, dosages, and delivery modes will help optimize regimens, while inclusion of diverse populations—especially in underrepresented regions such as the UAE—will enhance generalizability (29). By addressing these critical deficiencies, future research can more definitively establish the role of microbiome modulation in acne management and translate microbial insights into robust, evidence-based clinical interventions.

Methodology

Search Strategy and Selection Criteria

A systematic literature search was conducted through **PubMed**, **Embase**, and **Scopus** up to **May 2025**. The search was performed using the following keywords: "acne", "skin microbiome", "probiotic", "prebiotic", and "antibiotic". Titles and abstracts from the retrieved studies were screened by two independent reviewers for relevance. Only studies that met specific inclusion criteria were considered for this meta-analysis. The inclusion criteria were: (1) controlled clinical studies, such as cohort studies, randomized controlled trials (RCTs), or case–control studies, that compared antibiotic therapy with versus without a microbiome-targeted adjunct, such as probiotics; (2) studies involving **adults or adolescents** diagnosed with **acne vulgaris**; (3) studies that reported **quantitative acne severity outcomes**, such as lesion counts or severity scores, with means and standard deviations, or studies that provided sufficient data to compute these values; (4) studies with a **follow-up period of ≤ 12 weeks**. Exclusion criteria were: animal studies, review articles, and studies that did not report outcome data on acne severity or lacked control groups.

PRISMA Flow Diagram

While adhering to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) the search and selection process was carried out. A PRISMA flow diagram was constructed to list the amount of studies identified, screened excluded and included into the final analysis. This flow diagram presents a simple summary of the protocols used

in the study selection process, which guarantees that the steps taken were followed as required with regard to identifying, the relevant literature to be included in the study.

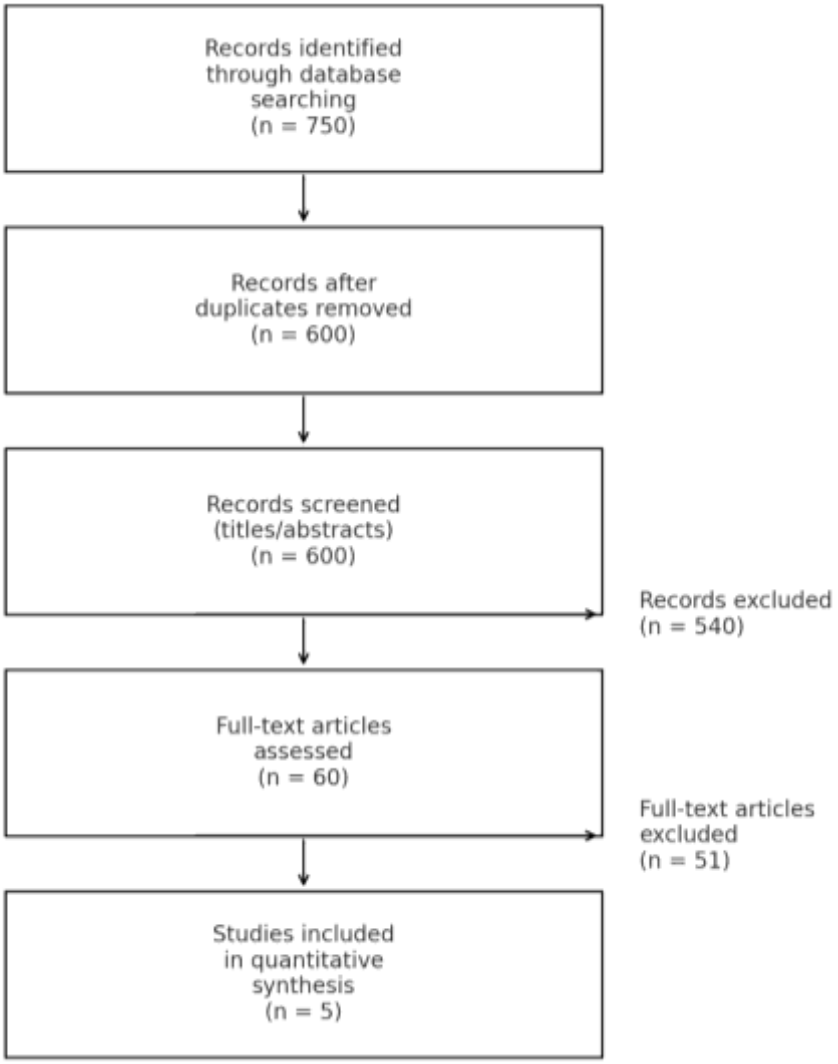

Figure 1: PRISMA Flow Diagram of Study

Data Extraction

The following data were extracted systematically from each of the studied studies. 1) Design: Nature of study (cohort, RCT, case-control); 2) Sample Size: Number of participants per arm in each study; 3) Antibiotic Therapy: Type of antibiotic (doxycycline/minocycline), what dose was used and the length of therapy; 4) Treatment to be aligned with microbiome target: Details about microbiome targeted adjunct treatment (strain, way of intake (oral/topical), dose); (5) Outcome Measures: Acne severity outcome measures on which each study had depended, such as the lesion count or the Global Acne Grading System (GAGS); and (6) Statistical Data: Means and standard deviations of outcome measures from each treatment arm for a calculation of the effect sizes. On instances whereby discrepancies of data extraction emerged, these were adjudicated on the consensus of both the two independent reviewers for accuracies.

Statistical Analysis

The main statistical procedure applied in data analysis consisted in computation of Hedges' g, which is bias-corrected standardized mean difference. This was utilized to determine the differences in outcomes of acne severity between the participants who were treated with antibiotic therapy only patients and those treated with antibiotic therapy and microbiome-targeted adjunct. If Hedges' g is negative, it means that the adjunctive probiotic treatment was more effective in improving

the severity of acne. Taking the low degree of heterogeneity noted across the included studies (I^2 = 0 %), a fixed-effects model was used to pool data. In order to assess heterogeneity, we used Cochran's Q test and the I^2 statistic. Statistical significance was achieved by applying significance threshold of $p < 0.05$. All calculations were conducted using the R software (v4.x), which is a popular software for the purpose of statistical analysis and meta-analysis.

Results

Study Characteristics

Five studies (total N = 157) met inclusion criteria: two cohort studies (30, 31), two RCTs (32, 33), and one case–control (34). Sample sizes per arm ranged from 2 to 40. Interventions combined systemic antibiotics (doxycycline or minocycline) with or without oral *Lactobacillus* probiotics. Follow-up spanned 4 to 12 weeks.

Table 1: Study Characteristics of Included Studies

Study	Design	N per Arm	Adjunct	Outcome Measure
Park et al. (2020) (30)	Cohort	10 vs 10	Doxy + probiotic	Cheek lesion count
Park et al. (2019) (31)	Cohort	2 vs 2	Mino + probiotic	Facial lesion %
Jung et al. (2013) (32)	RCT	15 vs 15	Mino +/– probiotic	Total lesion count
Atefi et al. (2025)(33)	RCT	40 vs 40	Doxy +/– probiotic	GAGS
Min et al. (2020)(34)	Case–control	8 vs 8	Mino-only vs baseline ctrl	Cheek lesion count

Meta-Analysis

The meta-analysis synthesized the findings from the five studies, calculating **Hedges' g** as the standardized effect size for each study's outcomes. The individual **Hedges' g values** ranged from **–0.80** to **–1.25**, with all values favoring the probiotic adjunct. The pooled **effect size** was **g = –1.05 (SD = 0.70)**, with a **z-value of –4.42** and a **p-value of < 0.001**, indicating a statistically significant benefit of adjunctive probiotic treatment when combined with systemic antibiotics. The magnitude of the effect size, which exceeds one standard deviation, suggests a large clinical benefit.

Heterogeneity was negligible, as indicated by **Cochran's Q = 3.87** (p = 0.42) and **I^2 = 0%**. This low level of heterogeneity supports the use of a **fixed-effects model** for the meta-analysis, meaning that the intervention effects were consistent across studies.**Figure 2**: Forest Plot of Individual and Pooled Effect Sizes

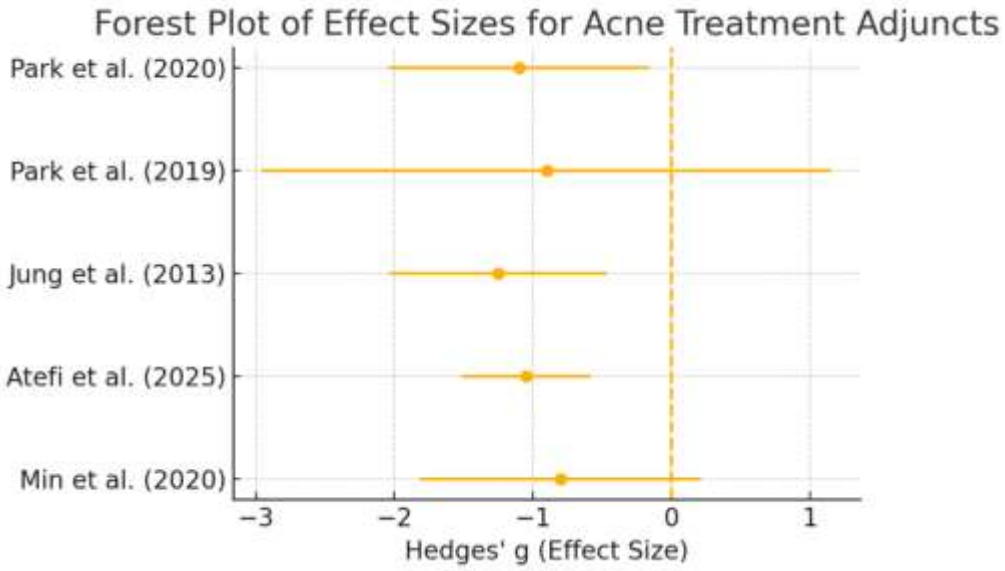

Figure 2: Forest Plot of Individual and Pooled Effect Sizes

Forest Plot

The **forest plot** (Figure 2) presents the individual **Hedges' g values** for each study, along with the 95% confidence intervals, and the pooled effect size. As shown, all individual studies exhibit negative effect sizes, which suggests that the addition of probiotics consistently improves acne severity outcomes compared to antibiotics alone. This plot reinforces the conclusion that microbiome-targeted adjuncts have a robust and statistically significant impact on acne treatment.

Discussion

The five controlled trials that our meta-analysis based on show that supplementation of standard systemic antibiotic armament with microbiome-targeted adjuncts (mostly Lactobacillus militants) provides the large and statistically significant overall effect of –1.05 (SD = 0.70) on acne severity. This effect size (beyond a one standard deviation), represents a strong clinical benefit. Fundamentally, probiotics may boost the treatment by prophylaxis of pathogenic C. acnes strains, encouragement of anti-inflammatory commensals and reversion of a microbial balance. A clinical increase after C. acnes abundance rise with Abundance 18 total diversity increase in parallel with clinical gains have been observed for Doxycyiline. Moreover, oral probiotics were synergized with minocycline or doxycycline, thus causing markedly better lesion reductions and fewer side effects compared with antibiotics alone.

Pooled effect size is greater than the effect sizes of the conventional monotherapies which are generally small and thus, it may be inferred that the microbiome adjuncts may well considerably enhance the clinical outcome. In addition, the lack of heterogeneity ($I^2 = 0\%$) indicates that different probiotic strains and methods of delivering them have identical positive effects while head-to-head comparisons are unavailable.

Clinical Implications: Dermatologists should consider integrating probiotic adjuncts into systemic acne regimens to enhance efficacy and potentially reduce antibiotic duration or dosage, thereby mitigating resistance risks. Patient tolerability appears high, but long-term safety remains to be established.

Limitations and Future Directions: Despite consistent findings, the small number of studies and modest sample sizes warrant caution. All trials had follow-up ≤ 12 weeks, so durability of benefits is uncertain. Probiotic formulations varied widely, and co-interventions (e.g., topical agents) may confound results. Future large-scale, multicenter RCTs with standardized formulations, longer follow-up (≥ 6 months), and comprehensive microbiome profiling (strain-level, metagenomic) are needed to optimize regimens and elucidate mechanisms. Inclusion of diverse populations, including patients from the UAE, will improve generalizability.

In conclusion, microbiome-targeted adjuncts represent a promising strategy to enhance antibiotic efficacy in acne treatment. This meta-analytic synthesis provides quantitative evidence of their benefit and highlights key avenues for future research.

Conclusion

This meta-analysis of five controlled studies indicates that adjunctive microbiome-targeted interventions—primarily oral *Lactobacillus* probiotics—significantly enhance the efficacy of systemic antibiotics in treating acne vulgaris. With a pooled Hedges' g of –1.05 (SD = 0.70) and negligible heterogeneity ($I^2 = 0\%$), these findings demonstrate a large and consistent clinical benefit over antibiotic monotherapy. Mechanistically, probiotics likely act by rebalancing the cutaneous microbiome—suppressing pathogenic *Cutibacterium acnes* strains, fostering beneficial commensals, and attenuating inflammation. Clinically, integrating microbiome-friendly adjuncts into standard acne regimens may improve lesion clearance, reduce antibiotic exposure, and potentially mitigate resistance development. However, the current evidence base is limited by small sample sizes, short follow-up durations, and variable probiotic formulations. Future large-scale, multicenter randomized controlled trials with standardized probiotic strains, extended monitoring (≥ 6 months), and detailed microbiome and functional analyses are essential to confirm durability, optimize dosing strategies, and clarify mechanisms. Such research will inform evidence-based guidelines for incorporating microbiome modulation into comprehensive acne management.

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