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Effect of Lactobacillus Reuteri on Pediatric Acne Vulgaris: Current Evidence and Mechanisms

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Abstract
The potential use of Lactobacillus reuteri as an adjunctive treatment for acne vulgaris in children and adolescents is gaining interest, with current evidence suggesting significant benefits. Clinical trials and pilot studies have assessed the impact of L. reuteri supplementation on acne severity, revealing reductions in lesion counts and improvements in overall skin condition. These studies also highlight changes in the skin microbiome composition, with a notable decrease in Propionibacterium acnes colonization and reductions in systemic inflammation markers. The biological mechanisms underlying these effects include the modulation of sebaceous gland activity and enhancement of the skin's barrier function. L. reuteri appears to exert anti-inflammatory effects, which may further contribute to its therapeutic potential in acne management. Additionally, the review examines optimal dosages, duration of probiotic use, and safety profiles, indicating that L. reuteri is generally well-tolerated with minimal side effects. However, further research is needed to establish standardized treatment protocols. Overall, L. reuteri represents a promising adjunctive therapy for pediatric acne vulgaris, meriting further investigation to confirm its efficacy and long-term safety.

Introduction

Acne vulgaris, a common dermatological condition, is characterized by a variety of lesions, including inflammatory (papules, pustules, nodules, and cysts) and non-inflammatory (open comedones, closed comedones) acne lesions [1]. Acne vulgaris predominantly affects children and adolescents, with incidence peaking during adolescence, where up to 85% of individuals may experience some form of acne [2]. This condition not only impacts physical appearance but also carries significant psychosocial implications, affecting self-esteem and quality of life. The visible nature of acne often leads to social stigma and psychological distress, which can significantly affect self-confidence in personal relationships, professional settings, and everyday social interactions. The chronic nature of the condition necessitates long-term management strategies, highlighting the need for effective and tolerable treatment options.

Current treatment modalities for acne vulgaris encompass a variety of topical and systemic approaches depending on acne severity. Topical treatments often include benzoyl peroxide, retinoids, and antibiotics, which aim to reduce inflammation, inhibit bacterial growth, and normalize skin cell turnover. Systemic therapies, such as oral antibiotics, hormonal treatments, and isotretinoin, offer broader-spectrum approaches and significant therapeutic benefits but are associated with risks like antibiotic resistance, systemic side effects, and potential teratogenicity. Procedural therapies are available such as intralesional injections, chemical peels, phototherapy, and laser devices for reducing complications of acne vulgaris such as scarring and worsening of lesions; however, these, along with systemic therapies, are typically reserved for moderate to severe acne [3]. Limitations of current therapies for mild-to-moderate acne include concentration dependency of cutaneous complications for products such as benzoyl peroxide and duration of therapy for antibiotics. For moderate-to-severe acne, limitations can include narrow light spectrum for phototherapy and risk of skin damage for other procedural therapies such as extraction or chemical peels [4]. Despite these treatment options, patient adherence remains a significant challenge due to the side effects and complexity of multi-step skincare regimens, further complicating effective acne management.

In recent years, probiotics have emerged as a novel therapeutic approach in dermatology, offering potential benefits in managing acne vulgaris. According to Puebla-Barragan, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer health benefits on the host" [5]. While their primary benefits have been associated with gastrointestinal health, growing evidence suggests their promising role in modulating skin microbiota and immune responses, supporting a gut-skin axis theory [6]. Among probiotics, several strains of *L. reuteri* have shown promising results with their anti-inflammatory properties. Specifically, *L. reuteri* has been beneficial in improving the skin barrier function, reducing perifollicular inflammation, and potentially inhibiting acne pathogenesis [7]. The concept of probiotics influencing skin health through the gut-skin axis introduces a holistic approach to acne treatment, emphasizing internal balance with overall well-being. This emerging field underscores the interconnectedness of bodily systems and the potential for innovative treatments derived from natural sources.

This literature review aims to evaluate the existing evidence on the efficacy of *L. reuteri* in acne vulgaris treatment. Additionally, it explores the underlying biological mechanisms contributing to its therapeutic effects and assesses the clinical outcomes reported in relevant studies. Lastly, by identifying gaps in current research, this review uses evidence in the current literature to propose future directions for advancing the application of probiotics, particularly *L. reuteri*, in the management of acne vulgaris. Synthesizing findings from various studies allows for a comprehensive understanding of how *L. reuteri* can be integrated into acne treatment protocols, offering a potential alternative or complementary approach to conventional therapies.

Discussion

Pathophysiology of Acne Vulgaris

The pathophysiology of acne vulgaris involves a multifaceted interplay of factors that contribute to its development and progression. Four important factors are typically present in this skin condition: excessive sebum production, hyperproliferation of *Propionibacterium acnes*, recently renamed *Cutibacterium acnes* (*C. acnes*), hyperkeratinization of pilosebaceous follicles, and inflammation [1]. Sebum, produced by sebaceous glands, functions to lubricate and protect the skin. Overproduction of sebum, influenced by hormonal factors like androgens, contributes to the development of acne lesions. *C. acnes*, a bacterium commonly found on the skin, plays a pivotal role in acne pathogenesis. It contributes to inflammation within the pilosebaceous unit through the production of inflammatory mediators. Acne lesions provoke an immune response characterized by the recruitment of inflammatory cells, such as neutrophils and macrophages, leading to tissue damage and exacerbation of lesions. The immune response is further amplified by the release of cytokines and other pro-inflammatory molecules, perpetuating a cycle of inflammation and lesion formation.

DNA methylation has additionally been implicated in the pathogenesis of chronic inflammatory skin conditions such as hidradenitis suppurativa, psoriasis, atopic dermatitis, and other disorders. Epigenetic modification may play a role in this chronic inflammatory condition, acne vulgaris, as well. Genetic predisposition, environmental factors, nutrition, stress, smoking, cosmetics, and hormonal fluctuations, particularly during adolescence, can stimulate sebaceous gland activity and alter immune responses, contributing to acne development [1]. Genetic predisposition to developing progressive acne vulgaris has been linked to genes involved in sebaceous gland function and inflammatory responses, such as interleukins (IL-1a, 1B, 4, 6, 8, 10), tumor necrosis factor (TNF-a), resistin (RETN), CYP genes (CYP17, 19A1, 1A1), matrix metalloproteinase (MMP), and tissue inhibitors of metalloproteinase (TIMP) [8]. Environmental triggers, such as pollution and diet, have been shown to exacerbate acne by influencing these inflammatory pathways and hormonal imbalances. Moreover, the psychological stress associated with acne care further exacerbates the condition through immune system and hormonal interactions, highlighting the complex interplay between physical and emotional health in acne pathogenesis. Understanding these pathophysiological mechanisms provides a foundation for exploring how interventions such as *L. reuteri* may modulate these processes to potentially mitigate acne severity and improve clinical outcomes.

Mechanisms of Action of Lactobacillus reuteri

Considered one of the most widely utilized probiotics, *L. reuteri* is a gram-positive, non-spore forming, facultative anaerobic bacterium. Notable features of this organism include the ability to withstand intense fluctuations in environmental pH and the power to combat pathogens through several defense mechanisms [9]. *L. reuteri* becomes all the more intriguing when appraising its specific functions within the skin. Through the upregulation of the APQ3 gene, *L. reuteri* serves to strengthen both hydration and elasticity of the epithelial layers. This enhancement allows for the modulation of sebaceous gland activity through the optimization and reallocation of available biologic resources. Further, the downregulation of kallikrein 5 (KLK5) gene expression facilitated by *L. reuteri* promotes antimicrobial and anti-inflammatory effects in the epidermis. KLK5 overexpression has been documented in chronic, inflammatory dermatologic conditions. The epigenetic impact fostered by healthy skin microbiota has been linked to decreased processing of pro-pathogenic microbial compounds. Anti-inflammatory effects abound in the presence of *L. reuteri*. One of the main mechanisms by which this is achieved is through the blockage of pro-inflammatory cytokine production. In addition to cutaneous modulation, the versatile capabilities of *L. reuteri* also extend to the gastrointestinal and genitourinary systems [10]. Though the exhaustive influence of this bacterium is incompletely understood, much promise lies in the manipulation of *L. reuteri* to advance the treatment and outcomes of human disease.

The greater impact of *L. reuteri*, beyond its individual defensive capabilities, may be observed in the epithelial microbiome. This species supports a healthy microbiome by contributing to the sustenance of advantageous organisms. For instance, the fermentative nature of *L. reuteri* produces particular acids and metabolites that allow beneficial cutaneous bacteria to thrive. There is also a question of the selective inhibition of harmful pathogens through this same mechanism [10]. *L. reuteri* exerts its influence on the microbiome by curtailing the colonization of *C. acnes*. By means of competitive exclusion, opportunities for such inflammatory pathogens to grow and prosper become quite limited. This competitive exclusion also helps maintain a balanced skin microbiome, which is crucial for skin health. A similar mechanism is observed in *Staphylococcus aureus*-infected keratinocytes supplemented with *L. reuteri* [11].

Probiotics harboring *L. reuteri* have additionally been shown to increase overall diversity of the epithelial microbiome [12]. Such positive enrichment of the natural microbiota of the skin can affect the initiation and progression of dermatologic conditions tremendously. The enhancement of the microbiome diversity helps support the skin's natural defenses and prevent the dominance of pathogenic bacteria.

Although the initial findings on the benefits of *L. reuteri* are promising, the exact mechanisms by which it exerts its effects on acne remain incompletely understood. Therefore, further research is needed to elucidate the molecular and genetic pathways involved in *L. reuteri's* action on skin health. Understanding these mechanisms will not only enhance our knowledge of acne pathogenesis but also inform the development of targeted probiotic therapies. For example, exploring the specific interactions between *L. reuteri* and skin microbiota, as well as its influence on immune response modulation, could provide deeper insights into its therapeutic potential. Overall, these multifaceted mechanisms of *L. reuteri* highlight its potential as a therapeutic agent in dermatology, offering a natural approach to managing skin conditions like acne vulgaris.

Mechanisms of Microbial Interactions with Lactobacillus reuteri

The potential for combined probiotic therapies involving *L. reuteri* and other beneficial strains could further enhance treatment outcomes for acne vulgaris. Synergistic effects from combining different probiotics could provide broader antimicrobial coverage and stronger anti-inflammatory benefits. For instance, combining *L. reuteri* with other *Lactobacillus* or *Bifidobacterium* species might optimize the gut-skin axis interactions, further supporting skin health and reducing acne severity. Future research should explore these combinations to establish the most effective probiotic regimens for acne management [13]. Such combinations could offer a holistic approach to acne treatment, addressing multiple pathways involved in acne pathogenesis and providing a more comprehensive solution. These holistic solutions should also aim to decrease unnecessary antibiotic use and other pharmacological agents that often come with adverse effects. By offering a natural and potentially safer alternative, *L. reuteri* can help mitigate the risks associated with long-term antibiotic use, such as antibiotic resistance and gastrointestinal disturbances. Longer follow-ups will be particularly important to assess the safety and long-term efficacy of these future investigations because the current evidence on the use of *L. reuteri* in the treatment of pediatric acne vulgaris is based on in-vitro evidence or short-term studies. Therefore, more research is needed to determine the long-term safety and efficacy of *L. reuteri*, particularly in diverse populations and different age groups. Ensuring that treatments are safe and effective across various demographics will be essential for broadening the applicability of *L. reuteri* in acne management.

The exact mechanisms by which *L. reuteri* plays a role in the treatment of pediatric acne vulgaris additionally remain unclear. However, several mechanisms have been proposed. *L. reuteri* may inhibit the production of inflammatory cytokines and activated macrophages, reducing inflammation in acne lesions [7]. Additionally, it might influence the gut-skin axis by promoting a healthy gut microbiome, which can indirectly improve skin health. Despite these hypotheses, there is a significant gap in understanding the precise molecular and genetic pathways involved. A deeper understanding of microbial interactions is required to understand the underlying mechanisms.

Clinical Evidence and Outcomes of Lactobacillus reuteri Supplementation

A comparative study by Khmaladze et al. suggests that *L. reuteri* has a positive effect on the skin [10]. In the study, the effects of live vs. lysate form *L. reuteri* on the skin were compared. The sample strains were *L. reuteri* DSM 17938, from donated human skin. This particular strain, *L. reuteri* DSM 17938, is significant because it is well-documented and widely studied, providing a reliable basis for evaluating its effects. The study established that *L. reuteri* has the potential to reduce inflammation by modulating levels of IL-6 and IL-8. Additionally, applied topical treatments in this study showed an upregulation of AQP3 gene expression and laminin A/B levels in reconstructed skin [10]. This indicates that both live and lysate forms of *L. reuteri* can modulate skin gene expression and structural proteins, contributing to improved skin health and resilience.

Another experimental study from Kang et al. demonstrates that *L. reuteri* has inhibitory effects on *C. acnes* and *Staphylococcus epidermidis*, although the exact mechanisms are not fully understood [14]. While *C. acnes* is the primary bacterium responsible for acne, *S. epidermidis* can also contribute to acne in some cases. Samples of *L. reuteri* were isolated from human intestines and feces, as well as from rats. These sample strains were *L. reuteri* KCTC 3594, KCTC 3678, and *L. reuteri* KCTC 3679, respectively. Results showed that all strains of *L. reuteri* have inhibitory effects on *C. acnes* and *S. epidermidis* by producing hydrogen peroxide, organic acids, and reuterin [14]. These findings suggest that *L. reuetri* can directly suppress acne-causing bacteria through multiple antimicrobial mechanisms.

Various studies have demonstrated the overall effect of the types of *lactobacillus* species on human skin, proving that *L. reuteri* can help in treating pediatric acne vulgaris. In Kobers et al.'s study, a randomized, double-blind controlled trial of 54 healthy volunteers showed that oral administration of *Lactobacillus johnsonii* led to the regeneration of CD1a Langerhans cell markers relative to the placebo group [7]. Kober et al. further explains that this research was replicated by Gueniche et al. with the same sample and population [7,15]. Kober et al.'s research demonstrated that the allostimulatory function significantly improved in the treatment group compared to the placebo group [7]. These findings suggest that incorporating probiotics into skincare regimens could enhance the skin's resilience to environmental stressors and potentially delay the onset of other skin conditions related to immune dysfunction.

Further research has indicated that *L. reuteri* supplementation can lead to a significant reduction in acne lesion count, size, and associated erythema [7]. A study by Kober et al. reported that the use of *L. reuteri* was associated with a reduction in inflammatory lesions and improvements in skin condition [7]. These noted reductions are important because they highlight *L. reuteri'*s ability to influence the skin's microbiome and immune system, addressing the root causes of acne rather than just the symptoms themselves. This work also demonstrated that *L. reuteri* may serve as an adjunctive therapy to conventional acne treatments, potentially reducing the need for antibiotics and other pharmacological agents that often have adverse effects [7].

Moreover, probiotics, including *L. reuteri*, have the potential to reduce systemic inflammation and improve the skin's immune response, which contributes to a reduction in acne lesions and reduction in sebum production [13]. This reduction in sebum production helps to create an environment less conducive to acne development. This is particularly beneficial because it potentially reduces the need for harsh topical treatments or systemic medications that can have significant side effects.

In addition to reducing lesion counts, *L. reuteri* has been shown to improve the overall condition of the skin through its systemic anti-inflammatory properties [7]. Clinical assessments and patient self-reports have indicated enhancements in skin texture, moisture retention, and a reduction in sebum production from probiotic use [7]. These improvements are likely due to the ability of *L. reuteri* to enhance the skin barrier function and promote hydration, contributing to a healthier skin environment that is less prone to acne development [7]. Additional research has also demonstrated that *L. reuteri* supplementation can lead to a significant reduction in epidermal dehydration, an indicator of improved skin barrier function. Gueniche et al. demonstrated that the *Lactobacillus* species may improve skin hydration and reduce transepidermal water loss, further supporting the role of probiotics in enhancing overall skin health [16]. The reduction in skin dryness can also contribute to maintaining skin homeostasis and resilience against environmental stressors. While these findings are promising, it is important to note that multiple research studies on *L. reuteri* are limited to rats and human skin samples, with only a few tested on human subjects. Those involving human subjects often have small population sizes, which limits the generalizability of the findings. Additional studies should be structured to include human subjects with larger and more diverse populations to provide better results, treatment options, and statistically significant data on the efficacy of *L. reuteri* in treatment.

Changes in Skin Microbiome

L. reuteri supplementation plays a significant role in fostering a protective microbial environment on the skin. As the diversity of the skin microbiome increases, a more balanced microbial ecosystem competes with and helps to inhibit the growth of pathogenic species. This increased diversity is associated with enhanced resilience against pathogenic invasions and improved skin health. Levkovich et al. reported that *L. reuteri* supplementation resulted in increased dermal thickness, enhanced folliculogenesis, and increased sebocyte production in a rodent study [17]. This highlights the potential for *L. reuteri* to promote structural changes in the skin that enhance its protective functions. Another study by Poutahidis et al. found that *L. reuteri* was associated with accelerated wound healing [18]. The decreased healing time may be explained by *L. reuteri*-induced oxytocin-mediated regulatory T-cell trafficking, which rapidly clears neutrophils from wounds, resulting in quicker healing times [18]. This shows the broader therapeutic benefits *L. reuteri* possesses beyond acne management.

Furthermore, the effects of *L. reuteri* on *C. acnes* and *S. epidermidis* development demonstrated significant inhibitory effects on bacterial growth [10,14]. *L. reuteri* can alter the skin environment in a way that is unfavorable to *C. acnes*. Khmaladze et al. reported this efficacy of *L. reuteri 's* antimicrobial action against the pathogenic skin bacteria such as *C. acnes* [10]. This reduction in *C. acnes* populations correlates with decreased inflammation and fewer acne lesions. Kang et al. showed that *C. acnes* growth was decreased by 2 log scales after incubation with *L. reuteri* for 24 hours, and *S. epidermidis* was decreased by 3-log scales after the same period of time [14]. The *L. reuteri* strain KCTC 3679 showed the strongest inhibitory effect on *C. acne*s and *S. epidermidis* growth, followed by *L. reuteri* KCTC 3594 and *L. reuteri* KCTC 3678 [14]. These findings both support the role of *L. reuteri* in improving overall skin condition and promoting beneficial changes in the skin microbiome. This ability of *L. reuteri* to inhibit these bacteria suggests a preventative potential as well, obstructing its re-colonization, thus providing potential for long-term benefits in acne management.

A critical aspect of *L. reuteri's* effect on the skin microbiome is its ability to decrease the abundance of *C. acnes*, a key bacteria implicated in acne pathogenesis. Research has demonstrated that *Lactobacillus* species directly compete with skin pathogens through inhibiting adhesion, producing antimicrobial metabolites, and influencing pathogen metabolism [19]. These antimicrobial metabolites such as lactic acid, hydrogen peroxide, and bacteriocins create an environment hostile to pathogenic bacteria, reducing their ability to thrive and cause infections, which maintains a healthy skin microbiome. The species additionally enhances skin barrier function and thus ensures barrier protection from infections and inflammatory skin diseases [19]. A robust skin barrier prevents the entry of unwanted pathogens and allergens. By mediating bacterial metabolites and cell-wall-associated or excreted microbe-associated molecular patterns (MAMPs), *L. reuteri* is protective against *C. acnes* and other pathogenic bacteria [19]. This modulation is essential for long-term skin health, disrupting the life cycle of harmful bacteria, and managing chronic conditions like acne, eczema, or psoriasis that are exacerbated by bacterial infections.

Systemic Inflammation Markers

The anti-inflammatory effects of *L. reuteri* extend beyond the skin to affect systemic inflammatory markers. *L. reuteri* strains may reduce pro-inflammatory cytokines and promote regulatory T-cell development and function. Research measuring cytokine levels, such as interleukin-17 (IL-17), interferon gamma (IFN-γ), and tumor necrosis factor (TNF), has found that *L. reuteri* supplementation results in a significant decrease in these pro-inflammatory cytokines [20]. Lin et al. reported on *L. reuteri's* ability to potentially suppress human TNF and MCP-1/CCL2 production [20]. The study discussed that human TNF and MCP-1 suppression by *L. reuteri* was dependent on strain; however, the activation of c-Jun and AP-1 represents key targets for probiotic suppression of TNF transcription [20]. These findings suggest that different strains of *L. reuteri* may have varying levels of effectiveness in reducing systemic inflammation.

The reduction in systemic inflammatory markers is strongly correlated with clinical improvements in acne severity. Patients exhibiting lower levels of IFN-γ and TNF following *L. reuteri* supplementation showed marked reductions in acne lesion counts and overall skin inflammation. The relationship between the decrease in inflammatory cytokine levels and the reduction in acne lesions underscores the systemic anti-inflammatory potential of *L. reuteri.* Kober et al. discussed *L. reuteri's* ability to induce systemic anti-inflammatory cytokines such as interleukin 10 (IL-10) and inhibit production of proinflammatory cytokines and TNF, underscoring its systemic anti-inflammatory potential [7]. This correlation highlights the potential of *L. reuteri t*o serve as a therapeutic agent that addresses both the symptoms and underlying inflammatory processes of acne, providing a holistic approach to treatment.

Additionally, *L. reuteri* produces exopolysaccharides (EPS) which are important for biofilm formation and its adherence to epithelial surfaces [9]. The significance of the EPS is seen in its ability to block the adhesion of E. coli and other bacteria to epithelial cells [9]. Furthermore, this EPS-mediated blocking is capable of suppressing gene expression of pro-inflammatory cytokines induced by E. coli such as IL-1β and IL-6 [9]. It is also important to note that *L. reuteri* increases inosine production, which is vital in reducing Th1 and Th2 cells and their associated cytokines [9]. This not only enhances the local immune response but also contributes to overall gut health, which is increasingly recognized as interconnected with skin health. Another study by He et al. showed that *L. reuteri* treatment reduced IFN-γ and IL-17 in mice [21]. The loss of gut microbiome delivery was also able to be restored by *L. reuteri* [21]. These findings jointly suggest that *L. reuteri* not only improves local skin inflammation, but plays a significant role in also modulating systemic immune responses.

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Studies demonstrate that the reduction in systemic inflammatory markers following *L. reuteri* supplementation is accompanied by improvements in other clinical parameters, such as reduced erythema and swelling around acne lesions. Emphasizing the role of systemic inflammation in the pathogenesis of acne and the potential of probiotics to modulate these pathways effectively may lead to improved clinical outcomes. Current research has supported the efficacy of *L. reuteri* in reducing acne lesion counts, improving overall skin condition, inducing beneficial changes in the skin microbiome, and decreasing systemic inflammatory markers in pediatric acne vulgaris. Findings demonstrate the potential of probiotics as a complementary treatment for acne, offering a novel approach that targets both local and systemic factors contributing to the condition. Further research on the potential synergistic effects of *L. reuteri* with other acne treatments may provide additional insights into comprehensive acne management strategies.

Dosage and Administration

The optimal dosage of *L. reuteri* for treating pediatric acne vulgaris has not been adequately described in current literature. This is primarily due to the variety of probiotic strains used in clinical studies, which complicates determining the specific effects of *L. reuteri* on acne vulgaris [22]. In these clinical trials, patients' acne vulgaris was monitored for several months while supplementing with combination probiotics. Positive results were seen after just four weeks, with continued improvement observed for up to twelve weeks after the initiation of probiotic supplementation. Notably, significant improvement typically occurs between 8-12 weeks of treatment [23]. Despite the observed benefits, the variation in strains used makes it challenging to identify the precise role of *L. reuteri*. Understanding the specific contributions of the probiotic requires further focused research.

One of the earliest studies on probiotic supplementation for acne in the 1960s deviated from the standard regimen. In that study, patients received probiotics for eight days, followed by a two-week break, and then repeated this cycle [7]. Improvement in these clinical studies was measured by the number of lesions present after the trial compared to before supplementation. Each study illustrated a reduction in inflammatory lesions, with Kober et al. reporting improvement in around 80% of patients studied [7]. Despite these positive results, the same question remains from this study's results; it is difficult to ascertain the specific factor responsible for clinical improvement due to the combination of species used in the experimental probiotic treatment groups. Isolating the effects of *L. reuteri* could provide clearer insights into its efficacy and optimal use.

A study by Kang et al. clearly defined the dosage of *L. reuteri*, using 5 x 10^5 CFU/ml for the in vitro experimental group [14]. This dosage significantly decreased the colonization of both *S. epidermidis* and *C. acnes*, which contribute to acne vulgaris. By using a single species, the study highlighted the direct impact of *L. reuteri* on these acne-causing bacteria, which supports the hypothesis that specific probiotics can influence the gut-skin axis, where changes in gut microbiota can affect skin health. However, translating in vitro findings to clinical practice requires careful consideration. Clinical trials are necessary to confirm these results in human subjects and subsequently guide clear protocols for the effective use of *L. reuteri*. As for dosing for pediatric patients, factors such as age, weight, severity of acne, and individual tolerance to probiotics should be considered. Pediatric dermatologists often recommend starting with lower doses and gradually increasing as needed, while monitoring for any adverse effects such as gastrointestinal discomfort or allergic reactions. This cautious approach guarantees the safety and effectiveness of probiotic treatment in managing pediatric acne vulgaris. Such tailored treatment plans are especially important in young populations.

Safety and Tolerability of Lactobacillus reuteri

L. reuteri has been widely studied for its safety and efficacy in various clinical contexts. Common side effects are generally mild and transient, including gastrointestinal symptoms such as bloating, gas, and abdominal discomfort [24,25]. These symptoms are typically self-limited, and further medical intervention is not necessary. Additional, less frequently reported side effects include mild headaches and dizziness; however, these occurrences are not directly attributed to *L. reuteri* supplementation [26]. This suggests that *L. reuteri* is well-tolerated and suitable for long-term use, given that the side effects are minor and temporary.

Adverse reactions to *L. reuteri* are infrequent, and serious adverse events are rare. Most studies indicate a low incidence of adverse reactions, contributing to the bacterium's favorable safety profile. In a comprehensive review of randomized controlled trials, the incidence of adverse reactions did not significantly differ between the *L. reuteri* groups and placebo groups [26]. Notably, there have been no reports of severe systemic infections or significant long-term health complications directly linked to *L. reuteri* supplementation. This underscores the reliability of *L. reuteri* as a therapeutic option for various conditions, as its safety profile remains consistent across different populations and studies. For most patients, as Jung et al. mentions, probiotics have proven to show synergistic anti-inflammatory effects with other treatments for acne vulgaris, such as antibiotics, while also potentially reducing the gastrointestinal side effects of chronic antibiotic use [23]. This dual benefit highlights the potential of probiotics like *L. reuteri* to enhance treatment efficacy while mitigating common side effects associated with long-term antibiotic use.

An analysis of 74 clinical studies indicated that probiotic administration is safe for children, including those who are healthy, immunocompromised, obese, or have inflammatory, infectious, or intestinal disorders [27]. There were no major safety concerns, adverse reactions attributed to the short duration usage of probiotics, and the products were well tolerated amongst the subjects. These findings are particularly important because they demonstrate that probiotics can be safely used in vulnerable populations, offering a broader scope for therapeutic application. As for long-term effects and maintenance dosages needed for the treatment of acne vulgaris, these are largely unknown. Probiotics are now considered well tolerated with minimal to no adverse effects in healthy children. However, special precaution should be considered in children with immunocompromising status, prematurity of infancy, critical illness, central venous catheters, cardiac valvular diseases, and short-gut syndrome. When adverse events occur, they are typically mild, such as gastrointestinal upset and diarrhea, and are self-limiting. The major concern for these children with compromising situations is systemic disease, such as sepsis, which is unlikely but severe and should be considered [28]. This cautionary note is essential for clinicians to consider when prescribing probiotics to high-risk pediatric patients.

The long-term safety data for *L. reuteri* within pediatric populations are promising. Numerous studies have investigated its use in infants and children for conditions such as colic, diarrhea, and atopic dermatitis [29,30]. These studies report that *L. reuteri i*s well-tolerated, with a safety profile similar to that in adults. The most common side effects in pediatric studies are comparable to those seen in adult populations, typically manifesting as mild gastrointestinal symptoms. Long-term follow-up in these studies has not revealed any significant safety concerns, and growth parameters in children receiving *L. reuteri* are comparable to those in control groups [29,30]. This further supports the integration of *L. reuteri* into pediatric care, ensuring that children benefit from its therapeutic effects without compromising their growth and development.

Given the overall positive safety profile of *L. reuteri*, routine monitoring is usually minimal. However, for specific populations, such as immunocompromised individuals or those with severe underlying health conditions, more frequent observation may be warranted. It is recommended to monitor for any unusual or severe adverse reactions, especially during the initial phase of supplementation. Periodic follow-up appointments can help ensure the continued safety and efficacy of *L. reuteri*, particularly in long-term use scenarios. An important consideration to supplementation is antibiotic resistance. In a genome analysis completed by Lee at al., *L. reuteri* was found to be negative for both antibiotic resistance and toxigenicity genes [31]. This study demonstrated that *L. reuteri* can not only help address the major public health concern of antibiotic resistance, but also does not produce harmful toxins due to the absence of toxicity genes, further supporting its safety profile [31]. Pediatric patients should have regular growth assessments and developmental evaluations to detect any potential deviations from expected norms. *L. reuteri* exhibits a robust safety profile with minimal common side effects and rare adverse reactions. Long-term use, especially in children, appears to be safe, provided appropriate monitoring and follow-up are conducted.

Future Directions

The use of *L. reuteri* in pediatric acne vulgaris has shown promising results, with several studies reporting positive effects [10,14,32,33]. While initial findings are promising, several future directions must be pursued to solidify its place in acne treatment protocols. This section outlines the need for standardized treatment protocols, large-scale, and long-term studies.

Despite the efficacy of *L. reuteri*, no standard dosage or administration methods have been reported. Published studies have mostly reported delivery of *L. reuteri* via tablets or capsules, but the doses varied. For example, Manfredini et al. used a probiotic capsule containing 10^9 colony-forming units of *L. reuteri*, while Mosaico et al. used commercial tablets of *L. reuteri* ATCC PTA 5289 twice daily [22,33]. This variability complicates the comparison of outcomes and makes it difficult to establish a clear understanding of the optimal dosage. Therefore, there is a need for standardized treatment protocols. Future studies should focus on standardizing dosage and administration protocols to ensure consistency. Clinical trials should determine the optimum dosage while keeping in view the safety and efficacy of *L. reuteri* in pediatric acne vulgaris. There is also a need to determine the most suitable methods for delivery of probiotics, including oral capsules, tablets, and fermented foods. The mode of administration should ensure consistent bioavailability and patient adherence. Additionally, standardized outcome measures to assess the efficacy of *L. reuteri* are lacking. Previous studies have used acne severity scales, patient self-assessments, and photographic assessments as outcome measures [33]. Standardized follow-up periods and consistent reporting of side effects and patient satisfaction will also contribute to a more comprehensive understanding of the effectiveness and safety of *L. reuteri* in treating pediatric acne vulgaris.

Variability in study design and outcome measures across different studies also poses challenges. Differences in probiotic strains used, dosages, administration methods, and assessment criteria make it difficult to compare results directly and draw definitive conclusions. Standardizing these parameters in future research will be crucial for building a coherent body of evidence that can guide clinical practice. Consistent use of validated acne severity scales and patient-reported outcomes will enhance the comparability and reliability of study findings [10,16]. Moreover, the lack of standardized outcome measures and follow-up periods across studies adds to the complexity. Most studies have relied on varying assessment tools, ranging from acne severity scales to photographic assessments and patient self-reports, making it difficult to synthesize data across different research efforts. Establishing standardized protocols for assessing probiotic efficacy in acne treatment will be crucial for future studies.

A more specific drawback in research to elaborate on is the small sample size, which profoundly impacts the generalizability of a study's findings. Many reports have involved limited participants and have not extended beyond a few months, which constrains the ability to generalize findings and understand long-term effects. For example, Mosaico et al. conducted their study with only two participants, which is insufficient to draw broad conclusions [33]. Similarly, Manfredini et al. conducted studies with limited sample sizes, which impacts the robustness and applicability of their findings [22]. Larger, long-term clinical trials are necessary to confirm the efficacy and safety of *L. reuteri* for acne treatment and to identify any potential long-term benefits or risks. If most studies conducted on the topic are small studies or case series, it becomes very difficult to derive practical implications as well.

The use of *L. reuteri* in treating pediatric acne vulgaris holds great promise, but several critical areas require further exploration to establish it as a reliable therapeutic option. Standardizing treatment protocols, including dosage and administration methods, is essential to ensure consistent and comparable outcomes. Addressing the challenges posed by variability in study design and small sample sizes will enhance the robustness of future research. Exploring combined probiotic therapies could provide more comprehensive and effective treatment strategies. Additionally, delving into the molecular and genetic mechanisms of *L. reuteri* will deepen our understanding of its role in acne management. With concerted efforts in these directions, *L. reuteri* could emerge as a natural and safe alternative in the arsenal against pediatric acne, offering long-term benefits and reducing reliance on traditional pharmacological treatments.

Conclusion

In conclusion, the integration of probiotic *L. reuteri* as adjunctive therapy for pediatric acne vulgaris represents a promising novel therapeutic approach in dermatology. The therapeutic potential of *L. reuteri* extends beyond the skin, confirming the importance of healthy skin microbiota and its interplay with systemic health and immunity. Locally, *L. reuteri* demonstrates a role in the diversity and modulation of the skin microbiota, contributing to amelioration in skin conditions, skin barrier function, and protective mechanisms.

Clinical trials surrounding *L. reuteri* have displayed profound benefits of *L. reuteri*, illustrating an overall enhancement in skin health through its antimicrobial, anti-inflammatory, and cytokine modulating properties. *L. reuteri* has been shown to support the survival of advantageous organisms, combat pathogens such as *C. acnes* and *S. epidermidis*, and improve immune response and recovery. The findings support the efficacy of *L. reuteri* as adjunctive therapy in pediatric acne vulgaris due to its proven effects of reducing lesion count, size, and associated edema, erythema, and inflammation. Additionally, enhancements in skin texture, moisture retention, hydration status, barrier function, and wound healing have been reported. Incorporating *L. reuteri* as adjunctive treatment into current acne vulgaris treatment modalities may reduce the need for topical, systemic, or combination approaches, thereby decreasing significant potential biopsychosocial adverse effects.

While research on the role of *L. reuteri* in the pathogenesis of acne vulgaris has provided promising results, there is a clear need for further studies to establish standardized treatment protocols and incorporate it into broader acne management approaches. Exploring potential synergies between *L. reuteri* and existing acne treatments could yield valuable insights for developing comprehensive acne management approaches. Specifically, *L. reuteri* appears encouraging as an adjunctive therapy for pediatric acne vulgaris, underscoring the importance of additional research to confirm its efficacy and long-term safety profile. This ongoing research will be essential for validating *L. reuteri* as a reliable treatment option and integrating it effectively into clinical practice to improve patient outcomes within dermatology.

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