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# Production And Formulation of Postbiotics for Treatment of Acne Vulgaris

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**ABSTRACT**

In dermatology, the development and formulation of postbiotics have gained significance for skincare treatment. Postbiotics, deceased organisms promoting host health, exhibit potential in modifying skin microbiota, enhancing the skin barrier, and reducing inflammation. Present research focuses on postbiotic production and their application in treating acne vulgaris. Although postbiotic use in skincare is nascent, acne, a chronic inflammatory condition, stems from factors like increased androgen-induced sebum production, altered keratinization, inflammation, and Propionibacterium acnes colonization. Nonetheless, implementing postbiotics faces challenges like nomenclature, regulatory issues, and safety concerns. Further exploration is essential to establish global standards and regulations, enabling the creation of safer, more sustainable postbiotic products. Addressing these aspects could revolutionize skincare, employing postbiotics responsibly and effectively, particularly for conditions like acne vulgaris. Achieving this requires consistent manufacturing, extensive clinical trials, and continuous research to comprehend mechanisms of action and validate the efficacy and safety of postbiotic-based skincare.

**Keywords:** postbiotics1, microbiomes2, skin care3, acne vulgaris4.

## 1.1 INTRODCUTION

Probiotic can alter the gut microbiota which has a number of positive effects of health. However, viability constraint and other technological restriction have prevented probiotic from being used to their full potential in the food and pharmaceutical industries. As a result, attention is increasingly turning away from probiotic bacteria that are still alive and towards non-viable para probiotic and are biomolecules made from probiotics which are referred to as postbiotic [1]. Compounds that are released are create microbial metabolism and have a positive impact on the host either directly or indirectly. One major benefit of the post biotic is that they do not contain live microbes which reduces the hazard involved with use [2]. Including dipeptide and short chain fatty acids may have a significant impact on metabolic process [3]. These include amino acid peptides organic acid a short chain fatty acid short chain protein vitamins biosurfactant enzyme and more [4]. These substances have antibacterial immunomodulatory anti-inflammatory and antioxidant properties [5]. Postbiotics obtained from fermentative process, but most companies prefer industrial process. Most of the companies prefer the lactic acid bacteria or saccharomyces cerevisiae. Postbiotics includes metabolite such as teichoic acid, polysaccharides and among others. It is having significant properties such as antioxidant, antiproliferative, immunomodulatory- for these reasons. It's using in cosmetic formulation. What's particularly unique approach in the cosmetic component industry since they do not require the viability in the topical formulation and have a longer shelf life than probiotic. Lipoteichoic acid having the property which effect the anti-aging [7]. The use of postbiotics for skin condition is still a beginning process [8]. Early Colonization with the acne P acne and family history could play a significant part in the illness precisely what triggers acne and what treatment means for the course of the disease state model. Different factor for example that have been suggest it entirely not understood facial scarring because of acne effect up to 20% of the young people. Acne can continue to adult with negative impact on confidence there is an optimal skin inflammation although it is reasonable for decreasing it can be found for most patient great quality proof on relative viability for normal effective and fundamental screen breakout treatment is scanned effective treatment including benzoyl peroxide retinoids and antitoxins when utilized in blend typically further develop direct or indirect acne treatment with consolidate oral contraceptive can assist ladies with skin inflammation patient with more extreme in incendiary skin inflammation for the most part need oral anti-microbial joint with effective benzoyl peroxidase to diminish antimicrobial safe organic entities. Oral isotretinoin is the best treatment and is utilized from to get gold in extreme illness although utilization is restricted by teratogenicity and opposite secondary effect. accessibility antagonist impact and cost limit utilization of photodynamic treatment new exploration is required into the remedial near advocacy and security of the numerous item accessible and to even more likely regular history subtype and triggers of skin inflammation [9].

**1.2. Concept related to the title:**

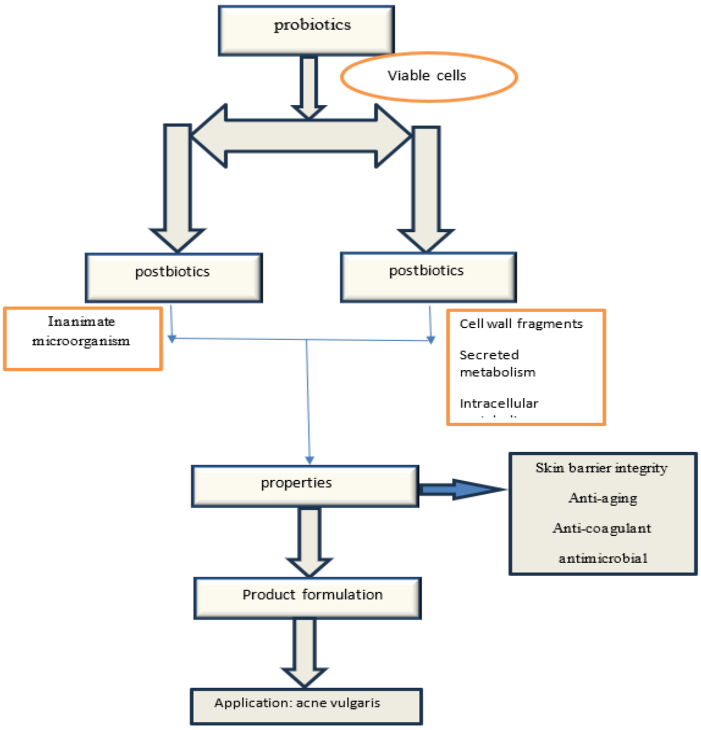


Fig 1: postbiotics schematic representation related to acne vulgaris.

**1.3 Mechanism of acne vulgaris:**

Acne affects the pilosebaceous units of the skin, resulting in a range of lesions at varying levels of inflammation, including acne scars and hyperpigmentation. Acne lesions are more typically found on the face, chest, upper back, and upper arms, which are known to have a high density of sebaceous glands.

Acne is caused by four major pathogenic factors: increased sebum production, irregular follicular desquamation, Propionibacterium acnes growth, and area inflammation.

**1. Excess sebum production:**

The synthesis and release of sebum are stimulated by androgen hormones, particularly testosterone.

**2. Epidermal hyper proliferation and formation of comedones:**

Acne is characterized by an abnormal accumulation of keratinocytes, lipids, and monofilaments in sebaceous follicles. This leads to the formation of microcomedones, which are the initial microscopic lesions. As they accumulate more lipids, they develop into visible comedones, known as blackheads (open comedones) or whiteheads (closed comedones). If sebum builds up further, closed comedones may rupture, leading to inflammatory acne lesions.

**3. Propionibacterium acne infiltration:**

It produces lipase enzymes that metabolize sebum into glycerol and fatty acids, contributing to the formation of comedones and subsequent inflammation. P. acnes is the primary target of oral and topical antibiotic treatments for Acne vulgaris. Individual immune response to P. acnes influences the development of acne in different individuals.

**1.4 Current synthetic treatment for acne vulgaris:**

**1. Topical Treatments:**

- Benzoyl Peroxide: It has antibacterial and anti-inflammatory properties, reducing acne-causing bacteria and promoting skin cell turnover. The medication is designed for the treatment of mild to severe acne vulgaris and contains anti-inflammatory, keratolytic, and comedolytic properties. As a larger concentration is not necessarily better and more effective, clinicians must strike a balance between the required concentration, the vehicle base, and the risk of side effects.
- Topical Retinoids: Derived from vitamin A, they unclog pores, reduce inflammation, and improve cell turnover. Over 30 years have passed since retinoids first came into usage. Topical retinoids are used to treat acne's microcomedo-precursor lesion. There is generally general agreement that topical retinoids should be used as the first treatment for mild-to-moderate inflammatory acne, either alone or in combination, and that they are also the preferable drug for maintenance therapy.
- Topical Antibiotics: Such as clindamycin or erythromycin, they help control bacterial growth and inflammation.
- Combination Topicals: Some treatments may combine two or more of the above components for enhanced efficacy.

**2. Oral Antibiotics:**

- Oral antibiotics like doxycycline, minocycline, or tetracycline may be prescribed for moderate to severe inflammatory acne to control bacteria and inflammation.

**3. Oral Contraceptives:**

- For females, oral contraceptives with anti-androgen properties can help regulate hormones that contribute to acne development.

**4. Isotretinoin (Accutane):**

- Reserved for severe, nodulocystic acne, isotretinoin is a potent oral medication that targets excessive sebum production and is often prescribed when other treatments have failed. Oral retinoids are prescribed for severe, moderate-to-severe acne, or cases where acne causes physical or psychological scarring, and does not respond to standard treatments. They stand out as the sole medication capable of targeting all four pathogenic factors involved in the development of acne.

**5. Procedural Treatments:**

- Chemical Peels: These helps exfoliate the skin and reduce the appearance of acne scars.
- Laser and Light Therapies: Various laser and light devices can target acne-causing bacteria and reduce inflammation.
- Extraction: Manual removal of comedones or cysts by a healthcare professional.
- Intralesional Injections: For large, inflamed cysts, corticosteroid injections can help reduce swelling and speed up healing.

6. Post-acne Care:

- After successful acne treatment, skincare and maintenance are essential to prevent future breakouts and manage residual scarring.

There is no evidence to support or refute the effectiveness of dietary control in the treatment of acne [10].

### 1.5. General production for postbiotics

The fermentation broth can be directly subjected to cell lysis without prior concentration. This cell inactivation step can be achieved using methods such as ultrasound, high-pressure breakage, or enzymatic treatment in the cell inactivation tank (CIT-01). As a result of this process, both intracellular and cell membrane/wall molecules are released into the solution, necessitating further removal of large cell debris through centrifugation (C-02) and filtration (F-02) before being directed to a homogenizing tank (HT-01).

Alternatively, the centrifuged biomass from C-01 can undergo cell lysis in a secondary pathway. This biomass can be combined with cell debris from other unit operations, such as filtration F-01, and then inactivated, leading to the production of a different postbiotic product. The same inactivation methods used for C-01 biomass can be applied in the cell inactivation tank (CIT-02). Additionally, specific extraction methods can be employed in the extraction tank (ET-01) if needed, using solvents like ethanol or ethyl acetate to remove particular molecules from the original solution due to their strong solubilizing properties. This extraction process may target molecules like carbenicillin, cephalexin, cephalothin, and tetracycline.After the inactivation, with or without extraction, the resulting metabolites are then directed to the homogenizing tank (HT-01) for further processing [5].

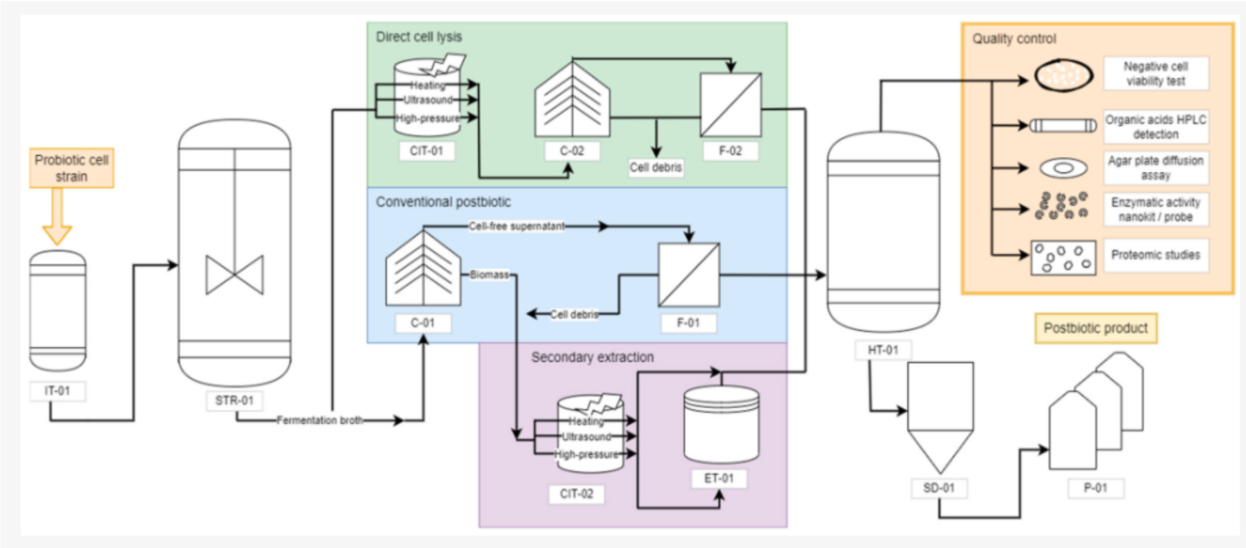


Figure 2: postbiotics production flowchart [5]

Each approach ends with the homogenizing tank, which ensures that the product will have a consistent composition throughout all fractions. Spray dryers (SD-01) and packing (P-01) are the two most viable alternatives when the intended product is in a solid particle state. Although hot air is used in the spray dryer, it is less severe other inactivation techniques and typically employs protective substances that are added to soluble starch, such as glucose, sucrose, lactose, and maltodextrin, before drying [10].

Before releasing a postbiotic into the market, it must undergo thorough quality control to ensure its composition meets the required standards. Apart from the standard beneficial feature characterization, which is similar to probiotic testing (evaluating non-toxicity, antipathogenic activity, and functional properties), an essential test is the negative cell viability test to confirm the absence of viable cells.

The recommended method for this test is direct plate cultivation without using various dilutions. Although alternatives like microscopies or real-time PCR exist, they may face challenges due to the presence of cell debris and remaining genetic material in the solution.

Additionally, further characterization of the postbiotic is vital. This includes evaluating saccharides, organic acids, antibiotics, bacteriocins, proteins, and enzymes. Chromatographic methods such as HPLC and thin layer chromatography can be used to detect monosaccharides, N-acetylglucosamine, alcohols, and organic acids. For antibiotics and bacteriocins, their activity is best tested using agar diffusion well tests against classical pathogens to ensure their biocidal properties remain effective [11].

### 1.6. Mechanism of action

Postbiotics can influence the skin's microbiome and restore microbial balance through several mechanisms:

1. Competition with Pathogenic Microbes: Postbiotics, which are metabolic byproducts of probiotic bacteria, can compete with and inhibit the growth of harmful or pathogenic microbes on the skin. By occupying the ecological niches on the skin's surface, postbiotics create an environment less favourable for the proliferation of harmful bacteria.
2. Production of Antimicrobial Substances: Some postbiotics release antimicrobial substances, such as bacteriocins or organic acids, that have selective antibacterial properties. These substances target specific harmful bacteria while sparing beneficial ones, contributing to a more balanced microbial

community.

3. Modulation of Immune Responses: Postbiotics can interact with immune cells in the skin, influencing the immune response. They may stimulate the production of anti-inflammatory cytokines while dampening the release of pro-inflammatory cytokines. This immune modulation helps to prevent excessive inflammation and supports a more harmonious microbial environment.
4. Promotion of Beneficial Microbes: Postbiotics can promote the growth and activity of beneficial bacteria on the skin, such as certain strains of commensal bacteria that contribute to skin health. By creating a favourable environment for these beneficial microbes, postbiotics help restore microbial balance.
5. Enhancement of Barrier Function: Postbiotics can reinforce the skin's natural barrier function. A healthy skin barrier is crucial for preventing the invasion of harmful microbes and maintaining a balanced microbiome. By improving the barrier function, postbiotics indirectly support the stability of the skin's microbial community.
6. Regulation of pH Levels: Postbiotics can influence the skin's pH levels, creating an environment that is less conducive to the growth of certain harmful bacteria. A balanced pH level is essential for maintaining a healthy skin microbiome.
7. Restoration of Homeostasis: Postbiotics aid in the restoration of microbial homeostasis, which refers to the natural balance and stability of the skin's microbial community. This equilibrium is crucial for overall skin health and defense against external threats.

By employing these various mechanisms, postbiotics help shift the skin's microbiome towards a more diverse and beneficial composition, promoting a healthier, more resilient skin barrier, and reducing the risk of skin issues such as acne, inflammation, and infection. However, it is important to note that research in this area is still ongoing, and more studies are needed to fully understand the complexities of postbiotic interactions with the skin microbiome [5].

Acne has long been linked to the proliferation of Propionibacterium acnes (also known as Cutibacterium acnes). However, recent studies utilizing metagenomics have challenged this association. They found that the abundance and bacterial load of C. acnes do not significantly differ between individuals with acne and those with healthy skin [12].

Specifically, Barnard et al., [19] using the WGS approach, reported that healthy individuals had a slightly higher relative abundance of C. acnes compared to acne patients (93.8% vs. 88.5%). Moreover, other cutaneous Propionibacterium species, such as P. humerusii, P. granulosum, and P. avidum, were also identified in both healthy and acne-afflicted individuals.

At the strain level, the C. acnes populations in older healthy individuals were found to be similar to those in younger healthy cohorts, predominantly consisting of RT1, RT2, and RT3 strains, with minimal to no presence of RT4, RT5, and RT8 strains. Using SLST markers targeting the tuf2 gene, researchers discovered that staphylococcal strains selectively exclude acne-associated C. acnes and coexist with the phylotypes associated with healthy skin, partly through the regulation of antimicrobial activity.

These findings emphasize the significance of skin-resident staphylococci and propose that selective microbial interference plays a role in maintaining healthy skin homeostasis. In essence, the relationship between C. acnes and acne is more complex than previously believed, and the interplay of various skin microbes likely contributes to the overall health of the skin [13].

### 1.7. formulation of postbiotics

Skin cosmetic products typically consist of a complex blend of approximately 20 different ingredients, carefully selected to ensure the desired effectiveness, safety, and market acceptance. Among these ingredients, key components include water, surfactants, preservatives, barrier agents, enhancers, humectants, and active ingredients. The specific concentrations of these chemical compounds determine the categorization of the final product, such as lotions, creams, or moisturizers [15].

Ultra-pure water serves as the fundamental foundation of skin products, acting as the solvent basis that influences the final consistency of the product. Additionally, it plays a crucial role in enhancing skin moisturization levels, contributing to the overall effectiveness of the cosmetic formulation [16]. Surfactants are versatile substances with both hydrophobic and hydrophilic moieties in their chemical structure, enabling them to reduce the surface tension between liquids with different polarities. This property contributes to achieving a smooth and uniform texture in the final cosmetic product [16].

Preservatives, such as parabens and formaldehyde, play a vital role in preventing the growth of harmful microorganisms, safeguarding the cosmetic from spoilage. They also counteract the generation of reactive oxygen species (ROS) and hinder the oxidation of the cosmetic formulation, ensuring its stability.

Barrier agents create a thin, hydrophobic layer over the skin, reducing water loss and minimizing direct contact with potential sensitizer, irritant, or allergen compounds present in the formula. This protective layer contributes to skin comfort and safety [15].

Enhancers, such as denatured alcohol, glycols, and esters, are added to improve the penetration of active ingredients into the skin. They achieve this by promoting lipid fluidization, lipid extraction, and lipid ordering mechanisms, enhancing the efficacy of the product. Humectants, as the name suggests, improve skin hydration by attracting water from deeper layers and facilitating its retention in the stratum corneum through the formation of hydrogen bonds. This helps to keep the skin surface moisturized.

Apart from the essential ingredients mentioned earlier, skin products designed to target specific skin disorders, such as acne vulgaris, may include additional synthetic-active ingredients. These ingredients encompass a range of compounds, including anti-inflammatory agents, corticosteroids, immunosuppressive agents, and antimicrobial agents. Incorporating these specific actives enhances the product's therapeutic properties, aiding in the effective treatment of various skin conditions [17].

Recent studies have brought attention to the potential risks associated with prolonged exposure to synthetic compounds when used as the sole treatment for various skin conditions. Adverse events, such as skin irritation, dryness, exfoliation, erythema, and striae, have been reported. These reactions can alter the structure of the skin's microbial community, impacting its biological functions and exacerbating the severity of conditions like acne vulgaris [17].

In response to these concerns and the growing demand for environmentally friendly products, the market has witnessed a shift towards the development of biocosmetics. Biocosmetics are formulations that incorporate natural, organic, and plant-derived ingredients. These products aim to offer effective and safer alternatives to traditional cosmetics, with a focus on minimizing negative impacts on the skin and the environment. By choosing biocosmetics, consumers seek to strike a balance between achieving desired skincare results and promoting skin health while supporting sustainable practices and reducing their ecological footprint [15].

Among the biotechnological solutions explored, incorporating postbiotics as active ingredients has emerged as one of the most promising approaches. The use of postbiotics offers significant advantages, such as the absence of risks associated with bacteremia and fungaemia. Additionally, postbiotics demonstrate inherent stability during industrial processes and extended shelf life [6].

Formulating cosmetic products with postbiotics has proven to be cost-effective, as there is no need to maintain cell viability during transportation and storage. This eliminates the need for specialized storage conditions and reduces production costs.

Majeed et al. [9] evaluated the direct addition of LactoSporin® (2% [w/w]), an extracellular, low-weight protein metabolite produced by the patented probiotic B. coagulans MTCC 5856, in the formulation of topical creams for the treatment of mild-to-moderate acne lesions.

Topical treatment remains the primary approach for managing acne. Benzoyl peroxide, clindamycin, and retinoids are among the most commonly prescribed topical medications for acne. While effective in treating mild to moderate acne vulgaris, these treatments can be irritating and historically linked to low tolerability and patient adherence. Therefore, selecting the appropriate formulation that ensures both efficacy and tolerability is crucial. Innovative formulations that optimize drug concentration and utilize improved delivery vehicles have made significant advancements in enhancing tolerability and effectiveness. These advancements also enable less frequent application or co-application of previously incompatible drugs, providing more effective and convenient treatment options for acne patients [18].

While direct addition of postbiotics is cost-effective, it exposes these substances to external conditions such as UV light, temperature, pH, and oxidation, which can lead to a loss of stability and biological activity in topical formulations. To overcome this challenge, encapsulation with microparticles and nanoparticles emerges as a viable solution. This protective encapsulation provides a shield for the active ingredients, preserving their stability and biological activity even when exposed to external factors. Moreover, encapsulation allows the postbiotics to be effectively delivered and retained in the top layer of the epidermis, enhancing their therapeutic efficacy in treating acne and other skin conditions [19]. By employing encapsulation technology, postbiotics can be safely and efficiently utilized in cosmetic and skincare products, maximizing their benefits for users.

### 1.8. Effect of postbiotics on treatment of acne vulgaris

Acne vulgaris is a chronic inflammatory illness that affects the pilosebaceous unit (skin hair follicles connected with a sebaceous gland) on the face, neck, chest, and seashore. In general, there is no perfect treatment for acne, however topical treatments combining retinoids, benzoyl peroxide, and antibiotics show success in mild and moderate instances. Postbiotics have been found to be a promising therapy option for acne [20, 21].

Majeed et al. tested the impact of LactoSporin® (a filtered extract produced from a fermented Bacillus coagulans MTCC 5856) to benzoyl peroxide in 64 people with mild and moderate acne. Both treatments significantly improved dermatological assessment of closed and open comedowns, as well as papule count [5].

- **SkinDuoTM**

Lactiplantibacillus plantarum, a species known to generate potent bacteriocin-like chemicals, can prevent dangerous commensal bacteria on the skin.In participants with mild-to-moderate papulopustular acne, a single strain of L. plantarum was used to modify and enhance host-skin microbiota interactions [22].

Lactobacillus species hinder pathogenic microbe colonization and modify the health-associated skin commensal bacteria. Our unique and revolutionary formulation contains solely natural components that increase and sustain the vitality of L. plantarum for up to 7 days [23]. SkinDuoTM is non-pathogenic and non-toxic to human health. The findings of this study reveal that lipid synthesis from human sebocytes is

reduced, which is further reduced in the presence of pro-inflammatory mediators. Acne is connected with increased sebum production, which uses metabolic substrates to support the development of C. acnes and S. epidermidis [24].
The metabolic activity was increased after SkinDuoTM serum administration, indicating an improvement in metabolic cellular status, which also represents inhibition of cellular activity and shows the absence of toxicity in the acne diseased model [25].

**Conclusion:**
This review represents a novel and emerging research area focusing on biomolecules derived from probiotics. However, it is essential to acknowledge certain limitations in the findings. Some clinical studies examined had small sample sizes, and the intervention periods were relatively short, potentially affecting the generalizability and long-term efficacy of the results. Additionally, the diverse factors, including various inactivation and extraction methods, specific characteristics of postbiotics, carrier systems, and biological losses during their biological properties and overall health impact. Addressing these limitations through larger and more extended clinical trials and standardization of methodologies will be critical to gaining a comprehensive understanding of the potential benefits of postbiotics and their optimal utilization in various health applications.
The application of postbiotics presents final challenges related to nomenclature, regulatory aspects, and safety in use. These aspects warrant further investigation by researchers to establish international standards and regulations, thus paving the way for the production of healthier, safer, and sustainable postbiotic products. By addressing these crucial issues, the skincare industry can unlock new possibilities for utilizing postbiotics as effective and responsible treatments for various health conditions, including acne vulgaris. This comprehensive approach will ensure consumer confidence, promote ethical practices, and contribute to the development of a thriving postbiotic-based skincare market.
Postbiotics show great promise as a treatment for various skin conditions, as they can positively influence the skin microbiome, strengthen the skin barrier, and alleviate inflammation. Clinical studies have provided substantial evidence supporting their effectiveness in enhancing skin health, particularly in conditions like acne, eczema, psoriasis, rosacea, and more. However, to fully harness the therapeutic potential of postbiotics in skincare products, additional research and formulation optimization are necessary. The use of postbiotics presents an encouraging avenue to address skin concerns and drive advancements in the field of dermatology.

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