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Review

Acne Vulgaris Topical Therapies: Application of Probiotics as a New Prevention Strategy

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Abstract: The skin microbiome is an essential barrier for preventing the invasion of pathogens and regulating the immune responses. When this barrier is disrupted, several dermatoses, including acne vulgaris, may arise. Most people will experience acne starting at the onset of puberty and continuing into adolescence; a significant percentage of those individuals continue to suffer from it into adulthood. Although common, this dermatosis usually has an enormous impact on the self-esteem and quality of life of individuals who suffer from it. An increase in consumer literacy regarding skincare leads buyers to seek out innovative products containing ingredients with proven benefits for their concerns. Probiotics have proven to be an alternative to the use of antibiotics, often associated with undesirable effects, in the treatment and prevention of dermatological disorders such as acne. This review provides a comprehensive analysis of the pathophysiology, risk factors, symptoms, conventional treatment recommendations and main studies emphasizing innovative topical products for acne-prone skin based on probiotics. In addition, the potential advantages, and limitations/challenges associated with the implementation and manufacturing of these innovative skin products are also highlighted.

Keywords: acne; topical therapies; probiotics; skin care; active ingredient

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1. Introduction

Human skin defends itself against microbes through secreted substances, such as sebum, proteases, antimicrobial peptides, and lisoenzymes, as well as with its pH, temperature and humidity levels. Despite this, commensal bacteria on the skin form complex ecosystems, and their competition with pathogens can prevent colonization by harmful bacteria [1]. As a result, most of the bacteria that colonize the skin are not harmful and some may even be beneficial to the host.

Over 1000 species of bacteria from 19 different phyla (of which the most representative are Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes) inhabit human skin, alongside dermatophytes and viruses, as result of constant exposure to microbes found in the external environment [2]. Other important factors that influence the skin microbiota throughout an individual's life include host factors, such as lifestyle, age, and gender, and environmental (socioeconomic and geographical) ones. At the onset of puberty, increased sebum production creates an environment favorable to the proliferation of lipophilic microbes, such as *Cutibacterium acnes* (formerly designated as *Propionibacterium acnes*), which compete with other commensal bacteria and dominate the areas of higher density in

sebaceous glands, leading to a decrease in the overall diversity of skin microbiota during puberty [2]. While the sebaceous areas of the skin are less diverse, harboring mostly bacteria from the Actinobacteria and Firmicutes phyla, such as *Propionibacterium* and *Staphylococcus* species, moist zones (the navel, soles of feet, skin folds and creases) tend to be richer in *Corynebacterium* and *Staphylococcus* species, and drier regions such as the buttock, forearm, and parts of the hand tend to present the highest phylogenetic diversity [3].

Women and men also have differences in their skin microbiome, due to variations in pH, sweat, thickness, hormones, and sebum production. pH is generally lower and sebum secretion is higher in men when compared to women of the same age. These anatomical and physiological factors account for some of the differences observed; beyond those features, some variations may be caused by gendered behavioral tendencies regarding hygiene and cosmetics use [3].

Regarding the impact of a Westernized lifestyle versus non-Westernized living conditions, comparisons have shown that people subjected to the former possess less diverse skin microbiomes, with higher percentages of Actinobacteria, and, more specifically, *Propionibacterium* species [2,4].

Cosmetics also have the potential to change the skin microbiome, especially when the daily frequency with which most people use them is considered. Although sterility is not required in cosmetic products, the likelihood that they will introduce infectious microbes is very low, provided the products comply with current legislation. However, the presence of antimicrobial preservatives in formulations may have an impact in the skin microbiome, with hard-to-predict long-term consequences that could entail the selection of resistant bacteria, depending on the residual activity of the preservatives on skin [5].

Given the impact of acne on the lives of those who suffer from it, there is a rising number of recent reviews exploring acne vulgaris [6–10]. However, to date, there has been no comprehensive investigation into the use of topical products for acne-prone skin based on probiotics as an alternative or adjuvant therapy. Therefore, a narrative review of the literature concerning acne pathophysiology, risk factors, symptoms, and conventional treatment recommendations was carried out. Furthermore, a compilation of current scientific evidence available up to date on topical probiotic formulations, as well as their impact and benefits on acne management, is provided. In addition, the advantages and limitations of these innovative skin products were also highlighted. Searches with Google Scholar and Pubmed from 1962 to 2023 were performed.

2. Acne Vulgaris

Acne vulgaris is a chronic inflammatory disease of the human pilosebaceous follicle. It has been reported that it affects 85% of Westernized adolescents, continuing into their twenties in 64% and into their thirties in 43% of individuals; as such, it is considered the most common skin disease [11,12]. The pathophysiology of acne is well-characterized, but despite its near universality in young individuals, the epidemiology of this disease remains uncertain; common risk factors have been difficult to confirm, and misconceptions about the causes of acne are still rather frequent [11].

2.1. Pathophysiology

Acne lesions, which can be divided into noninflammatory lesions (open or closed comedones) and inflammatory lesions (papules and pustules) are formed in two main stages. First, the keratinocytes lining the pilosebaceous unit undergo abnormal desquamation, resulting in the formation of a microcomedone. The follicle, which normally serves as an exit route for sebum secretions, becomes plugged due to the buildup of sebum and desquamated cells, and it eventually becomes swollen enough to become a visible comedone—a whitehead or a blackhead. If the microcomedone is colonized by bacteria, specifically *C. acnes*, an inflammatory process begins. *C. acnes* promotes pustule formation by releasing chemotactic factors that attract neutrophils, among other pro-inflammatory mediators [13].

As consequence, the four main processes via which acne lesions appear have been identified: altered keratinization forming comedones; increased sebum production controlled by androgens; *C. acnes* proliferation inside the pilosebaceous units; and the release of inflammatory mediators in the skin [14]. These events are not entirely sequential, as will be discussed below.

2.1.1. Follicular Hyperkeratosis

A follicle affected by hyperkeratosis undergoes a rapid proliferation of keratinocytes, which are normally loosely layered but grow densely packed in this situation, are now unable to desquamate normally and are carried to the surface of the skin by sebum flow. The keratinocyte plugs thus formed originate the microcomedones. The causes of this abnormal occurrence have been theorized to be the lipid composition of sebum, high androgen concentrations, endogenous inflammatory mediators, such as interleukin-1 (IL-1), and other comedogenic sebum components, such as the products of UV degradation of squalene and fatty acid peroxides [15].

2.1.2. Seborrhea

Sebum creates an anaerobic, lipid-rich environment, that is ideal for *C. acnes* to thrive within the pilosebaceous follicle. Thus, exacerbated sebum production is necessary for the development of acne, but by itself it is not enough to cause it [16].

There are several types of receptors that regulate sebum production and are controlled by diverse factors. Androgen receptors can be found in the basal cell layer and differentiating sebocytes of the sebaceous gland, hinting at the role of androgens in controlling their proliferation and lipogenesis [17]. This growth-stimulating effect can promote hyperkeratosis. In the skin, androgens produced in the gonads and adrenal glands are converted into testosterone and dihydrotestosterone by 5α-reductase; this enzyme, as well as the androgen receptors themselves, is more abundant in acne-prone skin, which is not necessarily related to higher levels of androgens themselves. It is more commonly due to the sensitivity of the sebocytes to these hormones. Nevertheless, increased androgen production during puberty has been linked to the onset of acne, and this skin affliction is notably absent in individuals with non-functional androgen receptors [15].

Another class of hormones that affect sebum levels are estrogens, which are known to suppress sebum production. Estrogens seem to have this effect not by acting directly upon the sebaceous glands, but rather by inhibiting gonadotropin secretion or increasing the binding of testosterone by globulins, thus decreasing androgen action on sebocytes [17,18].

Peroxisome proliferator-activated receptors, or PPARs, regulate sebocytes at the transcriptional level of lipid metabolic genes [17,19]. Dietary molecules, namely free fatty acids and cholesterol, activate PPARs [20]. Additionally, some neuropeptides such as melanocortins and corticotropin-releasing hormone (CRH), also affect the sebaceous gland function; CRH promotes sebocytes differentiation, lipid synthesis, and the conversion of dehydroepiandrosterone to testosterone, acting more directly than melanocortins do, which appear to stimulate androgen production. The sebotrophic action of these neurogenic factors reinforces the link between emotional stress and the exacerbation of acne breakouts which has often been observed [21].

Retinoids, on the other hand, have the opposite effect of inhibiting sebocyte differentiation, thus shrinking sebaceous glands as well as decreasing sebum secretion and, therefore, being helpful in the management of acne, as are estrogens, albeit in far higher doses than the physiological ones [18].

2.1.3. Colonization by *Cutibacterium acnes*

C. acnes are ubiquitous, commensal, Gram-positive bacteria that predominate in sebaceous skin areas such as the head, chest, and back, and can be found in the pilosebaceous follicles [22]. Based on recent genomic evidence, the *Propionibacterium* designation has been abandoned in favor of the newly created *Cutibacterium genus* [23].

C. acnes can be isolated from healthy skin and acne lesions alike, and acne is not always caused by a greater presence of these bacteria within the sebaceous glands. Rather, recent research suggests that it is due to the proliferation of specific phylotypes of *C. acnes* over others; in acne lesions, phylotypes IB and II are decreased whereas IA phylotypes, particularly IA1, are prevalent. These latter phylotypes appear to thrive in inflammatory microenvironments [24,25].

The ability of *C. acnes* to form biofilms (i.e., organized aggregates of bacteria within a secreted external matrix of polysaccharides) enables it to adhere to pilosebaceous follicle walls more effectively. *C. acnes* biofilms appear significantly more often in acne patients than in control groups. By increasing the stickiness of sebum, the extracellular polysaccharide of the biofilm can impede the normal desquamation of keratinocytes and promote the formation of the plug in comedones [24].

It has been theorized that the role of *C. acnes* in acne pathogenesis is due to the release of pro-inflammatory bacterial metabolites. Bacterial lipases can degrade the triglycerides present in sebum to free fatty acids, which have inflammatory and irritant properties at higher concentrations. Furthermore, other chemotactic factors, hyaluronidases and proteases stimulate the infiltration of neutrophils and macrophages into the follicle. This process leads to the formation of pustules and may cause the rupture of the follicular wall. The release of cytokines and chemokines promotes the synthesis of matrix metalloproteinases, which promote tissue breakdown and scarification. Once the bacteria are phagocytosed, the inflammatory reaction is reinforced via the release of hydrolytic substances [13,15].

Additionally, *C. acnes* has been linked to follicular hyperkeratosis due to its modulation of the expression of integrins and filaggrin. Integrins are heterodimeric transmembrane receptors that regulate keratinocyte differentiation and proliferation. These proteins gather keratin into macrofibrils and are associated with keratinization disorders when present in a disbalanced state. Filaggrins are present in higher levels within the pilosebaceous units of seborrheic and acne-prone skin, as keratinization occurs prematurely and forms microcomedones. Thus, *C. acnes* can be implicated in the pathogenesis of acne as early in the process as during the formation of the microcomedone itself [26].

2.1.4. Inflammation

As previously described, the inflammatory reactions that happen within an acne lesion are multifactorial in origin. Although they may stem from hormonal fluctuations or the release of bacterial metabolites, there is evidence that inflammatory processes are heightened in the clinically normal pilosebaceous follicles of acne patients, even before the onset of follicular keratosis, suggesting that inflammation plays a role in acne lesion formation from the very earliest moments. This may happen due to a naturally higher tendency towards inflammation in acne-prone skin [27].

Certain inflammatory mediators, such as leukotriene B4, which binds to PPARs in sebocytes, can also intervene in sebum production upregulation [13]. As such, all events that lead to acne development are interconnected and tend to reinforce one another when the necessary conditions and cutaneous characteristics are gathered in a synergistic dynamic.

2.2. Risk Factors

The physiological mechanisms underlying acne may be well-established, but the factors that may trigger it or lead to a higher propensity towards it are still hotly debated, and they are surrounded by many myths and misconceptions. Despite this, some correlations between certain characteristics or behaviors and an increased predisposition towards acne have been observed.

2.2.1. Genetics, Age, and Gender

Twin studies indicate that this skin condition has a genetic component. Although not much is yet known about its specific mechanisms of heredity, it appears likely that multiple genes, including ones that regulate adrenal androgen production, are involved [8].

Age and gender are also crucially important. Acne is generally a disease of adolescence (with some studies reporting a near-100% prevalence of comedones in adolescents of either gender), although girls tend to develop acne at a younger age and are also more prone to postpubescent acne; conversely, the severity of acne in late puberty is greater in boys [28].

2.2.2. Hygiene and Cosmetics

There is a popular belief that poor hygiene is at the root of acne, but current studies are still inconclusive. Although there is some weak evidence suggesting the benefits of medicated washes, no significant link between frequency of washing, sweat and acne has been established [11]. The previously discussed impact of highly hygienic Westernized lifestyles on cutaneous microbial diversity may still play a role in acne development, and it has been proposed that the traumatizing effect of strong facial washes employed by acne patients, as part of an oftentimes costly and burdensome regime, contributes to irritation which might worsen acne [29]. One unblinded, randomized study showed that using an acidic syndet cleanser (pH in solution: 5.5–5.6) on a regular basis, as opposed to a standard bar soap, reduced the number of inflammatory acne lesions after 4 weeks [30]. Current research has established that an acidic pH improves the barrier function of the skin, and that an impaired barrier function promotes inflammation and comedogenesis; thus, an acidic cutaneous pH would be beneficial for the management of acne, which may justify the observed results [31].

2.2.3. Chemical Triggers

Certain drugs can also be responsible for triggering acneiform eruptions, more commonly androgens, anti-epileptics, corticosteroids, lithium, or oral contraceptives containing progestins, which feature androgen-like activity, as well as certain anti-cancer drugs such as epidermal growth factor receptor antagonists. These eruptions form papules and pustules, usually without the formation of comedones [32].

2.2.4. Environmental Triggers

There is a common belief that sunlight exposure can help mitigate the severity of acne, but current evidence is insufficient to indicate that natural sunlight might be helpful, although light therapy with blue, blue-red or infrared light appears to have some short-term benefits [29,33,34].

Other climatic factors, such as humidity and hot weather, reportedly contribute to the formation of "tropical acne" breakouts [14].

2.2.5. Westernized Lifestyle

According to what has been discussed in terms of hygiene habits and diet, it appears that a Westernized lifestyle is among the factors with a higher correlation to the development of acne. The reduction in microbiome diversity associated with modern living conditions as opposed to those experienced in more agrarian, traditional societies can facilitate dysbiosis and the proliferation of *C. acnes* [2].

Acne has been associated with disrupted sleeping patterns [35], whether due to the physical discomfort caused by lesions [36] or to the psychological link between acne and anxiety, depression and self-esteem issues [37]. Another feature of a modern lifestyle that has been linked to acne is the heightened level of stress; acne itself is often a source of emotional distress, but fewer studies have focused on stress as a cause of acne rather than simply an outcome [11].

2.3. Symptoms and Treatment

Acne can be manifested on varying levels, ranging from mild to very severe, but even moderate cases can cause psychological and emotional suffering [13]. Beyond the physical discomfort caused by the lesions, acne patients of all ages and genders report feeling self-conscious and anxious due to the condition of their skin. Furthermore, regardless of the severity of the case, it can exacerbate depression, anxiety, anger and suicidal ideation [37]. Given the significant impact on the quality of life of sufferers, it is critical to provide an effective treatment course that can manage the development of new lesions while healing the pre-existing ones.

The clinical appearance of acne is polymorphic, with variable degrees of severity and both acute and chronic forms, as well as many subtypes. Acne vulgaris can be classified as inflammatory versus noninflammatory, comedonal, comedopapular, papular, papulopustular and cystic or nodular, though the definitions of what constitutes a papule versus a nodule, for instance, are not concordant [38]. Acne vulgaris proper usually refers to papulopustular acne, but more severe instances can fall under the designation of acne conglobata (nodular acne), infantile and juvenile acne, and acne tarda in patients older than the usual age range, that is, above 25 years of age [39]. Although acne is not often misdiagnosed, some conditions may have acneiform presentation and should be excluded, as is the case of grade 2 rosacea, *Staphylococcus aureus* folliculitis, milia, boils, acne agminata, syringomas, demodex folliculitis, pityrosporum folliculitis and perioral dermatitis [24].

Many scales for grading acne severity exist, but a review on their quality by Agnew et al. [40] indicated that most were poorly validated and their outcomes were inconsistent; lacking a gold-standard assessment scale, researchers and clinicians may resort to simplified methods, such as the classification of acne as mild, moderate, or severe in treatment guidelines. These methods present weak to moderate reliability [40].

Table 1 summarizes the current guidelines for the treatment of acne. Despite their effectiveness, many of these treatments have undesirable side effects. The retinoids used for more severe cases frequently cause erythema, stinging or burning sensations, xerosis and desquamation. Systemic retinoid therapy also leads to a high risk of teratogenicity. Additionally, it has been reported that isotretinoin (unquestionably the most effective oral treatment for severe acne), among other potentially dangerous side effects, can induce depression and suicidal ideation when used in the treatment of acne [41].

The increasing resistance of *C. acnes* has given rise to worldwide efforts to replace antibiotic therapies with other options, such as benzoyl peroxide, topical retinoids, azelaic acid or combinations thereof [14,39].

Regardless of severity, the development of acne cases can be improved if recommendations regarding maintenance, skin care and psychological support are followed. Maintenance therapy may rely on continued use of azelaic acid or topical retinoids. The remainders of lesions, such as post-inflammatory hyperpigmentation (PIH) and scarring, can also be addressed by therapeutics, in the former instance by the use of topical retinoids (which may be used in conjunction with benzoyl peroxide) and topical azelaic acid; the second line of treatment of PIH involves hydroquinone, sometimes in association with retinoic acid and a corticosteroid, and adjunctive therapies such as chemical peels may also be resorted to [24]. For scarring, other than the use of topical retinoids, there are many options, such as cryosurgery, dermabrasion, microneedling, punch excision, punch elevation and grafting of deep scars, laser therapy, and fillers [24,43].

Table 1. Summary of treatment recommendations according to the European S3 guideline, adapted from Nast et al. [42].

	Comedonal Acne	**Mild/Moderate Papulopustular Acne**	**Severe Papulopustular/Moderate Nodular Acne**	**Severe Nodular/Conglobate Acne** *4
Strong recommendation *1	No evidence	Adapalene + benzoyl peroxide (BPO) (f.c.) or Adapalene + clyndamycin (f.c.)	Isotretinoin *1	Isotretinoin *1
Moderate recommendation	Topical retinoids *3	Azelaic acid or BPO or topical retinoids *3 or systemic antibiotic *2 + adapalene *10	Systemic antibiotic *5 + adapalene *10 or systemic antibiotic *5 + azelaic acid *8 or systemic antibiotic + adapalene + BPO (f.c.)	Systemic antibiotic *5 + azelaic acid
Weak recommendation	Azelaic acid or BPO	Blue light or oral zinc or topical erythromycin + isotretinoin (f.c.) or topical erythromycin + tretinoin (f.c.) or systemic antibiotic *2 *5 + BPO *7 or systemic antibiotic *2 *5 + azelaic acid *10 or systemic antibiotic *2 *5 + adapalene + BPO (f.c.) *9	Systemic antibiotic *5 + BPO *7	Systemic antibiotic *5 + BPO *7 or systemic antibiotic *5 + adapalene *9 *10 or systemic antibiotic *5 + adapalene + BPO (f.c.) *9
Alternatives for female patients	—	—	Hormonal antiandrogens + topical treatment or hormonal antiandrogens + systemic antibiotics *6	Hormonal antiandrogens + systemic antibiotics *6

f.c.: Fixed combination; *1 use of a lower recommendation strength treatment may be necessary due to limitations (financial, legal, drug availability and licensing, etc.); *2 systemic treatment initiation can be recommended in case of more widespread/severe disease; *3 adapalene is preferable, rather than tretinoin/isotretinoin; *4 systemic treatment with corticosteroids may be considered; *5 doxycycline and lymecycline; *6 weak recommendation; *7 indirect evidence from a study also including chlorhexidine based on expert recommendation; *8 indirect evidence from nodular and conglobate acne and expert opinion; *9 indirect evidence from severe papulopustular acne; *10 only studies with systemic antibiotics + adapalene, isotretinoin and tretinoin (combination therapy) were considered based on expert recommendation.

3. Active Ingredients for Acne-Prone Skin

Formulations targeted towards acne frequently fall in a gray area between medications and cosmetic products; the term "cosmeceuticals" was coined in 1984 to describe such borderline products that "do more than coloring the skin and less than a drug". While the definitions of both "drug" and "cosmetic" are cemented in legislation and regulated by the authorities, there is no official definition for cosmeceuticals yet and, as such, no legislation specific to this category [44].

Given this, it is important that ingredients promoted as beneficial for acne by brands actually possess scientific research that can support the claims made in marketing briefs, in accordance with Commission Regulation (EU) no. 655/2013, which dictates that all claims on cosmetic products should conform to common criteria: legal compliance; truthfulness; evidential support; honesty; fairness; and informed decision-making [45]. Below, a selection of ingredients commonly used as anti-acne actives in cosmetic and cosmeceutical products

are indicated and the supporting evidence for their beneficial action in the treatment of acne is summarized in Table 2.

Table 2. Examples of active ingredients used in anti-acne formulations.

Active Ingredients	Actions	References
Glycolic acid [1]	Keratolytic	[46] **, [47] ****
Azelaic acid [1]	Antimicrobial; keratolytic; sebostatic	[48] *
Mandelic acid [1]	Antimicrobial; keratolytic	[49] **
Gluconolactone [1]	Epidermal turnover enhancer; hydrating; antioxidant	[50] **
Salicylic acid [1]	Keratolytic; sebostatic; anti-inflammatory	[51] ****
Nicotinamide [1,2]	Anti-inflammatory; sebostatic	[52] ****, [53] **
Retinol [1,2]	Antiproliferative	[54] ****
Zinc [1,2]	Anti-inflammatory; sebostatic	[55] ****, [56] ****
Sulfur [1]	Keratolytic	[57] **
Tea tree oil [1,2] (*Melaleuca alternifolia*)	Broad-spectrum antimicrobial; anti-inflammatory	[58] **, [59] ****
Tea extract [1,2] (*Camellia sinensis*)	Antioxidant; antimicrobial; antiandrogen; sebostatic	[60] *
Witch hazel extract [1] (*Hamamelis virginiana*)	Anti-inflammatory; antimicrobial	[61] ***
Cannabinoids [1]	Sebostatic; anti-inflammatory; antiproliferative	[62] **, [63] ***

[1] Topical, [2] systemic; * systematic review without or with meta-analysis; ** clinical trial; *** in vitro study; **** review/recommendations.

Some of the commonly used ingredients for acne are hydroxy acids, which can be divided into alpha- and beta-hydroxy acids (AHAs and BHAs, respectively). AHAs include glycolic acid, citric acid, malic acid, mandelic acid, tartaric acid, and lactic acid. They are considered chemical exfoliants due to their keratolytic activity [47]. More recently, a new generation of AHAs has emerged: polyhydroxy acids (PHAs), such as gluconolactone and lactobionic acid. Their effects are comparable to those of AHAs, but with less skin irritation [64] and without increasing sun sensitivity [65], suggesting that they may similarly possess benefits for acne-prone skin.

Although salicylic acid has been classified as a BHA, Kornhauser et al. [64] believe this classification is incorrect. Rather, it is a phenolic aromatic acid which, being liposoluble (unlike AHAs), is miscible with epidermal lipids and sebaceous excretions, giving it an advantage in the lipidic moiety of the pilosebaceous follicle [51].

Other classes of anti-acne actives with well-established benefits are vitamins and their analogs—these include retinoids (analogs of vitamin A) and nicotinamide (a water-soluble derivative of vitamin B3)—and inorganic elements, such as sulfur and zinc salts [56]. The unpleasant odor of sulfur, which is frequently used in combination with other topical agents (for example, salicylic acid), can limit its popularity as an acne care product. Zinc, on the other hand, has been incorporated into skin care products in combination with ingredients such as nicotinamide, but its benefits regarding acne have been studied primarily through oral administration [41].

There is a great number of plant-derived ingredients that have been used in cosmetic products claiming to have anti-acne properties. Table 2 also includes the reported properties of a few of those ingredients which have gained the most popularity. These active ingredients are attractive to consumers due to their natural origin and their history of use in traditional medicine. Many other plant extracts have been proposed as helpful for acne. However, the evidence supporting their use is limited, being frequently based solely on

in vitro results regarding antimicrobial or anti-inflammatory properties of the individual ingredient, and lacking clinical-strength, placebo-controlled trials on human skin.

A subset of plant-derived ingredients that have generated some controversies are those derived from Cannabis, which has been shown to have favorable effects on sebocytes that could imply a positive impact on acne. A cream containing 3% Cannabis seed extract has been reported to reduce facial sebum and erythema [62]. It should, however, be noted that not all phytocannabinoids are necessarily advantageous for acne; while cannabidiol, cannabichromene, cannabidivarin and tetrahydrocannabivarin showed promising anti-acne lipostatic activity, cannabigerol and cannabigerovarin were reported to possess the opposite (pro-sebaceous) effect, which may be useful for dry skin, xerosis and even skin aging, but is counterproductive in oily and acne-prone skin [63].

In most cases, acne-related skin issues do not end with the disappearance of inflammatory lesions and comedones; PIH spots give a blemished look to the skin, even after the resolution of acne breakouts [66].

Some of the aforementioned ingredients, for instance AHAs and retinoids, can be photosensitizing [67,68], leaving the skin more vulnerable to UV damage. In individuals who are prone to PIH, sunscreen is also the base for treating dark spots; without it, only minimal benefits will be attained from the use of skin-lightening cosmetics [66]. This strengthens the importance of sunscreen as a fundamental component of a skincare regimen for the management of acne-prone skin. The use of sunscreens can prevent photoaging and photocarcinogenesis, as well as reduce inflammation and the incidence of post-inflammatory hyperpigmentation/erythema. Based on acne pathogenesis, oily sunscreens should be avoided as they can aggravate acne symptomatology. Alternatively, emollient, antioxidant, non-comedogenic, water-based and broad-spectrum sunscreens (SPF $\geq$ 30) should be recommended [69].

As an alternative to the aforementioned active ingredients, products containing probiotics have also been used to prevent the development of acne vulgaris.

4. Topical Probiotic Formulations for Acne-Prone Skin

Owing to recent discoveries regarding the cutaneous microbiome, cosmetic and pharmaceutical brands have begun to develop and advertise products that seek to enrich and protect the diversity of healthy skin bacteria, making use of probiotics (i.e., live microorganisms that, when administered in adequate amounts, confer a health benefit on the host) [70]. Microorganisms must meet certain criteria in order to be designated as probiotics. The criteria include all information about the microorganism, such as its genus and species, having a scientifically valid nomenclature, and having validated health benefits with at least one study carried out in humans [71].

Probiotics have been the subject of study in what is called the gut–brain–skin axis theory. These studies have shown that probiotics are effective in the treatment of some dermatological disorders, such as acne and atopic dermatitis [72]. Effectively, the intestinal microbiota is responsible for the body's adequate immunity and defense against pathogenic microorganisms. Thus, variations considered harmful at the level of the intestinal microbiota could trigger inflammatory states and autoimmune diseases in various organs distant from the intestine, such as the skin [73]. Table 3 presents some of the main advantages and limitations associated with the topical administration of probiotics.

Topical probiotic treatments are considered safe and without adverse effects, when compared to topical and systemic standard therapies [74]. However, there are few human clinical trials based on probiotics in topical pharmaceutical formulas for the treatment of acne. Thus, there are insufficient clinical data to demonstrate effectiveness and a deep understanding of side effects of these products. Consequently, further clinical investigation is required, as well as better regulation of topical probiotic products, including those used in the treatment and prevention of acne. Patients seeking information about the use of topical probiotics should be informed not only about their clinical benefits, but also relevantly to

the lack of knowledge regarding its potential adverse effects. In fact, despite the promising findings, the side effects of topical probiotics are not well-known [75].

Table 3. Advantages and limitations of topical probiotic administration.

Advantages	Non-invasive Avoids gastrointestinal degradation Allows a controlled release High patient compliance Skin immunity regulation Skin pH reduction
Limitations	Low permeability of probiotics across stratum corneum Low probiotic stability in unfavorable skin environments Lack of scientifically validated clinical data about the efficacy and safety of topically applied probiotics

Zmora et al. [76] concluded that probiotics could potentially cause damage if not implemented correctly, mainly in the case of immunocompromised patients (e.g., patients with AIDS—acquired immunodeficiency syndrome). Additionally, the administration of probiotic species that are not native to a particular ecosystem can potentially cause adverse effects. Thus, extensive research is needed to safely administer different strains, which may have different effects depending on the individual. In addition, the quantity of probiotics being introduced was not regulated [77]. However, several in vitro studies have demonstrated interesting properties of some probiotic strains [78].

The most well-known probiotics are Gram-positive anaerobic bacteria, such as *Lactobacillus* and *Bifidobacterium*. Their use in oral preparations is well-regulated; however, there is no legal regulation for topical probiotics [75,79]. Lopes et al. [80] observed that many strains of *Lactobacillus* and *Bifidobacterium* had a good ability to adhere to keratin and inhibit pathogenic bacteria biofilm formation; however, these bacteria had a limited ability to adhere to *C. acnes*, which could be relevant to their potential use as topical probiotics [78].

In cosmetic products, probiotics were initially used as ingredients in creams, intimate hygiene products, shampoos, and toothpastes. The most common probiotic strains included in cosmetics are *Bacillus subtilis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Lactobacillus plantarum*. These probiotics stimulate the production of lipids, having a moisturizing effect on the skin. Other benefits include the reduction in toxic metabolites, the increase in antibody production, the restoration of the immune system's homeostasis, and the regulation of cytokine synthesis [81–83]. It is also worth noting that topically applied probiotics can also serve as a protective shield by functioning as a competitive inhibitor of binding sites, thereby preventing colonization by other potential pathogens [75].

Lactobacillus species are used in cosmetic products with anti-wrinkle, anti-aging, and moisturizing properties due to the production of lactic acid, which is one of the main components of skin's natural moisturizing factor. Furthermore, the use of *Streptococcus salivarium* and *Streptococcus thermophilus* S244 in cosmetics also leads to the production of skin moisturizing enzymes, reducing skin dryness and aging [84]. The use of probiotics also has a beneficial effect on the regulation of skin pH [85].

Bifidobacterium species may also enhance the production of hyaluronic acid, a glycosaminoglycan that contribute to skin elasticity. Studies have shown that the ability of bifidobacteria-fermented soymilk extract to stimulate hyaluronic acid-improved skin appearance [86,87].

In addition to the use of probiotics in cosmetic products, their topical application in skin diseases (use of *Lactobacillus bulgaricus*), including acne, has been reported since 1912 [78].

Park et al. [88] verified that probiotics modify several factors involved in the pathophysiology of acne development. Thus, topical products containing probiotics or their lysates have shown potential in acne prevention. Individuals with acne treated with topical

probiotics experienced a reduction in lesions, erythema, and pathogenic bacteria load with an improvement in the skin barrier. Because acne is associated with an overgrowth of pathogenic bacteria, and treatment often consists of antibiotics, topical probiotics can restore the skin's microflora, shrinking acne lesions without causing systemic side effects [89].

Di Marzio et al. [90] showed that when applied to the skin for seven days, *S. thermophilus* can increase ceramide production and that some of the ceramide sphingolipids, mainly phytosphingosine, would provide both anti-inflammatory activity and antimicrobial effect against *C. acnes*.

Staphylococcus epidermis is also an example of a bacterium that has shown promise in the treatment of acne. A study showed that this bacterium is present in the microbiota of the skin and mediates the fermentation of glycerol, which is naturally produced by the skin, inhibiting the growth of *C. acnes* [91]. It was shown that succinic acid, a product of glycerol fermentation, was responsible for the inhibitory effects on *C. acnes* [91] and that increasing it with probiotics can result in better outcomes for patients with acne. In addition to *S. epidermis*, *S. salivarius* is also a bacterium obtained through the oropharyngeal system that inhibits the proliferation of *C. acnes*, in this case, by producing a bacteriocin-like inhibitory substance (BLIS) [92,93]. The *S. salivarius* K12 strain was able to inhibit the production of pro-inflammatory cytokines, such as interleukin-8 (IL-8) in epithelial cells and keratinocytes, most likely by inhibiting the nuclear factor kappa B (NK-kappa B) pathway [94].

Lactobacillus vulgaris produces lactic acid, which increases the production of substances with antimicrobial action against *C. acnes* and reduces significantly the amount of papules and pustules. *Bifidobacterium longum* and *Lactobacillus paracasei* are other examples of probiotics used to attenuate inflammation mediated by substance P, i.e., a primary stress-induced mediator that leads to inflammatory states and sebum production [95]. It is well-known that acne can be exacerbated due to stress, as result of the release of substance P, which stimulates sebocytes to produce higher levels of pro-inflammatory cytokines such as IL-1, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). Gueniche et al. [95] demonstrated that *B. longum* extract applied to the skin improved sensitive skin in various parameters associated with inflammation, such as decreased vasodilation, edema, mast cell degranulation, and TNF-alpha release. These findings suggested that *B. longum* extract application contributes to reinforcing skin homeostasis and improves skin resistance to external environmental effects.

Kang and colleagues [82] performed a double-blind, randomized, placebo-controlled clinical trial in 70 patients with acne. These authors concluded that the activity against *C. acnes* produced by *Enterococcus faecalis* SL-5, a species of *Lactobacillus genus* extracted from human feces, has a potential role in acne treatment and could serve as an alternative to topical antibiotics. A lotion containing this probiotic significantly decreased the inflammatory acne lesions such as pustules when compared to a placebo lotion [82,96]. Natural antibiotics (bacteriocins) are preferable to synthetic antibiotics due to their lack of multidrug resistance and the presence of fewer adverse effects [97]. In other study, Tagliolatto et al. [98] used *Lactobacillus plantarum* GMNL06, a tyndallized bacteria produced from heat-treated probiotics. This heat treatment allows the release of bacteriocins from cell membranes. According to the authors, using *Lactobacillus plantarum* GMNL06 cream topically to treat mild to moderate acne was shown to be both safe and effective in the treatment of mild and moderate acne, even as monotherapy. It did not cause skin irritations or discomfort; it was not photosensitizing, and 90% of the volunteers who were tested showed positive findings.

To compare the efficacy of a lotion based on *L. paracasei* MSMC 39-1 versus a 2.5% benzoyl peroxide lotion in 104 patients with mild to moderate acne, Sathikulpakdee et al. [99] conducted a randomized clinical trial. In both groups, acne lesions and erythema decreased; however, a greater percentage of patients treated with benzoyl peroxide experienced treatment-related side effects compared to patients treated with probiotic-based lotion (26.92% vs. 7.69%). Therefore, these authors concluded that the lotion based on *L. paracasei* MSMC 39-1 could be a safer alternative compared to the 2.5% benzoyl peroxide

lotion [99]. In other clinical trial, involving 10 volunteers, Muizzuddin et al. [100] used *L. plantarum*-based aqueous lotion prepared in 1% and 5% concentrations of probiotics. While the formulation containing 5% of probiotics was effective at reducing acne lesion size, skin erythema and repairing the skin barrier, the lotion with a concentration of 1% did not present significant effects. This study suggested a dose-dependent effect of *L. plantarum* in mild acne treatment.

A study performed by Jung et al. [101] supported the conclusion that probiotics may also provide a synergistic anti-inflammatory effect with systemic antibiotics, such as minocycline, while also reducing potential adverse events associated with chronic antibiotic use.

It is described that nitrates participate in metabolic pathways, lead to nitrolipid formation, and regulate the inflammatory response. *Nitrosomonas eutropha* is a bacterium that converts ammonia to nitrite and nitric oxide. *N. eutropha* was an important bacterium usually found on human skin. However, due to the use of antibacterial soaps, and other hygienic practices, *N. eutropha* is no longer present on the skin in sufficient amounts to have a beneficial effect [102]. Thus, several researchers have hypothesized that the reintroduction of this bacterial strain to human skin may provide health benefits [103]. A randomized, double-blind, placebo-controlled, phase IIb/III study is currently underway to evaluate the safety, tolerability, and efficacy of B244 (topical *N. eutropha* D23) when used by subjects with mild to moderate acne over 12 weeks [103].

Several in vitro studies have shown the potential beneficial effects of probiotics in acne prevention; however, clinical trials with topical formulations containing probiotics are scarce, although they have shown positive results. Topical probiotics seem to produce their effects through the inhibition of growth of *C. acnes* in the pilosebaceous unit and decrease inflammatory responses.

Given the potential adverse effects caused by some standard acne treatments, probiotics have been investigated as an alternative or adjuvant therapy by employing less aggressive therapies and positive effects on the recovery of acne symptoms [78]. In fact, probiotics could complement the classical acne treatment by reducing the number of pathogens, lowering toxic metabolites, increasing antibody production, and regulating cytokine synthesis [101].

Prebiotics are specific fermented components that enhance changes in the composition and activity of the gut microflora in favor of the host [104]. Probiotics and prebiotics in association (i.e., synbiotics) have the capacity to maintain and restore the skin microbiota. In cosmetic formulations, prebiotics can selectively increase the activity and growth of beneficial skin probiotics. To study the symbiotic ability of probiotic bacteria (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus gasseri*, and *Lactococcus lactis*) in association with the prebiotic konjac glucomannan hydrolysates to inhibit *C. acnes* growth, an in vitro study was carried out by Al-Ghazzewi et al. [105]. These authors found that different probiotic bacteria strains were able to inhibit the growth of *C. acnes*, and the presence of the konjac glucomannan hydrolysates significantly enhanced the inhibition [105,106]. Bateni et al. [107] also proved that a formulation containing konjac glucomannan hydrolysate (5%, *w*/*v*) significantly improved the health of the skin of young women with acne.

It is also important to highlight that, especially in cosmetics, the application of live bacteria would require huge efforts to implement modified procedures for handling during the production, storage, and delivery of the products [108]. Given that formulation processes may inactivate probiotics and alter their functionality, it is critical to select suitable formulation techniques and manufacturing processes. Dehydration processes, such as spray-drying, freeze-drying, and fluidized bed-drying, are common practice used during the production of probiotics [109]. Unlike oral formulations, in which lyophilized probiotics can be packaged into capsules or tablets, topical probiotic formulations often require reconstitution to enable spreading onto the skin and/or incorporation into a pharmaceutical base (e.g., cream, emulsion, gel, and suspension) prior to use [110].

Another important issue is that these topical care products should be sterile and not contain antimicrobial preservatives that may affect probiotic strain viability and further alter the microbiota of the host [85].

5. Conclusions

The Westernized lifestyle, characterized by excessive exposure to soaps, cosmetics, pollution, and medicines, has caused significant skin microbiome alterations. Consequently, there has been an increase in research interest in finding methods to restore the skin microbiome. These methods have included the use of topical probiotics to treat skin microbiome problems such as acne vulgaris. Acne is a multifactorial disease, which can be improved through the daily use of adequate skin care products. The usage of novel cosmetic active ingredients for acne is often based solely on claims supported by in vitro studies. The comparative efficacy of an individual ingredient versus a placebo needs to be established by clinical-strength trials when dealing with borderline products (cosmeceuticals) such as those targeted to improve acne symptoms. Formulating products intended for acne prone skin requires particular care to avoid irritants, comedogenic ingredients, and ingredients that destabilize the microbiome, compromise the skin barrier function, or alter its pH.

The cosmetic industry is currently experiencing an extremely high rate of innovation. Given that acne is a very widespread disease that can be managed with the help of cosmetics, the high demand for products aimed at acne-prone skin indicates that it is an ideal target for expansion, particularly when taking in account recent innovations such as microbiome cosmetics, which could help achieve even better outcomes. Accordingly, a probiotic approach is obviously preferable to products which unselectively decrease bacterial growth using antibiotics or antimicrobial agents. Thus, probiotics can be considered an alternative approach for acne prevention because they directly prevent growth and colonization by pathogenic bacteria and control inflammation, constituting a less aggressive therapy, when compared to antibiotics, with less side effects. However, more clinical trials evaluating efficacy of topical formulations based on probiotics must be performed to broaden our understanding of their potential therapeutic application in acne treatment and prevention.

The delivery of probiotics through the skin is appealing since it is noninvasive and avoids gastrointestinal degradation. However, as living microorganisms are heat-sensitive and their growth is influenced by the content of water, there are some challenges associated with the formulation of these innovative skin products given that formulation and manufacturing processes may inactivate probiotics and alter their functionality.

Future topical probiotic solutions should aim to increase the biodiversity of the skin microbiome. Thus, emphasis is placed on the research and production of genetically modified microorganisms, as well as their incorporation into suitable dosage forms, which will allow the production of products tailored to the individual needs of each patient.

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