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REVIEW

Fermented Plant-Derived Phytoconstituents in Biocosmetics: Pharmacological Enhancements and Applications

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Abstract: The application of plant-derived extracts in dermatological and cosmeceutical formulations is often limited by poor bioavailability, low skin permeability, and the instability of bioactive compounds. Fermentation has emerged as a promising biotechnological approach to enhance phytochemical composition and biological activity through microbial biotransformation. This review aims to critically evaluate the effects of fermentation on plant-derived phytoconstituents and their relevance in cosmeceutical dermatology. A structured literature search was conducted using Scopus and PubMed databases for studies published between 2015 and 2025. A total of 32 records were initially identified. After screening titles and abstracts, 19 articles were assessed for full-text eligibility. Following full-text evaluation, 5 studies met the inclusion criteria and were included in the qualitative synthesis. The findings indicate that fermentation modifies phytochemical profiles, by converting glycosides into more bioactive aglycones resulting in improved skin permeability and biological activity. Fermented extracts demonstrate enhanced antioxidant capacity, increased tyrosinase inhibition, and improved photoprotective effects compared to non-fermented counterparts. Mechanistically, these effects were associated with modulation of oxidative stress pathways and inflammatory mediators, including upregulation of SOD and CAT and suppression of IL-6 and TNF-α. However, the available evidence is predominantly limited to in vitro studies, with variability in fermentation conditions and microbial systems. This review provides an integrated and critical perspective linking biochemical transformation, skin permeability, and dermatological relevance. Future research should prioritize standardization and clinical validation to support translational application.

Keywords: fermentation, phytochemicals, cosmeceuticals, skin permeability, antioxidant activity

Introduction

Skin aging is a complex biological process influenced by both intrinsic factors and extrinsic environmental stressors, with ultraviolet (UV) radiation recognized as the primary contributor to photoaging.[1] Unlike intrinsic aging, photoaging is characterized by structural and functional alterations in the skin, including wrinkle formation, loss of elasticity, and hyperpigmentation.[2] At the molecular level, UV exposure induces the generation of reactive oxygen species (ROS), leading to oxidative stress, extracellular matrix degradation, and disruption of cellular homeostasis.[3,4] These processes not only accelerate skin aging but also play a central role in the development of pigmentary disorders.[5]

Hyperpigmentation is one of the most prominent clinical manifestations of photoaging and is primarily associated with increased melanogenesis.[6] The enzyme tyrosinase plays a critical role in this process by catalysing the rate limiting

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steps in melanin synthesis.[7] Excessive UV exposure enhances tyrosinase activity through oxidative stress pathways, resulting in abnormal melanin accumulation and the formation of age-related pigmentation disorders.[8] Consequently, the inhibition of tyrosinase activity has become a key therapeutic target in dermatological and cosmeceutical applications.[9] Currently, the management of hyperpigmentation largely relies on synthetic agents such as hydroquinone, corticosteroids, and kojic acid. Although effective, these compounds are associated with safety concerns, including skin irritation, cytotoxicity, and long-term adverse effects such as ochronotic.[10,11]

In response to these limitations, there has been a growing interest in natural alternatives, particularly plant-derived compounds, due to their favourable safety profiles and bioactive properties.[12,13] Phytochemicals such as flavonoids, phenolic acids, and tannins have demonstrated significant antioxidant and anti-tyrosinase activities, making them promising candidates for skin related applications.[14,15] However, despite their therapeutic potential, plant-derived extracts face substantial challenges that limit their effectiveness in dermatological formulations.[16,17] Many phytochemicals exhibit poor bioavailability, low skin permeability, and instability under environmental conditions such as light, heat, and oxygen exposure.[18,19] Moreover, a large proportion of these compounds exist in glycosylated form with relatively high molecular weight, which restricts their ability to penetrate the stratum corneum and reach target sites within the skin.[20,21] These physicochemical limitations ultimately reduce their therapeutic efficacy and hinder their practical application in cosmeceutical products.[22,23]

Given these challenges, innovative strategies are required to enhance the bioavailability and functionality of plant-derived compounds.[24] In this context, fermentation has emerged as a promising biotechnological approach to overcome the inherent limitations of phytochemicals.[25] Through microbial activity, fermentation facilitates the bioconversion of complex phytochemicals into simpler, more bioactive forms.[26] Microorganisms such as lactic acid bacteria, yeasts, and fungi produce specific enzymes capable of hydrolysing glycosidic bonds, thereby converting glycosides into aglycones with improved physicochemical properties and biological activity.[27] In addition, fermentation can generate novel metabolites, including organic acids, vitamins, and potent antioxidants, which further contribute to skin health and protection against oxidative damage.[28]

Recent studies have highlighted the potential of fermented plant-derived compounds in enhancing antioxidant capacity, reducing inflammation, inhibiting tyrosinase activity, and improving photoprotection.[29] Nevertheless, the current body of literature remains limited by the predominance of in vitro studies and significant variability in fermentation conditions, microbial strains, and plant substrates.[30] Furthermore, previous reviews have often addressed phytochemical composition and biological activity separately, without adequately integrating fermentation mechanisms with their dermatological implications.[31]

Therefore, a clear research gap exists in understanding how fermentation-driven transformation of phytochemicals influences their bioactivity, skin permeability, and therapeutic potential within a unified framework. This review aims to critically evaluate the effects of fermentation on plant-derived phytochemicals and their relevance in cosmeceutical dermatology, with particular emphasis on mechanistic pathways, pharmacological activities, and translational potential. By linking biochemical transformations with dermatological outcomes, this review provides a more integrated perspective that supports the development of safer, more effective, and scientifically grounded biocosmetic formulations.

Methods

Search Strategy

A comprehensive literature search was conducted using Scopus and PubMed databases to identify relevant studies published between 2015 and 2025. The search strategy incorporated keywords including fermentation, medicinal plants, phytochemicals, and cosmeceuticals, along with their synonyms. Boolean operators ("AND" and "OR") were applied to refine the search. A total of 32 records were identified from the selected databases. Following title and abstract screening, all 32 articles were evaluated for relevance. Of these, 19 articles were assessed for full text eligibility. After full text evaluation, 13 articles were excluded due to not meeting the inclusion criteria. Ultimately, 5 studies were included in the qualitative synthesis. The study selection process followed the PRISMA framework, including identification, screening, eligibility, and inclusion stages, as illustrated in Figure 1.

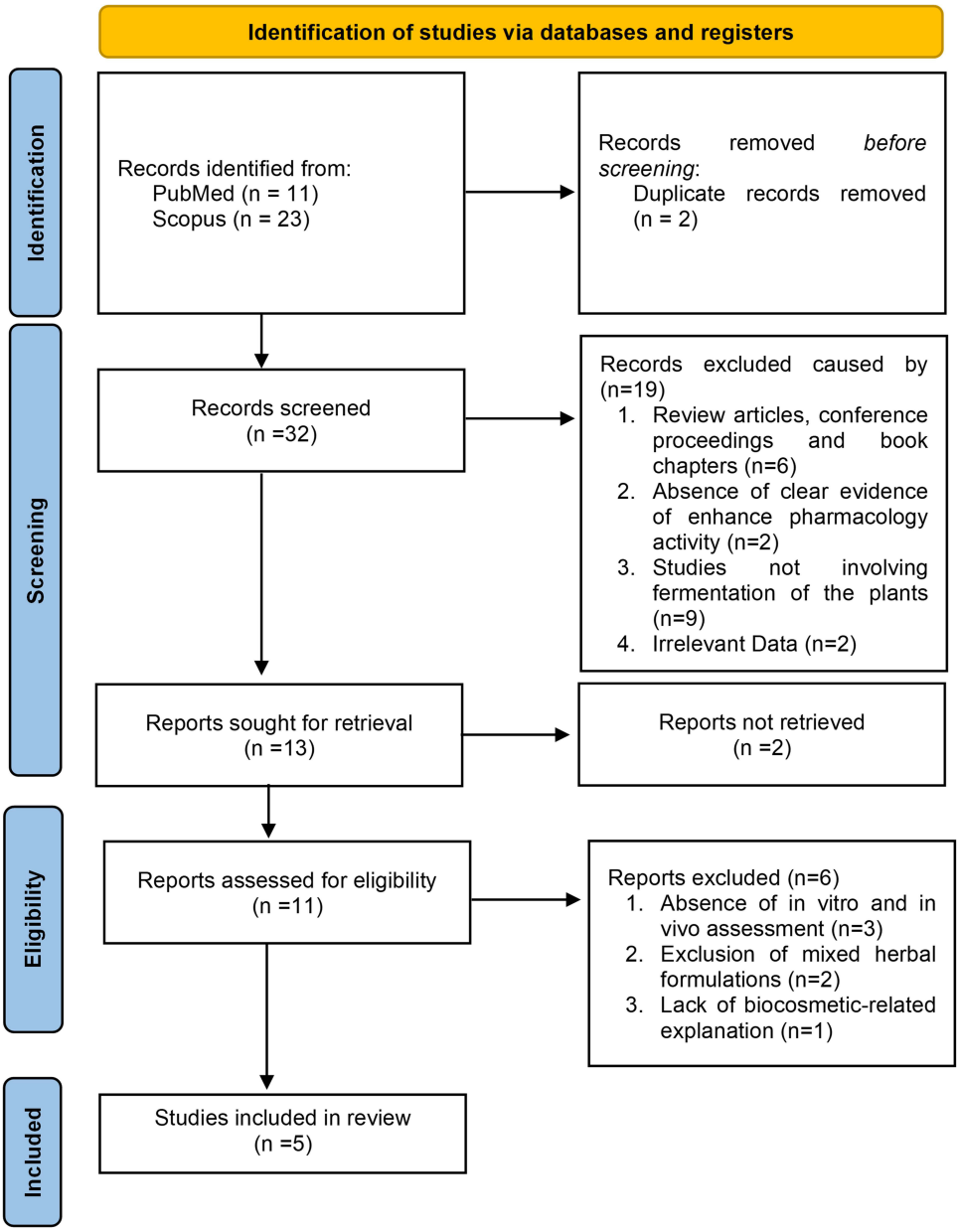

Figure 1 PRISMA flow diagram of the study selection process, adapted from the PRISMA 2020 guidelines (Page MJet al BMJ 2021;372:n71. doi: 10.1136/bmj.n71)., under the Creative Commons Attribution License.[32]

Data Collection Process

The study selection process was carried out systematically after removing duplicate records from the initial search results. Titles and abstracts of all identified articles were independently screened using the web-based tool Rayyan.ai (https://new.rayyan.ai/). Articles that met the initial criteria were then moved to thorough full-text assessment. To be eligible, articles needed to be discussed about the fermentation methods and their effects on phytoconstituents, as well as report preclinical findings, published in English between 2015 and 2025. The included studies needed to investigate extracts or isolated compounds derived from medicinal plants and to present outcomes related to fermented samples, particularly regarding their phytoconstituents and pharmacological properties or dermatological activity. Articles were excluded if they were reviews, commentaries or focused primarily on non-fermented plant materials. For each eligible study, key data were extracted including the medicinal plant family, collection location and year, plant parts used, fermentation methods, classes of metabolites or specific phytoconstituents, and quantitative comparisons of

phytoconstituents levels before and after fermentation. For in vitro studies, data such as the type of cell line, induction method, and exposure duration were also recorded. Based on these criteria, 5 articles were ultimately included for in-depth analysis.

Synthesis Methods

Due to the significant variability among the included studies and the differing outcome measures, we conducted a narrative synthesis of the evidence. The findings were qualitatively summarized and organized thematically based on the reported results. To provide a more comprehensive context and address gaps for a thorough review, this synthesis includes dedicated sections on the mechanisms of phytoconstituents towards skin permeability and the potential fermented plants for biocosmetic active pharmaceutical ingredients. This holistic approach is a valuable resource for researchers, integrating biological context with a systematic review of the most recent evidence.

Summary of Measures and Synthesis of Results

A total of 32 records were identified from the two selected databases. Following the screening of titles and abstracts, all 32 articles were evaluated for relevance. Of these, 19 articles were assessed for full-text eligibility. After full-text evaluation, 13 articles were excluded for not meeting the inclusion criteria. Ultimately, 5 studies were included in the qualitative synthesis. The study selection process is illustrated in Figure 1, which outlines the stages of identification, screening, eligibility assessment, and final inclusion in accordance with the PRISMA framework. In addition to the included studies, supplementary literature was reviewed to support the interpretation of mechanistic findings, particularly those related to skin permeability. These sources were not included in the PRISMA flow diagram, as they did not meet the predefined inclusion criteria for systematic analysis.

Results

The clinical efficacy of biocosmetic formulations is fundamentally dictated by the metabolic compatibility between plant phytochemical matrices and microbial enzymatic machinery.[33] Recent literature suggests a significant paradigm shift a departure from passive solvent extraction toward targeted biological activation.[34] Studies considered these fermented plant-based or fermented phytoconstituents work synergistically as a pharmaceutical ingredient in biocosmetic.[1] All of study, 5 articles discussed about in vitro studies in terms of fermented plants as potential in biocosmetics. Of these studies, we found that many plant materials demonstrated significant changes in phytochemical composition and biological activities following fermentation.[35,36] Overall, fermented plant extracts show considerable potential for biocosmetic application yet only a limited number of studies have explicitly elucidated the underlying mechanisms related to safety sustainability in fermented plant-based biocosmetics.[37] The findings presented in this review should be interpreted with caution due to the limited number of included studies and variability in experimental conditions.[38] Although several studies report enhanced bioactivity following fermentation, the magnitude and consistency of these effects differ across studies, depending on factors such as microbial strains, fermentation parameters, and plant substrates.[39,40] In addition, most available evidence is derived from in vitro models, which may not fully reflect clinical efficacy.[41] Therefore, a critical comparison of findings is necessary to better understand the scope and limitations of fermentation-based approaches in biocosmetic applications.

Fermentation Effects Toward Plant-Based or Phytoconstituents

Solid-state fermentation and submerged fermentation are two effective strategies for altering and improving the phytochemical composition of plants.[42,43] Throughout this process, bacteria including *Lactobacillus sp, Saccharomyces cerevisiae*, and *Aspergillus sp*, generate extracellular enzymes such as beta-glucosidase, cellulase, and xylanase, capable of degrading plant cell walls.[44] Biotransformation is the principal method via which bound phytochemicals are liberated from the cellular matrix.[45] Complex molecules such as flavonoid glycosides undergo hydrolysis to provide simpler and more bioactive aglycones.[46] In addition to enhancing bioavailability and antioxidant activity, this method can diminish antinutritional chemicals (such as phytates and tannins) and generate novel secondary metabolites absent in the original raw material.[47]

Fermentation has demonstrated its significance as an approach for enhancing the phytochemical composition of natural products for therapeutic purposes.[48] Metabolically designed microorganisms, such as *Saccharomyces cerevisiae*, facilitate the accurate synthesis of intricate bioactive chemicals like glycyrrhizin acid (GA) and cannabigerol (CBG), thereby surpassing the constraints of traditional plant extraction methods.[49,50] The incorporation of *Ganoderma applanatum* mycelia and lactic acid bacteria, such as *Lactobacillus paracasei*, in this biotransformation process enhances the polyphenol content and antioxidant capacity in diverse plant matrices, including *Morinda citrifolia* and fruit peel waste such as pineapple and pomegranate.[51] The breakdown of glycosidic linkages into more bioactive aglycone forms and the enhanced solubility of phytoconstituents in the solvent solution are two mechanisms that frequently contribute to this increase in activity.[52] Mechanically fermented phytoconstituents demonstrate enhanced anti-inflammatory efficacy by inhibiting significant pro-inflammatory mediators.[53] Research on extracts from *Chamaecyparis obtusa* leaves and a combination of nine anti-inflammatory herbs indicates that fermentation can suppress the expression of cytokines including IL-1, IL-6, and TNF-α. This is accomplished by modifying the Nuclear Factor-kappa B (NF-κB) and Mitogen-Activated Protein Kinases (MAPKs) signaling pathways.[23,54] This fermentation product effectively inhibits degradative enzymes, including collagenase and 5-alpha-reductase, while also diminishing nitric oxide (NO) generation.[55] In dermatological therapy, this protective function is vital as fermentation-derived chemicals can avert cellular damage and collagen degradation induced by H_2O_2 oxidative stress and UVB radiation. Advancements in fermentation technology, including the synthesis of sophorolipids using *Candida bombicola* via the bioconversion of macadamia oil and Korean traditional herbs, introduce a novel aspect in the development of topical medication delivery systems. This process augments the absorption of active compounds and fortifies epidermal barrier function by stimulating structural proteins such as filaggrin. Moreover, clinical evidence demonstrates that fermented oil can regulate alpha diversity and the diversity of skin microbiota. This fermented product, as a postbiotic, possesses a superior safety profile compared to synthetic materials and aids in restoring the equilibrium of the skin ecosystem, which is crucial for addressing many chronic dermatological diseases and premature aging.[56]

In vitro Studies

A transition is occurring from traditional plant extraction techniques to biosynthetic methods utilizing yeast platforms in the creation of cannabinoid-based medicinal molecules.[57] The research findings indicate that Cannabigrol (CBG) generated through fermentation surpasses CBD in anti-inflammatory efficacy and skin health restoration. Mechanistically, CBG derived from yeast biosynthesis has been demonstrated to be an exceptional component for cosmetic formulations due to its superior ability to protect the skin at the cellular level compared to CBD.[58]

Bioprocess interventions in a combination of Pomegranate skin (*Punica granatum*) and *Schisandra chinensis* by the fermentation of *lactobacillus* bacteria significantly increase the density of polyphenols and flavonoids.[59] According to research on Human Adult Keratinocyte Tumor (HaCaT), this fermentation process maximizes the antioxidant activity inside cell.Particularly, this fermentation product provides significant protection against oxidative stress caused by hydrogen peroxide (H_2O_2).[60] This indicates that the gradual optimization of the fermentation parameter is correlated with the improvement of the biological material's efficiency in reducing free radicals.[61]

The terpenoid and phenolic fractions were enhanced following the extraction of Chamaecyparis obtusa leaves and the fermentation of the mycelium with the useful fungus Ganoderma applanatum.[62] In vitro research has shown that the metabolites generated from this fermentation have potent anti-inflammatory qualities.[63] Mycelial fermentation seems to convert precursor chemicals into secondary metabolites that are more pharmacologically active and can effectively lower inflammatory mediators.[64] The findings demonstrate that fungal fermentation is a viable biotechnological technique for creating medications based on natural products. These observations suggest that the data presented in Table 1, offering a clear overview of the in vitro studies of fermented plant-based or phytoconstituents as potential for biocosmetics relevant to skin health.

Table 1 Effects of Fermented Plant-Based or Phytoconstituents as Biocosmetic Potential

Medicinal Plants, Collection Location, Year	Plant part Used or Compound Used	Fermentation or Extraction Method (Solvent-Used)	Type of Fermentation		Class of Metabolites	Type of Study	Results	Interpretation	Ref
			Microorganism Employed	Fermentation Conditions					
Cannabis sativa L. (Cannabiceae), China,2022	Purified Cannabigerol	Precision fermentation	Saccharomyces cerevisiae	Not reported	Cannabigerol	NHEKs (Human Epidermal Keratinocytes) stimulated by DPPH for 3 hours HFDs (Human Dermal Fibroblasts) induced by 5 ng/mL TPA induced IL-6 (12-O-tetradecanoyl-phorbol-13-acetate) for 24 hours NHEKs (Human Epidermal Keratinocytes) induced by 5 ng/mL TPA induced TNF-a (12-O-tetradecanoyl-phorbol-13-acetate) for 24 hours	CBG inhibiting UVB-induced TNFα release (IC50 = 14.7 nM), more potent than CBD (29.8 nM) and clobetasol (2142 nM). Against UVA-induced IL-6, CBG significantly reduced secretion (IC50 = 0.3 μM), whereas CBD and ascorbic acid were ineffective. In antioxidant assays, CBG also scavenged DPPH radicals (IC50 = 502 μM), showing ~2-fold greater potency than CBD (910 μM), but weaker than ascorbic acid (5 μM).	Cannabigerol (CBG) exhibits significant potential asin enhancing cutaneous hydration and fortifying the skin barrier function.	[65]
Punica protopunica (Punicaceae), China, 2021 *Schisandra chinensis* (Schisandraceae), China, 2021	Fruits Peels	Mixed culture LAB fermentation and Maceration	Lactobacillus plantarum and Sterptococcus thermophilus	Aqueous medium with glucose, sterilized by autoclaving, inoculated with L. plantarum and S. thermophilus, incubated at 37 °C for 24 h	Ellagic acid	HaCaT cells stimulated by H2O2 induced for 24 hours Chemical Reaction reduction (Redox) scavenging using DPPH Chemical Reaction reduction (Redox) scavenging using O2- Chemical Reaction reduction (Redox) scavenging using OH- Chemical Reaction reduction (Redox) scavenging using ABTS	Fermented broth (FB) from pomegranate peel and *Schisandra chinensis* showed strong antioxidant activity, with high scavenging of ABTS (EC50 = 0.033 mg/mL), DPPH (0.042 mg/mL, slightly stronger than vitamin C), OH^- (4.48 mg/mL), and $O2^-$ (6.00 mg/mL). Compared to water extract (WE), FB contained ~3-fold higher ellagic acid (99.49 vs. 34.88 mg/mL) and exhibited stronger radical scavenging. FB also showed lower cytotoxicity on HaCaT cells (≥90% viability at ≤8 mg/mL). Pretreatment with FB significantly protected HaCaT cells from H2O2-induced oxidative stress by reducing ROS levels, outperforming vitamin C at higher doses.	Potential as a high-value functional constituent in cosmeceutical formulations.	[66]

Chamaecyparis obtusa (Cupressaceae), Korea, 2022	Leaves	Maceration and Fungal fermentation (70% Ethanol)	Ganoderma applanatum mycelia	Inoculate at dose 10%, incubated at 25°C with 180 rpm (shaking incubation) for 3 weeks	Flavonoids (Quercetin) and Polyphenols	Mouse macrophage cells (RAW264.7) stimulated by LPS for 16hours Chemical Reaction reduction (Redox) scavenging using DPPH Chemical Reaction reduction (Redox) scavenging using ABTS	70CLGA altered composition (quercitrin 20.52% vs. 15.08%; amentoflavone 8.84% vs. 26.66%) and increased total phenolics/flavonoids compared that non-fermented extracts. 70COLGA showed stronger antioxidant activity than non-fermented extract (70COL) at low concentrations (DPPH, ABTS assays) and reduced cytotoxicity (≈100% cell viability up to 200 μg/mL vs. <80% at 25 μg/mL for 70COL). In RAW264.7 cells, 70COLGA suppressed LPS-induced iNOS, COX-2, NO, IL-1β, IL-6, IL-27, MIP-2, GM-CSF, and G-CSF	Potential as a high-value functional constituentin biocosmetic	[67]
Citrus maxima (Rutaceae), Vietnam, 2020	Fruit peels	Enzyme-assisted fermentation in Sodium citrate buffer (Pectinase, pH 4.8)	Pectinase enzyme (enzymatic bioconversion)	1000–6000 IU/g peel, incubation at 50 °C with 150 rpm of shaking incubation for 24 h	Flavonoids, Polyphenols, and Tannins	Chemical Reaction reduction (Redox) scavenging using DPPH Determination of Sun Protection factor	Fermented C. maxima peel exhibited moderate antioxidant capacity (IC50 range 37.98–55.79%), weak antibacterial effect against E. coli (inhibition zone 1.67–2.33 mm), and moderate UV protection (SPF = 26.84–29.28 depending on enzyme concentration).	The fermentation of *P.granatum* is one of the most important ingredients in skincare product development, offering a competitive advantage over *C. maxima* and *M. acuminata* in functional cosmetics.	[68]
Musa acuminata (Musaceae), Vietnam, 2020	Fruit peels	Enzyme-assisted fermentation in Sodium citrate buffer (Pectinase, pH 4.8)	Pectinase enzyme (enzymatic bioconversion)	1000–6000 IU/g peel, incubation at 50 °C with 150 rpm of shaking incubation for 24 h	Polyphenols, flavonoids, and Tannins	Chemical Reaction reduction (Redox) scavenging using DPPH Determination of Sun Protection factor	Fermented M. acuminata peel showed antioxidant activity with IC50 values between 34.69–49.12%, but no antibacterial effect against E. coli or S. aureus. UVB protection was weak compared to other peels, with SPF values ranging from 7.43–9.18.		
Punica granatum (Lythraceae), Vietnam, 2020	Fruit peels	Enzyme-assisted fermentation in Sodium citrate buffer (Pectinase, pH 4.8)	Pectinase enzyme (enzymatic bioconversion)	1000–6000 IU/g peel, incubation at 50 °C with 150 rpm of shaking incubation for 24 h	Polyphenols, flavonoids, and Tannins	Chemical Reaction reduction (Redox) scavenging using DPPH Determination of Sun Protection factor	Fermented P. granatum peel showed the strongest antioxidant effect (IC50 = 0.18% at 3000 IU), inhibited E. coli growth with inhibition zones up to 6.67 mm, and displayed the highest UVB protection (SPF = 36.58 at 1000 IU, 10% solution).		

(*Continued*)

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Table 1 (Continued).

Medicinal Plants, Collection Location, Year	Plant part Used or Compound Used	Fermentation or Extraction Method (Solvent-Used)	Type of Fermentation		Class of Metabolites	Type of Study	Results	Interpretation	Ref
			Microorganism Employed	Fermentation Conditions					
Morinda citrofolia L(Rubiaceae), Chiang Mai, Thailand, 2018	Fruits	*Lactobacillus piracies* HII01 30 ±2°C for 6 months	*Lactobacillus piracies HII01*	Samples were collected during fermentation (day 0, 4, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, and 180). Then, they were filtered through Whatman no. 42 filter paper, 1% (v/v) of each sample was aliquoted with sterile water and stored at −70°C	Comprised of carbohydrates, dietary fibers, vitamins (Vitamins C, E, B1, B2, B6, B12, biotin, pantothenic acid, folic acid, carotene, and niacin), proteins, minerals (calcium, potassium, sodium, phosphorus, iron, molybdenum, magnesium, and sodium chloride)	Antioxidant assays (TAC, FRAP)	L. paracasei HII01-mediated fermented of M. citrifolia fruits juice was enriched with phenolic compounds and antioxidants. The use of cane sugar as carbon source for the growth of L. paracasei HII01 facilitates the fermentation process compared to honey. Likewise, the study suggested that natural fermentation of noni with cane sugar was found to be relatively superior like L. paracasei HII01-mediated fermented juice. However, the use of probiotic strains as starter culture for the development of fermented juice.	Morinda citrofolia L. as a high value	[127]

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Mechanism of Fermented Plant Extracts in Enhancing Skin Permeability by Overcoming the Stratum Corneum Barrier Through Enzymatic Deglycosylation

The fundamental physicochemical characteristics of the source compounds are the main obstacle to the topical administration of botanical actives.[69] Most phytoconstituents, including those in *P. granatum, M. citrifolia*, and several Rosa species, are glycosides in their original, non-fermented state.[70] Due to the presence of sugar moieties, these glycosylated molecules have high molecular weights and considerable polarity, which form strong hydrophilic and steric barriers that stop them from passing through the lipophilic stratum corneum.[71]

The fermentation techniques covered in this review, particularly those that employ *Lactobacillus* strains, successfully overcome these limitations by enzymatic hydrolysis. Extracellular β-glucosidase produced by starting cultures facilitates O-glycosidic bond cleavage.[72] The related aglycones, such as free scopoletin or flavonoid aglycones, are bio-converted from bulky, hydrophilic glycosides.[73] Passive diffusion is governed by Fick's First Law, and the resulting aglycones have substantially lower molecular weights and optimal lipophilicity. Fermented extracts show more intracellular antioxidant activity in HaCaT cells than their non-fermented counterparts, serving as a biological stand-in for enhanced cellular absorption.[74]

Mechanism of Enhanced Skin Permeability in Fermented Plants via Lipophilicity Modulation Induced by Fungal Biotransformation

Beyond simple hydrolysis, fungal fermentation offers a structural alteration mechanism that directly impacts permeability*applanatum* fermentation of *C. obtusa* most likely involves terpenoid biotransformation.[75] Natural terpenes often contain functional groups that limit their compatibility with the skin's lipid bilayer. The fungal mycelia's enzymatic repertoire can modify these scaffolds, perhaps via hydroxylation or methylation, to create more hydrophobic metabolites. Because of this polarity shift, fermented chemicals can more easily partition into the skin's intercellular lipid matrix, allowing for deeper penetration to the viable epidermis, which is home to inflammatory mediators like NF-κB.[76]

The Role of Biosurfactants in Fermented Plant Delivery Systems for Improved Skin Permeation

Studies using the Oji complex and Macadamia oil fermented by *Candida bombicola* reveal a unique and extremely complex mechanism.[77] This bioprocess produces sophorolipids (SLs) in situ, as opposed to conventional extraction techniques that depend on solvent diffusion. These glycolipid biosurfactants serve as a green delivery method. Herbal actives and oils exist as distinct phases with little interaction in non-fermented combinations. But during fermentation, SLs create micellar structures that can contain both hydrophilic and hydrophobic phytoconstituents.[78] This micellar encapsulation improves the solubility of active ingredients and reduces interfacial tension. Furthermore, biosurfactants are known to interact with stratum corneum lipids, creating a transitory and reversible breakdown of barrier function, which dramatically enhances the flux of encapsulated actives into the dermis.[79] Chemical Loosening and Acidification of the Barrier Permeability is also significantly influenced by the formulation's physicochemical surroundings. *Citrus grandis* (Pomelo) peel ferments spontaneously to produce a filtrate with a pH range of 3.2–3.8 that is rich in organic acids like lactic and citric acid.[80] This acidic environment promotes a modest keratolytic action, in contrast to the neutral pH of non-fermented aqueous extracts.[81] The fermented filtrate effectively "loosens" the solid structure of the skin's outer layer by reducing the cohesive forces between corneocytes.[82] In addition to encouraging skin renewal, this method produces micro-channels that facilitate the more efficient penetration of other bioactive substances, such naringin, than they would in a non-acidified medium.[83] These results demonstrate that bioprocess technology, whether through yeast biosynthesis or microbial fermentation (lactic acid bacterial and fungal mycelium), effectively enhances the pharmacological profile of plant-derived substances.[84]

Pharmacological Applications in Biocosmetics

Currently, the emphasis in biocosmetics is predominantly on topical applications rather than cellular level interventions using fermentation technologies. Current research demonstrates that the bioaugmentation technique utilizing

microorganisms like *Lactobacillus* and yeast can enhance the bioavailability of phenolic chemicals, which are crucial for skin defense.[85] The fermentation of Schisandra chinensis and pomegranate peel exhibits a significant capacity to diminish intracellular oxidative stress. When human HaCaT keratinocyte cells are subjected to hydrogen peroxide, a byproduct of this fermentation exhibits a potent action against free radicals.[86] This safeguards DNA from harm that may lead to premature aging or photoaging.[87] Moreover, investigations into the manufacture of Cannabigerol from yeast produced unexpected new results. Its antioxidant effects surpass those of Vitamin C in diminishing Reactive Oxygen Species in skin fibroblasts.[88] This represents the benchmark for anti-aging. Fermented fruit peel possesses a sun protection factor (SPF) value of up to 36.5.[89] This illustrates the capacity of natural materials to physically and physiologically shield themselves from UV radiation. While skin pigmentation serves as a natural defensive mechanism, hyperpigmentation frequently signifies melanocyte dysregulation resulting from prolonged oxidative stress.[90] Research on the fermentation of *M. citrifolia* and pomegranate fruit demonstrated a correlation between antioxidant activity and the suppression of melanogenesis in the skin.[91] Free radicals frequently stimulate the enzyme tyrosinase, the primary catalyst for melanin synthesis. In an optimal fermentation method, such as a 15-day fermentation of Noni fruit, the concentrations of polyphenols and flavonoids markedly elevate.[92] The heightened concentration of these bioactive chemicals renders the atmosphere more reducing. This milieu eradicates free radicals that induce pigmentation and indirectly halts the enzymatic cascade of tyrosinase.[93] Consequently, facial skin tone becomes more uniform and luminous biologically due to the restoration of skin oxidative equilibrium. Biocosmetics provides targeted dermatological therapies for inflammatory disorders such as acne and dermatitis, minimizing the adverse consequences linked to prolonged corticosteroid application. A study of fermented *Chamaecyparis obtusa* leaf extract by Ganoderma fungal mycelia demonstrated a complex chemical pathway. This mechanism functions by obstructing the nuclear translocation of NF-κB and impeding the STAT signaling pathway.[94] This effectively halts inflammation at the genetic level. Cannabigerol performs effectively in its two notable roles when utilized. Firstly, it inhibits the proliferation of the bacterium *Cutibacterium acnes*; secondly, it obstructs the surge of pro-inflammatory cytokines such as IL-1β and TNF-α generated by immune cells in reaction to the bacteria.[95] Clinical evidence demonstrates that cannabigerol-based serum diminishes erythema in patients. This signifies a new epoch in acne therapy, emphasizing the modulation of the skin's immune response while specifically targeting bacteria.[96] While fermentation generally enhances the biological activity of plant-derived compounds, not all studies report consistent improvements. Variations in experimental design, microbial strains, and substrate composition contribute to differences in outcomes across studies. These inconsistencies highlight the importance of critically evaluating individual findings rather than drawing generalized conclusions.[97]

Despite the reported enhancements in bioactivity, the findings across studies are not entirely consistent. Variability in microbial strains, fermentation duration, and substrate composition contributes to differences in outcomes. While some studies demonstrate substantial improvements in antioxidant and anti-inflammatory activities, others report moderate or condition-dependent effects. Taken together, the available evidence suggests that fermentation outcomes are highly context-dependent and require careful optimization.[98]

Across the included studies, fermented extracts consistently demonstrated enhanced antioxidant and anti-inflammatory activities compared to non-fermented counterparts, although variability was observed depending on microbial strains and fermentation conditions. The available evidence suggests that the effects of fermentation are context-dependent and require process optimization.[99]

Discussion

The findings of this work validate that biotransformation via microbial fermentation is not solely a preservation method, but an essential molecular engineering approach for improving the bioavailability of botanical chemicals.[100] This research demonstrates a notable shift in the chemical composition of high molecular weight complicated glycosides towards more straightforward and physiologically active aglycone forms. The application of strains, *like Lactobacillus paracasei* in the fermentation of *M. centifolia* and Lactobacillus spp. in the exocarp of Punica granatum, consistently enhances the overall polyphenol content. This process is facilitated by the enzyme β-glucosidase, which cleaves glycosidic bonds, thereby activating the molecules at the skin receptor target. The benefits of the eukaryotic system are also apparent by the application of *G. applanatum* on various *C. obtuse* substrates in contrast to the prokaryotic

system.[101] Filamentous fungi possess a more extensive enzymatic repertoire, enabling alterations to lipophilic functional groups, hence enhancing the compound's affinity for the stratum corneum lipid matrix. This technique conforms to the tenets of contemporary drug design, emphasizing the enhancement of small molecules for improved tissue penetration.[102]

The therapeutic effectiveness of these fermented substances is facilitated by molecular signaling pathways. Plant-derived fermentation extracts influence skin inflammation by inhibiting NF-κB and MAPK.[103] A distillate from a fermented blend of nine herbs shown enhanced efficacy in safeguarding skin from UVB radiation by preventing collagen degradation facilitated by MMP-1. The results demonstrate that the fermentation process can generate secondary metabolites that function as photoprotective and anti-aging agents. Moreover, the de novo synthesis of CBG is achieved by metabolically altered *S. cerevisiae* yeast, addressing the issues related to variability in plant raw materials.[104] CBG is a biosynthetic product that displays in vitro anti-inflammatory properties, thereby showcasing the promise of cellular technology as a source of high-purity chemicals in comparison to unfermented extracts.[105]

One of the most groundbreaking contributions to the existing research is the utilization of *C. bombicola* for the in-situ production of sophorolipids biosurfactants. Enhanced natural infiltration of amphiphilic compounds.[106] This method lowers surface tension and reversibly alters intercellular lipid arrangement in the stratum corneum, facilitating the penetration of active compounds into deeper epidermal layers.[107] The enhanced permeability is further corroborated by the inherent pH management throughout the fermentation process, as seen by the research findings on Citrus grandis fermentation.[108] Adjusting the pH to the skin's physiological acidic range preserves the integrity of the skin barrier and facilitates the diffusion of phenolic compounds in a non-ionic state. The lowering of molecular weight via glycosylation, together with the penetration improvement provided by biosurfactants, establishes a pharmacokinetic synergy optimal for topical therapy.[109]

The research on product development transitioned from crude extract to a fermented active ingredient, yielding an improved safety profile.[110] Cytotoxicity assays on HaCaT cells and human dermal fibroblasts indicated that biotransformation frequently diminishes the irritation usually induced by certain chemical substances in native plants. Nonetheless, in vitro evidence has significant therapeutic potential akin to pharmaceuticals, as exemplified by CBG for acne and *Rosa spp*. for tyrosinase inhibition.[111]

Adherence to FDA criteria necessitates a distinct differentiation between assertions regarding enhancement of skin structure and those pertaining to improvement in appearance.[112] Despite the molecular mechanism suggesting significant enzymatic inhibition, present commercialization techniques favor a classification as functional cosmetics or cosmeceuticals.[113] This research yields a scientific foundation for the development of an active ingredient delivery system that is clinically efficacious, physically and chemically stable, and safe for prolonged usage in biocosmetic formulations.[114]

Despite the detailed mechanistic insights, the translational relevance of these findings remains limited. Most studies rely on in vitro models, which may not fully represent complex biological responses in human skin.[115] Therefore, further validation through in vivo and clinical studies is essential to confirm the practical applicability of fermented phytochemicals in dermatological settings.

The shift from laboratory size to industrial scale necessitates rigorous standardization of fermentation techniques to guarantee batch-to-batch uniformity. Within the biocosmetics sector, the use of this technology is transitioning from conventional open-tank fermentation to fully regulated bioreactors.[116] De novo production of CBG utilizing yeast *S. cerevisiae* exemplifies industrialization, wherein factors such as aeration rate, temperature, and food availability are optimized to enhance the yield of the desired metabolite, independent of seasonal or genetic variability in plants.

The scalability of liquid herbal fermentation (LHF) entails optimizing upstream processing, including the determination of suitable inoculum concentration and substrate ratio. The utilization of *C. bombicola* for sophorolipids extraction indicates that the industry is commencing the integration of carrier material and active ingredient production into a singular bioprocess step, thereby enhancing cost and energy efficiency in the sustainable cosmetics sector. Notwithstanding its significant bioactive potential, the downstream processing of fermentation products encounters intricate technical hurdles. A primary challenge is the elimination of leftover microbial biomass and undesirable secondary metabolites that may influence the product's sensory attributes color and scent. Membrane filtration and

distillation techniques, utilized for the nine-herb mixture, are essential for generating a clear and aesthetically stable filtrate while preserving the integrity of its active compounds.[117]

Moreover, standardizing the concentration of active compounds in intricate fermentation matrix presents a regulatory problem. The fermentation product constitutes a dynamic combination. The identification of certain biomarkers, such as quercetin or aglycone concentrations, is necessary as a quality control criterion. The susceptibility of active chemicals to oxidation during purification requires the implementation of encapsulation technologies or the incorporation of supplementary natural antioxidants to preserve product efficacy until it reaches the consumer.[118] The safety of fermentation-based biocosmetics is assessed both in vitro and through thorough clinical examination. Original research findings indicated that cytotoxicity tests on HaCaT cells and dermal fibroblasts consistently demonstrated that certain doses of the fermentation extract did not affect cell viability. The clinical assessment of biosynthesized CBG, which included a 48-hour patch test on human participants, verified that the substance is non-irritating and non-sensitizing.[119]

Prolonged usage necessitates assessment of skin barrier integrity. If the pH is not calibrated to the skin's buffering ability, fermentation producing elevated concentrations of organic acids may result in the thinning of the stratum corneum. To prevent phase separation or chemical degradation that may yield harmful byproducts, it is essential to conduct physicochemical stability studies, including accelerated stability testing at severe temperatures.[120] The Human Repeated Insult Patch Test (HRIPT) aims to mitigate the risk of enduring adverse effects, including photosensitivity resulting from the buildup of specific phenolic chemicals. Research on fermentation filtrates of Rosa spp. and *M. centifolia* indicates that biotransformation frequently eradicates possible allergens found in the original plants by modifying the enzymatic structure of proteins and terpenoids.[121] However, attention is necessary to guard against the potential for opportunistic microbial infection. Nonetheless, monitoring is essential to guard against potential opportunistic microbial infection.[122] Consequently, an appropriate preservation method for fermented organic materials must be meticulously engineered to guarantee microbiological safety throughout the product's shelf life.[123]

The application of fermentation technology in the synthesis of dermatological active compounds represents a notable progression in cosmetic pharmaceuticals.[124] Therapeutic agents with high molecular target precision, good skin penetration, and a clinically validated safety profile can be produced by integrating traditional herbal knowledge with contemporary bioprocessing technology.

A key limitation of the current evidence lies in the lack of direct comparability between studies. Differences in microbial systems, fermentation parameters, and plant substrates make it difficult to establish standardized conclusions. For instance, lactic acid bacteria mediated fermentation consistently enhances polyphenol release, whereas fungal fermentation appears to be more effective in modifying lipophilic compounds. This suggests that fermentation outcomes are not universally transferable and should be interpreted within specific experimental contexts.

Current Challenges and Safety

The stability and fermentation odor are physical and chemical attributes of the product associated with the bioconversion process. Research on Noni fruit indicates that the fermentation process inherently modifies the chemical composition of its components, resulting in a decreased pH and heightened acidity, which culminates in a distinctive sour aroma. These alterations indicate the emergence of active molecules rather than just side effects. This chemical environmental alteration enhances the stability of the finished product. Research on pomegranate peel and Schisandra chinensis indicates that fermentation effectively preserves and enhances antioxidant potential and phenolic components more efficiently than conventional water extraction techniques. Moreover, employing yeast biosynthesis for CBG manufacturing provides greater supply stability compared to dependence on crop harvests, which are subject to variability, hence maintaining the consistent quality of the finished product across time. This represents a benefit for the availability of raw materials. Fermentation is essential for dermatological safety as it diminishes irritation risk and enhances the biocompatibility of substances with human skin. Fermentation can eliminate the cytotoxic characteristics of certain plant extracts, *C. obtuse* extract safeguards cells from standard ethanol extract during fermentation with fungal mycelia. Clinical investigations on fermented serum containing Cannabigerol shown that it neither induced irritation nor facilitated the repair of skin damage resulting from contact to harsh chemicals such as SLS. The fermentation process converted the active component into a more dermally compatible form, facilitating tolerance for very sensitive skin.[125] Nonetheless, the

deployment of this technology in the sector encounters several intricate industrial challenges. The primary concerns are scalability and cost effectiveness. Due to the economic impracticality of directly extracting rare chemicals from plants, the industry is shifting towards bioprocess engineering, including the utilization of more scalable yeast. This necessitates a substantial initial investment in technology. Moreover, there are technical challenges associated with the optimization process. Parameters including temperature, duration, and inoculum size must be precisely determined with statistical techniques such as Response Surface Methodology. This is attributable to the potential for minor errors that may compromise product quality. Conversely, organic waste, like fruit peels, ought to be transformed into valuable resources. This signifies that this fermented product can be regarded as both a traditional processed item and a contemporary, validated cosmetic or therapeutic product.

A comparative evaluation of the included studies highlights variability in fermentation outcomes depending on microbial systems and process parameters. Fermentation mediated by lactic acid bacteria appears to consistently enhance polyphenol bioavailability through enzymatic hydrolysis, whereas fungal fermentation may induce broader structural modifications that improve lipophilicity. These differences suggest that microbial selection is a critical determinant of the pharmacological profile of fermented products. Despite these promising findings, not all studies reported consistent improvements following fermentation. In some cases, only moderate or condition-dependent effects were observed, indicating that fermentation does not universally enhance bioactivity. This variability underscores the importance of process standardization and careful optimization of fermentation conditions.

Limitations of the Study

Although the present review provides comprehensive insights into the biocosmetic's potential of fermented plant-based phytoconstituents, several limitations should be considered when interpreting the findings. The qualitative synthesis was limited in scope, and substantial heterogeneity in plant species, fermentation methods, microbial strains, and evaluation models restricted direct comparison across studies. As summarized in Table 2, these limitations were identified among

Table 2 Identified Limitations and Research Gaps Across the Studies Included

Author, year of Publication	Limitation Of Study	Limitation Detail
Liu et al, 2022;[66]	In vitro model limitations	Most studies predominantly utilize in vitro models (eg., HaCaT keratinocytes, RAW 264.7 macrophages) or animal models, which do not fully replicate the complexity and barrier function of human skin.
Perez et al, 2022;[65]	Small clinical sample size	Clinical studies often involve small sample sizes (eg., 20–21 participants), limiting statistical power and generalizability.
Chaiyasut et al, 2018;[126]	Microbial Strain Specificity	The production of bioactive compounds is highly dependent on specific microbial strains (eg., *Lactiplantibacillus plantarum, Saccharomyces cerevisiae*), reducing reproducibility across studies.
Kang et al, 2021[68]	Phytochemical Complexity	Multi-herb fermentation systems complicate the identification of active compounds responsible for observed biological effects.
Kim et al, 2024[67]	Raw material variability	The concentration of bioactive compounds is influenced by raw material quality, storage conditions, and preprocessing, posing challenges for standardization.
Chaiyasut et al, 2018;[126]	Scalability issues	Fermentation parameters optimized at laboratory scale may not be directly applicable to industrial-scale production.
Perez et al, 2022;[65]	Short-term evaluation	Most clinical studies are conducted over short durations, limiting understanding of long-term safety and efficacy.
Perez et al, 2022;[65]	By-Product Utilization	The use of agricultural by-products (eg., fruit peels) introduces variability in composition, affecting consistency of final products.

the 5 articles that met inclusion criteria. Importantly, these limitations do not reflect quality of the included studies but rather highlight current gaps in the literature. Future research with standardized methodologies and more comprehensive experimental designs is needed to strengthen the scientific basis and translational potential of fermented plant-based for biocosmetics applications. Several limitations should be considered when interpreting these findings that should be acknowledged. First, only five studies met the inclusion criteria, reflecting the limited availability of research specifically addressing fermentation-driven phytochemical transformation in dermatological applications. Second, most of the included studies were based on in vitro models, which may not fully represent clinical conditions. Third, variability in microbial strains, fermentation conditions, and plant substrates limits the comparability of findings. These limitations highlight the need for standardized methodologies and well-designed clinical studies.

Future Perspectives

The beauty and pharmaceutical industries are presently experiencing a substantial paradigm shift. This paradigm transitions from traditional extraction techniques to more sophisticated bioprocess engineering. Research on the manufacture of cannabigerol via yeast indicates that future production of active compounds will not just rely on agricultural modifications and the harvesting of seasonal crops. The industry will transition to mobile factories that utilize microbial fermentation as their foundation. These factories can ensure industrial scalability, excellent purity, and product uniformity independent of external factors.

This signifies a new epoch in which biomanufacturing will serve as an essential remedy to the shortage and elevated expense of uncommon phytochemical raw materials. In the future, the supply chain for raw materials will emphasize sustainability and the circular economy. Research indicates that fruit peel waste, including pomegranate, banana, and grapefruit, can be utilized to generate bioactive chemicals possessing antioxidant and photoprotective characteristics. In the future, the beauty and food sectors will progressively converge, transforming residual biomass from trash into a valuable enzymatic fermentation resource. This approach not only tackles environmental concerns but is also exceptionally economical.

Furthermore, scientific validation and toxicological modulation will enable the establishment of new standards to supplant conventional empirical assertions. Research indicates that mycelial fermentation can preserve the anti-inflammatory properties of hardwood extracts such as *C. obtuse* while diminishing their cytotoxic effects. This facilitates the creation of novel pharmaceuticals that exhibit great biocompatibility with human dermal tissue. In the future, product development will be guided by an evidence-based medical methodology. This method will enhance fermentation parameters through exact statistical techniques, including Response Surface Methodology, while standardized clinical studies will be imperative to guarantee the efficacy and safety of contemporary dermatological solutions.

Conclusion

This review underscores that fermentation represents a promising biotechnological strategy to enhance the functional performance of plant-derived phytochemicals in cosmeceutical dermatology, primarily by improving their bioavailability, skin permeability, and physicochemical stability.

The evidence synthesized in this review suggests that fermentation may improve antioxidant capacity, anti-inflammatory activity, and tyrosinase inhibition, which are mechanistically associated with modulation of oxidative stress pathways and inflammatory mediators, including SOD, CAT, IL-6, and TNF-α. These findings are aligned with the mechanistic insights discussed, particularly the role of enzymatic deglycosylation, lipophilicity modulation, and biosurfactant mediated delivery in enhancing skin permeability across the stratum corneum.

However, as highlighted in the Results and Discussion sections, the current evidence base remains largely derived from in vitro and limited in vivo studies, with substantial heterogeneity in microbial strains, fermentation conditions, and plant substrates. This variability constrains direct comparability and limits the translational applicability of the findings, indicating that fermentation outcomes are context-dependent rather than universally generalizable.

From a clinical and industrial perspective, fermentation offers a potentially valuable approach for developing safer, more stable, and functionally optimized biocosmetic ingredients. Its application may support the formulation of products

targeting oxidative stress-related skin conditions, such as photoaging and hyperpigmentation, while also aligning with sustainability principles and scalable production processes.

Future research should prioritize standardization of fermentation protocols, including microbial selection, substrate composition, and processing parameters; identification of reliable bioactive markers for quality control; integration of advanced in vitro, in vivo, and clinical models to validate dermatological efficacy, and addressing regulatory challenges related to product consistency, safety, and commercialization. Addressing these aspects will be critical to bridge the gap between experimental findings and real-world cosmeceutical applications.

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Disclosure

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