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Review

Precision Fermentation as a Tool for Sustainable Cosmetic Ingredient Production

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Abstract

Precision fermentation, a highly controlled process of microbial fermentation, is emerging as a transformative tool to produce cosmetic ingredients. This technology leverages engineered micro-organisms to produce high-value compounds with applications in skincare, hair care, and other cosmetic formulations. Unlike traditional methods of ingredient sourcing, which often rely on extraction from plants or animals, precision fermentation offers a sustainable and scalable alternative, minimizing environmental impact and enhancing the consistency of ingredient supply. This paper explores the potential of precision fermentation to revolutionize the cosmetic industry by enabling the production of complex molecules, such as peptides, proteins, and other bioactive compounds, which are essential for cosmetic efficacy. Using synthetic biology, micro-organisms such as yeast, bacteria, and fungi are programmed to biosynthesize specific cosmetic ingredients, which can include antioxidants, emulsifiers, and moisturizers. This technique not only ensures high purity and ingredients safety but also allows for the production of novel compounds that may be difficult or impossible to obtain through traditional methods. Furthermore, precision fermentation can be employed to address growing consumer demand for cruelty-free, vegan, and eco-friendly products, as it eliminates the need for animal-derived ingredients and reduces resource consumption associated with conventional farming and extraction processes. This review highlights key advancements in the field, discussing the challenges faced by industry, such as regulatory framework, and presents potential solutions for overcoming these obstacles. The paper concludes by examining the prospects of precision fermentation in cosmetics, forecasting how continued innovation in this area could further drive sustainability, ethical production practices, and the development of highly functional, scientifically advanced cosmetic products.

Keywords: precision fermentation; sustainable cosmetics; biotechnology in cosmetics; microbial fermentation; cosmetic ingredient production; synthetic biology; cosmetic ingredients regulatory framework; eco-friendly skincare; patented cosmetics

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1. Introduction

The escalating climate crisis, coupled with a rapidly growing global population and an increasing demand for rapidly depleting natural resources, has positioned sustainability as modern society's critical issue to be tackled. In turn, the manufacturing industry has been identified as one of the major contributors to environmental degradation due to its high resource consumption, energy use, and carbon emissions, which has made integrating sustainable practices into this sector an urgent challenge. However, challenges also present opportunities, as companies that adopt environmentally conscious strategies often gain a competitive edge, with reports suggesting that they have an enhanced brand reputation, improved customer satisfaction, and direct economic benefits through increased resource efficiency and waste reduction—factors that collectively contribute to long-term business success [1–3]. Given its intrinsic characteristics (namely, high demand for natural resources, continuous global expansion, and the significant influence of brand perception on consumer purchasing decisions), the cosmetics industry needs a long-term sustainability strategy, with the advancement of both social and environmental sustainability being fundamental aspects of its Green Transition. Moreover, cosmetic companies' decision to commit to sustainability is often driven by the expectation of economic benefits, as sustainable practices not only attract a larger customer base but also enable the development of higher-value products, thereby enhancing profitability [2,4]. One of the main areas being addressed in the attempt to improve the sustainability of the cosmetic industry relates to ingredient sourcing and production. One of the most promising strategies implies the use of renewable and/or waste-derived materials instead of virgin raw materials using circular-economy-based approaches to present solutions with a better and more responsible resource management while also reducing waste generation and minimizing environmental impact. However, there are other solutions that could allow for a more sustainable cometic industry, particularly biotechnology-derived ones. Fermentation is a prime example of this: fermentation has emerged as a sustainable alternative to cosmetic ingredients production because it allows for the production of bio-based compounds using less virgin raw materials, thus having a lower environmental impact. This highlights the importance of fermentative processes for the development of a more sustainable cosmetic ingredients and aligns the present manuscript, which will focus on fermentation, particularly precision fermentation, as a key strategy for the future sustainable ingredient production in the cosmetics industry [2,5,6].

Fermentation, a process where micro-organisms are used to generate the desired products, has been used practically since the dawn of civilization to produce foodstuffs like wine and beer. However, while the interest in fermentation started in foods, it later expanded into other fields, such as medicine, where fermentative processes allowed for the production of important ingredients, like antibiotics, on a larger scale. As technology evolved, fermentation became one of the cornerstones of the biotechnology industry, and the path to more precise applications opened. In fact, precision fermentation represents another significant leap in fermentation technology, with it exploiting the use genetically engineered micro-organisms to produce specific target compounds, such as enzymes or other ingredients [5,6]. A prime example of this is the production of recombinant insulin using genetically modified *Escherichia coli*, a development that resulted in a drastic improvement in insulin availability and had a significant impact on the welfare of diabetics. This example has proven that precision fermentation offers promising solutions in medicine, food, and cosmetics production via an environmentally sustainable process [7]. In fact, nowadays, precision fermentation appears as a particularly interesting alternative, not only because of its scalability but also because of its versatility [2,6,8,9].

Considering the aforementioned context, where the cosmetic industry needs more sustainable ingredients, fermentation has been identified as one of the possible solutions. The present work aims to explore how precision fermentation can be used as a sustainable biotechnological platform to produce cosmetic ingredients. Through a multidisciplinary approach, it provides strategic insights for both researchers, industrials, and innovators in a way that bridges biotechnology, sustainability, and cosmetic product development under the lens of precision fermentation [1,3,6]. To accomplish this, it is structured in different sections that aim to provide different insights into this topic. Section 2 aims to provide some market context and insights into consumer perspectives that will drive the development of new precision fermentation processes and contextualize its relevance within this frame. Section 3 gives an overview of the current research and innovation trends, showcasing the increasing commercial and scientific interest that surrounds fermentation-based cosmetic technologies. Section 4 dives into fermentation itself, contrasting the different aspects of traditional and precision fermentation and providing real case-studies of specific cosmetic ingredients with high market importance (like collagen, resveratrol, and hyaluronic acid). It also discusses the different types of biological platforms that can be used in precision fermentation processes, highlighting the importance of selecting adequate microbial hosts for each desired ingredient. The following section (Section 5) dives into the technological aspects of scaling-up this process, addressing several of the challenges that need to be considered (and overcome) for the successful translation of these technologies to a market reality. Section 6 delves into the regulatory framework that surrounds cosmetic ingredients produced via precision fermentation, highlighting the importance and requirements for regulatory compliance. And lastly, Section 7 discusses different future perspectives into the use of precision fermentation and their integration with different technologies and fields of study.

2. Market and Consumer Perspectives

The cosmetic industry is witnessing a growing economic and environmental interest in developing innovative and sustainable ingredients, driven by consumer demands, regulatory requirements, and technological advancements. Overall, it is a lucrative and rapidly expanding sector, valued at approximately $419.8 billion in 2024 and projected to grow at a compound annual growth rate (CAGR) of 4.6% through 2030. Furthermore, its future expansion is predicted to be particularly robust in segments that align with innovations that include eco-conscious formulations, digital-first brands, luxury cosmetics, and AI-integrated skincare [4,10]. Overall, cosmetic-related industries are expected to continue to embrace circular economy models, integrate biotech and fermentation-derived ingredients, and personalize consumer experiences.

Fueled by a strong culture of personal grooming, higher consumer-spending levels, and its retail ecosystem, North America currently represents the largest cosmetics market (valued at €102 billion in 2024), a position that is further cemented due to the presence of worldwide dominant brands, influencer marketing, and the rapid growth of e-commerce [10,11]. Europe has the second largest market share (valued at €96 billion in 2024), supported by a mature retail infrastructure, stringent and ever-evolving regulatory standards (details in Section 6) and requirements, and innovation-driven consumer preferences that drive this sector to reinvest 3–5% of their annual revenue in to R&D and result in an innovative pipeline that sees 25% of all products either upgrade or completely reformulated [10,11]. As the European markets emphasize the importance of quality, transparency, and sustainability, which not only aligns with emerging trends like clean/organic cosmetics but also with the underlying environmental advantages of considering the use of precision fermentation processes. Overall, the demand for clean, sustainable, health-conscious cosmetics is one of the key growth drivers that are accelerating the evolution of this industry, with 68% of European consumers considering sustainability to be a crucial factor in their purchasing decisions (and 66% of them being willing to pay more for products with positive social and/or environmental impacts) [4,11,12]. This has resulted in an increase in the scrutiny placed on ingredient lists and an increasing preference for organic, vegan, cruelty-free, ethically sourced formulations and an overall pressure on the industry towards more sustainable production practices. In fact, it represents a rapidly expanding sectors of skincare in Europe and is projected to reach a market value of >$362 billion by 2031 [6,10,11,13–16].

Considering the above-mentioned arguments, sustainability has become one of the key value drivers for the cosmetic industry, with forward-thinking companies looking at the entire life cycle to improve their overall value chain sustainability, from packaging to end-of-life management, as well as product design and ingredient sourcing [4,11,14,17,18]. And it is in the ingredient sourcing that precision fermentation has the potential to be a transformative solution. It enables the controlled and sustainable production of high-performance cosmetic ingredients (like those exemplified in Section 4.3) by engineering micro-organisms (using tools like BioBricks design, pathway engineering, modular assembly, and chassis fine-tuning) to function as biofactories, replacing conventional, resource-intensive sourcing with greener (and more ethical) solutions [19–21]. Squalane is one of the most compelling examples of this. Used in skincare products due to its emollient and antioxidant properties, it was traditionally sourced from shark liver oil (squalane accounts for 40–60% of shark liver biomass), thus contributing to the decline of deep-sea shark populations [22–27]. Using plant sources as alternatives had limited yields asides all those related to agricultural practices. In fact, amaranth oil only has around 5.9% squalane, and it is one of the richest sources of this compound, and olive oil has been reported as having amounts as low as 0.6% [28,29]. Here, precision fermentation has risen as a viable solution for its production, achieving high yields in a reproducible, scalable, and environmentally friendly manner. In fact, while a few wild-type yeasts have been reported to produce 0.2–14.3 mg/g of squalane on a cell dry weight base, their engineered forms have systematically resulted in increases in production ranging from 3.2-fold up to 115-fold [22,30–36]. Life Cycle Assessment (LCA) studies have also contributed to laying bare the environmental burden of cosmetic ingredient production, further emphasizing the need for upstream interventions to reduce raw material consumption, energy use, and waste generation. Once again, precision fermentation presents a possible solution for this, particularly if considering processes designed using renewable resources (like those sourced from agri-food wastes). Moreover, the generated ingredients also offer a strong performance and formulation compatibility given their similarity to their natural counterparts, which will facilitate the seamless integration into cosmetic formulations without compromising their efficacy or stability. This ensures both brand continuity and regulatory acceptance while also strengthening supply chain traceability and resilience. Furthermore, it also unlocks access to rare/novel compounds that are either difficult to isolate or too expensive to synthesize chemically [19,37].

In sum, as sustainability becomes one of the driving forces behind cosmetic innovation, precision fermentation presents itself as a forward-looking, scientifically robust solution for addressing the ingredient sourcing challenge.

3. Technological and Scientific Mapping of Fermentation-Based Innovations in the Cosmetic Sector

3.1. Bibliometric Networks Visualization (Fermentation Technologies into Cosmetic Industry) by VOS Viewer

The graphical bibliometric analysis was conducted by considering papers available in scientific databases on 14 March 2025 (ScienceDirect at www.sciencedirect.com and Scopus at www.scopus.com) using the keywords "Fermentation" and "Cosmetic Industry" or "Cosmetic industries", search that yielded 624 research documents (2021–2025). Subsequently, a file was created to avoid keywords repetitions in the co-occurrence analysis (e.g., Substrates/Substrate or antioxidant activities/antioxidant activity). Overall, this analysis divided the body of research into five clusters (Figure 1a), which demonstrated the convergence of cosmetics and fermentation research, particularly in sustainability, bioactive compounds, and functional applications. These insights provide a structured perspective of emerging trends and key areas for innovation.

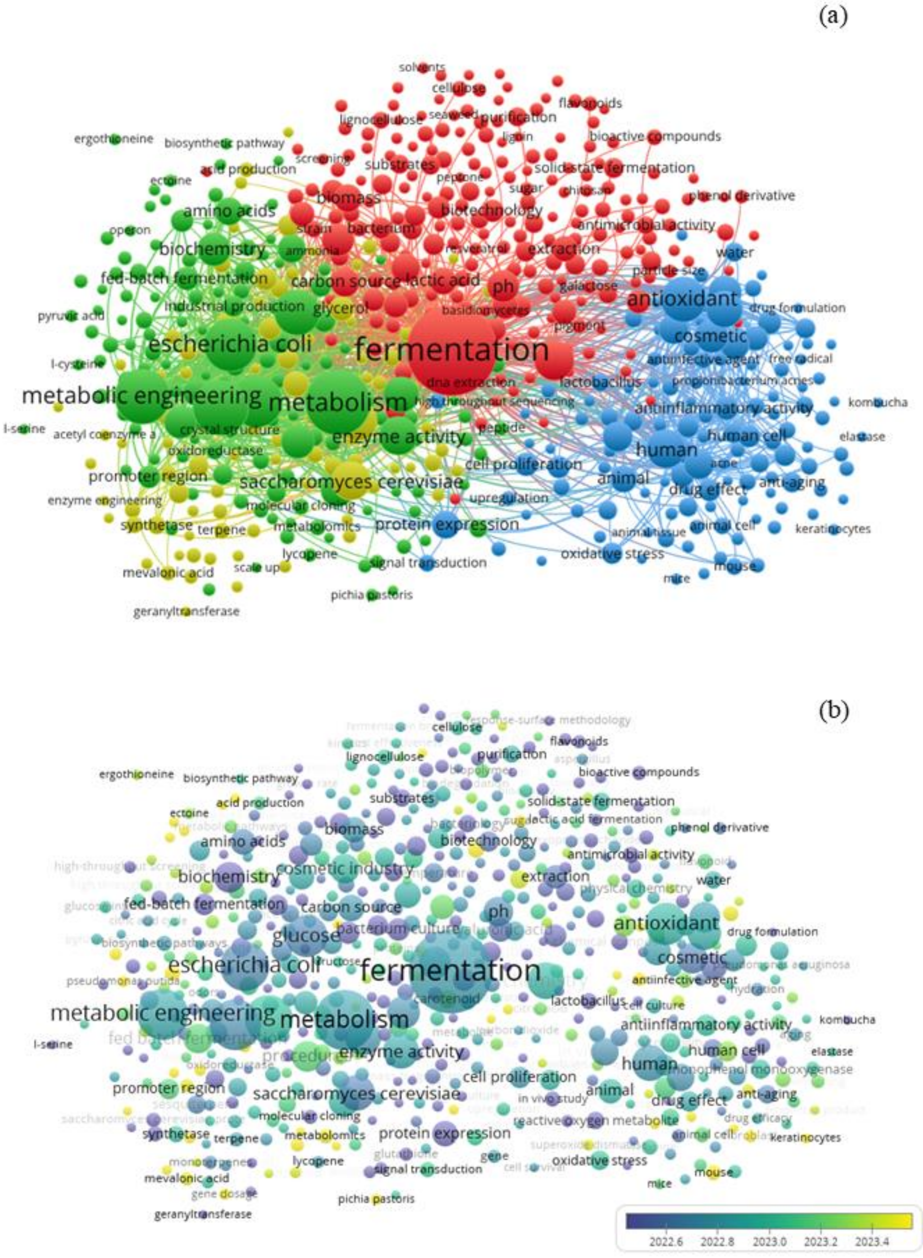

Figure 1. Network graph of fermentation in the cosmetic industry from 2021 to 2025 by VOSviewer version 1.6.20. (**a**) Cluster distribution of research information divided in 4 cluster: sustainable ingredients and functional additives (red), microbial bio-transformations (green), antioxidant activity and skin applications (blue), Volatile Compounds and Sensory Attributes (yellow); (**b**) time distribution of research information in fermentation into cosmetic industry between 2021–2025.

- The first cluster (red) was mainly related to sustainable ingredients and functional additives obtained by fermentation technologies with the following keyword: “absorption”, “additives”, “substrate”, and “agro-industrial by-products”, which indicates an emphasis on bio-based formulations and environmentally friendly processing. Thus, this cluster encompasses ongoing research interests in optimizing ingredient functionality while ensuring sustainability.

- The second cluster (green) focuses on the enzymatic, metabolic engineering, and microbial bio-transformations characterized by the following keywords: “acyltransferase”, “alcohol dehydrogenase”, “amino acids”, and “fermentation.” It encompasses the biochemistry process and the pathways involved in bioactive compounds production and aroma profiles in cosmetics.
- The third cluster (blue) is related to antioxidant activity and skin applications, with keywords such as “ABTS radical scavenging assay”, “acne”, and “antioxidant capacity”, encompassing research on oxidative stress mitigation and dermatological benefits. Additionally, it is interesting to note that it was possible to identify a higher frequency of reactive oxygen species related terms; this suggests that there is a current interest in developing novel formulations to improve skin health and longevity via oxidative stress modulation.
- The fourth cluster (yellow) is related to the obtention of “Volatile Compounds and Sensory Attributes”, with keywords such as “p2-phenylethanol”, “acetic acid”, and “aroma compounds”. This cluster highlights current research interest in the recovery of aromatic components by integrating fermentation technologies with potential applications in other sectors, such as the food industry, where the products’ sensory attributes play a crucial role in consumer acceptance.

The analysis of trends over time (Figure 1b) showed that the clusters related to “metabolic engineering” and “enzymatic and microbial bio-transformations” englobe areas with recent publications and lower density (green/yellow $\geq$ 2022). The lower density indicates an opportunity for new research aimed at increasing the novel potential metabolic engineering technologies to produce highly industrial attractive molecules through fermentation. This could be explained under the new sustainable trends looking for high-yield processes.

3.2. Intellectual Property Screening (Fermentation Technologies into Cosmetic Industry) by WIPO-Patentscope

Nowadays, the growth in scientific literature related to precision fermentation for production, conversion, and the recovery of cosmetic compounds has been associated with the development of patents registered with international organizations such as WIPO (International Intellectual Property Organization). The intellectual property analysis (Table 1) was performed using the intellectual property database (PATENTSCOPE) to elucidate technological growth over the past 20 years, using the terms “Heterologous expression”, “Precision fermentation”, and “Cosmetics”, limiting the search to specific uses in cosmetics or similar preparations (IPC: A61Q; International Patent Classification).

According to the patent databases search (carried out on 26 June 2025), twenty patents were registered from 1998 to 2025, which include various applications of precision fermentation taking advantage of heterologous expression (Table 1) for the recovery of molecules of interest for cosmetic use. For example, five patents can be grouped into a group called “Production or genetic engineering for the production of PUFAs” (20060051847, 1766023, WO/2005/118814, 2005250074, and 2016013126) focused on the production of polyunsaturated fatty acids, which have beneficial functions in human health and also strengthen the skin barrier. This last characteristic makes it interesting for the development of cosmetic products [38].

Table 1. Chronological evidence of the most representative patents on heterologous expression and precision fermentation in recent years.

Patent	Title	Main Core	Scope	Publication	Country
US20060051847	Metabolically engineered *Saccharomyces* cells for the production of polyunsaturated fatty acids	The present invention relates to the construction and engineering of cells, more particularly micro-organisms for producing PUFAs with four or more double bonds from non-fatty acid substrates through heterologous expression of an oxygen-requiring pathway.	PUFAs production	9 March 2006	USA
CN105969742	Arabidopsis thaliana SOD (Superoxide Dismutase)1 protein and application thereof in cosmetics	The invention relates to arabidopsis thaliana SOD (Superoxide Dismutase) protein and the application of the arabidopsis thaliana SOD1 protein in cosmetics and belongs to the technical field of gene engineering. The obtained protein can be applied to the development of the cosmetics.	Bioactive molecule production	28 September 2016	China
CN113234764	Heterologous expression method of gamma-polyglutamic acid	The invention discloses a heterologous expression method of gamma-PGA (gamma-polyglutamic acid) with different D/L monomer ratios from a saccharic raw material by one-step fermentation; a strain of *C. glutamicum* F343 with high yields of L-Glu is used as a chassis.	Bioactive molecule production	10 August 2021	China
CN116987179	Long-acting heat-resistant collagen as well as preparation method and application thereof	The invention relates to a long-acting, heat-resistant collagen, which comprises a collagen with an amino acid sequence and a nucleotide sequence for coding the collagen. The recombinant humanized collagen is obtained on the basis of human collagen sequence optimization and heterologous expression, and the collagen does not easily generate toxins, is safer to use, and has better heat resistance and certain long-term effect.	Structural protein production	3 November 2023	China
CN118480553	Recombinant silk fibroin as well as expression system and application thereof	The invention provides recombinant silk fibroin as well as an expression system and application thereof and belongs to the technical field of cosmetic raw material development. The method not only can solve the quality control problem of naturally extracted protein products but also can realize the effects of high-efficiency and high-purity heterologous expression and low large-scale production cost and has higher industrial application potential.	Structural protein production	13 August 2024	China

The focus on structural proteins, such as "collagen", has been explored through the development of four patents (116987179, 116082525, 118480553, and 106957803), among which patent 116987179 stands out focusing on the development of thermosetting collagen by *S. cerevisae* and the use of *E. coli* for the expression of silk fibroin (CN118480553). Similarly, the production of other compounds with biological activity (ten patents) have been explored, namely the heterologous expression of enzymes (e.g., mutanase) from *Trichoderma harzianum* with potential application in the development of oral care products (WO1998000528) or the production of enzymes with potential for application in medical cosmetology (Hyaluronic acid lyase, CN110527680). The expression of enzymes that modify compounds like polyphenols (flavonoids) has been explored in patent CN116855465, in which the biosynthesis of isorhamnetin from quercetin and adenosylmethionine, through the expression of flavonol 3′-O-oxymethyltransferase, was explored. Lastly, patent 202041054332 has a broader focus, describing the development of expression platforms that can be applied to multiple purposes.

In summary, the development of patents related to precision fermentation encompasses the production of various molecules with biological activity and potential for application in the development of cosmetic products. However, it is important to highlight that there are still a limited number of patents in the area, so the development of novel research that culminates in disruptive technological developments and innovations that allow for tech transfers to industries is needed.

4. Fermentation

Fermentation promotes not only the breakage of larger molecules (and a subsequent increase in bioavailability of active components) but also the formation of an array of metabolites that can be recognized by the human body. Thus, it offers a bio-based approach to ingredient production with a lower resource-dependency or less harmful production processes while still providing a scalable means to produce high-value compounds. It also has the possibility of aligning with circular economy principles by utilizing byproducts as raw materials for the fermentation process [4,6,39]. Several examples of ingredients produced via fermentation can already be found in the market. Pitera, the commercial name for a *Galactomyces* ferment filtrate, is a fermented product that has become the base upon which the cosmetic brand SKII was built. It has been reported as reducing oxidative stress and melanin synthesis (pigmentation) while also exhorting some anti-inflammatory effects, evidence that support its anti-aging, nourishing, and skin-soothing effects [6]. While this is an interesting example, other, more recognizable ingredients are also produced via fermentation, namely hyaluronic acid, resveratrol, and coenzyme Q10 (Q10; ubiquinone) [40–42].

4.1. Traditional Versus Precision Fermentation

Fermentation is an ancestral technology used for the production of molecules of interest in various industrial sectors (mainly food), presenting challenges related to the "natural" capacity of selected micro-organisms to produce metabolites of interest. However, the evolution of genetic editing has opened a new panorama of research and production, where, through "precise" editing of metabolic pathways, it is possible to increase the yield, speed, and production of specific molecules [19]. Additionally, editing allows for the design of bespoke protein structures with greater functionality, stability, improved digestibility, or reduced allergenicity [43]. These processes may also be more sustainable, since Knychala et al. [44] reported that the use of precision fermentation can, in some cases, reduce water consumption and greenhouse gas emissions by 90–97% when compared to animal-based protein production methods. From this perspective, and under the current environmental framework, precision fermentation presents itself as an interesting alternative for today's industry, particularly as recent scientific efforts have focused on the development of new synthetic biology and artificial intelligence strategies that are expected to spearhead the development of competitive technologies within the near future. In fact, precision fermentation is currently being exploited to produce several well-known cosmetic ingredients, with some of the most recognizable being listed in Table 2.

Table 2. Recent applications of precision fermentation as a strategy to produce more recognizable cosmetic ingredients.

Product	Micro-Organism	Media	Scale	Parameters	Yield	Reference
Hyaluronic acid (HA)	*Streptococcus zooepidemicus*	20 g/L peptone, 12.5 g/L phosphates, 10 g/L Pyruvate, 6 g/L Yeast extract, 3 g/L $MgSO_4 \cdot 7H_2O$, 1 g/L N-acetylglucosamine, 80 mg/L phosphatidylcholines and 80 g/L glucose.	3 L	pH 7.0–7.5 (37 °C), aeration rate 3 L/min, and 200 to 600 rpm DO 20–30%	1.01 gHA/L/h	[45]
Human collagen α1(III) chain with viral prolyl 4-hydroxylase	*P. pastoris* GS115	Buffered methanol medium (0.2% biotin, 1% methanol, 1% yeast nitrogen base, 1% yeast extract, 2% peptone, 100 mM potassium phosphate)	Flask	30 °C (200 rpm), Methanol supplementation (24 h, 1% methanol) and the culture lasted for 144 h.	0.7 mg/mL	[46]
Squalene	*P. pastoris* GS115	BMGY medium (1% glycerol, 1.34% YNB, 2% peptone, and 1% yeast extract).	Flask	250 rpm (30 °C); methanol addition (1%, 24 h), and dodecane (10%) were initially supplemented.	20.80 ± 0.02 g/L	[47]
	Yarrowia lipolyticae	YNB-60 (60 g/L glucose and contained 8 g/L yeast nitrogen base without amino acids, and 9 g/L yeast extract.	Flask	YNB-60 medium, a C/N ratio of 10:1, the addition of 1 mM isoprenol, no addition of terbinafine, and 28 °C	1628.2 mg/L	[48]
	S. cerevisiae C800	YPD medium (containing 10 g/L $CaCO_3$. Including 400 g/L glucose, 10.24 g/L $MgSO_4 \cdot 7H_2O$, 50 g/L $(NH_4)_2SO_4$, 18 g/L KH_2PO_4, 0.56 g/L Na_2SO_4, 7 g/L K_2SO_4, 20 mL/L vitamin solution, and 24 mL/L trace metal solution.	5 L	pH 5.5 (30 °C), dissolved oxygen (DO) at 50%, stirring rate (250–800 rpm) up to 72 h, then at 30% after 72 h. The feeding medium was added at 6 mL/h from 14 to 24 h, then 8 mL/h from 24 to 72 h for maintaining the cell growth.	8.2 g/L of squalene	[49]
	Rhodobacter sphaerodies BCRC 13,100	The basal medium: sucrose (20 g/L), molasses (44 g/L), corn steep liquor (35 g/L), Soytone (56 g/L), and $(NH_4)_2SO_4$ (2 g/L).	Feed batch	pH 7, 30 °C and 200 rpm; 2 g/L Vitamin B1 and 100% medium replacement at 48 h.	138.24 mg/L	[50]
Resveratrol	*E. coli* BL21 (DE3)	LB medium	Flask	30 °C for 48 h with shaking at 200 rpm, glycerol 8%	80.4 mg/L	[51]
	Scheffersomyces stipitis NBRC10063	YP medium (10 g/L yeast extract; 20 g/L peptone) containing 50 g/L of glucose, cellobiose, or sucrose.	Flask	30 °C, 100 rpm, Initial inoculum size: 0.1 OD_{600}	529.8 mg/L (cellobiose) 668.6 mg/L (Sucrose) 237.6 mg/L (glucose)	[52]
	Saccharomyces cerevisiae	Synthetic media (YPD20 (1% yeast extract, 2% peptone, 2% dextrose).	Flask	300 rpm at 30 °C or 39 °C	187.07 ± 19.88 mg/L	[53]
		Eucalyptus globulus wood (Pretreated with hydrothermal treatment)	NE	39 °C	151.65 ± 3.84 mg/L resveratrol from 2.95% of cellulose from *Eucalyptus globulus*	
	E. coli	EZ medium with 100 µg/mL ampicillin.	Flask	Initial inocolum size: 0.1 OD_{600}, 30 °C and IPTG 25 µm. Induction at 18 °C for 12 h, 60 µL of 10 mM resveratroil in DMSO, and 24 h at 30 °C	36.99%	[54]

4.2. Cost Effectiveness of Traditional Versus Precision Fermentation

Fermentation has long been recognized as a cost-effective method for the production of a range of food and cosmetic ingredients, relying primarily on naturally occurring microbial activity. Traditional fermentation processes (such as those used to create lactic acid, ethanol, or fermented botanical extract) are generally well-optimized and relatively low-cost due to decades of industrial development. These systems often employ inexpensive substrates like sugars or grains, and their operating parameters are simple enough to be handled with minimal automation. However, the major drawback is that traditional fermentation is limited in its ability to produce highly specific compounds. For cosmetic applications, where product consistency, purity, and bioactivity are paramount, these limitations can become significant economic barriers due to the need for additional downstream refinement steps that erode cost advantages [55,56]. In contrast, precision fermentation offers a compelling technological leap, as its usage of engineered micro-organisms to produce targeted biomolecules, such as elastin, collagen, or hyaluronic acid, enables the production of high-value cosmetic actives with exceptional purity and reproducibility. However, this specificity comes at a substantial cost. Unlike traditional fermentation, precision fermentation involves high capital expenditure (CapEx) in bioreactor design and operation, along with significant operating expenses (OpEx) linked to strain development, culture maintenance, and downstream processing. One of the most critical cost challenges is feedstock pricing as precision fermentation typically relies on refined sugars, which are more expensive and more resource-intensive than the simpler feedstocks used in traditional fermentation. The shift toward using agricultural residues or waste streams as alternative feedstocks may mitigate this issue, but only if compatible microbial strains and tailored bioprocesses are developed to handle them efficiently [55,57].

From an economic standpoint, the scale of production also plays a decisive role in cost per unit. Pharmaceutical-grade fermentations, where precision fermentation originally gained traction, are economically viable even at low volumes due to the high value of the final product. However, in the cosmetic market, unit costs must remain low enough to compete with both synthetic and naturally derived alternatives. It is estimated that for precision fermentation to match the cost of conventional protein production, production titers must increase by orders of magnitude, highlighting the urgent need for the improvement of bioprocess efficiency and strain robustness. These improvements will add layers of complexity and upfront investment that can delay returns on investment and increase financial risks [55].

In sum, while traditional fermentation remains more economically straightforward, it cannot meet the precision demands of high-performance cosmetic actives without substantial downstream processing. Precision fermentation, though currently more expensive, is steadily closing the cost gap through advances in metabolic engineering, alternative substrates, and computer-aided process design. Regardless, this sector presents a strategic opportunity for precision fermentation to establish economic traction, as these ingredients often command higher price points and face less regulatory burden when compared to food or pharmaceutical products, respectively.

An interesting case to consider is that of hyaluronic acid. Widely used in skin care products and dermal fillers, it has been manufactured via fermentation using natural hyaluronic-acid-producing micro-organisms, such as *Streptococcus zooepidemicus*. These bacteria can achieve titers of ca. 2.5 to 5 g/L in batch or fed-batch fermentations, with production costs around $946–1115 per kilogram for cosmetic-grade hyaluronic acid. This cost is consistent with the market price range of ca. $1000–2000/kg observed for this grade of hyaluronic acid; moreover, the cost of medical-grade hyaluronic acid (used in fillers) can exceed $40,000/kg. As it is a premium product with a high price, the production of this grade of hyaluronic acid, which demands higher purity and higher molecular weights, should also remain an economically viable option. However, while traditional fermentation production processes remain viable, they rely on complex media (harder to purify), which indirectly contributes to higher OpEx, particularly if aiming at medical-grade hyaluronic acid. In this scenario, as precision fermentation results in purer and more concentrated hyaluronic acid, it can be an interesting option to actually reduce the downstream processing costs and therefore the OpEx. Works using genetically engineered *Bacillus subtilis* strains reported titers above 7 g/L of hyaluronic acid after only 11 h of fermentation, nearly halving fermentation time when compared with *Streptococcus*-based fermentations. This, when also factoring in the use of a defined inorganic media, can result in a significant reduction in resource input (and related costs) and downstream purification needs. In fact, an economic analysis of this process at bench to pilot scale was estimated to double the operational profit when compared with *Streptococcus*-based fermentations [58–60].

Another example is Squalane. It is an emollient used extensively in moisturizers and serums that has historically been extracted from shark liver oil, a source that was controversial and had production costs reported between $15–25/kg. Following regulatory and consumer-driven shifts, most producers shifted to olive-derived squalane, which, while more ethically accepted, resulted in higher ingredient production costs (typically $50–80/kg) and made this ingredient susceptible to agricultural volatility. Precision fermentation offered a route to produce squalane from sugars using engineered yeast strains, with companies exploiting it to produce squalane with production costs between $20–40/kg, values that undercut olive-derived sources while maintaining consistent quality, quantity, and scalability. This cost reduction in relation to plant-derived squalane has already led to a translational adoption of this process by the cosmetic industry, particularly among brands seeking “vegan” or bio-based ingredient labels. Notably, these gains are primarily cost-driven rather than sustainability-driven, suggesting that precision fermentation can offer direct economic advantages even in the absence of environmental incentives [56,61,62].

4.3. Cosmetic Ingredients Produced via Fermentation

One of the first best-selling fermented cosmetic ingredients was Pitera by Procter & Gamble’s Japanese SKII. According to the International Nomenclature of Cosmetics Ingredients (INCI), Pitera is a *Galactomyces* ferment filtrate. The company claims that after realizing that the hands of elderly women working at a sake brewery were soft and youthful looking, they started examining the potential of yeast fermentation products as potent anti-aging ingredients. In recent years, advancements in biotechnology have enabled the incorporation of more efficient production methods aligned with sustainability trends. Specifically, precision fermentation technology has allowed for the targeted production of components that were previously derived from animal tissues with low yields [6,63,64].

4.3.1. Hyaluronic Acid

As previously mentioned, hyaluronic acid is a cosmetic ingredient of great interest with a wide range of applications, including its use in moisturizing creams, serums, and makeup. Its chemical structure comprises a disaccharide D-glucuronic acid (GlcUA) and N-acetylglucosamine linked with β-1, 3 and β-1,4 glycosidic bonds [65]. Hyaluronic acid has some advantages in the industry due to its mechanical stability, lack of immunogenicity, moisture retention, and lubricant capabilities [40]. The traditional technique to produce hyaluronic acid involved its extraction from rooster combs; however, given the rise in preference for non-animal-sourced ingredients, some of its production shifted, and fermentation was introduced as a novel technology with low-cost and high quality, particularly for cosmetic-grade hyaluronic acid. The natural synthesis involves the glycolytic pathway for the creation of 2 main precursors: UDP-glucuronic acid (UDP-GlcUA) and Uridine diphosphate-N-acetylglucosamine (UDP-GlCNAc) from glucose and fructose (-6-phosphate), following polymerization-mediated hyaluronic synthase [66].

The initial hyaluronic acid production Via traditional fermentation employed pathogenic bacterial strains, such as *Streptococcus* from groups A and C; however, over the years, it has shifted towards the use of safer genetically modified micro-organisms, such as *Lactococcus lactis*, *Bacillus subtilis*, and *Streptococcus thermophilus* [67]. Also, new sustainable strategies have been developed for the incorporation of agricultural by-products: Sugar beet pulp, corn steep liquor, distillery waste, and wheat bran have the potential to be used as a new substrate for the production of hyaluronic acid [40]. A critical challenge for its production using fermentation is related with the medium viscosity, as it has been reported that at concentrations ≥4 g/L of hyaluronic acid the increase in media viscosity, caused by this accumulation, results in a oxygen access limitation and the resulting anaerobic environment could result in the production of other compounds (e.g., lactate) [68]. To address this challenge, batch and semi-continuous processes have been developed to produce hyaluronic acid. An example is the work of Zhang et al. [45] that showed an efficient production system using a beneficial mutant (SZ07) of *Streptococcus zooepidemicus* ATCC 39920 and a semi-continuous two-stage fermentation, which resulted in higher production levels of hyaluronic acid, 29.38 g/L. Thus, although precision fermentation is an interesting tool for hyaluronic acid production, there are additional technological challenges that must also be addressed alongside strain manipulation to increase the production yield, particularly in seeking to produce the more expensive, medical-grade, high-molecular-weight (and higher viscosity) hyaluronic acid.

4.3.2. Collagen

Collagen is another remarkably interesting protein for industry that can be found in different cosmetic products (e.g., hydrated creams and gels) and has been gathering interest in the medical field. Conventional collagen production methods are animal-derived extractions, which are not only misaligned with consumer's demand for "animal-free" cosmetic products but also have the potential to trigger immunogenic reactions in addition to not being the correct collagen type to exert the desired effects. Using human collagen from relevant tissues (namely skin) could address some of these issues, but sourcing human-derived collagen has several drawbacks, with one of the most relevant, asides ethical issues, being the difficulty in finding human tissues in sufficient quantity for the extraction to support larger-scale production [69]. Fermentation has been introduced as a solution for this issue via the use of modified micro-organisms containing heterologous expression systems, targeting the specific types of desired collagen (or associated subunits) for each application. More specifically, recombinant collagen, attained using DNA-recombinant technologies could be divided into three classes: (1) Recombinant human collagen, defined as "*Physicochemical and biological function of 3-helix structure collagen*". (2) Recombinant humanized collagen, defined as "*Sequence of specific type of human collagen, or a combination of functional fragment*". (3) Recombinant collagen-like protein, defined as "*sequence with low homology with the gene-encoding human collagen*" [69]. Due to different pos-translational requirements, these different classes of collagen could be expressed with different systems. Xiang et al. [70] referred to a recombinant collagen-like protein as a "*sequence with low homology with the gene-encoding human collagen*", highlighting the advantages of using *Escherichia coli* as an expression system, namely the low fermentation costs, efficacy, reduced production time, and the clear expression mechanism and well-known genetics of this expression system. However, one major limitation of bacterial fermentation is the post-translational modification and the potential production of inclusion bodies in the cell. As an alternative, eukaryotic expression systems, such as *Pichia* spp., have been used for collagen production due to their suitability for high-density fermentation, higher protein secretion levels, and an effective post-transcriptional modification system [71].

Additionally, to address the challenge of producing high-quality collagen with adequate post-transcriptional modifications, the use of co-expression systems has been proposed to produce the desired collagen type. An example is the production of hydroxylated collagen (containing hydroxyproline), which presents a challenging target molecule due to its post-transcriptional requirements. A potential solution based on a co-expression approach was published by Fang, Ma, Liu, Wang, Cheng, Zheng, Wu, Xia, Chen, Yang, Hao, and Zhang [46], who proposed a co-expression system comprising recombinant human collagen $\alpha1$(III) chain and the viral prolyl 4-hydroxylase using the yeast *Pichia pastoris* GS115 strain, resulting in a protein yield of 0.7 mg/mL (not optimized conditions).

4.3.3. Squalene

Squalene is a triterpene hydrocarbon used in the cosmetic industry mostly due to its moisture retention properties, though it has also been associated with other bioactive properties, namely its capacity to act as a cardio-protective, anti-infection, and antioxidant agent. As previously mentioned, one of the main issues with squalane is its sourcing, as raw materials for extraction are either vegetable oils (low yield) or the liver of the deep-sea sharks. Thus, the use of fermentation has been explored for the heterologous production of squalene using different expression systems. It could be produced by both bacteria and archaea via the 2-C-methyl-D-erythritol 4-phosphate pathway or in eukaryotic systems by using the mevalonate pathway (MVA). Additionally, with the incorporation of metabolic engineering, some strains have been modified to improve squalene production, targeting the improvement of the mevalonate pathway, the inhibition of competing pathways, stimulating an increase in acetyl-CoA supply and other cofactor availability, the incorporation of the isopentyl pathway, or organelle engineering [72]. Squalane production in *Saccharomyces cerevisiae* has been reported using a strain modified through the integration of genes to eliminate the feedback inhibition induced by ergosterol and to increase the MVA pathway output, resulting in the production of 8.2 g/L squalene in a 5 L bioreactor [49]. Another expression system was explored by Zhang, Yang, Chen, Lin, Wu, and Liang [47], as they created a three-pronged metabolic engineering strategy for boosting squalane production in *Pichia pastoris.* The first step focuses on increasing the supply of squalane building blocks by improving the output from the mevalonate pathway; the second involves increasing the conversion of said components into squalane by over-expressing squalene synthase; and lastly, the methanol metabolism pathway was reconstructed to divert metabolites into squalane biosynthesis. These modifications resulted in fermentative production of 20.80 ± 0.02 g/L squalane using a fed-batch system. The development of a high-producing fermentative system encompasses a combination of different factors, like media components, compound concentration, gene expression, and micro-organisms, among others. This widespread approach has resulted in the production of 1628.2 mg/L of squalene using a *Yarrowia lipolytica* combining the overexpression of limiting enzymes, the improvement of precursor molecules as well as the optimization of culture medium and fermentation conditions [48]. Thus, precision fermentation offers a sustainable, viable alternative for industrial squalane production that can be optimized through metabolic engineering and selection of favorable fermentation conditions [48].

4.3.4. Ubiquinone (Coenzyme Q10)

Ubiquinone, also known as coenzyme Q10, has been used in the cosmetic industry due to its regenerative properties and its capacity to prevent cell membrane and low-density lipoprotein oxidation [73]. Conventional Q10 extraction implies the use of animal and plant tissues (e.g., liver, heart, leaves, and seeds) as source and has relatively low yields (15.5–172.6 μg/g). Chemical synthesis could also be a possibility, but its need for non-environmentally friendly reagents (petroleum ether or trichloromethane) and its long, complicated process have made it a less appealing alternative [74]. Sustainable trends have spotlit fermentation as a possibility for the development of greener producing lines, exploiting the presence of three major biochemical pathways related with Q10 production: the shikimate pathway (quinone ring), the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway (polyisoprene side chain), and the ubiquinone pathway [73,74]. Overall, two major strategies are used, either altering metabolic pathways in natural ubiquinone producers to induce its overexpression or the incorporation of these pathways non-natural Q10 producers.

In the case of natural Q10 producers, the optimization of fermentation parameters has also been studied with the addition of vitamins, amino acids, and other precursor molecules to the culture media, with the supplementation of 2 g/L of vitamin B1, resulting in an increase in production from 31.24 mg/L to 138.24 mg/L [50]. These results can then be further optimized using metabolic engineering by stimulating the overproduction of key enzymes, improvement of storage capacity, or the incorporation of heterologous expression [42].

On the other hand, when considering micro-organisms without a natural capacity to produce coenzyme Q10, *Corynebacterium glutamicum* (industrially used for amino acids production) has been genetically engineered to be able to carry out the heterologous expression of precursor molecules (farnesyl diphosphate, FPP; and p-hydroxybenzoate, pHBA), as well as carry out the prenylation of pHBA and subsequent reactions to produce Q10 [75]. In a similar approach, the heterologous expression of the Ubiquinone complex in *Escherichia coli* has been carried out to promote the production of up to seven-times-higher levels of coenzyme Q10 in comparison to the control, using an agrifood byproduct, hydrolysate from a wheat side stream, as the substrate [76].

4.3.5. Resveratrol

Resveratrol is a well-known aromatic compound known for its beneficial properties (e.g., antioxidant and anti-inflammatory properties): It is mainly found in grape, berries, and peanuts, though its recovery through these plant sources deals with potential seasonal variations as well as fluctuations in yield and purity [41]. As a response, the production by fermentation technologies could present a better approach for resveratrol recovery, with the required genetic modifications possibly being introduced in different systems, such as *Escherichia coli*, *Corynebacterium glutamicum*, *Lactococcus lactis*, *Pichia pastoris*, or *Saccharomyces cerevisiae*, among others [77]. Its biosynthesis pathway englobes the phenylpropanoid acid (cinnamic and *p*-coumaric acids) derived from aromatic amino acids: L-phenylalanine and L-tyrosine, which are further converted into cinnamoyl-CoA and p-coumaroyl-CoA by 4-coumarate-CoA ligase (4CL). Finally, a stilbene synthase (STS) will create one molecule of resveratrol by condensing three malonyl-CoA moieties with one 4-coumaroyl-CoA [77].

Production of resveratrol using bacterial strains was explored by Park, Lim, Ahn, and Kim [51], who reported that using an *E. coli* with genetic modifications related to the synthesis of precursor molecules (*p*-coumaric acid) and the manipulation of the shikimate pathway (addition of resveratrol synthesis) resulted in a production (in 48 h) of 80.4 mg/L resveratrol, using a specific growth broth. The role of the carbon source was studied by Kobayashi, Inokuma, Matsuda, Kondo, and Hasunuma [41] by comparing the capacity of a genetically modified yeast *Pichia stipites* to produce resveratrol using different carbon sources (glucose, fructose, xylose, sucrose, cellobiose, among others) with results showing that resveratrol production using cellobiose and sucrose (529.8 and 668.6 mg/L) was the highest (in 120 h) when comparing with glucose (237.6 mg/L). These authors attributed the differences to the prevention of catabolite repression, slow substrate consumption, and a lower accumulation of metabolites involved in the pathways. Under a sustainable, resource-efficiency perspective, the use of genetically modified *Saccharomyces cerevisiae* was considered to accommodate both the simultaneous saccharification and resveratrol-producing fermentation process using *Eucalyptus globulus* wood (an agrifood byproduct), showing that 151.65 mg/L resveratrol could be produced using 5% of *Eucalyptus globulus* wood in the medium [53].

Prenylated compounds are emerging as an interesting alternative to resveratrol, given their better cell permeability and enhanced bioactivity, and they can be produced Via precision fermentation. For instance, an *E. coli* modified with prenyltrasnferase gene (AmbP1) has been used for the biotransformation of resveratrol to prenylated resveratrol, resulting in a final conversion rate of 36.9%, and a new prenylated phenolic (3-O-geranyl resveratrol) with higher antioxidant activity than resveratrol [54]. Similarly, Wang et al. [78] developed a method for the biosynthesis of prenylated resveratrol using a modified *E. coli* capable of co-expressing both the *p*-coumaric acid to resveratrol pathway and the MVA pathway, with prenyltranferase IAcE converting resveratrol to 2-C-prenyl resveratrol (68.4 mg/L). These advancements underscore that developing resveratrol through fermentation is a dynamic field with considerable potential for improvements at the genetic and operational levels and even through exploring post-translational modifications to boost its bioactivities.

4.4. Selection of the Biological Platform for Precision Fermentations

Precision fermentation leverages a variety of engineered biological platforms to produce high-value cosmetic ingredients; thus, selecting the appropriate biological platform for any process is key, as it impacts the system capabilities, scalability, and regulatory framework of the final product, with each offering distinct advantages and challenges. Bacterial platforms, like *Escherichia coli*, are typically preferred due to their rapid growth, well-known genetics, and their capability to generate peptides and small molecules in larger-scale conditions. However, as we are talking of prokaryotic systems, they are only suitable systems when the target compounds require little to no eukaryotic post-translational modifications [79–82]. Yeasts, such as *Saccharomyces cerevisiae* or *Pichia pastoris*, are robust eukaryotic hosts that have the capacity to produce more complex molecules (e.g., recombinant proteins and enzymes), which often require glycosylation or other post-translational processing. Moreover, these systems have been widely used for this purpose, with their industrial maturity and versatile engineering strategies making them a potentially interesting staple for cosmetic ingredient production pipelines. Filamentous fungi (e.g., the yeast-like *Yarrowia lipolytica* fungus) naturally secrete large amounts of enzymes and lipid derivatives, which makes them particularly interesting systems if seeking to produce secreted proteins or lipid-based emollients. Moreover, the secretion of target ingredients into the culture media results in a simplifying of downstream purification processes and therefore a higher cost-effectiveness of the overall production process [83–87]. However, the challenges in the scale-up and process optimization when exploiting these platforms currently limit their industrial prevalence [88]. Among these potential platforms, yeasts and bacteria dominate commercial implementation, owing to their established processes, regulatory acceptance, and availability of advanced genetic tools for engineering them.

The current diversity of biological platforms enables precision fermentation to meet a broad spectrum of cosmetic ingredient needs, from simple small molecules to structurally complex ones. The choice of micro-organism or cellular system requires balancing multiple interrelated factors, which include yield, metabolic compatibility, process scalability, safety considerations, and downstream processing requirements. A comprehensive understanding of these criteria is key to guide the rational selection of platforms tailored to address the demands of cosmetic ingredient production.

4.4.1. Productivity

High productivity of target compounds (reflected in titers and volumetric yields) is fundamental for industrial relevance and economic viability and thus must be one of the core aspects to consider. Bacteria are frequently preferred, given their relatively fast growth rates, particularly when coupled with the ease of their genetic code manipulation. As an example, a *Corynebacterium glutamicum* engineered strain, devoid of peripheral and central degradation pathways for aromatic compounds and with incorporated pathways for stilbene synthesis has achieved resveratrol titers exceeding 150 mg/L in batch fermentation, underscoring its suitability for producing valuable polyphenols [89]. Similarly, *E. coli* strains have been engineered (in a plasmid-free manner) synthesize astaxanthin in concentrations up to 1.4 mg/g of cell dry matter [90].

4.4.2. Metabolic Compatibility, Engineering, and Post-Translational Requirements

Hosts possessing native or closely related biosynthetic pathways for the desired targets tend to be more efficient at producing complex products and thus have a lower metabolic burden related with heterologous expression [91,92]. This makes metabolic compatibility a key aspect to consider when seeking to develop precision fermentation processes. An example is the use of yeasts to produce terpenoids, flavonoids, and polyphenols, as by tinkering with their inherent mevalonate and shikimate pathways (which also makes them more resistant to the presence of the resulting fermentation products), it is possible to produce compounds of interest. One example is the engineering of *S. cerevisiae* and *Y. lipolytica* to produce β-farnesene, a fragrance precursor, through the modification of its endogenous terpene metabolism [93–95]. Similarly, some fungal strains (like *Y. lipolytica*), known for their capacity for lipid accumulation, are more suitable platforms to produce fatty acid derivatives integral to emollient and skin-conditioning formulations [96–98]. In fact, engineered strains have been reported to successfully produce ω-hydroxy fatty acids important for skin hydration [99,100]. Photosynthetic microalgae also offer attractive platforms for carotenoid and polyunsaturated fatty acid production due to their photosynthetic carbon fixation, though scale-up remains more challenging [101–103].

Beyond intrinsic metabolic compatibility, the maturity and sophistication of genetic engineering and synthetic biology toolkits available also impacts platform suitability. Well-known platforms like *E. coli* and *S. cerevisiae* benefit from mature, versatile tools (including CRISPR/Cas systems, synthetic promoters, and regulatory circuits) that facilitate rapid strain development and complex pathway engineering. In contrast, non-conventional yeasts, filamentous fungi, or microalgae, which often have less developed genetic engineering toolkits, imply longer development timelines and potential optimization hurdles. This will compromise the process implementation not only due to the timewise effects but also the unknown genetic stability of the resulting strains [104–106].

The need for post-translational modifications often dictates whether bacterial or eukaryotic hosts are preferred, as specific modifications are necessary for many cosmetic proteins to enhance their bioactivity, stability, and functionality. Bacterial systems generally lack eukaryotic post-translational modifications (e.g., glycosylation), and thus, when post-translational modifications are required, they are not selected as production platforms [107]. This has resulted in a steering of complex protein production towards yeasts, filamentous fungi, or even mammalian cells when more specific modifications are required. Recombinant collagen is both a key cosmetic ingredient and a great example of this. It has been successfully produced in *P. pastoris*, which performs appropriate post-translational modifications and secretes the protein extracellularly (which also reduces the purification burden) [108–111].

4.4.3. Suitability for Industrial-Scale Processes

Unlike lab-based production, translation into an industrial setting means that the platforms will be subjected to industrial stressors, which include shear forces, pH shifts, osmotic stress, and extended fermentation durations. Thus, a platform's robustness to these stresses is essential for a process scalability and operational stability. Micro-organisms like *Bacillus subtilis* and *S. cerevisiae* have demonstrated resilience in large-scale fermenters, facilitating high-yield recombinant hyaluronic acid production [112,113].

Cost and downstream processing considerations are also pivotal. Platforms capable of secreting target products directly into the medium result in simpler purification protocols and therefore lower production costs, which is particularly interesting in price-sensitive markets like the cosmetic ingredient's one [114]. With these types of platforms frequently being selected for recombinant collagen and enzyme production.

4.4.4. Regulatory Framework

The regulatory framework surrounding precision fermentation-derived ingredients (discussed in detail in Section 6) is complex. As safety and regulatory compliance are paramount, it frequently also has a significant impact on platform choice, particularly as organisms with GRAS or Qualified Presumption of Safety (QPS) status frequently enable smoother regulatory pathways. In fact, organisms such as *S. cerevisiae*, *Lactobacillus*, and *B. subtilis* are frequently also considered due to the regulatory familiarity and long histories of safe use in food and cosmetics [6,115].

4.4.5. Other Aspects

The intellectual property landscape and freedom to operate are also aspects one must frequently consider when carrying out platform selection. Well-characterized hosts are also frequently associated with broad existing patents or open-access genetic parts, which will possibly impact licensing risks and costs but can also expedite commercialization. On the other hand, emerging hosts often face more complex intellectual property environments requiring dedicated clearance strategies [116].

5. Technological Challenges in Scale-Up

Scaling up precision fermentation from laboratory to a reliable industrial production process presents a series of persistent technological and operational challenges that directly impact process economics, product quality, and the overall production scale one can achieve. One of the main challenges is maintaining consistent product quality and yield during scale-up to large-volume bioreactors, as non-linear changes in mass transfer, oxygen and nutrient availability, shear stress, and pH gradients can significantly affect metabolism and physiology, resulting in variations in parameters like titers produced and bioactivity. This is particularly crucial when considering the scale-up of high-value molecules, like recombinant collagen or hyaluronic acid [117–122]. Overall, parameters deemed critical at small scale, like oxygen mass transfer coefficient (kLa), typically require re-optimization for industrial bioreactor designs to avoid process inefficiencies and unforeseen yield drops [123]. Additionally, other variables like scale-dependent mixing heterogeneities, batch-to-batch variability, and medium formulation inconsistencies further complicate the upscale process and frequently demand iterative adjustments.

Another significant barrier that precision fermentation needs to overcome so its scale-up is viable is the genetic stability of engineered microbial strains, as when under prolonged or continuous fermentation conditions, the engineered traits may be lost (or silenced), resulting in lower-than-expected yields and product heterogeneity [19,124]. Strategies such as chromosomal integration, stable plasmid maintenance systems, or kill-switch regulatory elements are currently under development to enhance the robustness of the strains and facilitate larger-scale applications, but their industrial viability still requires validation [117–122].

Cost-efficiency is a critical aspect to consider when attempting to scale-up any process. This is particularly true when considering precision fermentation processes, since they depend on expensive feedstocks, such as culture media base, and require tightly controlled environmental conditions, which translates into increasing OpEx values. This may be further aggravated by downstream processing requirements, which can make up a large portion of the overall production cost [124–126]. Additionally, the need for initial CapEx may also be driven up due two major factors: the need for more advanced infrastructure and automation to meet the cosmetic-grade standards and additional R&D of the engineered strains to improve their growth kinetics and overcome any accumulated fermentation-byproduct-driven inhibition [124]. The advancement of continuous fermentation systems offers promising opportunities to intensify operations (and improve the economic return) by improving equipment utilization and reducing downtime compared to traditional batch processes, but continuous industrial-scale operation imposes elevated technical challenges, including sustained genetic stability, contamination control, and process monitoring to preserve consistent product quality over extended runtimes. Also, the contamination risk increases significantly with fermentation volumes and reaction duration increase, as maintaining aseptic conditions at scale is challenging. This means that production costs may be further driven up by the implementation of robust sterilization protocols, inline contamination detection systems, and rapid response strategies, which will be vital to avoid discarding batches and decontamination-related downtimes.

Beyond these factors, feedstock availability (resource competition) is an increasingly critical consideration as production scaling-up increases the demand for carbon sources like sugar-derived glucose, corn, or potato starch, which can potentially cause/intensify competition with food and biofuel sectors for these raw materials. This will not only drive their prices but also raise other ecological and social concerns about monoculture practices and land use. In this scenario, sustainable sourcing pathways, which include the valorization of agricultural waste streams, are becoming ever more interesting. These solutions foster circular bioeconomy principles and can result in a lower environmental impact, but their use not only implies the need for the establishment of new value-chains, but apports an additional level of complexity (and costs) to the production process.

6. Regulatory Framework

In Europe, to ensure consumer safety and transparency, cosmetic products and ingredients are regulated under Regulation (EC) No 1223/2009 [127]. In fact, all cosmetic ingredients (including those resulting from fermentative processes) must be in accordance with several regulatory frameworks, which are detailed in Table 3.

Precision fermentation is emerging as a new approach to be exploited by the cosmetic industry. However, while it presents numerous advantages, ensuring its compliance with European Union (EU) regulations is paramount for a successful entrance into the European market. This means adhering to safety, environmental, and labeling standards while understanding legal classifications and environmental compliance.

Table 3. Key European regulatory framework for cosmetic ingredients.

Regulation	Scope	Implications for precision Fermentation Ingredients
• Regulation (EC) No 1223/2009 on cosmetic products	• Governs the safety, marketing, and labeling of cosmetic products in the European Union (EU). Ensures consumer protection and establishes ingredient restrictions.	• Precision fermentation ingredients must undergo toxicological safety assessments (skin irritation, sensitization, etc.). • Compliance with Annexes II and III (list of banned and restricted substances). • Requires listing under International Nomenclature of Cosmetic Ingredients (INCI) for transparency.
• Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing a European Chemicals Agency	• Regulates the registration, evaluation, and authorization of chemicals used in the EU to ensure environmental and human health safety.	• If the ingredient is classified as a chemical substance, manufacturers must register it under REACH if imported or produced at $\geq$1 ton/year. • Toxicological and ecotoxicological data submission required for new substances. • May require a Chemical Safety Report (CSR).
• Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms	• Controls the deliberate release of genetically modified organisms (GMOs) into the environment and their use in industrial applications.	• If genetically modified micro-organisms (GMMs) are used in fermentation, compliance with GMO labeling and safety requirements is required. • If the final ingredient is free of GMO traces, it may be exempt from GMO-specific regulations.
• ISO 22716:2007 Cosmetics | Good Manufacturing Practices (GMP) | Guidelines on GMP	• Provides GMP guidelines for cosmetic production, ensuring ingredient quality, safety and traceability.	• Precision fermentation processes must follow strict GMP protocols for consistency and quality. • Batch traceability, contamination control, and hygiene standards are essential for compliance.
• Regulation (EU) No 655/2013 laying down common criteria for the justification of claims used in relation to cosmetic products	• Establishes common criteria for making claims about cosmetic products to prevent misleading marketing.	• If a product claims to use biotechnologically produced or sustainable ingredients, it must be scientifically substantiated. • Requires proof of efficacy for active ingredients derived from precision fermentation.
• Microbiological and Contaminant Safety Standards | EC No 1223/2009 Annex I	• Sets limits for microbiological contamination to ensure safety.	• Precision fermentation-derived ingredients must be free of pathogens, mycotoxins, and endotoxins. • Residual fermentation byproducts and purification methods must be validated to meet microbiological purity standards.
• Directive 2008/98/EC on Waste Management	• Regulates the handling, recycling, and disposal of industrial and hazardous waste to minimize its environmental impact.	• Fermentation residues must be classified and managed according to EU waste regulations. • Byproducts such as biomass, culture media, and solvents must be assessed for reusability, recycling, or safe disposal. • If using GMM, waste must be sterilized or inactivated before disposal to prevent environmental release.
• Directive IED 2010/75/EU on Industrial Emissions	• Establishes pollution prevention and control standards for industrial facilities to limit emissions, air pollutants, wastewater and solid wastes	• Fermentation facilities must comply with emission limits for volatile organic compounds, CO_2, methane, and nitrogen oxides. • Water discharge regulations apply to fermentation byproducts, requiring wastewater treatment to remove biological contaminants and residual media. • Requires manufacturers to implement Best Available Techniques for pollution reduction.
• ISO 14044/2006 Life cycle assessment (LCA) standards	• Establish guidelines to evaluate the environmental impact of processes, which include precision fermentation processes	• Manufacturers must conduct an LCA to quantify the carbon footprint, water usage, and resource efficiency of fermentation-derived ingredients. • LCA must be performed according to ISO 14044/2006 standards to validate sustainability claims. • Comparative LCA studies are required to demonstrate that precision fermentation is more sustainable than petrochemical, plant-derived, or animal-derived alternatives.

6.1. Classification and Registration of Precision Fermentation Ingredients

Precision fermentation ingredients' classification within the EU depends on several different factors like their chemical composition or production process. In its base, the regulation regarding cosmetic products (EC No 1223/2009) indicates that all ingredients to be used for cosmetic application must be assessed for safety and listed under INCI [127]. The INCI list is a globally recognized standard that was established to provide uniformity and transparency in ingredient listing on cosmetic product labels while ensuring consistency across international markets and promoting consumer trust. For innovative cosmetic ingredients, particularly those derived from precision fermentation, obtaining an INCI designation is a strategic move that facilitates commercialization while meeting stringent safety and labeling requirements. Falling within INCI has additional significance for precision fermentation ingredients because (i) the absence of genetically modified microorganisms on the final product has been demonstrated, (ii) the ingredient efficacy has been scientifically validated (to prove any made claim), and the ingredient has been approved by the PCPC or another regulatory body [127–129].

Additionally, precision fermentation ingredients are subjected to additional scrutiny because they are regarded as being of biotechnological origin. Here, a key distinction lies in whether the ingredient is classified as a natural derivative or a chemically modified substance. If the fermentation results in a substance with the same molecular structure as the naturally occurring one, the resulting ingredient is classified as natural-derived. On the other hand, should any molecular modifications occur, it is regarded as a chemically synthesized ingredient, and this means that it must also be compliant with the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation (EC No 1907/2006). If a substance is not already a part of REACH, i.e., it is not registered in the European Chemicals Agency (ECHA) database and does not fall into a regulatory exemption (naturally occurring substances; polymers; substances encompassed by EC No 1223/2009, or used exclusively in research and development–listed in the Annex Annexes IV and V or REACH), a compliance check and subsequent substance registration under REACH is mandatory. The requirements to do a full REACH registration encompass substance identity information, its physicochemical data, toxicological and ecotoxicological data, classification and labeling proposals as well as a guidance on safe use and exposure scenarios that are volume dependent [127,130].

6.2. Safety and Toxicological Assessment Framework for Precision-Fermentation-Derived Cosmetics

Safety and toxicological evaluation are critical requirements under EC 1223/2009, as this regulation stipulates that all cosmetic ingredients (regardless of whether they are produced by precision fermentation or not) must undergo rigorous scientific evaluation to ensure consumer safety and compliance with legal standards. Depending on their classification, as natural derivatives or chemically synthesized ingredients, the extent of toxicological assessment requirements varies significantly. The Cosmetic Product Safety Report (CPSR) is a key regulatory document that ensures the safety evaluation of cosmetic ingredients (including the precision fermentation ones) before their use in cosmetic products. It encompasses three major areas: Toxicological risk assessment, microbiological purity analysis, and stability studies [127].

6.2.1. Toxicological Evaluation

A comprehensive toxicological risk assessment is required for all cosmetic ingredients. In its simplest form, it encompasses dermal characterization studies, which include skin irritation and sensitization analysis (to determine potential allergenic reactions), genotoxicity and mutagenicity testing (to evaluate the risk of DNA damage or carcinogenicity), and repeated-dose toxicity studies to assess risks associated with chronic exposure. Also needed to ensure an adequate regulatory framework of the developed ingredients, is compliance with Scientific Committee on Consumer Safety (SCCS) guidelines whose aim is to ensure that dermal penetration, systemic toxicity, and cumulative exposure risks are adequately assessed. These evaluations are required regardless of whether the precision fermentation products are classified as a natural derivative or a chemically synthesized compound [127,131].

In the scenarios where modifications of molecular structure do occur (i.e., chemically synthesized), additional safety evaluations are required, thus ensuring that novel compounds that arise from their metabolization do not pose unforeseen risks (metabolic and degradation pathway analysis). If the ingredient is designed for leave-on formulations or sunscreens, there is also the need for phototoxicity studies (encompassing the effects of UV exposure upon its toxicity), and if it has no historical precedent of use, the execution of long-term toxicological testing is also required. If the precision fermentation ingredient is classified as a naturally derived, the overall regulatory burden may be reduced, as the existing body of knowledge on the naturally occurring molecule may be used to support safety claims, and some waivers may be made on the need for animal testing, particularly if alternative validated methods exist (in line with the EU animal testing bans). A summary of toxicological studies required according with the ingredient classification can be found in Table 3 [127].

6.2.2. Microbiological Risk Assessment and Contaminant Control

Precision fermentation is dependent on micro-organisms; therefore, a rigorous microbiological purity assessment is paramount to ensure ingredient safety and its compliance with Annex I of EC No 1223/2009 (Table 4). In fact, all fermentation-derived ingredients must be tested for the presence of pathogenic micro-organisms (encompassing bacteria, filamentous fungi and yeasts) to ensure their removal. If fungal fermentation is used, mycotoxins must also be assessed, while endotoxins are mandatory in bacterial fermentation (particularly when mediated by Gram-negative bacteria) to avoid the risk of inducing immune responses in sensitive individuals. In addition, depending on the fermentation/purification systems used, additional assessment of byproducts may be considered like the quantification and toxicity of non-target metabolites produced (e.g., secondary metabolites), the levels of residual host cell proteins and DNA must be confirmed to be in accordance current regulatory limits (particularly important for GMM used in precision fermentation), and all solvents used must also be below regulatory thresholds. For this last parameter, stricter limits on solvents levels may apply under REACH regulation when considering chemically synthesized ingredients [127,130].

Table 4. Summary of toxicological, stability, and microbiological control studies required for precision fermentation ingredients according to their classification of naturally derived or chemically synthesized.

	Assay	Natural Derivative	Chemically Synthesized
Toxicity assessment	• Skin irritation and sensitization	• Required, but historical safety data may allow waivers.	• Mandatory with in vitro and/or in vivo testing.
	• Genotoxicity	• Not required if structurally identical to a known safe natural substance.	• Required if the structure is new or chemically modified.
	• Repeated dose-toxicity	• Only required if new exposure routes (e.g., inhalation) are introduced.	• Required for systemic safety assessment.

Table 4. *Cont.*

	Assay	Natural Derivative	Chemically Synthesized
	Phototoxicity (UV exposure risk)	Only required if the ingredient is used in leave-on formulations exposed to sunlight.	Required if the new structure has aromatic rings or conjugated systems.
	Bioavailability and Metabolism	May use read-across data from natural sources.	Must be determined if the ingredient is novel.
	Ecotoxicity and Environmental fate	Not required unless the production process alters natural degradation pathways.	Required to assess persistence and bioaccumulation risks.
Stability assessment	Standard stability testing	Required under typical storage conditions.	Required, with additional chemical reactivity studies.
	Degradation pathway analysis	Only required if there are concerns about oxidation or shelf life.	Mandatory, especially if new chemical structures may form degradation products.
	Interaction with cosmetic formulations	Typically follows the known behavior of natural compounds.	Extensive formulation compatibility studies required.
Microbial and Contaminant control	Pathogen and Microbial contaminants	Must be tested but follows standard Annex I microbiological safety limits.	Must be tested with stricter purity standards due to increased regulatory scrutiny.
	Residual host cell proteins and DNA [1]	Removal below regulatory thresholds required.	Full documentation of removal and no bioactivity confirmation needed.
	Processing solvent and Purification residues	Standard limits apply (e.g., ethanol, water-based extractions).	Stricter limits apply if using synthetic solvents.
	Heavy metal and Impurity testing	Generally follows standard cosmetic ingredient limits.	Detailed impurity profiling required for novel ingredients.

[1] Specific for precision fermentation (GMO/GMM).

6.2.3. Stability Studies

To ensure that ingredients maintain their regulatory compliance and that they remain effective and safe for the consumers, the demonstration of their long-term stability is also a crucial aspect encompassed within the regulatory framework related to cosmetic ingredients (Table 3). Regardless of their classification as naturally derived or chemically synthesized ingredients, all precision-fermentation-derived ingredients must undergo two types of stability testing. The first is accelerated stability testing, which simulates storage conditions and focuses on characterizing physicochemical and microbiological stability. The second focuses on identifying the degradation pathway of relevance when considering active ingredients prone to hydrolysis, oxidation, or photodegradation.

If the ingredient falls within the natural derivatives category and has a history of use in the cosmetic industry, the stability assessment requirements can be more lenient. However, chemically synthesized ingredients require more analysis than just standard stability testing. Namely, to ensure that no toxic secondary compounds form over time, the degradation pathway must not only be identified, but also the degradation products must be analyzed over time. Also, in this scenario, the interactions with other cosmetic ingredients (like preservatives or emulsifiers) must be considered to evaluate the new ingredient's reactivity.

6.3. Environmental and Manufacturing Compliance Framework for Precision Fermentation Ingredients

Precision fermentation allows for the production of high-value cosmetic ingredients in a manner that neither relies on petrochemical synthesis nor depends on virgin raw materials (i.e., plants). This has resulted in its recognition as a sustainable biotechnological approach for cosmetic ingredient sourcing, but large-scale production must adhere to strict environmental and manufacturing compliance frameworks to ensure their safety, sustainability, and, subsequently, the regulatory approval of the ingredients/production processes. As shown in Table 3, the EU has a considerable regulatory framework that governs the assessment of the environmental impact and manufacture of precision-fermentation-derived ingredients that encompass EC No 1223/2009, REACH (EC No 1907/2006), Directives 2008/98/EC, IED 2010/75/EU, and ISO 22716:2007. In addition, if aiming to make any type of claim regarding the sustainability of the process/ingredient, it is also important to consider ISO 14044/2006, which contains the guidelines to carry out the evaluation of the environmental impact via an LCA of the precision fermentation process [127,130,132–135].

Despite being recognized as a green alternative to conventional ingredient sourcing practices, large-scale fermentations generate byproducts that must be managed in compliance with the relevant EU regulations to ensure responsible waste management, minimize pollution, and reduce carbon emissions. The Industrial Emissions Directive (IED 2010/75/EU) and the Waste Framework Directive (Directive 2008/98/EC) provide the most relevant framework, encompassing critical concerns like air and water emissions and microbial waste management [133,134].

The use of fermentation reactors typically implies the use of bioreactors that generate gaseous byproducts. In this scenario, under the framework of IED 2010/75/EU, there is the need for gas filtration systems that control the emissions of volatile organic compounds and relevant greenhouse gases like carbon dioxide. This framework also stipulates that should the risk for aerosolized bioactive compounds exists, systems must be in place to contain them within controlled environments to avoid unintentional environmental exposure [134].

Liquid effluents are a common (and large) byproduct generated during the fermentation process, and they must be treated to meet EU wastewater treatment standards before being released into the water systems. As precision fermentation implies the use of GMM, Directive 2001/18/EC stipulates the need to implement containment measures that prevent the release of GMM into the environment. Directive 2008/98/EC provides the framework for handling both solid (residual biomass) and liquid effluents. In traditional fermentation processes, the solid waste (typically microbial biomass) can be recycled as industrial compost to promote circular economy practices so long as it does not involve the use of toxic solvents, heavy metals, or other hazardous chemicals. However, in precision fermentation GMM are used, and that makes this recycling more complicated, particularly to avoid the deliberate release of GMO into the environment. While possible to do so, one must comply with specific biosafety and environmental conditions. Namely, they must be fully inactivated using approved sterilization methods (e.g., autoclaving ≥ 121 °C, 15–20 min), the inactivation efficiency must be verified (usually Via real time PCR targeting viable DNA), they must be free from hazardous contaminants (antibiotic residues, heavy metals, toxic metabolites, residual host cell DNA, pathogenic contaminants, or endotoxins), and a risk assessment for soil and environmental safety must be undertaken assessing site-specific risks, like potential gene transfer (even after inactivation), impact on soil microbiome, or long-term biodegradation and nutrient release profiles. Even so, local authorities may request the execution of pilot trials before allowing large-scale application as compost. In addition, under the framework of 2001/18/EC, the use of compost containing GMM may require notification/approval by local authorities. As an alternative to composting, while still attempting to promote a circular economy model for resource use, the GMM solid waste can either be used in anaerobic digestion processes towards the production of biogas or used as the raw material for the recovery of some (non-GMM) components of commercial relevance from the microbial biomass, such as proteins and cell wall components. Should any of these alternatives not prove viable, the regulations stipulate that the waste should be landfilled (in the appropriate containers) [130,133].

6.4. Labeling and Market Claims

Precision fermentation cosmetic ingredients, like all other cosmetic ingredients to be marketed within the European Union, must comply with EU No 655/2013, which specifies a set of common criteria for the establishment of cometic claims. This regulation aims to prevent deceptive practices that can misinform consumers regarding products composition, efficacy, or sustainability and thus ensure that all marketing statements made about any ingredient are truthful, non-misleading, and evidence-based.

As precision-fermentation-derived ingredients have additional connotations besides just their efficacy (namely their sustainability), the manufacturers of these ingredients must substantiate claims related not only with functionality but also with ingredient sourcing and environmental impact. As previously discussed, the ingredients registration in INCI is mandatory, and it goes a long way in ensuring that related claims are clear and that its identification across the different global markets remains the same (i.e., it has the same name in the labels worldwide). Additionally, as the ingredients are derived from GMM, the disclosure of this information to regulatory authorities is mandatory (upon request). In this case, it is also important to take into account regulation (EC) No 1830/2003, which specifies traceability and labeling requirements for products containing GMO.

If the ingredients are classified as naturally derived, and, overall, no traces of genetically modified DNA or proteins are found in the final product, it may be exempt from GMO-labeling requirements. However, as EU No 655/2013 requires all claims made to be truthful and evidence-based, the non-GMO claim must be scientifically substantiated, and care must be given, so consumers are not misled regarding the production process. It is also important to bear in mind that some certification bodies may disqualify ingredients as non-GMO based on their use of GMM, even if no traces of their genetic material are found in the final product. On the other hand, if the ingredient resulting from the precision fermentation process is classified as a chemically synthesized ingredient, the non-GMO claim cannot be made regardless of the absence of modified DNA or proteins. In sum, it is important to understand that the use of GMM in precision fermentation processes does not, on its own, require the addition of a GMO label, but the inclusion of a non-GMO one does imply compliance with the previously discussed regulation [136,137].

Another important aspect to consider under the transparency aspect of EU 655/2013 is the need for the disclosure of both ingredient sources and production methods used. This means that, if an ingredient is attained via precision fermentation, this must be made clear. So, referring to them as natural is not allowed (this may only be used regarding ingredients directly extracted from plants), and stating that they are an alternative to natural extracts implies providing comparative data that demonstrates that the precision fermentation ingredient has an equal (or better) performance than its natural counterpart. Also, claims of it being identical to natural products (nature-identic) or biomimetic must be accompanied by data that demonstrates that their chemical composition and function are equivalent to natural/endogenous molecules [136].

Marketing claims play an essential role in the consumers' decision-making process and the products' market success. Within the EU, to ensure all claims are truthful and substantiated by scientific evidence, clear, and readily understandable for consumers while avoiding misleading the consumer and remaining objective, all cosmetic claims are regulated by EC No 655/2013. If a product is marketed for a specific cosmetic benefit (e.g., antioxidant or anti-aging effects), the manufacturers must report data that demonstrates the alleged effects, namely in vitro studies that can be biochemically based, cell culture models, ex vivo works on skin explants or reconstructed human epidermis models, and clinical trials using volunteers (especially in scenarios were claims regarding hydration, wrinkle reduction, or skin elasticity improvements are made). To consider the reported data as valid regulators may require data to come in the form of peer-reviewed publications or as the results of reports made by independent, third-party institutions [136].

As previously mentioned, sustainability has become a well-established consumer priority, with sustainability-related allegations apporting significant value to both cosmetic products and their brands. Typically positioned as an alternative to petrol-based, animal- and plant-derived ingredients, manufacturers using precision fermentation frequently highlight the environmental benefits of their products. However, to ensure transparency and prevent misleading sustainability claims, manufacturers must substantiate them with scientific evidence. Namely, producers must provide quantifiable proof that their process has a lower environmental impact (e.g., lower carbon emissions, less land use, or less solvent consumption) as well as conduct comparative sustainability studies that demonstrate that their precision-fermentation-based process is more resource efficient than conventional ones. Also, an LCA (made in accordance with ISO 14044/2006 guidelines) must be used to quantify the carbon footprint, water usage, and waste generation associated with the ingredients. In fact, the LCA is crucial to substantiate claims that suggest that precision fermentation ingredients are safer or more sustainable than ones attained via conventional approach, as these claims require the existence of peer-reviewed data that compares data from new ingredients with traditional ones.

If a product misrepresents its environmental impact, it may face enforcement actions under EU's anti-greenwashing policies (e.g., label modifications, fines and financial penalties, product recalls, market restrictions, and even be subjected to legal actions) as well as subsequent brand/reputational damage and certification losses. Overall, this means that when ingredients are advertised as carbon neutral, this is supported by scientific evidence (and typically is only reachable by including carbon-offsetting programs). Similarly, claims identifying an ingredient as biodegradable or environmentally friendly need supporting data in the form of ecotoxicological testing made in accordance with OECD biodegradability protocols [135]. A more in-depth compilation of EU's anti-greenwashing regulatory framework and their main implications for precision fermentation ingredients are listed in Table 5.

Table 5. EU regulatory framework supporting anti-greenwashing policies and their implications for precision-fermentation-derived cosmetic ingredients.

Regulation	Scope and Relevance to Anti-Greenwashing	Implications for Precision Fermentation Ingredients
Directive (EU) 2005/29/EC on Unfair Commercial Practices	Prohibits misleading or unsubstantiated sustainability claims in marketing and product labeling.	• Any claim that precision fermentation is inherently more sustainable than traditional production methods must be backed by comparative LCA data. • The use of terms like nature-identical or biotechnologically derived must not mislead consumers into thinking the product is naturally extracted.

Table 5. *Cont.*

Regulation	Scope and Relevance to Anti-Greenwashing	Implications for Precision Fermentation Ingredients
Regulation (EU) No 655/2013 on Common Criteria for Cosmetic Claims	Stipulates the need for scientific validation for all claims used in cosmetic products.	• Manufacturers must provide LCA reports, resource efficiency studies, and ecotoxicology tests to support claims that precision fermentation ingredients have a lower environmental footprint than traditional alternatives. • If a precision fermentation ingredient is marketed as safer or purer than plant-derived ingredients, studies must confirm the absence of pesticides, heavy metals, or allergens.
Directive (EU) 2019/2161 (Omnibus Directive)	Strengthens consumer protection against deceptive green claims and introduces financial penalties for non-compliance (up to 4% of annual turnover).	• Companies promoting precision fermentation as a sustainable alternative must ensure carbon neutrality claims are substantiated with verifiable offset programs. Misleading claims about lower water usage, reduced energy consumption, or ethical advantages must be fully documented.
Directive 94/62/EC on Packaging and Packaging Waste	Ensures that packaging materials and sustainability claims are aligned with recyclability and environmental impact standards.	• Precision fermentation-derived ingredients must comply with biodegradability and packaging sustainability standards. If a product is marketed as plastic-free or zero-waste, it must meet packaging life-cycle requirements.
Directive (EU) 2018/851 on Waste Framework (Circular Economy Directive)	Prevents false claims about circular economic benefits by requiring scientific evidence for waste reduction and sustainability claims.	• If precision fermentation ingredients are marketed as zero or low waste manufacturers must disclose the disposal, byproduct recovery, and waste treatment methods used. Claims related to reduced land use or agricultural impact must be substantiated with quantifiable metrics.
Regulation (EU) 2018/848 on Organic Production and Labeling of Organic Products	Defines the use of the term organic in food and cosmetics, restricting its use to products that meet organic certification criteria.	• Precision fermentation-derived ingredients cannot be labeled as organic unless the fermentation feedstock itself is certified organic. Terms such as eco-derived or naturally fermented should be used with caution to avoid misleading consumers.
Directive 2014/95/EU on Non-Financial Reporting [1]	Requires large companies to disclose sustainability, environmental, and ethical impact data.	• Companies using precision fermentation must include LCA data, carbon footprint disclosures, and sustainable sourcing reports in their corporate sustainability statements. If precision fermentation claims are linked to ethical sourcing or biodiversity protection, supporting data on raw material sourcing impact must be provided.
Directive 2024/825/E Green Claims Directive	Introduces stricter regulations on environmental claims, requiring all sustainability statements to be independently verified before being used in marketing. Ensures that terms like "carbon neutral", "eco-friendly", and "biodegradable" are scientifically substantiated and prevents misleading greenwashing practices.	• Manufacturers of precision fermentation-derived ingredients must provide third-party verification for all sustainability claims, including carbon footprint reduction, waste minimization, and water efficiency. Claims related to environmental benefits must be backed by robust scientific methodologies, such as LCAs, and must comply with new pre-approval and transparency requirements before being marketed in the EU.

[1] To be replaced by Corporate Sustainability Reporting Directive.

6.5. Market Authorization and Notification

Regulation (EC) No 1223/2009 stipulates that all cosmetic ingredients, which includes those attained Via precision fermentation, must undergo a comprehensive safety evaluation (detailed previously). Additionally, manufacturers must submit a regulatory dossier as well as notify the commission through the Cosmetic Product Notification Portal (CPNP). The regulatory dossier will serve as the base to demonstrate compliance with safety, quality, and environmental impact requirements, and it is named the Product Information File (PIF). It must contain detailed ingredient information (Table 6) provided in accordance with the specific regulatory demands of each parameter, which vary depending on the ingredient classification. Once completed, the PIF must be submitted to the CPNP (mandatory for all cosmetic ingredients within the EU), along with the specification of the ingredient's function in the cosmetic formulation, expected concentration levels within the finished products, information on the manufacturer, responsible person, and the identification of EU distributors, all of this along with a summary of the safety information contained in the PIF and any existing SCCS opinion on the ingredient's safety. If the ingredient has no history of use, it is considered novel and it may also require an independent review by the SCCS. This review is particularly crucial for chemically modified ingredients produced via precision fermentation (e.g., bioactive peptides) due to their potential unforeseen toxicological risks [127].

Table 6. List of information required in a PIF dossier.

Specific Information Needed	
Ingredient identity and characterization	• Chemical characterization • Source (specify if GMM) • INCI name (or registration)
Toxicological and safety assessment	• Toxicological profile • Microbial safety data • Stability results
Environmental impact	• Biodegradability and ecotoxicity under REACH • Industrial emission assessment • Waste management assessment • Sustainability measures assessment (particularly if it is to be marketed as environmentally friendly)
Compliance with GMP	• ISO 22716:2007 certification for cosmetic ingredient production • Batch traceability records

Once an ingredient hits the European market, manufacturers must implement post-market surveillance programs that track any real-world adverse effects that may appear, monitor ingredient stability throughout its shelf life and, under Article 23 of EC 1223/2009, they must report any serious undesirable effect to relevant authorities within the member states. This also means that even when they reach the market, the precision fermentation ingredients (just like all other cosmetic ingredients) may be subjected to reevaluation, should any safety concern be raised. This can imply the request for additional testing (to verify continued compliance), the imposition of restrictions on ingredient's use, or even (if later identified as carcinogenic, mutagenic, or reprotoxic) the prohibition of its use [127].

7. Future Perspectives

7.1. Digital–Biotech Fusion and AI-Driven Optimization in Precision Fermentation

Looking ahead, the future of precision fermentation for cosmetic ingredients production is set to be transformed into a space where biotechnology meets advanced digital technologies, with this interaction possibly resulting in cutting-edge developments that will dramatically enhance process efficiency, sustainability, and scalability. The integration of artificial intelligence and machine learning opens innumerous new possibilities on how fermentation workflows are designed and managed. Platforms developed by companies such as TeselaGen, Ginko Bioworks, and Zymergen leverage AI algorithms to optimize strain development, media formulations, and process conditions in a way that was previously impossible. By using techniques like Bayesian optimization and deep learning, these technologies have cut the traditional design–build–test–learn cycle by up to 70%, greatly accelerating innovation, which means that new cosmetic actives can be developed and scaled more quickly, efficiently, and without sacrificing reproducibility [138].

7.2. Advances in Bioreactor Technologies, Real-Time Monitoring, and Adaptative Automation

Another promising advance comes from the evolution of next-generation bioreactor systems. These systems are becoming increasingly sophisticated, featuring modular designs equipped with a variety of sensors that provide real-time data on critical parameters like pH, dissolved oxygen, and cell density. This dynamic feedback enables the process to adapt on the fly, optimizing conditions to maximize yields. These adaptive systems are particularly valuable when working with delicate or high-density cultures, common in cosmetic ingredient production that demand precise handling to maintain ingredient quality. Additionally, real-time monitoring and automation may further enhance this transformation via the incorporation of inline biosensors coupled with sophisticated spectroscopic techniques like Raman and fluorescence sensing. This will allow for the continuous observation of metabolic changes; it can create closed-loop systems, where any deviations or byproduct accumulation are detected immediately and corrected automatically [139–143]. Such precise control not only improves consistency but is vital to meet the stringent quality standards required for cosmetic applications, particularly when considering expensive ingredients like injectable high-molecular-weight hyaluronic acid fillers.

7.3. Circular Bioeconomy and Sustainable Feedstocks

In precision fermentation, complex but well-defined culture media are often preferred because they provide consistent, optimized conditions for microbial growth and product synthesis. However, the cost and sustainability implications of using refined sugars are prompting a shift toward more circular, low-carbon alternatives like agrifood byproducts [44,115,144,145]. This redirection of resources into high-value applications not only improves resource efficiency but also supports broader circular economy goals by reducing reliance on virgin raw materials [144,145]. It also apports an additional layer of technical complexity (which motivates its placement under future perspectives instead of as a current reality) driven by their high technical complexity that requires complex, frequently tailor-made strategies (e.g., enzymatic hydrolysis or steam explosion) to unlock their full fermentative potential [144,145]. Emerging solutions are making these complex substrates more accessible, with techniques like CRISPR/Cas9 editing, adaptive laboratory evolution, and modular pathway design being increasingly used to equip micro-organisms with the tools they need to metabolize or tolerate the inhibitory compounds found in waste streams [144,145]. An example is the work of Rafieenia et al. [146], who demonstrated that the use of adapted microbial consortia (capable of mitigating citric acid accumulation), thereby improving carbon conversion efficiency, an innovation that could be central to future waste-based fermentation systems. Moreover, matching substrates to specialized microbial hosts will also be a key aspect. For instance, lipid-rich byproducts are especially compatible with oleaginous yeasts, which can convert them into valuable cosmetic metabolites such as lipophilic antioxidants and pigments [145,147,148].

This approach also brings additional challenges to table that will need to be addressed. First, it may negate one of the advantages of using precision fermentation since the previously easier-to-purify fermentation broths morph into highly complex matrixes whose purification will be both technologically and economically demanding [144,147]. It will also bring additional safety aspects into consideration, as the risk for contamination and the presence of pesticide residues or heavy metals increases. This may not only imply the need for the implementation of more stringent quality control measures, but it may also pose additional regulatory challenges for ingredient approval [115,144,145,147].

All these technological advances together signal a strategic shift. By adopting these cutting-edge solutions, companies are poised to move precision fermentation from a lab bench to robust, sustainable commercial manufacturing. Moreover, it promises to do so with shorter development timelines, enhanced product quality, and more readily scalable processes that will expand the array of innovative, bio-based ingredients available to formulators. Ultimately, the fusion of biotechnology, engineering, and digital innovation is paving the way for a more sustainable and creative future in cosmetic ingredient production, which will benefit producers, consumers, and the environment alike.

8. Conclusions

Precision fermentation has emerged as an innovative sustainable technology that can be exploited towards the production of cosmetic ingredients. It allows for bioactive ingredients production (e.g., peptides and antioxidants) using microbial-based processes designed to achieve higher purity and efficacy. In addition, its perceived sustainability fully aligns with the growing consumer demand for greener, more ethical cosmetic products, particularly when conventional sourcing strategies are becoming associated with resource depletion and higher environmental impacts. This places precision fermentation in a position poised to become a major mainstream strategy for the cosmetic industry. However, several hurdles need to be overcome to allow for larger industrial adoption, including navigating the complex EU regulatory framework needed to validate any new ingredient, working on improving consumers' perspective into biotechnologically derived ingredients (particularly when processes use GMO), and the need to adapt infrastructure towards large-scale production. Still, as regulations and consumers pressure the global industry to shift towards a greener, more environmentally sustainable model, precision fermentation holds the promise of transforming the cosmetic industry sector by reducing the reliance on petrochemical, plant-, and animal-derived ingredients in a manner that enhances the supply chain's sustainability and allows for the development of novel ingredients and formulations with better performance.

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Abbreviations

The following abbreviations are used in this manuscript:

GlcUA	D-glucuronic acid
MVA	Mevalonate pathway
FPP	Farnesyl diphosphate
MEP	2-C-methyl-D-erythritol 4-phosphate
pHBA	p-hydroxybenzoate

EU	European Union
INCI	International Nomenclature of Cosmetic Ingredients
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
CSR	Chemical Safety Report
GMO	Genetically Modified Organisms
GMM	Genetically Modified Micro-organisms
GMP	Good Manufacturing Practices
GRAS	Generally Recognized as Safe
LCA	Life Cycle Assessment
PCPC	Personal Care Products Council
ECHA	European Chemicals Agency
CPSR	Cosmetic Product Safety Report
OECD	Organization for Economic Co-operation and Development
QPS	Qualified Presumption of Safety
SCCS	Scientific Committee on Consumer Safety
IED	Industrial Emissions Directive
PCR	Polymerase Chain Reaction
PIF	Product Information File
CPNP	Cosmetic Product Notification Portal

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