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Review

The Benefits of Using Exosomes in Professional Cosmetic Products: From Theory to Practice

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Abstract

The integration of exosomes into professional cosmetics marks a significant paradigm shift from traditional passive formulations to advanced regenerative esthetics. Rather than being defined solely by their nanometric dimensions or classical association with endosomal biogenesis, these vesicles function as highly targeted intercellular messengers capable of delivering complex bioactive payloads to modulate tissue repair and collagen synthesis. While robust preclinical and clinical trials validate their remarkable potential in skin rejuvenation, hair restoration, and hyperpigmentation management, significant translational barriers remain. A critical analysis of the current literature reveals that successful clinical outcomes frequently rely on physical penetration enhancers, such as microneedling or fractional lasers, making it challenging to isolate the autonomous efficacy of topical vesicles from the trauma-induced regenerative response. Furthermore, commercial viability is dictated by stringent regulatory frameworks. In the European Union, Regulation (EC) No 1223/2009 strictly prohibits human-derived biologicals, while the US Food and Drug Administration (FDA) aggressively monitors the unsubstantiated marketing of cellular therapies. To navigate these biosafety and legal constraints, the aesthetic industry is increasingly pivoting toward non-human and legally compliant alternatives. Consequently, Plant-Derived Extracellular Vesicles (PDEVs), microbiome-derived exosomes (such as those obtained from bacterial fermentation), and bioengineered synthetic analogues have become the focal point of market innovation. A practical evaluation of the MCCM Medical Cosmetics portfolio illustrates this strategic shift, demonstrating the clinical versatility of botanical sources. To secure the long-term credibility of exosome technology, the industry must overcome current manufacturing heterogeneity by aligning with international standardization frameworks, such as the MISEV2023 guidelines, thereby ensuring reliable delivery systems, batch-to-batch consistency, and uncompromised consumer safety. This review provides a comprehensive overview of the biological mechanisms, clinical efficacy, and translational challenges associated with exosome-based cosmetics.

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1. Introduction

In recent years, our comprehension of intercellular communication has experienced a significant advancement due to the identification of Extracellular Vesicles (EVs), specifically exosomes. These particles, secreted by various cellular sources—including both animal and plant cells—and found in numerous biological fluids, are non-replicative and exhibit considerable heterogeneity [1,2].

Beyond their nanometre-scale dimensions, they are defined by a double-layered lipid membrane and a specific molecular signature of proteins and nucleic acids [1,3,4]. Once thought to serve only in cellular waste removal, exosomes are now recognized as powerful messengers between cells, with far-reaching effects on both health and disease [5,6]. This shift in perspective has attracted increasing interest not only in biomedical research but also in applied fields such as professional cosmetics [7,8].

A persistent challenge in dermatological science is overcoming the barrier function of the stratum corneum, the outermost layer of the skin, to ensure the effective delivery of active ingredients to targeted tissues [9]. Although traditional nanocarriers, such as synthetic liposomes, are extensively employed to enhance permeation, they frequently lack the inherent biological targeting capabilities necessary for precise cellular modulation [10]. In contrast, exosomes exhibit a distinctive surface architecture enriched with specific ligands and membrane proteins that promote receptor-mediated endocytosis and superior tissue penetration [6,8]. Due to their high biocompatibility and structural complexity, exosomes serve as highly efficient, natural delivery vehicles, representing a fundamental shift from passive topical skincare to advanced regenerative esthetic therapies [10,11].

The cosmetics industry persistently seeks innovative strategies to mitigate skin ageing, reverse photodamage, and promote tissue repair [7,12]. Unlike conventional monotherapeutic approaches, such as hyaluronic acid, retinoids, and standard peptides, which generally target isolated biochemical pathways, exosomes operate as dynamic, multifaceted nanocarriers [13,14]. By delivering intricate bioactive payloads, including structural lipids, regulatory proteins, and microRNAs, they concurrently modulate multiple biological processes. These encompass the downregulation of pro-inflammatory cytokines to maintain immune equilibrium [14,15], the stimulation of fibroblast proliferation to improve extracellular matrix (ECM) remodelling [16,17], and the precise regulation of cellular senescence and regenerative responses [12,18].

Translating this biological potential into commercial cosmetics is profoundly influenced by the origin of vesicles. Initially, research predominantly concentrated on exosomes derived from mammalian and human stem cells, due to their potent tissue-repairing capabilities [19]. However, increasing ethical, scalability, and regulatory concerns—particularly strict prohibitions on human-derived biologicals within the European cosmetic market—have prompted a strategic realignment within the industry [20,21]. Accordingly, there is a rising scientific interest in alternative, legally compliant sources, such as Plant-Derived Extracellular Vesicles (PDEVs) and microbiome-derived exosomes, which present promising bioactive synergies while reducing zoonotic and immunogenic risks [22–24].

Bridging theory and application, the integration of these nanovesicles into advanced cosmetic formulations presents both substantial opportunities and considerable challenges [12,13,25]. On the one hand, these nanovesicles demonstrate promising potential for augmenting skin regeneration and rejuvenation therapies. However, various factors,

including large-scale production, purification, standardization, safety considerations, and regulatory oversight, presently impede their wider application [13].

This study will systematically analyze multiple aspects of exosomes, starting with their fundamental biological properties and advancing through their mechanisms of action, cosmetic uses, supporting clinical evidence, and prevailing regulatory policies.

2. Principal Biological Properties of Exosomes

2.1. Structure and Molecular Composition

According to the Minimal Information for Studies of Extracellular Vesicles 2023 (MISEV2023) guidelines, extracellular vesicles (EVs) are the generic term for particles enclosed by a lipid bilayer [2]. Exosomes constitute a highly specific subclass within EVs. Rather than being identified solely by their nanometric size, which typically ranges from 30 to 100 nm, or by their classical association with intracellular endosomal biogenesis, they are primarily distinguished by their functional role in mediating intercellular signalling through the delivery of bioactive biomolecules [2,26,27]. Regarding their structural composition, these nanovesicles possess a phospholipid bilayer that largely reflects the membrane composition of their parent cell [2,26,27].

Exosomes were once regarded as a redundant mechanism for cellular waste disposal; however, contemporary proteomic and lipidomic analyses have reclassified them as intricate biological carriers. They are now acknowledged for their ability to transport a diverse array of molecular payloads, including structural lipids, functional proteins, and genetic material such as DNA, messenger RNA (mRNA), and microRNA (miRNA). This complex configuration facilitates the targeted transfer of encapsulated substances to both neighbouring and distant cellular environments [3,4].

As illustrated in Figure 1, animal-derived exosomes are encapsulated within a cholesterol-enriched lipid bilayer, which imparts membrane fluidity and structural stability. These nanovesicles encompass a diverse array of biomolecules, including proteins and various RNA species. Their surface is distinguished by a specific repertoire of ligands and membrane proteins that serve as molecular "zip codes," facilitating selective recognition and internalization by target cells [6].

A comparable yet distinct structural organization is observed in Plant-Derived Extracellular Vesicles (PDEVs), as illustrated in Figure 2. While sharing the fundamental 30 to 100 nm lipid bilayer architecture, PDEVs exhibit a unique and intimate association with plant cell wall components, which is presumed to be a fundamental factor in their biogenesis and release into the apoplastic space. Functionally, they act as robust biological nanocarriers for a diverse array of biomolecules, including mRNA, miRNA, proteins, and plant-specific bioactive compounds. Surface-associated ligands and membrane proteins further facilitate intercellular signalling within plants and support their emerging role in cross-kingdom communication [22].

In contrast to synthetic delivery systems such as liposomes, exosomes are naturally produced by cells, thereby conferring high biocompatibility and low immunogenicity. These attributes render them especially suitable for applications demanding close interaction with biological tissues [12].

A significant advantage resides in their capacity to encapsulate a broad spectrum of bioactive compounds, including both hydrophilic and hydrophobic molecules. Upon encapsulation, these molecules are preserved from enzymatic degradation and environmental instability, a factor particularly pertinent for delicate cosmetic active ingredients such as vitamin C or retinol, which may otherwise diminish in efficacy within traditional formulations. Additionally, exosomes can effectively engage with target cells via receptor-mediated

endocytosis or membrane fusion, thereby facilitating the release of their bioactive contents into the cytosol [12].

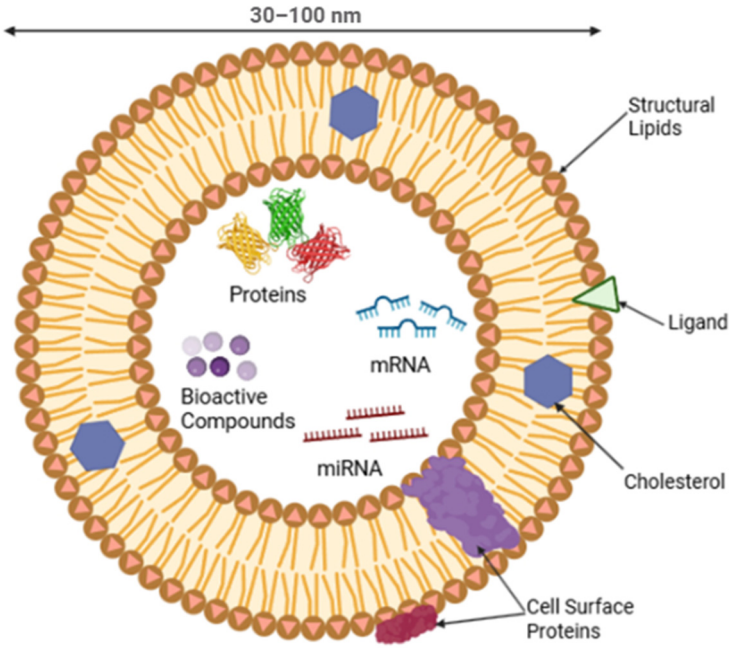

Figure 1. Schematic representation of the structural organization and molecular composition of an animal-derived extracellular vesicle (exosome).

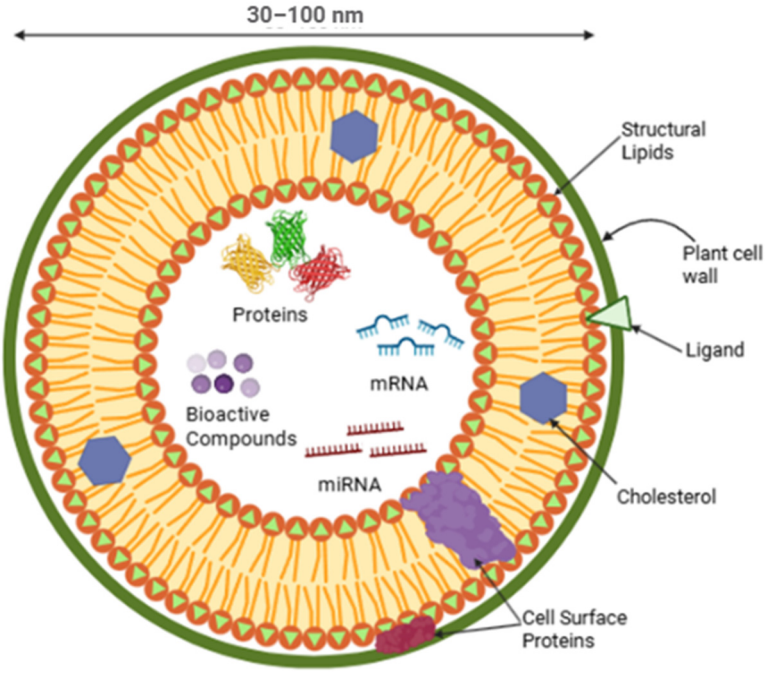

Figure 2. Structural architecture and molecular composition of a plant-derived extracellular vesicle (PDEV).

Another significant characteristic is their intrinsic targeting ability. The variety of proteins and lipids on the exosomal surface facilitates selective interactions with particular cell types, thereby enhancing delivery accuracy. Furthermore, they demonstrate a superior capacity to traverse biological barriers compared to many conventional delivery systems, thereby reinforcing their application in sophisticated topical and transdermal formulations [8].

2.2. Biogenesis of Animal-Derived Exosomes

The biological properties of exosomes are intimately connected to their mechanism of formation. These nanovesicles are derived within the endosomal system of the cell via a highly regulated process referred to as exosome biogenesis, which influences their composition and, thereby, their biological functionality [28].

Exosome biogenesis comprises three principal stages: formation, intracellular trafficking, and secretion. The process commences with the inward budding of the cytoplasmic membrane, whereby a segment of the cell membrane folds inward toward the cytoplasm, forming a cup-shaped invagination that internalizes various extracellular constituents, including proteins, lipids, metabolites, and surface molecules. This event leads to the formation of early endosomes, which subsequently mature into late endosomes through a series of morphological and molecular transformations. During this developmental process, the endosomal surface continues to invaginate internally, encapsulating cytoplasmic material and generating intraluminal vesicles (ILVs) within the endosomal interior. These ILVs selectively accumulate specific constituents, such as proteins, lipids, and nucleic acids, via specialized sorting mechanisms. Once populated with ILVs, these late endosomes are designated as multivesicular bodies (MVBs), and their ultimate fate is determined by the molecular profile of their surface proteins, which facilitate their routing through distinct intracellular pathways [26]. They are either targeted for proteolytic degradation through fusion with lysosomes and autophagosomes or, alternatively, directed toward the cell surface. In the latter scenario, fusion with the plasma membrane results in the secretion of ILVs as exosomes [26,29].

2.3. Biogenesis of Plant-Derived Extracellular Vesicles

While sharing fundamental similarities with the endosomal pathways observed in animal cells, the biogenesis of plant-derived extracellular vesicles (PDEVs) exhibits unique regulatory mechanisms tailored to plant physiology. As depicted in Figure 2, a significant challenge is their interaction with the plant cell wall during secretion. Evidence indicates that these nanovesicles originate through inward folding of the multivesicular body (MVB) membrane, a process akin to the animal pathway, yet specialized for the transport of plant-specific bioactive compounds and defence-related proteins. A crucial distinction is found in the final secretion phase: they must be released into the apoplastic space, where the cell wall may serve as a selective filter, potentially influencing the ultimate size and composition of the secreted nanovesicles, as suggested by experimental evidence from apoplastic vesicles [22,30]. This regulated biogenesis ensures that PDEVs can effectively mediate both internal signalling and inter-species communication [22,30].

3. Types of Exosomes

Virtually all cell types are capable of generating exosomes, which originate from diverse tissues and fulfil multiple biological functions. Among the known cellular populations in animals that secrete exosomes are components of the nervous system, such as neurons, oligodendrocytes, and Schwann cells, as well as immune effectors including lymphocytes, platelets, and mast cells. Furthermore, cells with potent regenerative properties, notably mesenchymal stem cells (MSCs) and induced pluripotent stem cells, have also been identified as significant sources of exosome secretion [10,31]. Their presence has been detected across a variety of biofluids, including blood plasma, urine, saliva, amniotic fluid, and breast milk [10,31].

A growing variety of exosome types has captured significant attention of the cosmetic industry, largely because each source appears to confer a distinct biological signature with specific benefits for skin health. Among the most extensively explored are those derived

from MSCs, which are known for carrying a rich combination of growth factors, ECM modulating proteins, and anti-inflammatory molecules that collectively support tissue regeneration and improve the overall quality of ageing skin [14,19]. Those derived from fibroblasts constitute another important group. They often contain proteins directly involved in collagen synthesis and dermal remodelling, making them especially relevant for formulations targeting firmness and wrinkle reduction. Those originating from epidermal cells, such as keratinocytes, also hold value because they tend to influence barrier restoration, cellular turnover, and the response to environmental stressors. In parallel, those released by immune-related cells, including macrophages or dendritic cells, have attracted interest for their capacity to modulate inflammatory pathways and soothe irritated or hypersensitive skin [32].

Beyond traditional animal sources, research has increasingly concentrated on Plant-Derived Extracellular Vesicles (PDEVs) obtained from fruits, leaves, or roots. These vesicles are often fortified with antioxidants, bioactive lipids, and small RNAs that can facilitate skin protection and regeneration, devoid of the ethical or regulatory issues associated with human-derived materials [23,24]. Furthermore, alternative sources such as milk-derived exosomes are gaining prominence due to their high biocompatibility and low immunogenicity, as well as their capacity to strengthen the skin barrier [33]. Additionally, those derived from yeast, produced via fermentation processes, are gaining popularity owing to their compatibility with the microbiome [34].

Complementing these natural categories, rapid advances in biotechnology have led to the emergence of engineered exosomes. These originate as natural nanovesicles but are subsequently modified through the loading of specific peptides, nucleic acids, or antioxidants to improve stability or to target particular cosmetic outcomes more effectively. Collectively, these varied platforms constitute a rapidly expanding toolkit that presents new opportunities for skin rejuvenation, repair, and protection within professional cosmetic applications [35].

A comparative summary of these diverse exosome sources is presented in Table 1, correlating their specific origins and bioactive payloads with their targeted cosmetic applications to illustrate their therapeutic versatility.

Table 1. Categorization of exosome sources and their primary biological targets in skin health.

Source Category	Specific Origin	Bioactive Payload	Principal Cosmetic Application
Animal (Stem cell)	Mesenchymal stem cells	Growth factors (TGF-β, VEGF)	Tissue regeneration & anti-ageing
Animal (Dermal)	Fibroblasts & keratinocytes	Collagen-related proteins	Firmness & barrier restoration
Animal (Immune)	Macrophages	Anti-inflammatory cytokines	Soothing hypersensitive skin
Plant	Fruits, roots, and leaves	Antioxidants and small RNAs	Antioxidant protection & repair
Microbial/Yeast	Fermentation products	Microbiome-modulating peptides	Hydration & skin microbiome balance
Biotechnological	Engineered vesicles	Loaded peptides/antioxidants	Targeted therapy & enhanced stability

Note: TGF-β: Transforming Growth Factor beta; VEGF: Vascular Endothelial Growth Factor.

4. Methods of Production, Isolation, Preservation and Quality Control

4.1. Production Methods

For applications necessitating large-scale production, cell culture systems are generally favoured owing to their operational and technical benefits, although the inherent low yield of exosome isolation remains a significant challenge [25]. Typically, achieving clinical efficacy requires substantial doses of exosomal protein, which in turn demands a robust expansion of large cell populations. In systems utilizing animal-derived cells, the composition of the culture medium plays a vital role in this process. When serum-containing media are employed, their preparations are often contaminated with serum-derived extracellular vesicles (EVs), thereby compromising product purity. Conversely, serum-free or Xeno-free

conditions, characterized as culture environments devoid of animal-derived components, may induce notable cellular stress and consequently alter exosome secretion patterns, such as an increase in oxidative stress markers. To mitigate these limitations, strategies frequently involve the implementation of two-stage culture protocols. This method typically comprises an initial expansion phase, during which cells are cultivated in nutrient-rich media to attain high confluence, followed by a collection phase. In the latter stage, cells are transitioned to a serum-free or chemically defined medium to ensure that the isolated vesicles are strictly cell-derived, thus preventing contamination from exogenous serum-derived vesicles and maintaining a balance between cell viability and exosomal purity [25].

Regardless of the cultivation strategy, the scalability of production requires a transition from static to dynamic systems. While static cultures in conventional flasks are technically simple, they provide limited control over environmental parameters such as pH and dissolved oxygen. Consequently, industrial production favours dynamic systems such as hollow-fibre (HF) and stirred-tank bioreactors (STRs) [36]. An HF system, composed of semi-permeable capillary fibres, maximizes surface area and facilitates the production of concentrated conditioned media, often resulting in a five- to ten-fold increase in yields when using cell lines such as HEK293, which are human cell lines widely employed particularly in drug delivery research [36]. For STRs, their utilization permits precise environmental monitoring and has been effectively adapted for mesenchymal stem cells (MSCs) under Good Manufacturing Practice (GMP) standards [37].

Ultimately, regardless of the production platform utilized—be it HF systems, microcarrier-supported cultures, or suspension-based bioreactors—the transition to large-scale manufacturing plays a crucial role in increasing exosome yield. However, meticulous optimization of the culture medium, production system, and operational mode remains vital for each specific cell line to guarantee consistent quality, safety, and therapeutic efficacy of the final product [38].

As summarized in Table 2, exosome production platforms exhibit considerable variation in their scalability, process control levels, and yield outcomes, thereby indicating that no singular system is universally optimal for large-scale manufacturing.

Table 2. Overview of exosome production systems and yield potential.

Production System	Characteristics	Yield Potential (Particles/mL)	Purity & Consistency	Advantages	Limitations
Static cell culture (flasks)	Adherent cells cultured under static conditions with limited environmental control	Low (10^8–10^9)	High consistency; easy monitoring	Technically simple and widely accessible	Poor control of pH and oxygen; low yield
Stirred-tank bioreactors	Dynamic, well-mixed systems with controlled pH, oxygen, and nutrient supply	High (10^{10}–10^{11})	Moderate; risk of shear stress-induced debris	Precise environmental control; GMP-compatible	Shear stress; higher technical complexity
Hollow-fibre bioreactors	Semi-permeable capillary fibres providing high surface area	Very High (10^{12}–10^{13})	High; concentrated media with low protein waste	High cell density; concentrated conditioned media; increased yield	Complex setup; limited direct cell access
Microcarrier-supported or suspension cultures	Cells grown on microcarriers or in suspension under dynamic conditions	Moderate-High (10^{10})	Variable; depends on agitation	Enables scale-up of adherent cell lines	Requires optimization for each cell type
Mechanical extraction (PDEV)	Vesicles isolated directly from plant biomass (e.g., fruit juice or pulp)	Extremely High (Massive biomass)	High stability; low zoonotic risk	High scalability; low cost; reduced biosafety risks	Limited standardization; biological heterogeneity

Note: PDEV: Plant-derived extracellular vesicles.

As summarized in Table 2, exosome production platforms vary considerably in terms of scalability, process control, and yield, indicating that there is no single system that is universally optimal for large-scale manufacturing [25,38].

The technical selection of a production system is inherently connected to the necessary Yield Potential and the specific requirements of the final cosmetic or therapeutic applica-

tion. While static cell cultures (flasks) continue to be regarded as the gold standard for preliminary biological characterization, owing to their high consistency, they generally produce lower concentrations (10^8–10^9 particles/mL), which are inadequate for industrial-scale manufacturing [25,36]. Conversely, hollow-fibre bioreactors denote a substantial advancement in efficiency, facilitating cellular densities significantly greater than those attainable with static systems and often producing concentrations surpassing 10^{12}–10^{13} particles/mL [25,36].

The production of plant-derived extracellular vesicles (PDEVs) presents an alternative paradigm emphasizing sustainability and safety. Unlike mammalian cell lines, which necessitate costly synthetic media and complex bioreactors to sustain cellular phenotype, PDEVs are generally isolated directly from the juice or pulp of organically cultivated biomass [39,40]. This mechanical extraction technique capitalizes on substantial agricultural biomass to achieve an "Extremely High" yield potential and cost efficiency, while also avoiding the risks associated with zoonotic viral transmission [22,41]. Accordingly, PDEVs offer a highly scalable solution that produces vesicles enriched with plant-specific bioactive metabolites, circumventing the technical challenges posed by shear stress and extensive cell expansion protocols inherent to animal-derived systems [41,42].

4.2. Isolation Methods

The translation of exosomes into viable cosmetic or therapeutic agents necessitates not only a high-yield source of producer cells but also a reproducible, scalable, and efficient isolation protocol. Although most cell types secrete exosomes, the quantity, composition, and functional properties of these nanovesicles vary substantially depending on cellular origin and culture conditions. The coexistence of non-vesicular macromolecular structures, such as protein aggregates and lipoproteins, in conditioned media complicates the recovery of pure populations, making the selection of an appropriate isolation strategy a critical determinant for downstream applications [37,38].

Historically, differential ultracentrifugation (UC) has served as the benchmark method for exosome recovery, employing sequential centrifugation steps to separate vesicles according to density and size [41,43]. Despite its extensive application, UC is labour-intensive, reliant on costly equipment, and presents significant challenges for scalability. Furthermore, the high centrifugal forces involved may adversely impact vesicle integrity and biological activity [43].

To address these limitations, size-based separation methods have become increasingly prominent. Ultrafiltration (UF) employs semi-permeable membranes distinguished by specific molecular weight cut-offs to concentrate exosomes and eliminate soluble impurities. In comparison to ultracentrifugation (UC), UF is more economical and scalable; nevertheless, challenges such as membrane fouling and incomplete separation from protein aggregates of similar size underscore the importance of meticulous optimization of filtration parameters [44].

Alternatively, Size-Exclusion Chromatography (SEC) discriminates between particles according to their hydro-dynamic radius, utilizing a column packed with a porous resin to achieve separation. SEC is widely praised for its ability to preserve nanovesicle integrity and yield high-purity fractions, though its scalability is often limited by the long processing times associated with gravity-driven flow [39]. For applications requiring speed, polymer-based precipitation is frequently employed. While commercially available kits based on this principle allow for rapid processing, they are prone to the co-isolation of soluble proteins and other non-exosomal particles, which can compromise sample purity [38]. On the other hand, immunoaffinity-based isolation, which targets specific surface markers (e.g., CD9, CD63), offers superior specificity but is restricted by high costs and low yields.

Recent technological strides have also introduced microfluidic platforms that integrate physical and biochemical separation properties, yet current designs remain limited in throughput [36].

Based on the data presented in Table 3, no solitary isolation method entirely satisfies the criteria for purity, scalability, and vesicle integrity preservation, thereby highlighting the necessity for meticulous optimization and, in numerous instances, the integration of complementary techniques.

Table 3. Overview of exosome isolation methods and their main advantages, limitations, yields and purity profiles.

Isolation Method	Principle of Separation	Average Yield (Particles/mL)	Purity Profile (Particle/Protein Ratio)	Key Advantage	Main Limitation
Ultracentrifugation (UC)	Size- and density-based separation under high centrifugal forces	High (10^{10}–10^{12})	Low-Medium (<10^{9})	Widely established reference method	Labour-intensive and poorly scalable; potential vesicle damage
Ultrafiltration (UF)/TFF	Size-based separation using membranes	Moderate-High (10^{10}–10^{11})	Medium (10^{9}–10^{10})	Rapid and scalable concentration	Membrane fouling and co-isolation of proteins
Size-Exclusion Chromatography (SEC)	Separation by hydrodynamic volume	Low-Moderate (10^{9}–10^{10})	High (>3 × 10^{10})	High purity and preservation of vesicle structure	Limited scalability and long processing times
Polymer-based precipitation	Polymer-induced reduction in vesicle solubility	High (10^{11}–10^{12})	Low (<10^{8})	Simple and rapid processing	Co-precipitation of non-exosomal contaminants
Immunoaffinity-based isolation	Antibody-mediated capture of surface markers	Low (10^{7}–10^{9})	Very High (Specific marker-based)	High specificity	High cost and low yield
Microfluidic platforms	Integrated physical and biochemical separation on chip	Low (Sample dependent)	High (Precision recovery)	High precision with low sample volume	Limited throughput and early-stage scalability

Note: TFF: Tangential Flow Filtration.

The comparative analysis presented in Table 3 employs two primary metrics to assess the effectiveness of isolation protocols: Average Yield and Purity Profile. Consistent with the MISEV2023 guidelines, the purity of an exosomal preparation is quantitatively characterized by the particle-to-protein ratio [2]. A ratio surpassing 3 × 10^{10} particles per milligram of protein is conventionally regarded as indicative of high purity, reflecting a substantial reduction in co-isolated non-vesicular proteins and aggregates [2,38].

The Average Yield pertains to the final concentration of vesicles (particles/mL) recovered. As demonstrated in the clinical trials discussed in Section 6.2, therapeutic efficacy is frequently dose-dependent, with successful human studies generally employing concentrations within the range of 10^{11} particles/mL [45]. Consequently, the selection of an isolation method constitutes a strategic trade-off: whilst techniques such as ultracentrifugation (UC) provide a high yield suitable for preliminary research, size exclusion chromatography (SEC) is preferred in instances where high-purity signalling is imperative to ensure consistent biological activity and to minimize potential immunogenic interference arising from protein contaminants [38,39,43].

Therefore, an optimal exosome isolation methodology must maintain vesicle integrity while ensuring high specificity, reproducibility, scalability, and cost-effectiveness [36,38]. Despite the extensive range of available strategies, many established approaches continue to be time-consuming, economically burdensome, or insufficiently selective for clinical-

grade applications. The incomplete removal of soluble contaminants or the presence of degraded nanovesicles may provoke undesirable biological effects, thereby confounding therapeutic outcomes. Consequently, the meticulous optimization of existing techniques, along with the strategic integration of multiple isolation methods, remains imperative to obtain high-purity exosome preparations suitable for safe and effective application in both in vitro and in vivo therapeutic and diagnostic contexts [38,44].

4.3. Critical Quality Parameters of Exosomes

The translation of exosome-based products for therapeutic or cosmetic applications necessitates a rigorous quality control (QC) process to guarantee batch-to-batch consistency, safety, and functional integrity. Since variations in cell culture and isolation procedures can significantly alter nanovesicle composition, a standardized QC framework is imperative to validate the final product.

The initial step in quality control (QC) involves verifying the identity and purity of the sample. In accordance with the international MISEV2023 guidelines, issued by the International Society for Extracellular Vesicles [2], this process entails confirming the presence of specific exosomal surface markers characteristic of human and mammalian exosomes. These markers include the positive expression of the mammalian tetraspanin family (CD9, CD63, CD81) and cytosolic protein components (Alix, TSG101), while ensuring the exclusion of non-vesicular impurities such as calnexin or GM130. Standard techniques such as Western blotting and flow cytometry are routinely utilized for this immunophenotyping analysis [37,38].

However, the growing commercial integration of PDEVs and yeast-derived nanovesicles necessitates origin-specific QC profiling. For instance, PDEVs lack mammalian tetraspanins [2,24,39,46]. Although analytical platforms such as Western blotting and flow cytometry remain widely used, the targeted reagents (e.g., primary antibodies) must be adapted to identify plant-specific membrane proteins, including TET8 (a plant tetraspanin ortholog), PEN1, and specific aquaporins [2,24,39]. Similarly, yeast- or fungal-derived exosomes require distinct markers, specifically cell wall remodelling enzymes such as Fks1 and Chs3/Chs1. Proteomic analyses also reveal that, unlike mammalian exosomes, yeast-derived vesicles are depleted of classic ESCRT components, such as Alix and TSG101 [2,34]. Applying mammalian immunophenotyping standards to botanical or fungal formulations constitutes a significant methodological flaw. Therefore, adapting the biomarker panel to the biological source is indispensable for accurate quality validation [2,46].

To evaluate physical properties, techniques such as Nanoparticle Tracking Analysis (NTA) and Transmission Electron Microscopy (TEM) are essential. NTA offers data regarding particle size distribution and concentration, while TEM verifies the morphological integrity of the characteristic lipid bilayer structure [22,37].

In addition to physical characterization, the biochemical and functional competencies of exosomes must be evaluated. Proteomic and RNA profiling techniques can identify stress-related biomarkers resulting from suboptimal production conditions [25]. Functional assays, tailored to the specific application, are essential to verify potency, such as cellular uptake efficiency or the capacity to stimulate collagen synthesis in skin models. For clinical and high-grade cosmetic applications, strict adherence to Good Manufacturing Practice (GMP) standards is mandatory, ensuring sterility, the absence of endotoxins, and the removal of xenogeneic components to mitigate safety risks [47].

4.4. Preservation Strategies and Formulation Stability

From a practical perspective, the commercial viability and clinical efficacy of exosome-based products are fundamentally determined by their stability. Exosomes are biologically

delicate entities; their phospholipid bilayers, RNA, and protein contents deteriorate swiftly in aqueous solutions at ambient temperatures. To address this issue, the industry has implemented various preservation strategies that directly influence clinical logistics, shelf life, and storage conditions [11,38].

The diverse approach currently utilized in esthetic market is summarized in Table 4.

Table 4. Comparative analysis of exosome product formulations, highlighting the relationship between physical state, biological preservation, and logistics requirements.

Product Form	Characteristics	Storage Requirement
Lyophilization	Most common for professional use; ensures stability of bioactive factors by removing water; requires reconstitution with a specific diluent, such as sterile/distilled/deionized water or a buffer solution.	Refrigerated (2–8 °C) or Ambient (depending on stabilizers)
Cryopreservation	Maintains highest biological integrity but requires complex cold chain logistics and specialized equipment.	Deep Freeze (−20 °C to −80 °C)
Liquid/Serum/Cream Stabilization	Formulated for ease of use and home application; often stabilized using specific polymers, high-viscosity carriers or PDEVs.	Ambient

Note: PDEV: Plant-Derived Extracellular Vesicles.

Currently, lyophilization, or freeze-drying, has established itself as the standard for professional clinical use. This method achieves an optimal balance between biological potency and logistical ease, requiring only standard refrigeration or, in specific stabilized formulations, ambient storage [48,49]. This ensures that the regenerative signals remain intact until the moment of application.

Conversely, products that necessitate the preservation of maximum biological integrity without dehydration depend on cryopreservation at extremely low temperatures. Although this method maintains vesicles in their most native condition, it presents significant logistical challenges concerning the cold chain and mandates immediate utilization upon defrosting to avert rapid degradation [12].

5. Mechanisms and Applications in the Cosmetic Field

5.1. Skin Regeneration and Anti-Ageing

Dermal regeneration and the mitigation of skin ageing are associated with the maintenance of extracellular matrix (ECM) homeostasis and the effective coordination of cellular repair mechanisms [50]. In this context, exosomes have increasingly been recognized as promising biological mediators due to their capacity to transport functional molecules that influence key regenerative pathways in the skin [16,17]. These nanovesicles, secreted by diverse cell types, participate in intercellular communication and contribute to tissue repair by modulating inflammation, cellular turnover, and matrix remodelling [12].

One of the central mechanisms underlying skin regeneration involves collagen dynamics. Collagen represents the most abundant structural protein within the dermal ECM and plays a fundamental role in preserving skin firmness, elasticity, and mechanical strength. During tissue repair, fibroblasts are activated to synthesize and deposit collagen, particularly types III and I [51]. Type III collagen predominates in the early phases of wound healing, providing a provisional framework that supports cellular migration. As regeneration progresses, Type I collagen progressively replaces Type III, conferring tensile strength and structural stability to the newly formed tissue [16].

Exosomes facilitate this process by delivering growth factors and regulatory molecules capable of stimulating fibroblast activity and promoting extracellular matrix (ECM) remodelling, as illustrated in Figure 3. Through interactions with cell surface receptors,

exosome-mediated signalling can influence keratinocyte proliferation and fibroblast function, which are essential for coordinated dermal repair. Concurrently, specific exosomal materials have been linked to the stimulation of elastin production, a critical determinant of skin elasticity. Enhanced elastin synthesis enables the skin to more effectively restore its original structure following mechanical stress, thereby contributing to a more supple appearance [17].

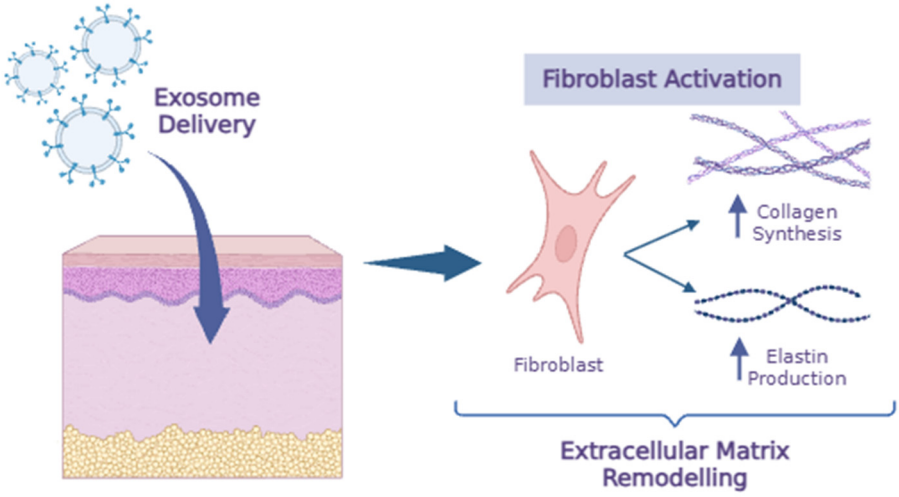

Figure 3. Schematic representation of exosome-mediated skin rejuvenation. The diagram illustrates the delivery of exosomes into the dermal layers, triggering fibroblast activation and the subsequent up-regulation of collagen synthesis and elastin production.

Regarding skin ageing, exosomes have shown the ability to mitigate age-related phenotypic characteristics, such as dermal rugosity and texture loss. Senescent skin is characterized by decreased collagen and elastin levels, diminished cellular turnover, and heightened oxidative stress [50,52,53]. These nanovesicles may counteract these effects through intercellular transfer of functional materials crucial for sustaining physiological balance and improving resilience against oxidative damage, thereby promoting extracellular matrix (ECM) renewal and overall physiological regeneration [54].

5.2. Wound Healing

While anti-ageing focuses on maintenance, wound healing entails restoring tissue integrity following injury. Exosomes serve as pertinent mediators within this process owing to their capacity to coordinate the intricate biological stages of tissue repair [8,16]. In the realm of cosmetology, this regenerative potential has garnered interest for enhancing skin recovery, diminishing scar prominence, and facilitating the healing of minor cutaneous lesions.

Cells derived from MSCs constitute one of the most extensively examined sources. They comprise a significant portion of the paracrine activity of their parent cells and facilitate tissue regeneration through promoting angiogenesis, augmenting cell proliferation, and stimulating collagen synthesis [54,55]. Moreover, they modulate inflammatory responses, thereby aiding the transition from a pro-inflammatory state to a reparative phase, which is crucial for effective wound healing.

Angiogenesis plays a pivotal role in wound repair by restoring the perfusion of oxygen and metabolic substrates to regenerating tissues. These nanovesicles facilitate this process through the transportation of pro-angiogenic signalling molecules, which effectively induce endothelial proliferation and neovascularization [15]. Furthermore, exosomes contribute to wound contraction and closure by enhancing the migratory capabilities of keratinocytes and myofibroblasts. Their molecular content, including specific microRNAs, supports progeni-

tor cell differentiation and promotes controlled collagen deposition, potentially reducing the incidence of excessive scarring and keloid formation [51,55]. The multifaceted role of exosomes in coordinating these stages of tissue repair, from inflammatory modulation to structural closure, is extensively depicted in Figure 4.

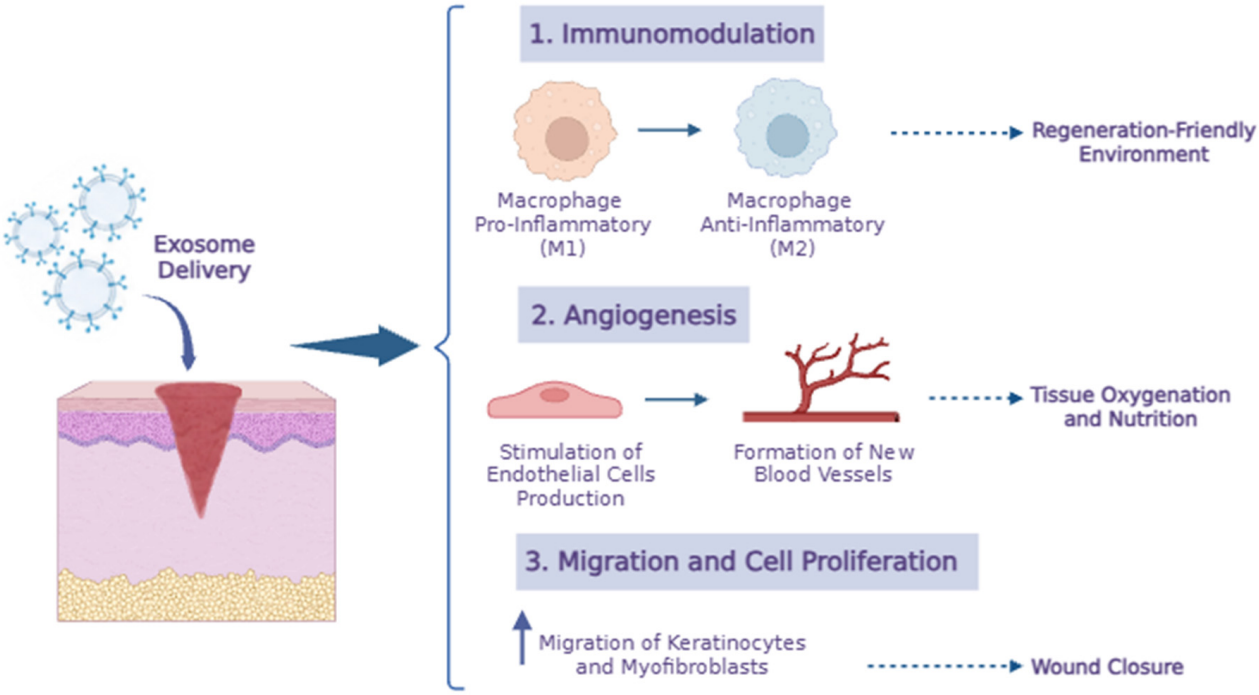

Figure 4. The exosome-driven regenerative cascade in cutaneous wound healing. The schematic illustrates the transition from an inflammatory to a proliferative phase, mediated by: (1) Immunomodulation, through the conversion of M1 macrophages into the M2 reparative phenotype to create a regeneration-friendly environment; (2) Angiogenesis, promoting tissue oxygenation via endothelial cell stimulation; and (3) Tissue Closure, driven by the accelerated migration and proliferation of keratinocytes and myofibroblasts.

5.3. Skin Pigmentation

Skin pigmentation is governed by the synthesis and distribution of melanin, a pigment generated by melanocytes located in the basal epidermal layer. Changes in melanogenesis may lead to hyperpigmentation or irregular skin tone. Recently, exosomes have gained recognition as critical regulators of pigmentation processes, due to their essential role in mediating molecular communication within the skin microenvironment [56].

Exosomes, secreted by keratinocytes, play a role in modulating melanocyte activity, especially in response to ultraviolet radiation. They are capable of transporting pro-melanogenic factors that stimulate melanocyte activation, thereby contributing to the skin's intrinsic protective barrier against solar damage [53]. Furthermore, exosomes derived from mesenchymal stem cells (MSCs) and certain plant sources have been shown to exhibit inhibitory effects on melanogenesis [57]. These exosomes frequently carry regulatory microRNAs and anti-inflammatory mediators that suppress key melanogenic pathways, including those involving tyrosinase. Through these mechanisms, MSC-derived exosomes may mitigate excessive melanin production and counteract oxidative stress, thus promoting skin brightening and tone uniformity [58].

In addition to their inherent biological roles, exosomes are becoming increasingly investigated as delivery systems for depigmenting agents. By encapsulating compounds such as tyrosinase inhibitors, these engineered vesicles can enhance targeted delivery to melanocytes, thereby improving bioavailability relative to traditional topical formulations.

This approach holds promise for the management of pigmentation disorders [12,58]. The mechanism through which exosomes influence the melanogenic pathway, especially via tyrosinase inhibition, is illustrated in Figure 5.

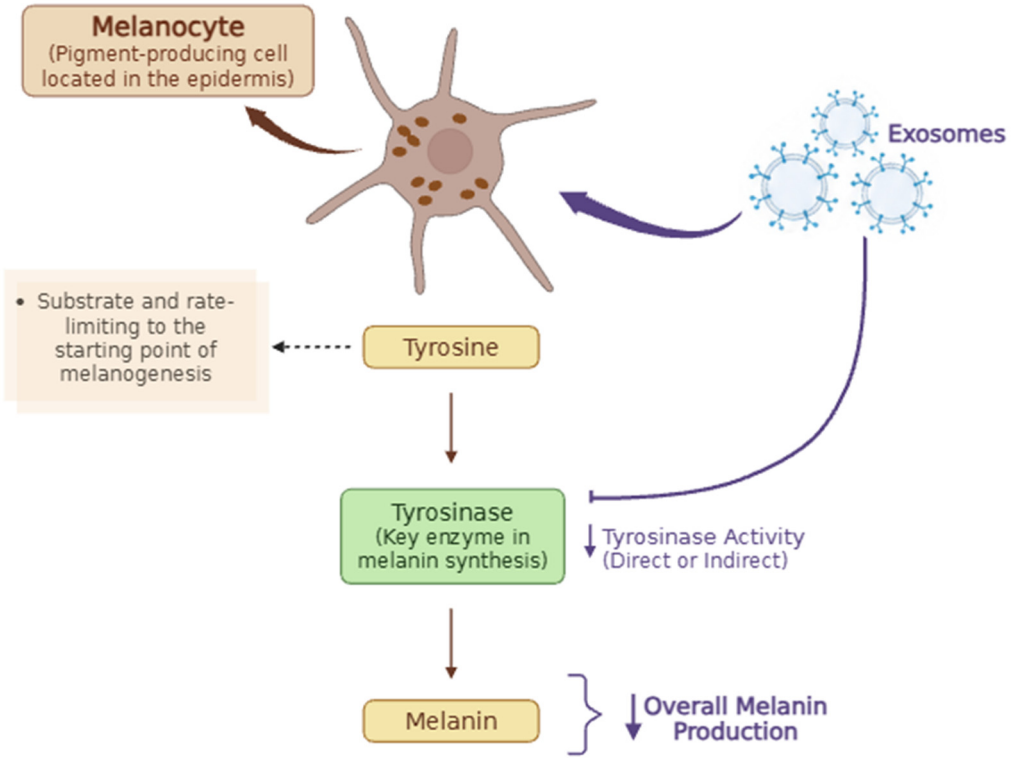

Figure 5. Exosomal regulation of the melanogenesis pathway. The diagram shows the targeted interaction of exosomes with melanocytes and their role in suppressing tyrosinase activity. By inhibiting this rate-limiting enzyme, exosomes effectively reduce overall melanin production, offering a targeted approach for managing hyperpigmentation.

5.4. Skin Hydration

Skin dehydration is a multifactorial condition characterized by a reduction in water content within the stratum corneum, often presenting as dryness and diminished comfort. Ensuring adequate hydration primarily relies on the integrity of the skin barrier and the organization of the extracellular matrix (ECM). In this context, exosomes function as biologically active mediators capable of supporting skin hydration through coordinated molecular mechanisms [52]. They contribute to the maintenance of cutaneous moisture balance by reinforcing the structure of the ECM. Their bioactive components can stimulate fibroblast proliferation, thereby promoting the synthesis of vital constituents such as hyaluronic acid, which plays a central role in water retention due to its high hygroscopic capacity [50].

Beyond ECM modulation, exosomes support the maintenance of the epidermal barrier, a critical factor in preventing transepidermal water loss (TEWL). By enhancing keratinocyte function and differentiation, exosomes contribute to barrier integrity, reducing moisture evaporation. This barrier's supportive role is especially relevant in dehydrated skin, where barrier disruption is a primary contributor to water loss [53].

6. Clinical Evidence

6.1. Preclinical Foundations and Delivery Optimization

A substantial body of preclinical evidence has elucidated the mechanisms by which exosomes influence skin regeneration, primarily through the modulation of inflammation,

stimulation of collagen synthesis, and promotion of angiogenesis. However, ensuring the effective occurrence of these molecular mechanisms in a clinical setting remains a significant challenge, as the method of delivery is as critical as the bioactive payload itself [59]. Unformulated exosomes, when applied topically without a suitable carrier, are susceptible to rapid clearance from the skin surface [59,60].

6.1.1. Delivery Systems and Skin Permeation

The primary challenge for any topical cosmetic treatment lies in overcoming the stratum corneum, the skin's outermost barrier that prevents the entry of foreign substances [9,61]. A common scepticism regarding topical exosome products addresses their ability to effectively penetrate this barrier [9,48]. However, recent findings suggest that these vesicles possess intrinsic permeation properties superior to those of conventional actives [9,48]. While stem cells remain a prominent source, novel and accessible alternatives, such as bovine milk, have demonstrated remarkable capabilities [47,48,61]. Wu et al. (2024) [47] confirmed that bovine milk-derived extracellular vesicles (mEVs) possess the unique ability to cross this barrier [47]. Utilizing confocal laser scanning microscopy to track fluorescently labelled mEVs, researchers observed that these vesicles successfully penetrated the stratum corneum and reached deeper dermal layers within one to four hours of topical application [47]. Beyond penetration, a complementary study by Lu et al. (2024) [61] demonstrated that the application of mEVs resulted in the significant up-regulation of CD44 (Hyaluronic acid receptor) and Filaggrin in keratinocytes [61]. Also, in fibroblasts exposed to UV radiation, mEVs restored the expression of Type I and Type III collagen, suggesting a direct reversal of photoageing signs at the cellular level [61].

Expanding on this intrinsic capability, Cho et al. (2021) [18] provided critical evidence regarding botanical sources [18]. Their study on *Panax ginseng*-derived exosomes demonstrated that these vesicles could effectively traverse the epidermal barrier to interact with human skin cells [18]. Once internalized, the ginseng exosomes exerted significant anti-senescence effects by suppressing senescence-associated β-galactosidase activity, thereby confirming the potential of plant-derived substances to serve as effective anti-ageing agents devoid of animal sources [18].

For specific applications such as hair restoration, the efficacy of topical application relies heavily on the trans follicular route. Research by Li et al. (2022) [62] on exosomes derived from dermal papilla cells has elucidated the mechanism behind this delivery [62]. These vesicles have been demonstrated to mediate the proliferation of hair follicle stem cells specifically via the Wnt3a/β-catenin signalling pathway, indicating that exosomes inherently accumulate within the follicular niche and thereby serving as ideal candidates for non-invasive hair therapy [62].

Despite this intrinsic permeability, ensuring sustained release and stability remains a priority [14,60]. To address the limitations in unformulated topical delivery, encapsulation strategies are utilized [12,32,63]. Ding et al. (2023) [16] provided extensive evidence on the efficacy of encapsulating exosomes within hydrogels, such as chitosan, alginate, and Gelatin methacryloyl (GelMA) hydrogels [16]. These biomaterial scaffolds serve a dual purpose: they protect the structural integrity of the exosomes and facilitate a sustained, controlled release directly into the dermis [16]. In preclinical trials with diabetic wound models, these exosome-loaded hydrogels demonstrated superior therapeutic outcomes compared to control groups [16]. The treatment groups consistently showed accelerated re-epithelialization and enhanced angiogenesis [16]. Crucially, the study observed a significant immunomodulatory effect characterized by a shift in macrophage phenotype from pro-inflammatory (M1) to pro-restorative (M2) [16]. This confirms that the vehicle acts synergistically with the exosome to create an optimal microenvironment for tissue regeneration [16,60,64].

To maximize permeation in professional clinical settings, physical enhancement methods, such as microneedling and fractional lasers, are often employed [11,45]. By creating temporary micro-channels, these devices bypass the stratum corneum entirely, ensuring the delivery of the exosome payload to the deep dermis [8,11,45]. This targeted depth is crucial for optimal efficacy, as highlighted by Kim et al. (2017) [65], when exosomes derived from human umbilical cord blood mesenchymal stem cells successfully penetrate the skin barrier. They fundamentally stimulate rejuvenation by promoting the synthesis of collagen and elastin, underscoring the necessity of these advanced protocols to ensure deep dermal access [65].

Table 5 presents a comparative summary of preclinical studies evaluating the dermatological applications and efficacy of exosomes from various biological sources.

Table 5. Comparative Analysis of Selected Preclinical Exosome Studies.

Author (Year)	Origin	Model	Analysis	Results
Wu et al. (2024) [47]	Bovine milk (mEVs)	Topical (ex vivo/in vitro screening)	Confocal laser scanning microscopy (fluorescently labelled vesicles)	Penetration into the stratum corneum and deeper dermal layers within 1 to 4 h
Lu et al. (2024) [61]	Bovine milk (mEVs)	In vitro (cells exposed to UV radiation)	RT-qPCR and Western blotting (for CD44, Filaggrin, and Collagen I/III)	Restoration of collagen (I and III) and increase in hydration markers (CD44 and Filaggrin)
Cho et al. (2021) [18]	PDEVs (*Panax ginseng*)	In vitro (interaction with human skin cells)	Senescence-associated β-galactosidase activity, Melanin content, and RT-qPCR	Suppression of cellular degradation markers (such as β-galactosidase)
Li et al. (2022) [62]	Dermal papilla cells	In vitro (focus on the transfollicular route)	Western blotting (protein expression) and Flow cytometry (apoptosis)	Hair follicle stem cell proliferation
Ding et al. (2023) [16]	MSCs	Topical (hydrogel delivery)	Review of in vivo preclinical wound models and molecular signalling pathways	Acceleration of re-epithelialisation and angiogenesis; immune transition from a pro-inflammatory (M1) to a restorative (M2) state
Kim et al. (2020) [65]	Umbilical cord stem cells	Topical (associated with deep delivery)	qRT-PCR, Procollagen Type I/MMP-1 ELISA, and histological analysis	Stimulation of deep structural protein synthesis following barrier penetration

Note: mEVs: milk-derived Extracellular Vesicles; PDEVs: Plant-Derived Extracellular Vesicles; MSCs: Mesenchymal Stem Cells.

Despite the promising results summarized in Table 5, a critical analysis of these specific studies reveals methodological limitations and potential biases that challenge the direct translation of these preclinical data into clinical practice. Firstly, two-dimensional (2D) cultures of isolated cells, as utilized by Lu et al. (2024) [61] and Cho et al. (2021) [18], largely ignore the complexity of the cutaneous microenvironment, such as the three-dimensional architecture of the ECM and the intricate signalling network of the immune system [18,61].

Similarly, laboratory permeation models, such as the ex vivo skin assessments employed by Wu et al. (2024) [47] and Kim et al. (2017) [65], fail to replicate the physiological dynamics of living human skin, neglecting factors such as occlusion, sweat production, or the rapid natural clearance of the vesicles on the cutaneous surface [47,65].

Another significant obstacle lies in the reliance on animal models to assess wound healing, as extensively reviewed by Ding et al. (2023) [16]. The anatomy and repair mechanisms of rodents differ drastically from those of humans due to the presence of the panniculus carnosus muscle, which promotes wound closure predominantly through muscle contraction (accounting for approximately 90% of the process), thereby limiting the translation of re-epithelialization data to humans [16,62]. In the field of trichology, in vitro models based solely on isolated dermal papilla cells, as seen in Li et al. (2022) [62], are insufficient to capture the endocrine and systemic complexity that defines conditions such as human androgenetic alopecia [62].

Furthermore, research involving plant-derived extracellular vesicles (PDEVs), such as the *Panax ginseng* vesicles examined by Cho et al. (2021) [18], encounters the potential for methodological bias if universal mammalian markers are improperly employed to verify the purity of botanical formulations. Additionally, such studies frequently lack comprehensive in vivo permeation data [18]. Ultimately, the therapeutic efficacy demonstrated in numerous studies is heavily reliant on physical delivery techniques or adjuvants, exemplified by the hydrogel encapsulation highlighted by Ding et al. (2023) [16]. This reliance raises legitimate questions regarding whether these exosomes could maintain sustained autonomous efficacy in the absence of delivery vehicles that mitigate rapid topical clearance [16]. The successful translation of these advanced delivery protocols has facilitated the progression toward rigorous clinical validation in human subjects, as discussed in the subsequent section.

6.1.2. Transition to Clinical Application

Notwithstanding these insights, it is essential to recognize that most of these findings are derived primarily from in vitro experiments and animal models. While such studies are crucial for understanding biological functions, they do not fully capture the complexity, variability, and safety considerations of human skin [66,67]. Therefore, the application of these mechanistic findings to clinical practice requires rigorous validation through well-designed human studies [52,68]. Clinical evidence remains the ultimate prerequisite for the safe and effective incorporation of exosomes into dermatological applications. In the absence of such data, their integration into cosmetic products cannot be thoroughly substantiated or reliably regulated [11,66].

6.2. Clinical Validation in Human Subjects

To address the inherent limitations of in vitro and ex vivo preclinical models, establishing robust in vivo evidence is paramount. Consequently, the current literature indicates a significant shift towards in vivo human clinical trials, with a focus largely on topical applications for skin rejuvenation, hair restoration, and inflammatory conditions [7,27]. This in vivo clinical validation is essential to confirm reproducibility, safety, and real-world performance in human skin, providing the necessary substantiation for the integration of exosomes into professional cosmetic formulations [11,66].

To advance beyond subjective patient satisfaction, recent research has adopted objective biophysical metrics to assess the effectiveness of exosome therapies. According to the systematic review by Bai et al. (2024) [52], numerous key clinical trials have employed instrumental analysis to substantiate outcomes, such as the split-face study conducted by Park et al. (2023) [52,69]. In a prospective split-face study, Park et al. (2023) [69] demonstrated

that the combination of microneedling with human adipose-derived stem cell exosomes (ASCE) yielded superior clinical results compared to microneedling with saline. At Week 12, the side treated with exosomes exhibited a statistically significant reduction in wrinkle parameters (Ra: 12.4%, $p = 0.031$) and a notable increase in skin elasticity (11.3%, $p = 0.002$), while the control side showed a decrease in elasticity. Additionally, instrumental analysis indicated a 6.5% increase in hydration ($p = 0.037$) and a 9.9% decrease in the melanin index ($p = 0.044$). Histological examinations supported these findings, revealing a higher density of newly synthesized collagen and elastic fibres on the exosome-treated side [52,69].

In a pivotal 12-week prospective, double-blind, randomized, split-face study, Kwon et al. (2020) [45] examined the synergistic effects of combination therapies by evaluating the efficacy of ASCE as an adjunct to fractional CO_2 laser treatment for atrophic acne scars [45]. The ASCE employed in the study was characterized by a mode size of approximately 117.4 nm and a concentration of 3.26×10^{11} particles/mL. At the final follow-up, the ECCA score exhibited a reduction of 32.5% (95% CI: 24.8–40.2%) on the side treated with ASCE, compared to a 19.9% reduction on the control side, with this difference reaching statistical significance ($p < 0.01$) [45]. Objective three-dimensional image analysis (Antera 3D®) confirmed significant decreases in depressed scar volume, mean pore volume, and skin surface roughness specifically on the ASCE-treated side, whereas the control side did not demonstrate significant improvements in these parameters. Superior clinical outcomes were also observed in the Investigator's Global Assessment (IGA) scores ($p = 0.02$), with 64% of the ASCE-treated sides achieving a grade 2 or higher improvement [45].

The versatility of exosomal signalling is further corroborated by the data from Proffer et al. (2022) [70], who utilized the VISIA-CR imaging system to quantify improvements in overall skin health through a Skin Health Score. The results revealed a statistically significant mean improvement of 224.2 ± 112.8 ($p \leq 0.0001$) at 6 weeks compared to the baseline. This progression correlated with measurable reductions in erythema ($p = 0.005$), wrinkles ($p = 0.0023$), and melanin production ($p \leq 0.0001$) across all cosmetic units, alongside significant enhancements in luminosity and colour uniformity ($p \leq 0.001$) [52,70].

Beyond conventional mammalian sources, microbiome-derived innovations have demonstrated promising clinical outcomes. Jo et al. (2022) [71] examined *Lactobacillus plantarum* exosomes, characterized by a concentration of 2.53×10^{11} particles per milligram of protein. Clinical evaluations conducted after four weeks indicated that exosome administration enhanced epidermal elasticity by 27.07% and skin hydration by 21.40%. Ultrasound imaging revealed a skin density improvement rate of 39.30%, markedly surpassing the 15.19% observed in the placebo group. Furthermore, Antera 3D analysis recorded a 15.89% reduction in periorbital wrinkle depth and an 8.7% decrease in pigmentation [52,71].

This clinical versatility is underscored by a comprehensive review of 15 distinct human studies conducted by Rodriguez et al. (2024) [11], which delineates applications ranging from the treatment of acne scars as an adjunct to fractional CO_2 lasers to the management of atopic dermatitis through barrier repair and inflammation modulation [11,52].

The maturity of the exosome market is further evidenced by the increasing number of officially registered clinical trials. Li W et al. (2025) [12] provide a comprehensive overview of ongoing investigations identified by their NCT identifiers, affirming that the industry is diligently working to validate exosomes not merely as cosmeceuticals but as potent therapeutic agents for complex pathologies [11,12]. These registered trials encompass research into androgenetic alopecia, diabetic wound healing, and chronic conditions such as melasma and psoriasis. The presence of Phase I and II trials affirms that the application of exosomes has become a medically recognized area of investigation, evolving from experimental trends to fundamental components of regenerative esthetics [27,37].

Table 6 presents a comparative analysis of recent human trials evaluating the dermatological applications of exosomes.

Table 6. Comparative Analysis of Clinical Exosomes Applications.

Author (Year)	Origin	Model	Analysis	Quantitative Outcomes and Statistics	Results
Park et al. (2023) [69]	Human adipose tissue (ASCE)	Microneedling (Prospective split-face study)	Cutometer, Corneometer, and histological analysis	Wrinkles: −12.4% Ra ($p = 0.031$); Elasticity: +11.3% ($p = 0.002$); Hydration: +6.5% ($p = 0.037$); Melanin: −9.9% ($p = 0.044$)	Significant overall improvement (GAIS $p = 0.005$) and superior dermal density compared to control.
Kwon et al. (2020) [45]	Human adipose tissue (ASCE)	Fractional CO_2 laser (Prospective double-blind split-face study)	Antera 3D® imaging system (scar volume/roughness), ECCA score, and subjective downtime evaluation	ECCA score reduction: 32.5% (ASCE) vs. 19.9% (Control) ($p < 0.01$).	Significant reduction in depressed scar volume, skin surface roughness, and mean pore volume (Antera 3D®). Superior IGA scores ($p = 0.02$)
Proffer et al. (2022) [70]	Human platelets	Topical application	VISIA-CR (imaging system)	Skin Health Score: $+224.2 \pm 112.8$ ($p \leq 0.0001$) at 6 weeks	Significant reduction in redness ($p = 0.005$), wrinkles ($p = 0.0023$), and melanin ($p \leq 0.0001$)
Jo et al. (2022) [71]	Micro-biome (*Lactobacillus plantarum*)	Topical application	MARK Vu (LED skin analyser) and F-ray equipment (skin contour analyser)	Elasticity: +27.07%; Density: +39.30%; Moisture: +21.40% (4 weeks)	Significant improvement in eye-wrinkles (−15.89%) and barrier repair (Filaggrin mRNA upregulation)

Note: ASCE: Adipose-derived Stem Cell Exosomes; ECCA: Échelle d'Évaluation Clinique des Cicatrizes d'Acné; GAIS: Global Aesthetic Improvement Scale; IGA: Investigator's Global Assessment.

Although Table 6 underscores notable clinical improvements, a rigorous examination of these trials uncovers methodological biases that warrant careful consideration. Firstly, the employment of mechanical interventions, such as the microneedling device utilized by Park et al. (2023) [69], introduces a confounding variable; microneedling inherently causes controlled skin injury, which naturally stimulates neocollagenesis, thereby complicating the attribution of the increase in collagen solely to the exosomes as opposed to the needle-induced trauma [69]. Similarly, the study conducted by Kwon et al. (2020) [45] exhibits thermal and synergistic biases. Considering that the fractional CO_2 laser is already regarded as a standard treatment for atrophic scars, the data suggest that exosomes may primarily serve as an adjunct to repair acute thermal damage and minimize downtime, rather than functioning as an independent rejuvenating agent [45].

Furthermore, the evaluation methods and product formulations themselves present inherent limitations. In the study of Proffer et al. (2022) [70], the outcomes measured by the VISIA-CR imaging system can potentially be influenced by the transient hydrating or illuminating effects of the serum vehicles used in daily skincare regimens, which does not necessarily demonstrate deep, autonomous structural remodelling by the exosomes [70]. Finally, concerning non-human sources, the absence of rigorous international standardization—such as strict compliance with the MISEV2023 guidelines—for bacterial-derived exosomes, like the *Lactobacillus plantarum* vesicles investigated by Jo et al. (2022) [71], raises substantial concerns. This regulatory deficiency may result in toxicological inconsistencies, batch-to-batch heterogeneity, and limited reproducibility in clinical

contexts, highlighting the necessity for additional standardization prior to widespread dermatological application [2,71].

6.3. Market Landscape, Intellectual Property, and Formulation Stability

The progression from clinical evidence to market availability requires a meticulous classification of the leading solutions in the global market [10]. To address the disparity between clinical research and the existing market offerings, it is imperative to assess the landscape of prominent commercial solutions. As demonstrated in Tables 7–9, the market is presently segmented based on the biological source of the exosomes: plant-derived, human-derived, and synthetic.

Table 7. Comparative Overview of Commercially Available Plant-Derived Extracellular Vesicles (PDEVs) Products.

Product	Brand/Company	Exosome Source	Formulation/Storage	Target Indication
Licorice Exosome Orbs	Snow Fox Skincare	Plant-derived: Licorice root (*Glycyrrhiza glabra*)	Topical Treatment Orbs (Ambient)	Skin Brightening
EXO ⁞ E Revitalizing Complex	Croma Pharma	Plant-derived: Ashwagandha (*Withania somnifera*), Black pepper (*Piper nigrum*), and botanical ferment (*Ustilago cynodontis*)	Topical Serum (Ambient)	Skin Rejuvenation and Post-Procedure Recovery
Pluryal Mesoline Exoyouth	Pluryal (MD Skin Solutions)	Plant-derived: *Centella asiatica* exosomes, combined with *Rosa centifolia* and *Centaurea cyanus* extracts	Sterile Topical Serum (Vials, Ambient)	Skin Rejuvenation, Deep Skin Hydration, and Acne Scar Reduction
Exosome Regenerating Serum (Private Label)	Thea Janus	Plant-derived: Rice, Green Tea, and Aloe Vera	Topical Serum/Creams (Ambient)	Anti-ageing, Skin Regeneration and Skin Hyperpigmentation Reduction
ASCE+ (SRLV, HRLV, IRLV)	ExoCoBio/BENEV	Plant-derived: Rose (*Rosa damascene*) and Adipose-derived MSCs	Lyophilized Powder (2–8 °C)	SRLV: Skin Rejuvenation and hydration HRLV: Hair regrowth and scalp care IRLV: Intimate care

Note: The data presented were synthesized from open-access digital databases and primary source materials, including commercial product inserts and labelling specifications. SRLV: Skin Rejuvenation Lyophilized Vial; HRLV: Hair Rejuvenation Lyophilized Vial; IRLV: Intimate Rejuvenation Lyophilized Vial; MSC: Mesenchymal Stem Cell.

Human-derived sources, including MSCs, platelets, and placental tissues, predominantly occupy the high-performance esthetic sector. These products are often marketed under stringent professional protocols, as exemplified by the ASCE+ line from ExoCoBio, the Plated Intense Serum from Rion Aesthetics, and AnteAge MDX. Concurrently, there is a growing emergence of plant-based and synthetic analogues, such as Inno-Exoma® by INNOAESTHETICS (NARBEX technology, Barcelona, Spain), Snow Fox's Licorice Exosome Orbs, and the EXO ⁞ E Revitalizing Complex. These alternatives are strategically formulated to navigate the intricate regulatory landscapes of Europe and North America within the

global cosmetic industry, providing diverse options concerning ethical acceptance and lower perceived biological risk profiles.

Table 8. Comparative Overview of Commercially Available Human-Derived Exosome Products.

Product	Brand/Company	Exosome Source	Formulation/Storage	Target Indication
Plated Intense Serum	Rion Aesthetics	Human Platelets (Renewosome™ technology)	Topical Serum (Ambient)	Skin Anti-Ageing, Redness, Texture and Photodamage
AnteAge MDX	AnteAge	Bone Marrow and Umbilical Cord MSCs	Lyophilized Powder (2–8 °C)	Skin Regeneration and Anti-inflammation
ELEVAI Enfinity	ELEVAI Skincare	Umbilical cord MSCs	Topical Serum (Ambient)	Skin Healing and Rejuvenation (Post-procedure care)
Age Zero™ Exosomes	Resilielle	Umbilical cord MSC	Cryopreserved Solution (−20 °C to −80 °C)	Skin Regeneration
NGF-574H	Medipost	Umbilical cord (MSC with conditioned media)	Topical Solution (Ambient)	Hair Growth in androgenetic alopecia (Mesotherapy)
Exovex Revive	Exocel Bio	Placental MSCs	Cryopreserved Solution (−20 °C to −80 °C)	Skin Regeneration
MSC-Exosome Advanced Complex (Private Label)	Thea Janus	MSCs	Topical Serum/Lyophilized (2–8 °C/Ambient)	Intensive Tissue Repair, Skin Rejuvenation and Collagen Stimulation

Note: The data presented were synthesized from open-access digital databases and primary source materials, including commercial product inserts and labelling specifications; MSC: Mesenchymal Stem Cell.

According to the data, a distinct dichotomy is evident in product positioning. Brands such as Resilielle and Exocel Bio utilize the high potency of perinatal tissues, including the placenta and umbilical cord, for advanced tissue regeneration, thereby positioning their portfolios more prominently within the field of regenerative medicine [11].

Innovations such as Rion Aesthetics' Plated Intense Serum demonstrate the feasibility of alternative human-derived sources, employing proprietary platelet-derived technology in lieu of traditional mesenchymal stem cells (MSCs). Conversely, brands like ExoCoBio (ASCE+) and Snow Fox utilize adipose-derived or plant-based sources to provide versatile solutions for skin brightening and hydration, often encountering fewer regulatory challenges within specific jurisdictions [49,53]. Products such as the EXO | E Revitalizing Complex and Pluryal Mesoline Exoyouth exemplify this strategic approach. By harnessing sophisticated botanical sources such as *Withania somnifera* and *Centella asiatica*, these brands deliver potent anti-inflammatory and regenerative benefits while adhering fully to cosmetic regulatory standards [11,56]. Notably, brands like ExoCoBio (ASCE+) navigate this domain through the development of hybrid formulations that combine rose-derived vesicles with adipose-derived MSCs to optimize esthetic results across various clinical indications, including skin, hair, and intimate rejuvenation. Furthermore, the prominent role of B2B (Business to Business) private label manufacturers, such as Thea Janus, underscores the industry's transition towards scalable global production across all biological origins. This encompasses the development of fully synthetic, bottom-up engineered biomimetic vesicles, exemplified by INNOAESTHETICS' NARBEX technology and Thea Janus' private label formulations, which address the increasing demand for consistent batch quality and

precise active ingredient delivery [16,25,58]. Additionally, brands such as Promoitalia and MartiDerm actively utilize this synthetic approach to encapsulate specific active payloads, including polydeoxyribonucleotide (PDRN) or depigmenting agents, thereby creating highly customized and synergistic formulations [12,58,66].

Table 9. Comparative Overview of Commercially Available Synthetic (Bioengineered) Exosome Products.

Product	Brand/Company	Exosome Source	Formulation/Storage	Target Indication
Inno-Exoma Exo-skin	INNOAES-THETICS	Synthetic (NARBEX™): Lipid-based biomimetic nanovesicles encapsulating recombinant growth factors, hyaluronic acid, and peptides.	Lyophilized Powder (2–8 °C)	Skin Revitalization
Synthetic Nano-Exosome Formula (Private Label)	Thea Janus	Synthetic: Engineered phospholipid bilayers encapsulating customizable recombinant proteins, signalling peptides, and hyaluronic acid.	Topical Serum/Creams (Ambient)	Skin Repair
V-Tech System	Promoitalia	Synthetic (SuperExo™): Biomimetic liposomal nanovesicles combined with Polynucleotides (PDRN), oligopeptides, and hyaluronic acid.	Topical Serum and Gel Mask (Ambient)	Intense Tissue Regeneration, Skin Biolifting and Wrinkle Reduction
DSP-Exo Melan Serum	MartiDerm	Synthetic: Phospholipid/phytosterol nanovesicles encapsulating Tranexamic Acid (TRX), Kojic Dipalmitate, and Niacinamide.	Topical Serum (Ambient)	Skin Hyperpigmentation Reduction and Skin Tone Uniformization

Note: The data presented were synthesized from open-access digital databases and primary source materials, including commercial product inserts and labelling specifications. The term 'Synthetic' denotes lab-created vesicles utilizing non-human structural components and proteins.

From a clinical perspective, the stability of the formulation is a decisive factor in ensuring reproducible results [72]. As observed in the data, storage requirements vary drastically depending on the structural complexity of the vesicles. This dependence on structural integrity justifies the common practice of reconstituting lyophilised powders, seen in ASCE+, AnteAge, and Inno-Exoma, at the point of care using functional diluents, such as sterile/distilled/deionized water or a buffer solution. By performing this procedure immediately prior to application, the practitioner ensures the delivery of a fresh, functional bioactive payload, mitigating the degradation risks associated with pre-mixed serums and aqueous environments [11,13]. Conversely, maintaining the viability of certain high potency MSC exosomes requires strict cold chain logistics, evidenced by the cryopreserved solutions (−20 °C to −80 °C) utilized by Resilielle and Exocel Bio [11,38]. To streamline professional workflows without compromising safety or requiring specialized clinical freezers, manufacturers are increasingly developing ready-to-use, sterile serums (such as Pluryal line) and ambient-stable topical solutions (like Snow Fox and ELEVAI). These formats are specifically designed for safe, immediate application possibly following physical enhancement methods like microneedling [11,13,53]. This convergence of biotechnological stability and practical handling protocols is essential for clinical validation and defines the current

maturity of the market, allowing exosome technology to position itself as a reliable and fundamental pillar of contemporary regenerative esthetics [11,50,66,73].

6.4. Industrial Case Study: Synergistic Application of PDEVs in Multi-Target Formulations

The practical application of exosome technology within professional cosmetics can be assessed through a technical analysis of the synergistic strategies utilized in the MCCM Medical Cosmetics portfolio, which employs carrot root extract, Daucus carota sativa, and (PDEV) formulations [74]. This case study exemplifies a commercially implemented strategy rather than a controlled experimental validation, with the intention of observing how biotechnological theory is integrated into targeted esthetic treatments. This approach reflects a strategic commitment to maintaining high safety standards and ensuring regulatory compliance within the European market, thereby avoiding immunogenic risks and ethical dilemmas often associated with animal or human-derived materials. In these frameworks, the PDEV fraction is hypothesized to serve as a biological modulator designed to prime the cellular environment, potentially enhancing the receptivity of the substrate to established bioactive compounds such as polynucleotides (PDRN), tranexamic acid (TRX), and specific enzymatic complexes, thus aiming to support their regenerative or corrective potential. This convergence facilitates a multi-target approach to the treatment of dermal concerns.

A principal example of the proposed synergy is the interaction between carrot-derived exosomes and structural proteins or humectants in trichological treatments. By incorporating PDEVs with hydrolyzed collagen and sodium hyaluronate [75], the formulation seeks to mitigate oxidative stress within the follicular microenvironment, thereby theoretically enhancing scalp vitality and hair shaft resilience through improved nutrient absorption pathways [9,50,60]. The documented variations in hair density and scalp coverage throughout the treatment cycle are depicted in Figure 6.

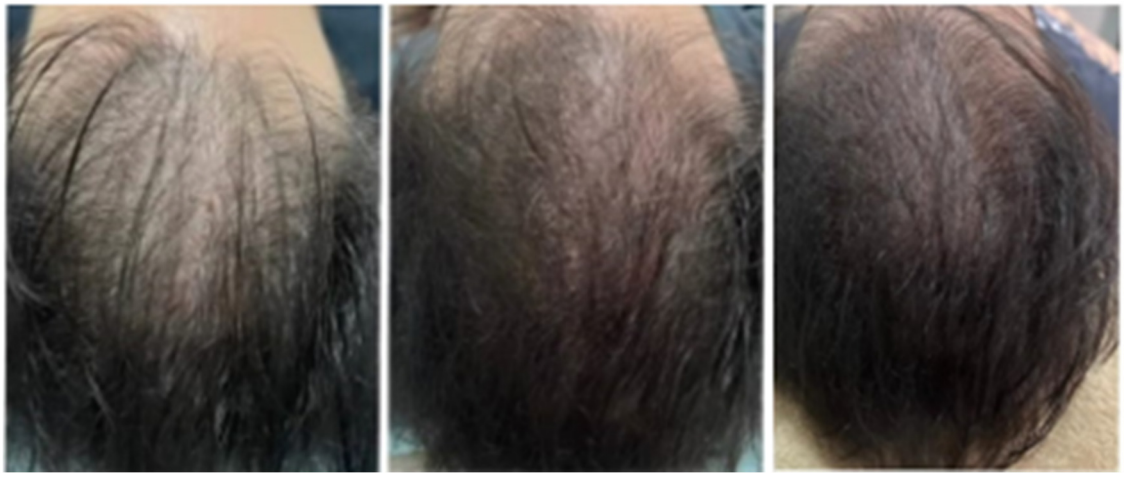

Figure 6. In vivo assessment of follicular density and scalp coverage following topical application of PDEV formulation (Frequency: 1/week; Dosage: 10 mL; Microneedling delivery).

Similarly, the convergence of enzymatic action and exosomal signalling is observed in body contouring applications. In this biochemical framework, hyaluronidase functions by temporarily depolymerising hyaluronic acid polysaccharides within the extracellular matrix (ECM), which correlates with decreased tissue viscosity and the drainage of retained fluids [59]. This enzymatic activity may prepare the tissue, potentially facilitating more effective penetration of carrot-derived exosomes to deliver their regenerative signals [9,66]. Subsequently, these exosomes may contribute to cellular renewal and collagen synthesis, thereby aiding the skin in attaining increased firmness and a smoother texture [49,56].

Evidence of the resulting improvement in skin texture and reduction in edematous markers can be observed in Figure 7.

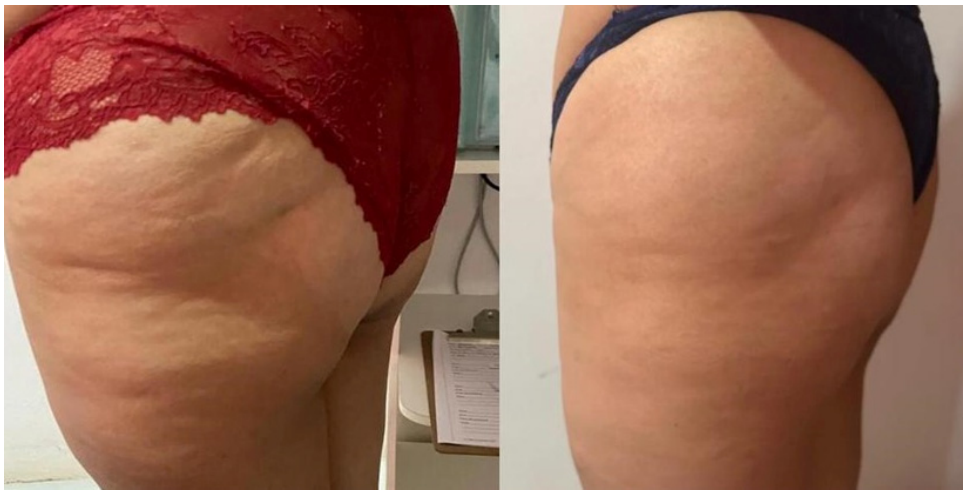

Figure 7. Clinical progression of cutaneous texture and edematous cellulite reduction through sequential hyaluronidase and PDEV-mediated signalling (Frequency: 1/week; Microneedling delivery).

The integration of PDEVs with PDRN exemplifies a dual-action repair mechanism. PDRN functions as a source of nitrogenous bases, providing essential components for nucleic acid synthesis and cellular repair [12]. Exosomes may serve a complementary role by priming fibroblasts, thereby potentially enhancing their receptivity to these nucleotides and facilitating the endogenous production of collagen and elastin [56,76]. Furthermore, a high concentration of sodium hyaluronate ensures significant hygroscopic action, thereby restoring the skin's water reserves and improving viscoelasticity [9,61]. The effects of this PDRN-PDEV synergy on facial rejuvenation, particularly concerning skin turgor and radiance, are documented in Figure 8.

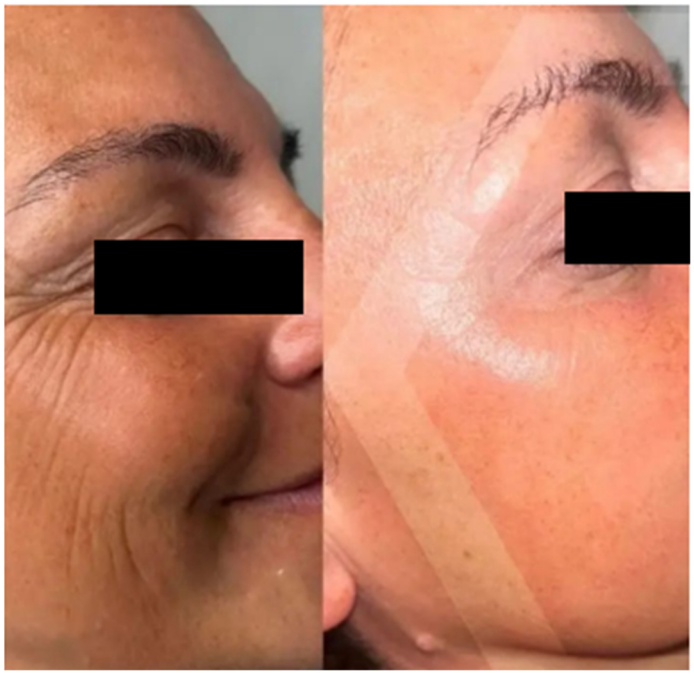

Figure 8. Evaluation of facial rejuvenation and epidermal radiance following the synergistic application of PDRN and PDEV-based metabolic priming (Frequency: 1/week; Microneedling delivery).

The multi-pathway modulation strategy is further applied to the management of hyperpigmentation, where PDEVs are combined with a complex of TRX, niacinamide, and allantoin. In this synergy, the carrot-derived exosomes are hypothesized to act as bioactive modulators that prime the melanocytes, possibly reducing the pro-inflammatory signals that trigger melanin overproduction [56,76]. The TRX may further complement this action by inhibiting the plasminogen/plasmin pathway, effectively reducing the vascular component of melasma and dark spots [77]. Simultaneously, niacinamide (Vitamin B3) prevents the transfer of melanosomes to the upper layers of the epidermis [77], while allantoin provides a soothing effect, promoting cellular renewal and maintaining the skin's barrier integrity [78]. The reported uniformity in skin tone and mitigation of photo-ageing signs are presented in Figure 9.

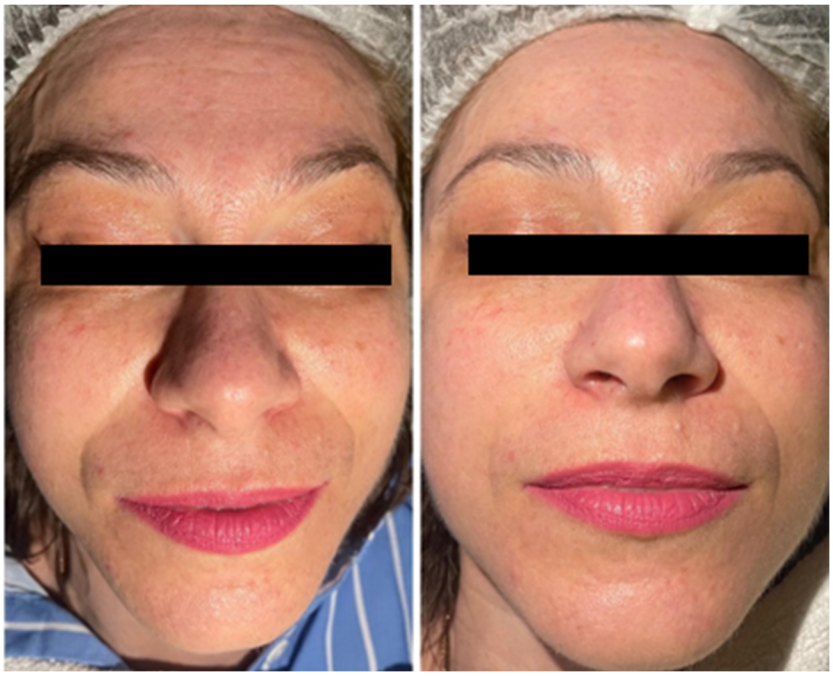

Figure 9. Qualitative analysis of skin tone uniformity and photo-ageing mitigation using a multi-pathway PDEV and TRX complex (Frequency: 1/week; Microneedling delivery).

Methodological Considerations and Confounding Variables

Notwithstanding the favourable clinical results depicted in Figures 6–9, it is imperative to consider certain methodological variables to facilitate a meticulous interpretation of the data. It is noteworthy that the PDEVs within these formulations are administered alongside highly potent pharmacological agents, including PDRN, TRX, and Hyaluronidase.

The clinical protocol used microneedling as the delivery method. The mechanical trauma caused by micro-needling is a well-documented inducer of the skin's innate wound-healing response, independently initiating neo-collagenesis and modulating inflammation [8,69]. Therefore, in the absence of a control group employing isolated PDEVs or microneedling with a neutral vehicle, it is not possible to definitively determine the specific contribution of the carrot root vesicles separate from the synergistic effects of the bioactive co-ingredients or the regenerative stimulus provided by mechanical trauma [45,69].

These observations exemplify a genuine clinical synergy within real-world settings rather than a controlled isolation of exosomal efficacy. They underscore the necessity for additional comparative studies to accurately quantify the specific bioactivity of plant-derived vesicles within complex cosmetic matrices [11,66].

7. Regulatory and Safety Concerns of the Use Exosomes in Cosmetic Products

7.1. The European Regulatory Framework: Regulation (EC) No 1223/2009

A fundamental element in safeguarding consumer safety within the European cosmetic industry is the European Union (EU) Cosmetics Regulation (EC) No 1223/2009. This regulation delineates rigorous standards concerning ingredients, safety evaluations, labelling, and market surveillance for cosmetic products distributed across EU Member States [21].

This regulation is applicable to all cosmetic formulations introduced into the European Union (EU) market. It defines a cosmetic product as any substance or mixture intended for application onto the human epidermis or external parts of the body, with the primary purpose of cleansing, perfuming, protecting, or altering appearance. This definition explicitly excludes effects that are primarily pharmacological, immunological, or metabolic in nature [21]. Compliance with these regulations is obligatory. Furthermore, the competent authorities within Member States are tasked with enforcing adherence to safety standards and ensuring the proper maintenance of technical documentation.

In addition to compositional safety, European regulatory interpretation emphasizes the significance of the intended use of cosmetic products, as biological materials capable of exerting pharmacological or metabolic effects may inadvertently cause a formulation to fall outside the scope of cosmetic regulation, even when marketed under esthetic claims [11,21].

7.2. Prohibition of Human-Derived Biological Materials

Within the framework of Regulation (EC) No 1223/2009, the European Union enforces rigorous controls on the utilization of materials derived from human origin in cosmetic products. Current interpretations and enforcement practices suggest that exosomes obtained from human tissues or cells are not authorized for use in cosmetic formulations and are consequently prohibited under the regulation's safety and ingredient listing provisions (Annex II) [20,21].

This restrictive stance reflects not only ethical and biosafety concerns but also the current absence of harmonized standards for the isolation, characterization, and quality control of human-derived extracellular vesicles (EVs), which constrains regulators' capacity to uniformly evaluate their safety and biological behaviour [11,20].

7.3. Novel Ingredients and Safety Assessment

According to Regulation (EC) No 1223/2009, each cosmetic product marketed within the European Union is mandatory to possess a Product Information File (PIF), which must incorporate a Cosmetic Product Safety Report (CPSR). The safety evaluation of the final product is primarily predicated on the toxicological profiles of its constituent ingredients [20,21].

For conventional ingredients, safety assessors typically rely on established historical data and bibliographic databases. However, exosomes and PDEVs are regarded as novel ingredients that lack a documented history of safe use in cosmetic applications. Therefore, the manufacturer is responsible for generating primary data to thoroughly characterize the ingredient before its incorporation into a formulation. This data should be used to determine toxicological endpoints, such as the No Observed Adverse Effect Level (NOAEL), and to facilitate the calculation of the Margin of Safety (MoS) [20,21].

Considering the stringent European prohibition on animal testing for cosmetic ingredients, these toxicological evaluations must depend solely on validated in vitro methodologies, which are typically directed by the Organisation for Economic Co-operation and Development (OECD) guidelines [20,21]. For exosome-based novel ingredients, the most

pertinent assessment parameters encompass testing for skin sensitization, phototoxicity, and local tolerance (irritation) utilizing 3D reconstructed human epidermis (RhE) models [20,67]. Additionally, due to the complex payload of active proteins and nucleic acids (such as miRNAs) contained within these vesicles [3,4], meticulous in vitro mutagenicity and genotoxicity screenings, including the Ames test (OECD 471) or the in vitro mammalian cell micronucleus test (OECD 487), are essential [20].

Recent scholarly works exemplify this meticulous methodology; for example, the comprehensive toxicological evaluation of small extracellular vesicles derived from umbilical cord blood has adeptly employed these OECD-validated in vitro models to empirically verify the absence of skin sensitisation, ocular irritation, and genotoxicity [79]. These specific in vitro parameters guarantee that the vesicles do not induce DNA damage upon repeated topical application, thereby constituting the essential empirical foundation necessary for precise MoS computation within the PIF [20,21].

In this context, the significant heterogeneity concerning manufacturing and profiling protocols continues to be a critical limitation. Absent a standardized definition of the ingredient's purity and biological activity, the toxicological data lack consistency, thereby directly compromising the reproducibility and validity of the final risk assessment [11,20].

7.4. Plant-Derived and Non-Human Exosomes: A Different Regulatory Space

While human-derived exosomes face substantial regulatory obstacles, PDEVs hold a more favourable regulatory standing under the European cosmetic regulatory framework. These nanovesicles are not subject to bans on materials of human origin and are widely accepted owing to their natural prevalence and reduced biosafety concerns [20,21].

Within the European Union, these non-human vesicles are authorized as cosmetic ingredients provided that their safety is sufficiently demonstrated through appropriate toxicological assessments. This regulatory distinction has positioned plant-derived and microbial vesicles as the primary focus of innovation within the European cosmetic industry [11].

7.5. Global Regulatory Interpretation and Enforcement

European regulators generally interpret exosomes derived from human sources as falling outside the scope of standard cosmetic ingredients due to their potential pharmacological activity, reflecting a precautionary regulatory approach grounded in consumer safety principles [21,80]. While the European framework addresses these human-derived exosomes with a structural prohibition under cosmetic law, the landscape in the United States offers a complementary perspective. Rather than imposing a merely cosmetic prohibition, the FDA (Food and Drug Administration) has actively overseen the proliferation of these products, classifying them as Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) pursuant to Section 351 of the Public Health Service Act [81]. Consequently, the Food and Drug Administration (FDA) has issued explicit safety notifications concerning the risks of infection and the absence of approved, safe products, warning against the utilization of unverified exosome therapies [82,83]. This contrast illustrates that, whereas Europe relies on cosmetic regulations to restrict human-derived products based on their origin and pharmacological classification, the United States concentrates its efforts on regulating the unsubstantiated marketing of 'cellular therapies' and enforces the stringent Biologics License Application (BLA) process for any regenerative claims [81].

European Union authorities also diligently monitor imported products to prevent circumvention of these restrictions. They emphasize the significance of standardized characterization, traceability of ingredients, and quality assurance throughout the supply chain [20,21]. The absence of harmonized international standards for extracellular

vesicle characterization remains a persistent challenge for regulatory enforcement and market transparency.

Future regulatory convergence will probably hinge on the establishment of clearer classification criteria that differentiate between cosmetic, therapeutic, and hybrid applications of extracellular vesicles. Such initiatives would gain from the harmonization of international quality and safety standards to guarantee consistent consumer protection while fostering responsible innovation within the cosmetic industry.

7.6. Critical Regulatory Gaps and the Borderline Paradox

While the frameworks delineate the fundamental legal boundaries, the swift commercial integration of exosome technology reveals substantial regulatory challenges and "borderline" paradoxes within the existing European landscape.

Firstly, Regulation (EC) No 1223/2009 characterizes a cosmetic product as a substance intended for external application on the human epidermis [21]. Nonetheless, as evidenced in current clinical protocols, the effectiveness of exosome-based formulations is often linked to physical permeation enhancers, such as microneedling [8,69]. This delivery technique aims to circumvent the stratum corneum, which may result in a conflict with the legal definition of a topical cosmetic application. The utilization of such puncturing devices could potentially place these protocols into a regulatory grey area between cosmetics and medical procedures, thereby challenging their classification as solely topical agents [11,59].

Secondly, a significant legislative vacuum persists concerning the classification of these vesicles as nanomaterials. Considering that exosomes are characterized by their nanometric dimensions, typically ranging from 30 to 150 nanometres, their commercialization inherently intersects with the stringent European Union regulations pertaining to nanomaterials [1,59]. Current legislation requires specific pre-market notifications and comprehensive toxicological assessments for nanoscale components due to the hypothesized risks of systemic absorption [21]. However, the precise legal categorization of organic, plant-derived, or synthetic biological nanovesicles under these directives remains unclear, thereby generating uncertainty for manufacturers concerning long-term regulatory compliance [59].

Ultimately, a significant regulatory challenge pertains to the borderline product paradox. By legal standards, European cosmetics should not primarily exert pharmacological, immunological, or metabolic effects [21]. Nonetheless, the scientific value of exosomes, whether derived from plants or synthesized, is believed to reside in their capacity to modulate cellular behaviour and inflammatory pathways [13,14]. Accordingly, the industry faces a paradoxical risk: demonstrating substantial biological efficacy could prompt health authorities to reclassify these formulations as medicinal products, thereby subjecting them to the rigorous pharmaceutical licencing procedures typical for advanced therapies [11,80]. Moreover, while scientific consortia such as MISEV2023 provide essential guidelines, these currently lack legally binding authority within the EU cosmetic regulatory framework, necessitating that manufacturers approach these developments with utmost caution [2,21].

7.7. Long-Term Safety, Immunogenicity, and Oncogenic Risks

Despite the promising clinical outcomes, the incorporation of bioactive nanovesicles into routine cosmetic procedures warrants a thorough assessment of their long-term safety profile. A primary concern pertaining to human and animal-derived exosomes is their inherent immunogenic potential. While exosomes are generally regarded as less immunogenic than their parent cells due to reduced expression of major histocompatibility complex (MHC) proteins, repeated topical applications of xenogeneic or allogeneic vesicles may still induce cumulative allergic contact dermatitis or broader immune hypersensitivity

over time [12,15]. Although PDEVs diminish mammalian biosafety risks and prevent zoonotic transmission, their long-term cross-kingdom immunogenicity affecting the human cutaneous immune system necessitates comprehensive longitudinal investigations [22,29].

A significant gap in toxicological understanding persists concerning the potential oncogenic risks associated with exosome-mediated cellular reprogramming [1,11]. The primary efficacy of exosomes in wound healing and anti-ageing applications stems from their capacity to stimulate fibroblast proliferation, upregulate matrix metalloproteinases, and promote extensive angiogenesis by transporting potent growth factors such as VEGF and TGF-β [16,55]. Nonetheless, persistent and unregulated cellular proliferation and angiogenesis are fundamental characteristics of oncogenesis [1].

Although the systemic absorption of topical cosmetics is inherently limited by the stratum corneum, the extensive clinical application of physical penetration enhancers—such as microneedling—circumvents this barrier, potentially enabling these mitogenic signals to enter the systemic circulation [8,69]. Consequently, sustained long-term exposure to these highly proliferative signals may hypothetically induce hyperproliferation of dysplastic cells or facilitate the vascularisation of undiagnosed pre-malignant cutaneous lesions, such as actinic keratosis [11]. Accordingly, establishing strict No Observed Adverse Effect Level (NOAEL) thresholds and executing comprehensive genotoxicity, mutagenicity, and long-term dermal carcinogenicity assessments are critical prior to the broad commercialisation of exosome-based therapies [20,21].

8. Conclusions and Future Perspectives

The integration of exosomes into professional cosmetics signifies a substantial paradigm shift in regenerative esthetics. Moving beyond conventional formulations that merely conceal cutaneous imperfections, exosomes serve as intricate biological messengers capable of engaging directly with cellular receptors. By delivering complex bioactive payloads, including lipids, functional proteins, and nucleic acids, these nanovesicles effectively reprogram cellular behaviour to promote collagen synthesis, modulate inflammatory responses, and expedite tissue repair.

Nevertheless, as illustrated throughout this review, the transition from compelling biological theory to dependable clinical practice is accompanied by considerable challenges. Although robust preclinical and human clinical trials affirm their remarkable potential in skin rejuvenation, hair restoration, and hyperpigmentation management, their clinical efficacy remains fundamentally dependent on structural stability and delivery mechanisms. Formulations must effectively safeguard these fragile vesicles, often employing advanced preservation techniques such as lyophilization. Moreover, successful dermal penetration often necessitates physical enhancement methods, such as microneedling or fractional lasers, thereby emphasizing the essential need to distinguish the autonomous efficacy of exosomes from the regenerative response prompted by physical barrier disruption.

From a commercial and regulatory standpoint, the landscape is shaped by stringent safety requirements. In the EU, Regulation (EC) No 1223/2009 strictly prohibits the use of human-derived biological materials in cosmetics, while in the US, the FDA aggressively monitors unverified cellular therapies. Rather than stifling innovation, this regulatory constraint has driven the industry toward highly effective, legally compliant alternatives. The MCCM Medical Cosmetics portfolio case study perfectly illustrates this strategic adaptation. By utilizing PDEVs sourced from carrot roots (*Daucus carota sativa*), the brand successfully avoids mammalian biosafety risks while demonstrating remarkable clinical synergies with established active ingredients, such as PDRN and TRX.

Moving forward, the primary challenge for the industry lies in standardization and safety validation. The notable heterogeneity in large-scale production, isolation, and

profiling methodologies continues to hinder absolute batch-to-batch consistency. To secure the long-term credibility of exosome-based cosmetics, manufacturers must align with international standards, such as the MISEV2023 guidelines, and adapt these rigorous quality control frameworks specifically for emerging botanical and synthetic sources. As these formulations navigate a complex 'borderline' regulatory space involving nanomaterial classifications and potent cellular reprogramming, demonstrating short-term efficacy is no longer sufficient. The industry must establish strict toxicological profiles, employing OECD-validated in vitro genotoxicity and mutagenicity screenings to unequivocally exclude long-term oncogenic and immunogenic risks.

Exosomes have unequivocally transitioned from a theoretical concept to a foundational pillar of modern esthetic dermatology. Future progress will depend on the continuous refinement of scalable isolation technologies, the development of non-invasive yet highly permeable topical delivery vehicles, and international regulatory convergence. Overcoming these technical, toxicological, and legal hurdles will ensure that exosome technology delivers safe, evidence-based, and highly targeted regenerative solutions to the cosmetic market.

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Abbreviations

The following abbreviations are used in this manuscript:

ASCE	Adipose tissue Stem Cell-derived Exosomes
CPSR	Cosmetic Product Safety Report
EC	European Commission
ECCA	Échelle d'Évaluation Clinique des Cicatrizes d'Acné
ECM	Extracellular matrix
EU	European Union
GAIS	Global Aesthetic Improvement Scale
GeIMA	Gelatin methacryloyol
GMP	Good manufacturing practice
HF	Hollow-fibre
IGA	Investigator's Global Assessment

ILVs	Intraluminal vesicles
mEVs	milk-derived Extracellular Vesicles
MHC	Major Histocompatibility Complex
miRNA	micro RNA
MISEV	Minimal International Studies of Extracellular Vesicles
MoS	Margin of Safety
mRNA	messenger RNA
MSCs	Mesenchymal stem cells
MVBs	Multivesicular bodies
NOAEL	No Observed Adverse Effect Level
NTA	Nanoparticle tracking analysis
OECD	Organisation for Economic Co-operation and Development
PDEVs	Plant-derived extracellular vesicles
PDRN	Polydeoxyribonucleotide
PIF	Product information file
QC	Quality control
RhE	Reconstructed Human Epidermis
SEC	Size-exclusion chromatography
STRs	Stirred-tank bioreactors
TEM	Transmission electron microscopy
TEWL	Transepidermal water loss
TFF	Tangential flow filtration
TRX	Tranexamic acid
UC	Ultracentrifugation
UF	Ultrafiltration

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