cosmetics

MDPI

Review

The Transformative Impact of Extracellular Vesicles on the Cosmetics Industry: A Comprehensive Review

Valéria Dal Col [1], Fábio Fernandes Ribas [1] and Rodrigo Pinheiro Araldi [2,3,*]

[1] GEC Cosmetics Enterprise, Vitória 29055-620, ES, Brazil; leiadalcol@gmail.com (V.D.C.); fabio.ribas@gmail.com (F.F.R.)
[2] Postgraduate Program in Endocrinology and Metabolism, Paulista School of Medicine, Federal University of São Paulo, São Paulo 04023-062, SP, Brazil
[3] BioDecision Analytics, São Paulo 01451-917, SP, Brazil
* Correspondence: rodrigo.araldi@unifesp.br or rodrigo.araldi@biodecisionanalytics.com

Abstract

Extracellular vesicles (EVs) have gained attention in the cosmetics industry for their role in intercellular communication and tissue regeneration. They transfer bioactive molecules such as proteins, lipids, and nucleic acids, promoting skin repair, rejuvenation, and anti-aging effects. Human mesenchymal stem cell-derived EVs are particularly valued for their ability to enhance collagen production, reduce inflammation, and improve skin texture and hydration. However, their use is prohibited by regulatory agencies. Plant- and bacterial-derived EVs are being explored to meet the demand for innovative cosmetics. Despite their potential, challenges such as regulatory approval, high production costs, and product stability need to be addressed to fully realize the benefits of EV-based cosmetics. This paper examines the mechanisms, benefits, market trends, and prospects of EV-based skincare products, highlighting their transformative impact on the cosmetic industry.

Keywords: exosomes; cosmetics; dermatology; plant-derived exosomes; bacterial-derived exosomes

Academic Editor: Xinghua Gao

Received: 25 July 2025
Revised: 20 August 2025
Accepted: 26 August 2025
Published: 2 September 2025

Citation: Col, V.D.; Ribas, F.F.; Araldi, R.P. The Transformative Impact of Extracellular Vesicles on the Cosmetics Industry: A Comprehensive Review. *Cosmetics* **2025**, *12*, 191. https://doi.org/10.3390/cosmetics12050191

1. Extracellular Vesicles in Cosmetology: The New Global Market Trend

Cosmetics have evolved significantly, transforming from simple beauty enhancers to sophisticated formulations with multiple purposes. Changes in cosmetology are driven by consumer demand for new products, particularly those free from harmful chemicals and synthetic ingredients. The search for these new products based on natural and organic ingredients for skin and hair care is responsible for the expected 6.1% compound annual growth rate (CAGR) from 2025 to 2030 in cosmetic market, which showed a global market size estimated at USD 295.95 billion in 2023 [1].

In an attempt to meet this demand, the global cosmetic global market has sought for innovative trends, including formulations based on (i) probiotics and postbiotics, which can enhance skin health and balance the microbiome [2–4], (ii) extracellular vesicles (EVs) from human cells (particularly derived from mesenchymal stromal cells (MSCs)), bacteria and plants, which can serve as vehicle for delivering functional bioactive molecules [5–7]; and (iii) devices that enhance product application [8–10]. Among these trends, the cosmetic exploration of EV-based formulations stands out, with a projected compound annual growth rate (GAGR) of 28.73% from 2025 to 2030 and showing a global market valued at USD 117.4 million in 2024 [11].

Despite the numerous new products based on exosomes proposed in the last decade (Table 1), few have properly characterized exosomes according to the recommendations of the Minimal Information for Studies of Extracellular Vesicles (MISEVs) guidelines [12]. Moreover, many of these products lack adequate safety and/or efficacy testing [12]. Therefore, this review aims to provide a concise overview of the research, development, and innovation (RDI) of cosmetic formulations based on EVs, focusing on the technical aspects and potential applications of the human-, bacterial-, and plant-derived EVs for skin and hair care.

Table 1. Number of articles published regarding exosomes and exosome-based cosmetic applications from 2014 to 2024.

Exosomes-Based Skin Cosmetics Applications								
Year	**Exosomes**	**Regeneration**	**Antiaging**	**Hydration**	**Pigmentation**	**Wound Healing**	**Nanodelivery of Molecules**	**Total**
2024	4982	26	25	2	7	309	31	5382
2023	5099	17	11	2	4	282	28	5443
2022	5226	15	11	1	2	258	30	5543
2021	5075	11	4	1	1	190	27	5309
2020	4299	5	4	1	4	145	22	4480
2019	3281	4	4	0	2	92	15	3398
2018	2573	1	3	0	1	61	10	2649
2017	2040	0	0	0	1	41	13	2095
2016	1560	1	0	0	1	36	4	1602
2015	1126	1	0	0	1	20	5	1153
2014	912	0	0	0	0	4	2	912
Total	36,173	81	62	7	24	1438	187	37,972

Data obtained from Villarreal-Gòmez et al. [12].

2. A Brief History of the Extracellular Vesicles

Extracellular vesicles (EVs) are a heterogeneous group of small, lipid bilayer-enclosed particles ranging in diameter from 10 to 10,000 nm. They are produced and secreted by nearly all cell types, including prokaryotes [13–17].

These particles were first reported in 1945 by the biochemist Erwin Chargaff. While studying coagulation, Chargaff observed the presence of "*membrane debris*" sediments in platelet-free plasma supernatant subjected to high-speed centrifugation [18].

One year later, working together with Rudolph West, Chargaff demonstrated that "*the addition of the high-speed sediment to the supernatant plasma brought about a very considerable shortening of the clotting time*" [19]. This observation led to the conclusion that "*the particulate fraction probably includes, in addition to the thromboplastic agent, a variety of minute breakdown products of blood corpuscles*" with high clotting potential [19].

However, the first EV images were recorded in 1967 by Peter Wolf [20]. Using transmission electron microscopy (TEM), Wolf described a "*material in minute particulate form, sedimentable by high-speed centrifugation and originating from platelets, but distinguishable from intact platelets*", which he named "*platelet dust*" [20].

Novel EV images were obtained in 1971 by Neville Crawford, who introduced the term "*microparticles*" to refer to these particles isolated from platelet-free plasma [21]. Crawford also demonstrated that these microparticles contained lipids and carried adenosine triphosphate (ATP) and contractile proteins, pioneering the description of the presence and coarse structure of such cell-free components [21].

Between the mid-1960s and early 1980s, several studies using TEM described structures consistent with EVs [22]. Among these, Nunez et al. [23] reported the presence of multivesicular bodies (MVBs) close to the apical membrane within the cytoplasm. The

authors proposed that "*fusion of the outer or limiting membrane of the multivesicular body with the apical plasma membrane might lead to the release of the vesicles contained within the structure into the luminal space*". This finding contributed to the identification of a subtype of nanosized EVs (30–150 nm) known as exosomes.

The discovery of EVs is closely linked to virology. In the 1960s and 1970s, scientists examined biofluids for virus-like particles (VLPs) with the aim of associating viruses not only with infections but also with other diseases such as cancer [24,25]. However, particles identified in patient biofluids from various diseases, including cancer, exhibited unique characteristics that differed from typical VLPs [24,26–28]. This observation led to the consensus that these particles were artifacts resulting from the separation process [28].

This consensus changed in 1975, when Dalton studied fractions of filtered and unfiltered fetal bovine serum (FBS) and demonstrated that the sera contained particles similar to those found in epithelial cell lines [29]. Dalton stated that "*to call structures with the morphology of normally occurring vesicles of multivesicular bodies and of microvesicles associated with epithelial cells 'virus-like' is unwarranted*", effectively ending the era of VLPs [29].

The early 1980s saw significant advances in extracellular vesicle (EV) biology. Using reticulocyte maturation to study membrane trafficking, research groups led by Stahl and Johnstone demonstrated that the transferrin receptor is lost through vesicle release. Stahl's group published a paper providing transmission electron microscopy (TEM) images showing that these EVs are released from the multivesicular body (MVB) lumen upon fusion with the plasma membrane [30]. In contrast, Johnstone's group described a novel intracellular sorting and trafficking pathway [31]. These EVs were named exosomes by Rose Johnstone in 1987 [22].

In 1991, Johnstone et al. demonstrated the presence of transferrin and nucleoside transporters on exosomes. They also reported that various cellular stresses induced both the release and internalization of exosomes [32]. From these historical papers, it was observed that there was a massive interest in EV research. This interest was driven from around 1993 with a paper demonstrating an elevated number of microparticles (a subtype of EV) in transient brain ischemia and other infarctions [33] and later confirmed in Crohn's [34]. At the same time, studies described the physical and biochemical characteristics of EVs [35] and the immunomodulatory properties of EVs [36].

Although previously called "*membrane debris*", "*platelet dust*", "*small particles*", and even "*virus-like particles*", and later classified into different subtypes according to their size, marker expression, and biogenesis (Table 2), the MISEV2023 discourages the EV nomenclature for terms related to the biogenesis, like exosomes, microvesicles, and apoptotic bodies [17,37].

Table 2. Extracellular vesicle classification based on biogenesis, cell surface expression, and size.

EV Category	Name	Size (nm)	Markers	Biogenesis
Exosomes	Classical	30–200	$CD63^+/CD9^+/CD81^+$	MVE
	Non-classical	30–200	$CD63^+/CD9^+/CD81^-$	MVE
Microvesicle	Classical	150–1000	Annexin A1, ARF6	PMS
	Oncosomes	1000–10,000	Annexin A1, ARF6	PMS
	ARMN	40–100	ARRDC1, TSG101	PMS
Apoptotic	Apoptotic body	1000–5000	Annexin V, PS	Apoptosis
	Apoptotic vesicle	100–1000	Annexin V, P5	Apoptosis
Autophagic	Autophagic EV	40–1000	LC3B-PE, p62, dsDNA/histones	Amphisome
Stressome	Stressed EV	40–1000	HSP90, HSPs	PMS
	Damaged EV	40–1000	$CD63^+/CD9^+/CD81^+$	PMS
Matrix vesicles	Matrix vesicles	40–1000	Fibronectin, Proteoglycan	Matrix binding release

MVE—multivesicular endosome; ARMM—arrestin-domain-containing protein 1 (ARRDC1)-mediated microvesicle; PMS—plasma membrane shedding; Amphisome—Autophagosome–endosome fusion.

3. Exosomes to Extracellular Vesicles: A Nomenclature Change Proposed by MISEV2023 That Directly Impact the EV-Based Cosmetic Market

Hypothetically, exosomes are the most explored subtype of EVs [38], including in cosmetic formulations [12] (Figure 1). But without an orthogonal characterization test to prove the exosomal nature of these vesicles, most formulations may contain other EV subtypes.

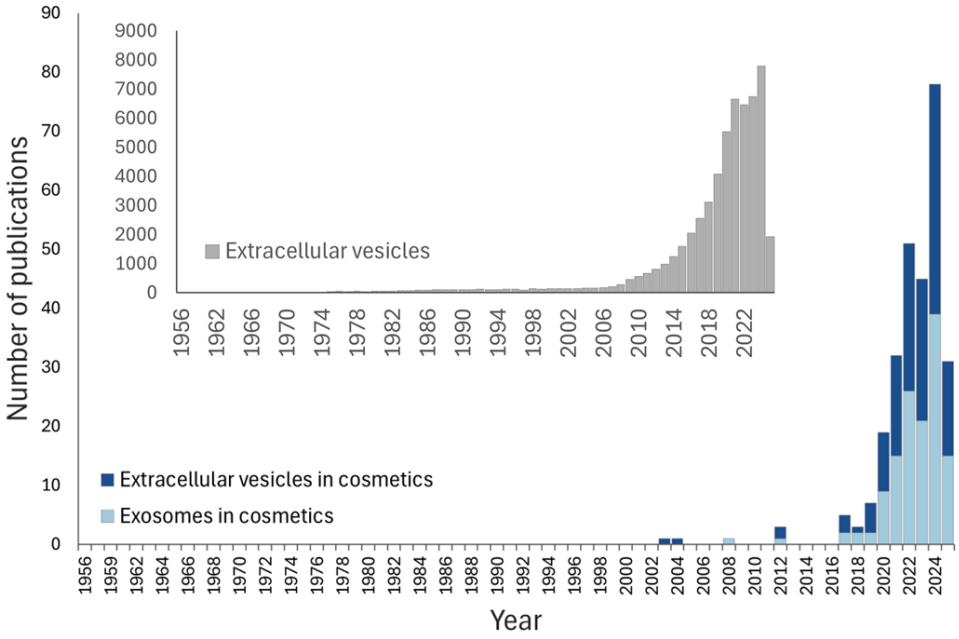

Figure 1. Number of publications about extracellular vesicles available on the PubMed database. Graphics clearly show an increased interest in EVs, particularly from 2010 (gray bars). Despite the reduced number of publications about EVs in cosmetology, it is possible to verify an increasing interest in these vesicles since 2020 (blue bars). Graphs obtained using the total number of publications available on the PubMed database until 17 March 2025.

Since MISEV2018, the International Society for Extracellular Vesicle (ISEV) has encouraged the use of the generic term EV to avoid the misuse of the term "exosome" (Table 3). Despite this recommendation, which was endorsed in MISEV2023 [17], and the lack of regulatory guidance, the term "exosome" has been strategically coined, especially by the cosmetic industry to refer to EVs.

Considering exosomes are a subtype of EVs, what drives the specific focus on exosomes rather than EVs in cosmetology?

This focus can be justified by the small diameter of the particles (30–200 nm), which confers the capability to cross different tissue barriers, including the skin [5,7]. This is a desired characteristic, since it enables exosomes to be used in topical formulations, serving as nanocarriers for natural active biomolecules and synthetic compounds.

Another reason that justifies the interest in exosomes is their biogenesis. Exosomes are generated from the endosomal compartment and contain phosphatidylserine, phosphatidylcholine, sphingomyelin, ceramides, and cholesterol in their lipid bilayer, ensuring structural integrity [39,40]. The combination of these characteristics with the nanosized diameter ensures the stability of these vesicles for up to 20 months at 4 °C or up to four years at −20 °C [17,41].

Table 3. Changes in EV nomenclature in MISEV in ten years (2014–2024).

MISEV2014	**Definition:** EVs are secreted membrane-enclosed vesicles **Nomenclature:** No recommendation
MISEV2018	**Definition**: EVs are particles naturally secreted from cells, defined by a lipid bilayer, and cannot replicate **Nomenclature**: Unless the authors do not establish specific markers of subcellular origins, they urged to consider operational terms for EVs subtypes based on their physical characteristics and biological constituents. The authors also suggest the replacement of terms such as "exosomes" and "microvesicles" with descriptions of the conditions or cellular origins
MISEV2023	**Definition**: EV are particles released from cells, delimited by a lipid bilayer, and cannot replicate on their own **Nomenclature**: Authors recommended the use of generic term "EV" (as previously suggested in MISEV2018) rather than inconsistently defined and sometimes misleading terms such as exosomes

Table adapted from Zhang et al. [37].

In addition, initially it was proposed that exosomes contain evolutionarily conserved surface proteins, such as tetraspanins (CD9, CD63, and CD81), heat shock proteins (HSP60, HSP70, and HSP90), major histocompatibility complex (MHC) class I and II, Alix, and TSG101 that could serve as putative exosomal markers [38]. This led to the idea that, through the immunodetection of these proteins (particularly CD63), it should be possible to distinguish exosomes from other EVs [13,42]. However, MISEV2023 recognized that immunodetection of tetraspanins CD9, CD63, and CD81 does not allow us to ensure exosomal nature of EVs, since other EV subtypes can also express these surface proteins [17].

Furthermore, exosomes count on exclusive sorting mechanisms during their biogenesis that cargo selective biomolecules such as nucleic acids (coding and non-coding RNAs, double- or single-strand DNA), proteins, metabolites, and lipids that make these nanosized vesicles more homogeneous in terms of content than other EVs [38]. This characteristic is particularly beneficial for the RDI of cosmetic products, as formulation homogeneity is a required feature in any product.

The sorting mechanism is part of several coordinated processes involved in exosome biogenesis [38]. This process begins with the formation of multiple intraluminal vesicles (ILVs) within the MVBs. ILVs form by inward budding of the endosome's limiting membrane, involving sorting-related proteins like the endosomal sorting complex required for transport (ESCRT). During ILV formation, cytosolic components are also captured within these structures [38].

Upon maturation, MVBs are transported to the plasma membrane via the cytoskeleton and microtubules. After fusion with the cell membrane, ILVs are released as exosomes into the extracellular space (secretory pathway). Alternatively, MVBs can fuse with lysosomes or autophagosomes for degradation (degradation pathway). The mechanisms governing these pathways are not fully understood but coexist [14,42].

Upon release into the extracellular space, EVs interact with recipient cells through different mechanisms, such as adhesion to cellular surface receptors (receptor-mediated uptake), endocytosis (phagocytosis), and fusion with the plasma membrane [43]. Transmembrane ligands on the extracellular vesicle (EV) surface can directly bind with receptors in recipient cells through direct interaction [44]. This binding initiates a downstream signaling cascade, resulting in the activation of the target cell [44]. This interaction mainly occurs in immunomodulation and apoptosis [44].

Altogether, these characteristics suggest that exosomes can be additional advantages to other subtypes of EVs. However, obtaining pure exosomal suspensions at a large scale imposes some technical limitations ranging from isolation to characterization. In this context, the central question is the following: Do we need to focus our attention on exosomes, or should we look for formulations based on EV?

Given the lack of regulatory guidelines for EV-based products and the importance of MISEV to provide technical recommendations and guidance on EV-related studies, the answer to this question is clear on MISEV2023, which discouraged the use of "exosome" and strongly suggested the use of the generic term EV.

Moreover, most EVs isolated from cells under physiological conditions have an average diameter of 100 nm [17], which is within the desired size to ensure these vesicles can cross epithelial layers, serving as a vehicle for the delivery of molecules of cosmetic interest.

In this sense, although the sorting mechanism can address specific nucleic acids to the exosomes, in cosmetology, the main purpose of the use of these nanosized vesicles is to explore their potential as a vehicle for the delivery of natural and/or synthetic compounds that are combined with these vesicles in multiple formulations.

In addition, the appropriate replacement of the term "exosome" by EV can be interesting from a manufacturing point of view of these vesicles. This is because, although it is strongly recommended that all EVs be characterized by orthogonal methods [17], the adoption of EV term does not limit the quality control process to the immunodetection of surface markers that, as previously mentioned, are not specific for exosome characterization and can negatively impact batch release, causing significant economic losses.

4. Exploring the EV Biotechnological Applications in Cosmetic Products

Since the first studies showed that EVs facilitate cell-to-cell communication by transferring bioactive molecules [45–51], these vesicles have been explored as potential carriers of molecules [52–55]. This is because EVs have all the features sought in a delivery vehicle, which include stability, little or no immunogenicity, biodegradability, low production cost, easy of fabrication, and tolerability [14].

However, EVs are biotechnological products isolated from human cells, bacteria, and plants, each one possessing unique benefits and limitations, as summarized in Table 4. Considering that the EV cargo (nucleic acids, proteins, metabolites, and even lipids) reflects the transcriptomic nature of the origin cells, it is not surprising that human-, plant-, and bacteria-derived EVs can offer different therapeutic and cosmetic opportunities. For this reason, this review provides a concise summary about the cosmetic applications of human-, plant-, and bacteria-derived EVs.

Table 4. Benefits and limitations offered by human-, plant-, and bacterium-derived EVs.

EV Source	Benefits	Limitations
Human-derived	-Can be isolated from plasma and MSCs -High potential for therapeutic and cosmetic applications due to their similarity to human cells	-Regulatory restrictions in many regions due to potential disease transmission -High production costs and complex quality control processes
Plant-derived	-Can be isolated from various plants, each offering unique bioactive functions -Rich in secondary metabolites with proven skin benefits (anti-aging, moisturizing, etc.) -Generally considered safe and non-immunogenic	-Limited comprehensive (pre)clinical studies -Variability in bioactive functions depending on the plant source -Less transcriptional similarity to human cells, potentially affecting efficacy
Bacterium-derived	-Specific strains like *Lactiplantibacillus plantarum* show anti-inflammatory and anti-aging benefits -Potential for drug delivery and immunomodulatory properties -Can be produced on a large scale	-Presence of lipopolysaccharides (LPS) or lipoteichoic acids (LTA) may cause immune reactions -Limited clinical evidence for cosmetic applications

4.1. Human-Derived EVs

Although there are no cosmetic products based on human-derived EVs approved to date, at least 81 clinical trials analyzing the safety and efficacy of human-derived EVs/exosomes for the treatment of several diseases are ongoing worldwide, as data available on ClinicalTrial.gov (accessed on 10 March 2025, Table 5).

EVs can be isolated from various human tissues. However, there are concerns regarding the use of human-derived EVs. These concerns include the potential risk of disease transmission, as EVs can carry virus particles and genetic material (DNA or RNA) of different viruses [56–58]. However, this concern can be mitigated through virological analysis of donors, a practice that is already commonly used for the tissues obtained for the isolation of mesenchymal stem/stromal cells (MSCs) for cellular therapy.

For cosmetic purposes, platelet-rich plasma (PRP) can be considered a primary source of EV obtaining [59].

PRP is an autologous treatment that already has multiple applications in dermatology, particularly in the areas of hair restoration, skin rejuvenation, acne scars, dermal augmentation, and striae distensae [60,61]. PRP therapy is a method that uses a centrifugated blood fraction containing a high concentration of platelets in a small volume of plasma [59,60]. The optimal platelet concentration recommended for high-quality PRP treatment in skin diseases is 1–1.5 million platelets/μL [62,63].

Platelets are small blood cell fragments derived from megakaryocytes that play a key role in hemostasis [63]. These fragments carry two types of storage granules: alpha-granules and dense granules [63,64]. Alpha-granules are the most relevant to PRP therapy since they contain multiple growth factors such as vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), platelet-derived angiogenesis factor (PDAF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), glial cell line-derived neurotrophic factor (GDNF), platelet factor 4 (PF4), interleukin 8 (IL-8), and β-thromboglobulin (or CXCL7) [63]. Dense granules are the second-most abundant granules, and storage of ADP, ATP, calcium, serotonin, and glutamate, which is released after PRP treatment, plays a complementary beneficial effect of this therapy [60,62–64].

Table 5. Ongoing clinical trials involving EVs.

NCT Number	Conditions
NCT05658094	Hair Loss, Alopecia
NCT06568653	Fistula Perianal
NCT04500769	Metabolism
NCT05043181	Familial Hypercholesterolemia
NCT04529915	Lung Cancer
NCT04965961	Sports Drug Abuse
NCT04544215	Drug-resistant
NCT04969172	COVID-19 Disease
NCT02957279	Sepsis
NCT05402748	Fistula Perianal
NCT06853522	Ulcerative Colitis (UC)
NCT02147418	Oropharyngeal Cancer
NCT04270006	Periodontitis
NCT06138210	Acute Ischemic Stroke
NCT05475418	Wounds and Injuries
NCT03478410	Atrial Fibrillation
NCT05499156	Perianal Fistula in Patients With Crohn's Disease
NCT05871463	Decompensated Liver Cirrhosis

Table 5. *Cont.*

NCT Number	Conditions
NCT06609785	Diabetes, Exercise, Lifestyle Intervention
NCT06810869	Stable Vitiligo
NCT06072794	Premature Ovarian Insufficiency, Diminished Ovarian Reserve
NCT06298682	Platelet Thrombus
NCT05616234	Exosomes, Connective Tissue, Exercise
NCT04636788	Pancreas Adenocarcinoma
NCT04602104	Acute Respiratory Distress Syndrome
NCT03985696	Lymphoma, B-cell, Aggressive Non-Hodgkin (B-NHL)
NCT06697080	Androgenic Alopecia
NCT04657406	COVID19
NCT06536712	Rectal Cancer
NCT02748369	Normal Cellular Metabolism
NCT04747574	SARS-CoV-2
NCT06764004	Apical Periodontitis
NCT06221787	Melasma
NCT05933707	Obesity
NCT03392441	Diabetes Mellitus
NCT06496451	Friedreich Ataxia
NCT06330922	Cerebral Palsy, Spastic
NCT04081194	New Tumor Diagnostics From Human Plasma Samples
NCT03106246	Type1 Diabetes Mellitus
NCT05559177	Recurrent or Metastatic Bladder Cancer
NCT04595903	COVID-19
NCT06598202	Amyotrophic Lateral Sclerosis
NCT05228899	COVID-19
NCT04384445	COVID-19
NCT06773572	Infertility
NCT05375604	Advanced Hepatocellular Carcinoma (HCC)
NCT04167722	Prostate Cancer
NCT02797834	Extracellular Vesicles
NCT06824285	Aging
NCT03255408	Obstructive Sleep Apnea of Adult
NCT04664738	Skin Graft
NCT03854032	Oral Cavity Squamous Cell Carcinoma
NCT06615531	Intensive Meditation in Novice and Experienced Meditators
NCT06536374	Prostate Cancer
NCT04134676	Chronic Ulcer
NCT01550523	Malignant Glioma of Brain
NCT04924504	Diabetes Mellitus, Type
NCT02507583	Malignant Glioma
NCT04617405	Diabetes Mellitus, Type 2
NCT05937594	Neonatal Opioid Withdrawal Syndrome
NCT06821243	Squamous Cell Carcinoma of Oropharynx
NCT06319742	Stroke, TIA, Stroke-mimics, Stroke Biomarkers
NCT02935816	Prostate Cancer
NCT00285805	Insulin Resistance
NCT00578240	Prostate Cancer
NCT06504485	Hepatitis D
NCT00001888	Asthma
NCT02653339	Rhinitis, Allergic, Perennial
NCT02063464	Ovarian Cancer
NCT05624203	Myocardial Reperfusion Injury

Table 5. *Cont.*

NCT Number	Conditions
NCT06633003	Spinocerebellar Ataxia
NCT06654167	Cognitive Function
NCT03406780	Muscular Dystrophies
NCT06652425	Cardiovascular System
NCT05575752	Cardiovascular System
NCT03459703	Obesity
NCT03410030	Pancreatic Cancer
NCT04350177	Parkinson Disease
NCT06219850	Diabetes Mellitus, Type 2
NCT04153539	Cardiovascular System
NCT02737267	Body Weight Changes

The mechanism of action (MoA) of PRP has been attributed to the secretion of growth factors and ATP, which begins 10 min after PRP injection [63–65]. Combined, these molecules induce multiple responses in cells within the injection site, resulting in cellular proliferation, matrix formation, regulation of inflammation, angiogenesis, osteoid production, collagen synthesis, and the remodeling of novel tissues [63–65]. PRP therapy is safe, with few contraindications, limited to patients with critical thrombocytopenia, platelet dysfunction, hemodynamic instability, sepsis, and local infection at the site of PRP administration [63].

However, current studies have provided evidence that EV ("exosomes") are the main effectors of PRP activity, mediating the intercellular communication process and serving as a vehicle for the delivery of platelet-derived growth factors and other biomolecules, including ATP [66–68]. In this regard, Guo et al. [66] provided strong evidence that intra-articular injection of PRP-EVs can significantly promote the repair of articular cartilage defects in murine models. These data make PRP-EVs potential candidates for cosmetic products. Moreover, these EVs can be easily isolated using already well-established protocols based on ultracentrifugation or tangential flow filtration (TFF). Moreover, for being an autologous treatment, PRP-EVs can be considered safety. On the one hand the PRP-EVs use represents a landmark in personalized cosmetology; on the other hand, the use of these vesicles requires the adoption of rigorous protocols to ensure the safety and efficacy of PRP-EV-based treatments.

Alternatively, MSCs emerge as a useful source of EVs obtained on large scale to supply the cosmetic market, which increases yearly. This is because these cells can be easily isolated from different tissues [13,69,70].

MSCs were first described in the 1960s by Soviet scientist Alexander Friedenstein, who demonstrated that bone marrow and other blood-forming organs contain clonogenic progenitor cells that, under in vitro conditions, can give rise to fibroblasts and other mesenchymal cells [71]. Friedenstein also showed that these cells (not belonging to the hematopoietic lineage) could also form bone and cartilage-forming cells [71–74].

Because of these characteristics, these cells were called "mesenchymal/stromal stem cells" by Prof. Dr. Arnold Caplan in 1991 [75].

In subsequent studies, Haynesworth et al. [76] showed that MSCs express unique surface antigens that could be used to identify and characterize MSC populations. A few years later, Barry et al. [77,78] reported that, using monoclonal antibodies, it would be possible to identify these antigens (CD105 and CD73), allowing the identification of MSC populations. From this moment, MSCs began to be characterized by (i) their capacity for adhesion and proliferation in culture (known since 1966), (ii) expression of the surface

markers CD73, CD90, CD105, CD44, and CD124 and (iii) the capacity to differentiate in vitro into mesodermal lineages.

Due to the increased clinical interest in MSCs and the need to establish broad and unambiguous criteria for defining MSCs, the International Society for Cellular Therapy (ISCT) has established minimum criteria for defining MSCs [79]. These criteria include (i) adhesion (to the plastic), (ii) expression of the surface antigens CD105, CD90, and CD73 in more than 95% of the cell population, and CD45, CD19, CD14, CD11b, CD34, CD79α, and HLA-DR limited to a maximum of 2% of the cell population, (iii) ability to differentiate in vitro into osteoblasts, chondrocytes, and adipocytes (multipotency) [79].

The main advantage of these cells as a source of EVs is that they can be cultivated on a large scale [80] and, under specific stress conditions, can produce high amounts of EVs to supply the cosmetic market [81–83].

Other relevant aspects that make MSC potential candidates for EV obtaining are the safety and tolerability of these cells, which have been investigated for over 15 years in multiple clinical trials [15,69,84–86].

Although MSCs can be isolated from different tissues, as they share transcriptional signatures with their tissue of origin [87–89], it is not surprising that the therapeutic potential of MSCs may vary according to their origin and even donors, as recently shown by a comparative transcriptomic analysis among different MSC types by Araldi et al. [70].

Despite the therapeutic potential of MSCs have already been widely demonstrated in different systematic reviews and meta-analyses, the MoA of these cells remains not completely elucidated [13,42,90–92].

Based on cumulative evidence showing that, after intravenous transplantation, MSCs migrate and transmigrate across the endothelium to sites of injury/inflammation, where they attach to target tissues (homing) [93,94], and differentiate into specialized cell types [15,16,95–97], initially, it was postulated that the therapeutic action of these cells was mediated by the ability of MSCs to replace dead and/or injured cells [96,98].

However, a study involving renal injury induced by injections of toxic doses of glycerol showed that transplanted MSCs remained at the site of injury for a few days, suggesting that the therapeutic benefits of MSCs do not necessarily depend on cell replacement [99]. Confirming this hypothesis, subsequent studies have shown that only 0.1–2.7% of transplanted MSCs are able to attach to the target tissue [100–102] and only 1–2% of transplanted MSCs survive for more than a week after systemic administration [98,103–107]. Therefore, given the low percentage of MSCs that attach to the target tissue, the replacement of injured cells by differentiated MSCs (initially postulated as the MoA of MSCs) would not be able to justify the therapeutic benefits of these cells.

In 1996, Haynesworth et al. showed that MSCs secrete a series of growth factors and cytokines that could act in a paracrine manner on recipient cells [108]. This discovery led to the formulation of the theory of paracrine stimulation. However, this theory was only confirmed ten years later, when Takahashi et al. [109] showed that growth factors and cytokines present in the conditioned medium of MSCs can increase the density of blood capillaries and improve cardiac function, reducing the damage caused by acute myocardial infarction in rats. Since then, it has been recognized that the therapeutic effects of MSCs are due to the paracrine action of the biomolecules secreted by these cells [95,96,105,110–114]. Such effects are mediated by cytokines, growth factors, lipids, nucleic acids, ions, and metabolites produced and secreted by these cells, which act in signaling and intercellular communication processes [98,115,116].

As observed in PRP, these biomolecules can be found in free form and contained in EVs secreted by cells [117]. However, the molecules present in free form are easily hydrolyzed or oxidized, while the molecules contained in EVs are less susceptible to degradation [14,42].

This observation has driven the biotechnological interest in exploring the use of EVs in a new therapeutic modality known as cell-free therapy [14,15,42,52,95,118].

However, the MSC production for the large-scale EV obtaining can be limited by the cost of production of these cells, which can make it economically unviable for cosmetic purposes. This is because the productive chain of MSCs requires multiple cell expansion steps and quality control processes to ensure the maintenance of MSC phenotype according to the minimum criteria defined by ISCT. These steps commonly involve an open process (except for MSC production in bioreactors) that also requires extensive microbiological vigilance. These processes represent important challenges for the sterile EV solution obtained for injectable cosmetic products. However, open processes may not represent a problem for obtaining MSC-derived EVs for cosmetic formulation destinated for topic use.

4.2. Plant-Derived EVs

Human-derived EVs have garnered significant interest and have been extensively studied in recent years. Conversely, plant-derived EVs (also known as plant-derived exosome-like nanoparticles—PELNs) have received comparatively less attention and remain under-researched. Although several investigations have highlighted their promising health benefits and drug delivery potential, comprehensive (pre)clinical studies are still limited [119].

Plants survive by defending themselves against biological and non-biological stress or adapting to the environmental conditions through various secondary metabolites, such as alkaloid, flavonoid, polyphenol, terpenoid, and quinone [120]. These secondary metabolites are commonly explored as nutritional supplements or active ingredients in multiple cosmetic formulations [120]. This is because they exert proven beneficial effects on human skin, providing antiaging, moisturizing, whitening, regeneration properties, and nutritional supply [120].

Besides secondary metabolites, plants produce defense against biological and non-biological threats though EV-mediated mechanisms [121,122]. Like human cells, plant cells, cultured in vitro also release EVs containing nucleic acids, proteins, lipids, and substances with protective functions into the growth medium, which can be harvested for pharmaceutical applications [119,123].

As observed with MSC-derived EVs, plant-derived EVs have various bioactive functions according to the plant they are derived from [120]. Exemplifying these differences, it was demonstrated that blueberry-derived EVs increase the survival rate of cells by regulating the expression of genes that affect inflammation and oxidation stress [124]; strawberry-derived EVs were reported to prevent oxidative stress in human MSCs [125]; grape-, grapefruit-, ginger-, and carrot-derived EVs were reported to help maintain intestinal homeostasis owing to their anti-inflammatory functions [126].

Although extensive evidence suggests that plant secondary metabolites are the primary agents responsible for the mechanism of action of plant-derived extracellular vesicles, Woith et al. [119] showed that these metabolites are not actively packaged into EVs but become enriched in the membrane when sufficiently lipophilic. This is because lipophilic compounds were found associated with nanovesicles, whereas more hydrophilic structures were not consistently observed [119]. This evidence reinforces that plant-derived EVs offer additional therapeutic benefits to secondary metabolites that are already extensively used in cosmetic formulations.

Confirming this hypothesis, analyzing the transcriptome of keratinocytes treated for six hours with plant-derived EVs or conventional plant secondary metabolites from different plants, including ginseng (*Panax ginseng*) and green tea (*Camellia sinensis*), Cho et al. [120] showed that EVs promoted more expressive transcriptional changes. In the

comparative analysis of expression of genes that are known to affect aging, regeneration, skin barrier, and moisturization (*MP12*, *MMP13*, *NOTCH3*, *FGF12*, *HS3ST3A1*, *LOX*, *VIM*, *ELOVL3*, and *KRTI*), the study showed that EVs are more effective than plant secondary metabolites in contributing to maintaining healthy skin [120]. These results demonstrate that plant-derived EVs have the potential to be commercialized as a cosmeceutical product [120].

4.3. Bacterial-Derived EVs

Bacterial-derived EVs are classified into Gram-negative and Gram-positive bacteria-derived EVs. EVs from Gram-negative bacteria contain lipopolysaccharides (LPS) [127], while EVs from Gram-positive bacteria contain lipoteichoic acids (LTA) [128]. These EVs are involved in the communication process between bacteria [129,130]. For this reason, bacterial-derived EVs have been investigated as mediators of drug delivery [131–134].

Lactiplantibacillus plantarum (previously *Lactobacillus plantarum*) is a Gram-positive bacterium belonging to the genus *Lactiplantibacillus* [135]. *L. plantarum* is found in many fermented products and has been associated with reducing allergic reactions as a probiotic and lowering cholesterol and triglyceride levels [129,136–140]. *L. plantarum*, which is an aerotolerant Gram-positive bacterium, is also found on the skin, controlling various harmful Gram-positive and Gram-negative bacteria [141–143].

In 2022, Kurata et al. [144] showed that *L. plantarum*-derived EVs (LpEVs) have immunomodulatory properties. These properties were confirmed in 2024 by Gong et al. [145], who showed that LpEVs lead to increased expression of Arg-1 and anti-inflammatory cytokines IL-10 and decreased expression of iNOS and surface marker protein CD86 in RAW 264.7 cells (murine macrophages) exposed to LPS, causing significant morphological changes in these cells. These results demonstrate that LpEVs can suppress inflammatory responses and promote the polarization of macrophages toward the anti-inflammatory M2 phenotype. These findings support the anti-inflammatory activity of *L. plantarum*-derived EVs [144].

Still in 2022, Jo et al. [129] provided in vitro and clinical evidence that *L. plantarum*-derived EVs (LpEVs) modulate the mRNA expression of extracellular matrix (ECM), suppressing skin wrinkle formation and pigmentation. These results show that LpEVs offer benefits against skin aging.

Currently, Kang et al. [146] showed that *Lactobacillus*-derived artificial EVs (LAEs) effectively improve wound healing in fibroblasts, modulating aging-related genes. These results make LAEs a promising alternative to natural EVs for skin rejuvenation and anti-aging.

Exosomes from other species, such as fungi and algae, have also been identified and may possess bioactive properties. However, this review will not explore their use due to the current lack of supportive data demonstrating their efficacy or safety in cosmetic contexts. To date, there is insufficient evidence validating their stability, bioavailability, or dermatological benefits, and no regulatory consensus regarding their safe incorporation into consumer products.

5. Potential Risks and Adverse Effects of Human-, Plant-, and Bacterial-Derived EVs in Cosmetics Applications

The incorporation of EVs into cosmetic formulations has garnered significant interest due to their capacity to modulate cellular communication, promote skin regeneration, and deliver bioactive molecules. However, despite their promising therapeutic potential, the use of exosome, particularly those derived from human, plant, and bacteria, raises important safety considerations that must be critically evaluated.

Human-derived EVs, often isolated from MSCs or other donor tissues, such as plasma, may carry risks related to immunogenicity and pathogen transmission [147,148]. Although purification protocols aim to eliminate contaminants, residual proteins, nucleic acids, or membrane-bound molecules could provoke unintended immune responses or inflammatory reactions, especially when administered intradermally [149,150]. Additionally, donor variability and the lack of standardized manufacturing practices may result in inconsistent bioactivity and safety profiles [151].

Plant-derived EVs are generally considered less immunogenic due to their phylogenetic distance from humans [152,153]. However, they may contain plant-specific secondary metabolites, allergens, or enzymatic compounds that could irritate sensitive skin or trigger allergic reactions upon topical application [120,153]. The stability of these vesicles in human skin environments and their ability to penetrate the epidermal barrier remain poorly understood, raising concerns about their efficacy and long-term safety [154,155].

Bacterial-derived EVs, or outer membrane vesicles (OMVs), pose unique challenges. While some OMVs have demonstrated beneficial effects such as anti-inflammatory or antimicrobial activity [156,157], they may also contain lipopolysaccharides (LPS), peptidoglycans, or other immunostimulatory components capable of inducing strong inflammatory responses [156,157]. Intradermal administration of bacterial EVs could heighten the risk of systemic immune activation or localized adverse reactions, including erythema, edema, or granuloma formation [158,159].

Across all sources, the route of administration significantly influences the risk profile. Topical application generally presents a lower risk due to limited systemic absorption, though compromised skin barriers may increase permeability [160,161]. In contrast, intradermal delivery bypasses the protective epidermal layer, introducing exosomes directly into the dermis, where they may interact with immune cells, vascular structures, and connective tissue—potentially amplifying adverse effects [7,148].

6. Challenges in EV Large-Scale Production for Cosmetic Purposes

Despite the increasing interest in biotechnology exploring EV, many technical challenges can limit the EV applications in cosmeceutical products. The first and most discussed technical challenge is EV isolation.

Although there are several methods for isolating EVs, such as ultracentrifugation (UC), ultrafiltration (UF), precipitation, isolation kits, and several novel techniques such as microfluidic chips (MFC), size-exclusion chromatography (SEC), field-flow fractionation (FFF), hydrostatic filtration dialysis (HFD), and immunoaffinity precipitation (IP) kits [162], each method has pros and cons that can limit their use for EV obtaining for clinical purposes [162]. For this reason, the best choice depends on the intended downstream application, the type of EV (exosome, microvesicle or apoptotic body), and the homogeneity levels desired.

Centrifuge-based methods separate EVs from a solution according to their size, shape, density, and the viscosity of the medium [162]. Thus, the greater the difference in density, the faster they separate [118,162,163].

UC became the gold standard method for EV isolation, especially for clinical purposes [162]. Three different UC-based techniques can be used for EV isolation: differential ultracentrifugation (DUC), density gradient centrifugation (DGC), and rate-zonal centrifugation (RZU) techniques [164,165].

Historically, DUC was the first technique used to isolate EVs [162]. This technique is based on the density, size, and shape of the EVs [164,166–169]. The main advantage of this technique is that it does not require the addition of any chemical compound that can result in eventual contaminants that can limit the EV clinical application, since the EV-

containing solution is directly subjected to high-speed centrifugation (generally higher than 100,000× *g* (RCF)). However, the development of DUC-based protocols requires expertise in both high-speed centrifugation and EV biology, since the duration (of ultracentrifugation), temperature, and sample dilution are critical factors for the separation efficiency [170,171]. On the one hand, this technique is scalable, being perfectly adequate for large-scale production to attempt clinical demands; on the other hand, it is not adequate for small sample volumes [172,173]. Another important consideration about this technique is that DUC causes the precipitation of various EV subtypes [174].

In this regard, DGC emerges as an alternative technique for reaching higher purification of specific types of EVs [164]. This is because unlike DUC, DGC occurs in an ultracentrifuge tube containing a preconstructed density gradient medium of sucrose or iodixanol (OptiPrep®) [167,174]. Thus, EVs can be separated from proteins [174] and purified according to their density to obtain most homogeneous isolations of exosomes, oncosomes, microvesicles, or apoptotic bodies [175]. However, by requiring longer durations and larger volumes of samples in relation to DUC [176,177], the application of this technique is not indicated for clinical purposes.

Rate-zonal centrifugation (RZC) is an alternative technique to obtain purified populations of exosomes (that represents the focus of study due to their nanosized diameter). In this technique, the sample is added to the top of the ultracentrifugation tube, and through centrifugation, higher-density compounds go through the dense layer more than lighter compounds [162]. Thus, particles with the same density and different diameters (size) can be separated [178], with more extracellular recovery in comparison with DGC [174]. However, this method is laborious and can leave potential contaminants that can limit the clinical use of these vesicles.

An alternative to methods based on centrifugation is precipitation. This method works based on dispersibility alteration. For this, a polymeric water-excluding compound (generally polyethylene glycol—PEG or lectin) is added to the sample. Next, the sample is centrifuged or filtered. The polymer dries the sample and leads to the EV precipitation [163,179]. Although considered a quick and easy method, since it does not require ultracentrifugation, this method does not offer selectivity and quality for clinical purposes. This is because the polymer leads to the precipitation of multiple types of vesicles simultaneously. Moreover, even using immunoaffinity techniques to purify the exosomal population of EVs [14,163,164], the polymer residues represent important contaminants to exosomal suspension that limit its clinical use. For this reason, precipitation should always be followed by centrifugation and filtration to eliminate contaminants [180,181].

Ultrafiltration (UF) is the most employed size-based isolation method. In this method, samples are filtered through membrane filters with different pore sizes that separate the EVs according to their size and molecular weight [164]. Although simple, this method can be limited by EV clogging and trapping in the membrane. For this reason, it is strongly recommended that samples be initially filtered using large pore filters [164,182]. However, filter plugging-related poor efficiency limits the use of this method for large-scale production [164,183,184]. Moreover, UF can also deform the EVs due to the pressure applied during the filtration process [14,42].

Tangential flow filtration (TFF) is a rapid and efficient method for isolating and purifying exosomes from biological fluids. More efficient than high-speed centrifugation-based methods, TFF uses tangential flow to isolate exosomes. Through this method, the media flows parallel to the membrane, making it more suitable for large-scale research applications [185]. The major advantage of this method is that it can be connected to a mechanical system for large volumes, avoiding eventual contamination by working a closed system [185]. Moreover, TFF can be combined with size-exclusion chromatography (SEC)

to remove host–cell protein (HCP) and DNA [185]. However, this method is more complex to operate, since it requires precise control of multiple parameters, such as transmembrane pressure, crossflow velocity, and temperature [185].

In this sense, sequential filtration can be alternatively used to simplify this process. In this method, the sample is filtered by different filtration steps. In each step, particles with large-size than the membrane pores are trapped, whereas smaller particles go through it [184]. However, in a similar way to other filtration-based methods, sequential filtration can be limited by filter trapping that leads to yield rate reduction [184,186,187].

Size-exclusion chromatography (SEC) in turn can be used to purify exosomes isolate by TFF or directly employs as a method to isolating these nanoparticles. SEC is a size-based separation method that employes a stationary phase often consisting of gel polymers through which the mobile phase transverses and is eluted [188]. This molecular sieve separates molecules by Stokes radii, leading to the elution of larger particles first, while the smaller molecules navigate through the pores of the resins (Biogel P, Sephadex, Sepharose, or Sephacryl) and are eluted later [188]. Although this method preserves the integrity of exosomes and their cargos, SEC is not applicable for a large-scale isolation [164,188,189].

Immunoaffinity-based methods also been also used for exosome isolation. These methods are based on the recognition of antigens present on the exosomal surface. These antigens are captured by specific antibodies [164,190]. Although simple, this method requires clearance pretreatment to remove cell debris [164]. On the other hand, this method allows us to obtain highly purified exosomes. The low harvest rate imposes limitations on its large-scale employment. Despite this disadvantage, this method has been explored in several magneto-immunoprecipitation commercial kits applicable to scientific purposes [164,191].

In this sense, methods based on micro- and nano-fluidic chips using acoustic, electrophoretic, and electromagnetic technologies can be efficiently used on small samples [164,192].

Thus, to date, DUC is the most appropriate isolation method for large volumes of samples, and TFF is the most promising method for scaling up the exosomal production for clinical purposes.

7. Regulatory Issues

The use of cosmetic products containing allogenic EVs derived from MSCs in moisturizers and serums is a growing trend in the cosmetic global market [7]. However, in Europe and the United States (U.S.), the use of the cosmetic based on products derived from humans is prohibited due to the possibility of transmission of viral or prion diseases [7]. In December 2019, the U.S. Food and Drug Administration (FDA) issued a safety warming regarding the use of exosomes following multiple reports of unspecified serious adverse events in patients in Nebraska treated with unapproved exosome-containing products [193]. Despite this, six companies in U.S. produce and supply exosome-containing products for clinical use, all from human origin, but with no information about their tissue origin [7].

In Brazil, the National Health Surveillance Agency (ANVISA, *Agência Nacional de Vigilância Sanitária*) authorized the use of exosomes of non-human origin in the group of grade 2 cosmetics [7]. Thus, these exosome-containing products are exclusively authorized for external use and can only be applied to the skin with an intact epidermis [7]. However, the presentation in sterile vials encourages their use by injection procedures that cause disruption of skin barriers, such as microneedling or fractional lasers [7].

The products authorized by ANVISA as cosmetics include Inno-Exoma® Exo-Skin by INNOASTHETICS and marketed by Suprema Marcas, ASCE Plus SRLV (for skin), HLRV (for hair), and ILRV (INTIMATEPRODUCTS) by BENEV Inc. in partnership with Exo-CoBio, GFCCELL™ EXO SCALP Pep9 (for hair) by GFC Life Science Co. (Hwaseong-si,

South Korea), EVO EXO ONE HAIR (for hair) by Evopharma Ltd. (Guaxupe, Brazil), Exocoll and exo.reset, both by Valéria Dal Col. The Inno-Exoma® Exo-Skin was developed using NARBEX (Non-Animal Regenerative Bioengineering Exosome) technology and utilizes synthetic exosomes obtained by bioengineering to mimic cell-derived exosomes [7]. Since these synthetic vesicles do not carry biomolecules as observed in EVs secreted by cells, the product is presented in a 10 mL sterile vial containing lyophilized exosomes associated with a complex of amino acids and peptides, mannitol, and hyaluronic acid, accompanied by a 2 mL vial of saline solution for dilution. However, to date, there are no published clinical studies on this product.

ASCE Plus is comprised by exosomes derived from *Rosa damascena* (plant), unlike the exosomes derived from adipocyte-derived MSCs marked by ExoCoBio in South Korea. The product is presented in a sterile vial containing a complex of amino acids and peptides and other active ingredients, such as ascorbic acids, retinol, nicotinamide, and thiamine, accompanied by a 5 mL vial of diluent containing water, sodium bicarbonate, sodium chloride, sodium hyaluronate, and an amino acid complex. However, there are no published studies demonstrating the safety and efficacy of the product. The only published study by ExoCoBio describes beneficial therapeutics of the product based on MSC-derived EVs (not approved by ANVISA) for the treatment of atopic dermatitis [194].

Exocoll is a treatment protocol designed to reverse and treat signs of facial aging [195]. Using a powerful combination of peptides, NMN, NADH, and exosomes, Exocoll aims to restore skin elasticity, reduce atrophy, maintain bioactive cells and produce collagen, promoting an improvement in the overall appearance of the skin, in addition to enhancing the effects of in-office treatments (https://valeriadalcoll.com.br/exocoll, accessed on 20 May 2025) [195].

8. Perspectives About the Cosmetic Use of EVs

The global market for EV/exosome-based cosmetics is experiencing significant growth, driven by increasing consumer interest in advanced skincare solutions that leverage the regenerative properties of EV. According to the market size and growth projections, it is expected that by 2032, the global EV skincare market reaches USD 809.5 million. However, the production of EV-based cosmetics faces several significant challenges, primarily revolving around safety and efficacy concerns. One of the main issues is the lack of appropriate regulatory guidelines for the industry.

Currently, the use of human-derived EVs in cosmetics is prohibited by regulatory agencies due to the potential risk of viral transmission. This restriction forces industry to rely on plant- and bacterial-derived EVs, which, despite offering various clinical benefits, have limited transcriptional similarities to human cells. This limitation can negatively impact the potential applications of these vesicles, thereby affecting the dynamics of the cosmetic market. The absence of comprehensive regulations that could make the use of allogenic MSCs for large-scale EV production viable further complicates the scenario. Without these regulations, industry cannot fully explore the potential of human-derived EVs, which represent a promising alternative due to their closer resemblance to human cells.

Another critical challenge is ensuring the safety and efficacy of EV-based cosmetics. The risk of viral transmission through human-derived EVs necessitates specific regulations, including virological analyses of cell donors, to guarantee the safety of these products. However, the lack of such regulations means that the industry must consider alternatives like PRP, which is already regulated by sanitary authorities and naturally contains EVs. The autologous administration of EVs in PRP mitigates the risk of viral transmission, making it a suitable alternative for personalized skincare protocols. Nevertheless, the industry still faces the challenge of proving the efficacy of these alternatives in delivering

the desired cosmetic benefits. The limited transcriptional similarities between human and non-human EVs may affect their performance, and without robust regulatory guidelines, the industry struggles to establish standardized methods for evaluating the safety and efficacy of these products.

In this regard, the release of the *Guideline on Quality, Non-clinical and Clinical Assessment of Extracellular Vesicle Therapy Products* by Korea's National Institute of Food and Drug Safety Evaluation (NIFDS) in September 2024 marks a pivotal moment in the global regulatory landscape for advanced biologics. This document establishes a comprehensive framework for the evaluation of therapies based on EVs, including exosomes derived from human cells, and sets a precedent for international harmonization in this rapidly evolving field.

This guidance is the first of its kind to systematically address the unique challenges posed by EV-based therapeutics. While regulatory agencies such as the EMA, FDA, and Anvisa have issued general recommendations for advanced therapy medicinal products (ATMPs), the NIFDS document is distinguished by its specificity and depth regarding EVs. It provides a blueprint that other regulatory bodies can adapt, fostering consistency in product development, safety evaluation, and clinical translation.

Among the main contributions of the *Guideline on Quality, Non-clinical and Clinical Assessment of Extracellular Vesicle Therapy Products* are (i) the definition and classification of EVs, positioning exosomes as therapeutic agents, (ii) standardization of quality attributes, including particle size distribution, surface markers, and cargo characterization, (iii) risk-based non-clinical evaluation, tailored to the biological complexity of EVs and, (iv) clinical trial design considerations, including dose rationale, biodistribution, and immunogenicity.

Although the Korea's 2024 guidance on extracellular vesicle therapy products represents a landmark achievement in the regulation of next-generation biologics, it is not applied for cosmetic products. However, it provides a robust and detailed framework, it not only accelerates the safe development of exosome-based therapies but also serves as a model for global regulatory convergence for cosmetic industry. As the therapeutic promise of EVs continues to unfold, this guidance will be instrumental in shaping the future of EV-based products.

Author Contributions: Conceptualization, writing and review V.D.C., F.F.R. and R.P.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: V.D.C. and F.F.R. the authors are employees of GEC Cosmetics Enterprise. The author R.P.A. was employer of BioDecision Analytics. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Grand View Research Cosmetics Market Size, Share & Trends Analysis Report By Product (Skin Care, Hair Care), By End-User (Men, Women), By Distribution Channel (Offline, Online), By Region (North America, Europe), And Segment Forecasts, 2024–2030. Available online: https://www.grandviewresearch.com/industry-analysis/cosmetics-market (accessed on 25 August 2025).
2. Han, J.H.; Kim, H.S. Skin Deep: The Potential of Microbiome Cosmetics. *J. Microbiol.* **2024**, *62*, 181–199. [CrossRef] [PubMed]
3. Woolery-Lloyd, H.; Andriessen, A.; Day, D.; Gonzalez, N.; Green, L.; Grice, E.; Henry, M. Review of the Microbiome in Skin Aging and the Effect of a Topical Prebiotic Containing Thermal Spring Water. *J. Cosmet. Dermatol.* **2023**, *22*, 96–102. [CrossRef] [PubMed]
4. Lolou, V.; Panayiotidis, M.I. Functional Role of Probiotics and Prebiotics on Skin Health and Disease. *Fermentation* **2019**, *5*, 41. [CrossRef]
5. Thakur, A.; Shah, D.; Rai, D.; Parra, D.C.; Pathikonda, S.; Kurilova, S.; Cili, A. Therapeutic Values of Exosomes in Cosmetics, Skin Care, Tissue Regeneration, and Dermatological Diseases. *Cosmetics* **2023**, *10*, 65. [CrossRef]

6. Queen, D.; Avram, M.R. Exosomes for Treating Hair Loss: A Review of Clinical Studies. *Dermatol. Surg.* **2024**, *51*, 409–415. [CrossRef]
7. Dal'Forno-Dini, T.; Birck, M.S.; Rocha, M.; Bagatin, E. Exploring the Reality of Exosomes in Dermatology. *Bras. Dermatol.* **2025**, *100*, 121–130. [CrossRef]
8. Cohen, M.; Austin, E.; Masub, N.; Kurtti, A.; George, C.; Jagdeo, J. Home-Based Devices in Dermatology: A Systematic Review of Safety and Efficacy. *Arch. Dermatol. Res.* **2022**, *314*, 239–246. [CrossRef]
9. Scott, J.A.; Banga, A.K. Cosmetic Devices Based on Active Transdermal Technologies. *Ther. Deliv.* **2015**, *6*, 1089–1099. [CrossRef]
10. Hamed, R.; Abu Nahia, B.J.; Alkilani, A.Z.; Al-Adhami, Y.; Obaidat, R. Recent Advances in Microneedling-Assisted Cosmetic Applications. *Cosmetics* **2024**, *11*, 51. [CrossRef]
11. Grand View Research Exosomes Market Size, Share & Trends Analysis Report by Product & Service (Kits & Reagents, Services), by Workflow (Isolation Methods, Downstream Analysis), by Application, by End-Use, by Region, and Segment Forecasts, 2025–2030. Available online: https://www.grandviewresearch.com/industry-analysis/exosomes-market (accessed on 25 August 2025).
12. Villarreal-Gómez, L.J.; Origel-Lucio, S.; Hernández-Hernández, D.A.; Pérez-González, G.L. Use of Exosomes for Cosmetics Applications. *Cosmetics* **2025**, *12*, 9. [CrossRef]
13. Kerkis, I.; Araldi, R.; Wenceslau, C.; Mendes, T. Advances in Cellular and Cell-Free Therapy Medicinal Products for Huntigton's Disease Treatment. In *From Physiopatology to Treatment of Huntigton's Disease*; InTech: Penang, Malaysia, 2022; pp. 1–27.
14. Da Costa, V.R.; Araldi, R.P.; Vigerelli, H.; D'Ámelio, F.; Mendes, T.B.; Gonzaga, V.; Policíquio, B.; Colozza-Gama, G.A.; Valverde, C.W.; Kerkis, I. Exosomes in the Tumor Microenvironment: From Biology to Clinical Applications. *Cells* **2021**, *10*, 2617. [CrossRef]
15. Teixeira, M.R.; Alievi, A.L.; da Costa, V.R.; Dias Pinto, J.R.; Araldi, R.P. Therapeutic Potential of Extracellular Vesicles in Parkinson's Disease. *Explor. Neurosci.* **2023**, *2*, 106–122. [CrossRef]
16. Araldi, R.P.; Delvalle, D.A.; da Costa, V.R.; Alievi, A.L.; Teixeira, M.R.; Dias Pinto, J.R.; Kerkis, I. Exosomes as a Nano-Carrier for Chemotherapeutics: A New Era of Oncology. *Cells* **2023**, *12*, 2144. [CrossRef]
17. Welsh, J.A.; Goberdhan, D.C.I.; O'Driscoll, L.; Buzas, E.I.; Blenkiron, C.; Bussolati, B.; Cai, H.; Di Vizio, D.; Driedonks, T.A.P.; Erdbrügger, U.; et al. Minimal Information for Studies of Extracellular Vesicles (MISEV2023): From Basic to Advanced Approaches. *J. Extracell. Vesicles* **2024**, *13*, e12404. [CrossRef] [PubMed]
18. Chargaff, E. Cell Structure and the Problem of Blood Coagulation. *J. Biol. Chem.* **1945**, *160*, 351–359. [CrossRef]
19. Chargaff, E.; West, R. The Biological Significant of the Thrombopastic Protein of Blood. *J. Biol. Chem.* **1946**, *166*, 189–197. [CrossRef]
20. Wolf, P. The Nature and Significance of Platelet Products in Human Plasma. *Br. J. Haematol.* **1967**, *13*, 269–288. [CrossRef]
21. Crawford, N. The Presence of Contractile Proteins in Platelet Microparticles Isolated from Human and Animal Platelet-free Plasma. *Br. J. Haematol.* **1971**, *21*, 53–69. [CrossRef]
22. Couch, Y.; Buzàs, E.I.; Di Vizio, D.; Gho, Y.S.; Harrison, P.; Hill, A.F.; Lötvall, J.; Raposo, G.; Stahl, P.D.; Théry, C.; et al. A Brief History of Nearly EV-erything—The Rise and Rise of Extracellular Vesicles. *J. Extracell. Vesicles* **2021**, *10*, e12144. [CrossRef]
23. Nunez, E.A.; Wallis, J.; Gershon, M.D. Secretory processes in follicular cells of the bat thyroid. III. The occurrence of extracellular vesicles and colloid droplets during arousal from hibernation. *Am. J. Anat.* **1974**, *141*, 179–201. [CrossRef]
24. Levine, P.H.; Horoszewicz, J.S.; Grace, J.T.; Chai, L.S.; Ellison, R.R.; Holland, J.F. Relationship between Clinical Status of Leukemic Patients and Virus-like Particles in Their Plasma. *Cancer* **1967**, *20*, 1563–1577. [CrossRef]
25. Seman, G.; Gallager, H.S.; Lukeman, J.M.; Dmochowski, L. Studies on the Presence of Particles Resembling RNA Virus Particles in Human Breast Tumors, Pleural Effusions, Their Tissue Cultures, and Milk. *Cancer* **1971**, *28*, 1431–1442. [CrossRef]
26. Fawcett, D.W. Electron Microscope Observations on Intracellular Virus-Like Particles Associated with The Cells of The Lucké Renal Adenocarcinoma. *J. Cell Biol.* **1956**, *2*, 725–742. [CrossRef] [PubMed]
27. Lunger, P.D.; Lucas, J.C.; Shipkey, F.H. The Ultramorphology of Milk Fractions from Normal and Breast Cancer Patients. A Preliminary Report. *Cancer* **1964**, *17*, 549–557. [CrossRef] [PubMed]
28. Prince, A.M.; Adams, W.R. Virus-like Particles in Human Plasma and Serum: Role of Platelet Lysosomes. *J. Natl. Cancer Inst.* **1966**, *37*, 153–166. [PubMed]
29. Dalton, A.J. Microvesicles and Vesicles of Multivesicular Bodies Versus "Virus-Like" Particles. *J. Natl. Cancer Inst.* **1975**, *54*, 1137–1148. [CrossRef]
30. Harding, C.; Heuser, J.; Stahl, P. Receptor-Mediated Endocytosis of Transferrin and Recycling of the Transferrin Receptor in Rat Reticulocytes. *J. Cell Biol.* **1983**, *97*, 329–339. [CrossRef]
31. Pan, B.-T.; Johnstone, R.M. Fate of the Transferrin Receptor during Maturation of Sheep Reticulocytes in Vitro: Selective Externalization of the Receptor. *Cell* **1983**, *33*, 967–978. [CrossRef]
32. Johnstone, R.M.; Mathew, A.; Mason, A.B.; Teng, K. Exosome Formation during Maturation of Mammalian and Avian Reticulocytes: Evidence That Exosome Release Is a Major Route for Externalization of Obsolete Membrane Proteins. *J. Cell Physiol.* **1991**, *147*, 27–36. [CrossRef]
33. Lee, Y.J.; Jy, W.; Horstman, L.L.; Janania, J.; Reyes, Y.; Kelley, R.E.; Ahn, Y.S. Elevated Platelet Microparticles in Transient Ischemic Attacks, Lacunar Infarcts, and Multiinfarct Dementias. *Thromb. Res.* **1993**, *72*, 295–304. [CrossRef]

34. Powell, J.J.; Harvey, R.S.; Thompson, R.P. Microparticles in Crohn's Disease—Has the Dust Settled? *Gut* **1996**, *39*, 340–341. [CrossRef]
35. Johnstone, R.; Bianchini, A.; Teng, K. Reticulocyte Maturation and Exosome Release: Transferrin Receptor Containing Exosomes Shows Multiple Plasma Membrane Functions. *Blood* **1989**, *74*, 1844–1851. [CrossRef]
36. Raposo, G.; Nijman, H.W.; Stoorvogel, W.; Liejendekker, R.; Harding, C.V.; Melief, C.J.; Geuze, H.J. B Lymphocytes Secrete Antigen-Presenting Vesicles. *J. Exp. Med.* **1996**, *183*, 1161–1172. [CrossRef] [PubMed]
37. Zhang, Y.; Lan, M.; Chen, Y. Minimal Information for Studies of Extracellular Vesicles (MISEV): Ten-Year Evolution (2014–2023). *Pharmaceutics* **2024**, *16*, 1394. [CrossRef] [PubMed]
38. Lee, Y.J.; Shin, K.J.; Chae, Y.C. Regulation of Cargo Selection in Exosome Biogenesis and Its Biomedical Applications in Cancer. *Exp. Mol. Med.* **2024**, *56*, 877–889. [CrossRef] [PubMed]
39. Di Bella, M.A. Overview and Update on Extracellular Vesicles: Considerations on Exosomes and Their Application in Modern Medicine. *Biology* **2022**, *11*, 804. [CrossRef]
40. Skotland, T.; Hessvik, N.P.; Sandvig, K.; Llorente, A. Exosomal Lipid Composition and the Role of Ether Lipids and Phosphoinositides in Exosome Biology. *J. Lipid Res.* **2019**, *60*, 9–18. [CrossRef]
41. Kumeda, N.; Ogawa, Y.; Akimoto, Y.; Kawakami, H.; Tsujimoto, M.; Yanoshita, R. Characterization of Membrane Integrity and Morphological Stability of Human Salivary Exosomes. *Biol. Pharm. Bull.* **2017**, *40*, 1183–1191. [CrossRef]
42. Araldi, R.P.; D'Amelio, F.; Vigerelli, H.; de Melo, T.C.; Kerkis, I. Stem Cell-Derived Exosomes as Therapeutic Approach for Neurodegenerative Ddsorders: From Biology to Biotechnology. *Cells* **2020**, *9*, 2663. [CrossRef]
43. Ogorevc, E.; Kralj-Iglic, V.; Veranic, P. The Role of Extracellular Vesicles in Phenotypic Cancer Transformation. *Radiol. Oncol.* **2013**, *47*, 197–205. [CrossRef]
44. Gurung, S.; Perocheau, D.; Touramanidou, L.; Baruteau, J. The Exosome Journey: From Biogenesis to Uptake and Intracellular Signalling. *Cell Commun. Signal.* **2021**, *19*, 47. [CrossRef]
45. Liu, S.-L.; Sun, P.; Li, Y.; Liu, S.-S.; Lu, Y. Exosomes as Critical Mediators of Cell-to-Cell Communication in Cancer Pathogenesis and Their Potential Clinical Application. *Transl. Cancer Res.* **2019**, *8*, 298–311. [CrossRef] [PubMed]
46. Lee, K.S.; Choi, J.S.; Cho, Y.W. Reprogramming of Cancer Stem Cells into Non-Tumorigenic Cells Using Stem Cell Exosomes for Cancer Therapy. *Biochem. Biophys. Res. Commun.* **2019**, *512*, 511–516. [CrossRef] [PubMed]
47. Mittelbrunn, M.; Gutiérrez-Vázquez, C.; Villarroya-Beltri, C.; González, S.; Sánchez-Cabo, F.; González, M.Á.; Bernad, A.; Sánchez-Madrid, F. Unidirectional Transfer of MicroRNA-Loaded Exosomes from T Cells to Antigen-Presenting Cells. *Nat. Commun.* **2011**, *2*, 282. [CrossRef] [PubMed]
48. Peak, T.C.; Praharaj, P.P.; Panigrahi, G.K.; Doyle, M.; Su, Y.; Schlaepfer, I.R.; Singh, R.; Vander Griend, D.J.; Alickson, J.; Hemal, A.; et al. Exosomes Secreted by Placental Stem Cells Selectively Inhibit Growth of Aggressive Prostate Cancer Cells. *Biochem. Biophys. Res. Commun.* **2018**, *499*, 1004–1010. [CrossRef]
49. Showalter, M.R.; Wancewicz, B.; Fiehn, O.; Archard, J.A.; Clayton, S.; Wagner, J.; Deng, P.; Halmai, J.; Fink, K.D.; Bauer, G.; et al. Primed Mesenchymal Stem Cells Package Exosomes with Metabolites Associated with Immunomodulation. *Biochem. Biophys. Res. Commun.* **2019**, *512*, 729–735. [CrossRef]
50. Sato, Y.; Yaguchi, M.; Okuno, Y.; Ishimaru, H.; Sagou, K.; Ozaki, S.; Suzuki, T.; Inagaki, T.; Umeda, M.; Watanabe, T.; et al. Epstein–Barr Virus Tegument Protein BGLF2 in Exosomes Released from Virus-Producing Cells Facilitates de Novo Infection. *Cell Commun. Signal.* **2022**, *20*, 95. [CrossRef]
51. Lee, M.; Ban, J.-J.; Kim, K.Y.; Jeon, G.S.; Im, W.; Sung, J.-J.; Kim, M. Adipose-Derived Stem Cell Exosomes Alleviate Pathology of Amyotrophic Lateral Sclerosis in Vitro. *Biochem. Biophys. Res. Commun.* **2016**, *479*, 434–439. [CrossRef]
52. Maas, S.L.N.; Breakefield, X.O.; Weaver, A.M. Extracellular Vesicles: Unique Intercellular Delivery Vehicles. *Trends Cell Biol.* **2017**, *27*, 172–188. [CrossRef]
53. Yuan, Z.; Kolluri, K.K.; Gowers, K.H.C.; Janes, S.M. TRAIL Delivery by MSC-Derived Extracellular Vesicles Is an Effective Anticancer Therapy. *J. Extracell. Vesicles* **2017**, *6*, 1265291. [CrossRef]
54. Mukhopadhya, A.; Tsiapalis, D.; McNamee, N.; Talbot, B.; O'Driscoll, L. Doxorubicin Loading into Milk and Mesenchymal Stem Cells' Extracellular Vesicles as Drug Delivery Vehicles. *Pharmaceutics* **2023**, *15*, 718. [CrossRef]
55. Haney, M.J.; Zhao, Y.; Jin, Y.S.; Li, S.M.; Bago, J.R.; Klyachko, N.L.; Kabanov, A.V.; Batrakova, E.V. Macrophage-Derived Extracellular Vesicles as Drug Delivery Systems for Triple Negative Breast Cancer (TNBC) Therapy. *J. Neuroimmune Pharmacol.* **2020**, *15*, 487–500. [CrossRef]
56. Alkhilaiwi, F.; Yuan, H. Detection of HPV RNA in Extracellular Vesicles from Neuroendocrine Cervical Cancer Cells. *Viruses* **2022**, *14*, 2226. [CrossRef]
57. Kouroumalis, E.; Tsomidis, I.; Voumvouraki, A. Extracellular Vesicles in Viral Liver Diseases. *Viruses* **2024**, *16*, 1785. [CrossRef]
58. Zhao, M.; Nanbo, A.; Sun, L.; Lin, Z. Extracellular Vesicles in Epstein-Barr Virus' Life Cycle and Pathogenesis. *Microorganisms* **2019**, *7*, 48. [CrossRef] [PubMed]

59. Gupta, A.K.; Wang, T.; Rapaport, J.A.; Talukder, M. Therapeutic Potential of Extracellular Vesicles (Exosomes) Derived From Platelet-Rich Plasma: A Literature Review. *J. Cosmet. Dermatol.* **2025**, *24*, e16709. [CrossRef] [PubMed]
60. Hesseler, M.J.; Shyam, N. Platelet-Rich Plasma and Its Utility in Medical Dermatology: A Systematic Review. *J. Am. Acad. Dermatol.* **2019**, *81*, 834–846. [CrossRef] [PubMed]
61. Sakata, R.; Reddi, A.H. Platelet-Rich Plasma Modulates Actions on Articular Cartilage Lubrication and Regeneration. *Tissue Eng. Part. B Rev.* **2016**, *22*, 408–419. [CrossRef]
62. Dashore, S.; Chouhan, K.; Nanda, S.; Sharma, A. Preparation of Platelet-Rich Plasma: National IADVL PRP Taskforce Recommendations. *Indian. Dermatol. Online J.* **2021**, *12*, 12. [CrossRef]
63. Vladulescu, D.; Scurtu, L.G.; Simionescu, A.A.; Scurtu, F.; Popescu, M.I.; Simionescu, O. Platelet-Rich Plasma (PRP) in Dermatology: Cellular and Molecular Mechanisms of Action. *Biomedicines* **2023**, *12*, 7. [CrossRef]
64. Heijnen, H.; van der Sluijs, P. Platelet secretory behaviour: As diverse as the granules . . . or not? *J. Thromb. Haemost.* **2015**, *13*, 2141–2151. [CrossRef]
65. Hesseler, M.J.; Shyam, N. Platelet-Rich Plasma and Its Utility in the Treatment of Acne Scars: A Systematic Review. *J. Am. Acad. Dermatol.* **2019**, *80*, 1730–1745. [CrossRef]
66. Guo, S.-C.; Tao, S.-C.; Yin, W.-J.; Qi, X.; Yuan, T.; Zhang, C.-Q. Exosomes Derived from Platelet-Rich Plasma Promote the Re-Epithelization of Chronic Cutaneous Wounds via Activation of YAP in a Diabetic Rat Model. *Theranostics* **2017**, *7*, 81–96. [CrossRef]
67. Torreggiani, E.; Perut, F.; Roncuzzi, L.; Zini, N.; Baglìo, S.; Baldini, N. Exosomes: Novel Effectors of Human Platelet Lysate Activity. *Eur. Cell Mater.* **2014**, *28*, 137–151. [CrossRef]
68. Iyer, S.R.; Scheiber, A.L.; Yarowsky, P.; Henn, R.F.; Otsuru, S.; Lovering, R.M. Exosomes Isolated From Platelet-Rich Plasma and Mesenchymal Stem Cells Promote Recovery of Function After Muscle Injury. *Am. J. Sports Med.* **2020**, *48*, 2277–2286. [CrossRef]
69. Kerkis, I.; Valverde Wenceslau, C.; Pinheiro Araldi, R. Stem Cells from Dental Pulp of Deciduous Teeth: Twenty Years of Experience. In *Recent Update on Mesenchymal Stem Cells*; IntechOpen: London, UK, 2024.
70. Araldi, R.P.; Viana, M.; Colozza-Gama, G.A.; Dias-Pinto, J.R.; Ankol, L.; Valverde, C.W.; Perlson, E.; Kerkis, I. Unique Transcriptional Signatures Observed in Stem Cells from the Dental Pulp of Deciduous Teeth Produced on a Large Scale. *Pharmacologia* **2023**, *14*, 72–95. [CrossRef]
71. Friedenstein, A.J.; Piatetzky-Shapiro, I.I.; Petrakova, K. Osteogenesis in Transplants of Bone Marrow Cells. *J. Embryol. Exp. Morphol.* **1966**, *16*, 381–390. [CrossRef] [PubMed]
72. Friedenstein, A.J.; Chailakhjan, R.K.; Lalykina, K.S. The Development of Fibroblast Colonies in Monolayer Cultures of Guinea-Pig Bone Marrow and Spleen Cells. *Cell Prolif.* **1970**, *3*, 393–403. [CrossRef]
73. Friedenstein, A.J.; Chailakhyan, R.K.; Gerasimov, U. V Bone Marrow Osteogenic Stem Cells: In Vitro Cultivation and Transplantation in Diffusion Chambers. *Cell Prolif.* **1987**, *20*, 263–272. [CrossRef] [PubMed]
74. Friedenstein, A.J.; Chailakhyan, R.K.; Latsinik, N.V.; Panasyuk, A.F.; Keiliss-Borok, I.V. Stromal Cells Responsible for Transferring the Microenvironment of the Hemopoietic Tissues. *Transplantation* **1974**, *17*, 331–340. [CrossRef]
75. Caplan, A.I. Mesenchymal Stem Cells. *J. Orthop. Res.* **1991**, *9*, 641–650. [CrossRef] [PubMed]
76. Haynesworth, S.E.; Barer, M.A.; Caplan, A.I. Cell Surface Antigens on Human Marrow-Derived Mesenchymal Cells Are Detected by Monoclonal Antibodies. *Bone* **1992**, *13*, 69–80. [CrossRef] [PubMed]
77. Barry, F.P.; Boynton, R.E.; Haynesworth, S.; Murphy, J.M.; Zaia, J. The Monoclonal Antibody SH-2, Raised against Human Mesenchymal Stem Cells, Recognizes an Epitope on Endoglin (CD105). *Biochem. Biophys. Res. Commun.* **1999**, *265*, 134–139. [CrossRef] [PubMed]
78. Barry, F.; Boynton, R.; Murphy, M.; Zaia, J. The SH-3 and SH-4 Antibodies Recognize Distinct Epitopes on CD73 from Human Mesenchymal Stem Cells. *Biochem. Biophys. Res. Commun.* **2001**, *289*, 519–524. [CrossRef]
79. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E. Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells. *Int. Soc. Cell. Ther. Position. Statement. Cytotherapy* **2006**, *8*, 315–317. [CrossRef]
80. Lizier, N.F.; Kerkis, A.; Gomes, C.M.; Hebling, J.; Oliveira, C.F.; Caplan, A.I.; Kerkis, I. Scaling-up of Dental Pulp Stem Cells Isolated from Multiple Niches. *PLoS ONE* **2012**, *7*, e39885. [CrossRef]
81. Qu, Q.; Fu, B.; Long, Y.; Liu, Z.-Y.; Tian, X.-H. Current Strategies for Promoting the Large-Scale Production of Exosomes. *Curr. Neuropharmacol.* **2023**, *21*, 1964–1979. [CrossRef]
82. Almouh, M.; Pakravan, K.; Ghazimoradi, M.H.; Motamed, R.; Bakhshinejad, B.; Hassan, Z.M.; Babashah, S. Exosomes Released by Oxidative Stress-Induced Mesenchymal Stem Cells Promote Murine Mammary Tumor Progression through Activating the STAT3 Signaling Pathway. *Mol. Cell Biochem.* **2024**, *479*, 3375–3391. [CrossRef]
83. Feng, Z.-Y.; Zhang, Q.-Y.; Tan, J.; Xie, H.-Q. Techniques for Increasing the Yield of Stem Cell-Derived Exosomes: What Factors May Be Involved? *Sci. China Life Sci.* **2022**, *65*, 1325–1341. [CrossRef]

84. Lee, H.; Cho, H.-J.; Han, Y.; Lee, S.H. Mid- to Long-Term Efficacy and Safety of Stem Cell Therapy for Acute Myocardial Infarction: A Systematic Review and Meta-Analysis. *Stem Cell Res. Ther.* **2024**, *15*, 290. [CrossRef]
85. Hoang, D.M.; Pham, P.T.; Bach, T.Q.; Ngo, A.T.L.; Nguyen, Q.T.; Phan, T.T.K.; Nguyen, G.H.; Le, P.T.T.; Hoang, V.T.; Forsyth, N.R.; et al. Stem Cell-Based Therapy for Human Diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 272. [CrossRef]
86. Wang, Y.; Yi, H.; Song, Y. The Safety of MSC Therapy over the Past 15 Years: A Meta-Analysis. *Stem Cell Res. Ther.* **2021**, *12*, 545. [CrossRef] [PubMed]
87. Brooke, G.; Tong, H.; Levesque, J.-P.; Atkinson, K. Molecular Trafficking Mechanisms of Multipotent Mesenchymal Stem Cells Derived from Human Bone Marrow and Placenta. *Stem Cells Dev.* **2008**, *17*, 929–940. [CrossRef] [PubMed]
88. Sakai, K.; Yamamoto, A.; Matsubara, K.; Nakamura, S.; Naruse, M.; Yamagata, M.; Sakamoto, K.; Tauchi, R.; Wakao, N.; Imagama, S.; et al. Human Dental Pulp-Derived Stem Cells Promote Locomotor Recovery after Complete Transection of the Rat Spinal Cord by Multiple Neuro-Regenerative Mechanisms. *J. Clin. Investig.* **2012**, *122*, 80–90. [CrossRef]
89. Shamir, C.; Venugopal, C.; Dhanushkodi, A. Dental Pulp Stem Cells for Treating Neurodegenerative Diseases. *Neural Regen. Res.* **2015**, *10*, 1910–1911. [CrossRef] [PubMed]
90. Hmadcha, A.; Martin-Montalvo, A.; Gauthier, B.R.; Soria, B.; Capilla-Gonzalez, V. Therapeutic Potential of Mesenchymal Stem Cells for Cancer Therapy. *Front. Bioeng. Biotechnol.* **2020**, *8*, 43. [CrossRef]
91. Archambault, J.; Moreira, A.; McDaniel, D.; Winter, L.; Sun, L.; Hornsby, P. Therapeutic Potential of Mesenchymal Stromal Cells for Hypoxic Ischemic Encephalopathy: A Systematic Review and Meta-Analysis of Preclinical Studies. *PLoS ONE* **2017**, *12*, e0189895. [CrossRef]
92. Cai, Z.; Liu, D.; Yang, Y.; Xie, W.; He, M.; Yu, D.; Wu, Y.; Wang, X.; Xiao, W.; Li, Y. The Role and Therapeutic Potential of Stem Cells in Skeletal Muscle in Sarcopenia. *Stem Cell Res. Ther.* **2022**, *13*, 28. [CrossRef]
93. Guo, M.; Yin, Z.; Chen, F.; Lei, P. Mesenchymal Stem Cell-Derived Exosome: A Promising Alternative in the Therapy of Alzheimer's Disease. *Alzheimers Res. Ther.* **2020**, *12*, 109. [CrossRef]
94. de Souza, C.F.; de Napoli, P.; Han, S.W.; de Lima, V.C.; Carvalho, A.C.d.C. Células-tronco mesenquimais: Células ideais para a regeneração cardíaca? *Rev. Bras. De Cardiol. Invasiva* **2010**, *18*, 344–353. [CrossRef]
95. Baek, G.; Choi, H.; Kim, Y.; Lee, H.C.; Choi, C. Mesenchymal Stem Cell-Derived Extracellular Vesicles as Therapeutics and as a Drug Delivery Platform. *Stem Cells Transl. Med.* **2019**, *8*, 880–886. [CrossRef]
96. Cheng, L.; Zhang, K.; Wu, S.; Cui, M.; Xu, T. Focus on Mesenchymal Stem Cell-Derived Exosomes: Opportunities and Challenges in Cell-Free Therapy. *Stem Cells Int.* **2017**, *2017*, 6305295. [CrossRef]
97. Evangelista, A.; Soares, M.B.P.; Villarreal, C.F. Cell-Free Therapy: A Neuroregenerative Approach to Sensory Neuropathy? *Neural Regen. Res.* **2019**, *14*, 1383–1384. [CrossRef]
98. Gomzikova, M.O.; Rizvanov, A.A. Current Trends in Regenerative Medicine: From Cell to Cell-Free Therapy. *Bionanoscience* **2017**, *7*, 240–245. [CrossRef]
99. Duffield, J.S.; Park, K.M.; Hsiao, L.-L.; Kelley, V.R.; Scadden, D.T.; Ichimura, T.; Bonventre, J.V. Restoration of Tubular Epithelial Cells during Repair of the Postischemic Kidney Occurs Independently of Bone Marrow-Derived Stem Cells. *J. Clin. Investig.* **2005**, *115*, 1743–1755. [CrossRef]
100. Chapel, A.; Bertho, J.M.; Bensidhoum, M.; Fouillard, L.; Young, R.G.; Frick, J.; Demarquay, C.; Cuvelier, F.; Mathieu, E.; Trompier, F.; et al. Mesenchymal Stem Cells Home to Injured Tissues When Co-Infused with Hematopoietic Cells to Treat a Radiation-Induced Multi-Organ Failure Syndrome. *J. Gene Med.* **2003**, *5*, 1028–1038. [CrossRef]
101. Devine, S.M.; Cobbs, C.; Jennings, M.; Bartholomew, A.; Hoffman, R. Mesenchymal Stem Cells Distribute to a Wide Range of Tissues Following Systemic Infusion into Nonhuman Primates. *Blood* **2003**, *101*, 2999–3001. [CrossRef] [PubMed]
102. Kristocheck, M.; Dias, L.D.; Ghem, C.; Eibel, B.; Kalil, R.A.K.; Markoski, M.M. The Homing of Bone Marrow Stem Cells Is Differentially Activated in Ischemic and Valvular Heart Diseases and Influenced by Beta-Blockers. *J. Transl. Med.* **2018**, *16*, 133. [CrossRef] [PubMed]
103. Biancone, L.; Bruno, S.; Deregibus, M.C.; Tetta, C.; Camussi, G. Therapeutic Potential of Mesenchymal Stem Cell-Derived Microvesicles. *Nephrol. Dial. Transplant.* **2012**, *27*, 3037–3042. [CrossRef]
104. Eggenhofer, E.; Benseler, V.; Kroemer, A.; Popp, F.C.; Geissler, E.K.; Schlitt, H.J.; Baan, C.C.; Dahlke, M.H.; Hoogduijn, M.J. Mesenchymal Stem Cells Are Short-Lived and Do Not Migrate beyond the Lungs after Intravenous Infusion. *Front. Immunol.* **2012**, *3*, 297. [CrossRef] [PubMed]
105. Fujita, Y.; Kadota, T.; Araya, J.; Ochiya, T.; Kuwano, K. Clinical Application of Mesenchymal Stem Cell-Derived Extracellular Vesicle-Based Therapeutics for Inflammatory Lung Diseases. *J. Clin. Med.* **2018**, *7*, 355. [CrossRef]
106. Gao, J.; Dennis, J.E.; Muzic, R.F.; Lundberg, M.; Caplan, A.I. The Dynamic in Vivo Distribution of Bone Marrow-Derived Mesenchymal Stem Cells after Infusion. *Cells Tissues Organs* **2001**, *169*, 12–20. [CrossRef]
107. Lee, R.H.; Pulin, A.A.; Seo, M.J.; Kota, D.J.; Ylostalo, J.; Larson, B.L.; Semprun-Prieto, L.; Delafontaine, P.; Prockop, D.J. Intravenous HMSCs Improve Myocardial Infarction in Mice Because Cells Embolized in Lung Are Activated to Secrete the Anti-Inflammatory Protein TSG-6. *Cell Stem Cell* **2009**, *5*, 54–63. [CrossRef]

108. Haynesworth, S.E.; Baber, M.A.; Caplan, A.I. Cytokine Expression by Human Marrow-Derived Mesenchymal Progenitor Cells in Vitro: Effects of Dexamethasone and IL-1α. *J. Cell Physiol.* **1996**, *166*, 585–592. [CrossRef]
109. Takahashi, M.; Li, T.-S.; Suzuki, R.; Kobayashi, T.; Ito, H.; Ikeda, Y.; Matsuzaki, M.; Hamano, K. Cytokines Produced by Bone Marrow Cells Can Contribute to Functional Improvement of the Infarcted Heart by Protecting Cardiomyocytes from Ischemic Injury. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *291*, H886–H893. [CrossRef] [PubMed]
110. Joladarashi, D.; Kishore, R. Mesenchymal Stromal Cell Exosomes in Cardiac Repair. *Curr. Cardiol. Rep.* **2022**, *24*, 405–417. [CrossRef]
111. Vizoso, F.J.; Eiro, N.; Cid, S.; Schneider, J.; Perez-Fernandez, R. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. *Int. J. Mol. Sci.* **2017**, *18*, 1852. [CrossRef] [PubMed]
112. Wendt, S.; Goetzenich, A.; Goettsch, C.; Stoppe, C.; Bleilevens, C.; Kraemer, S.; Benstoem, C. Evaluation of the Cardioprotective Potential of Extracellular Vesicles—A Systematic Review and Meta-Analysis. *Sci. Rep.* **2018**, *8*, 15702. [CrossRef]
113. Pishavar, E.; Trentini, M.; Zanotti, F.; Camponogara, F.; Tiengo, E.; Zanolla, I.; Bonora, M.; Zavan, B. Exosomes as Neurological Nanosized Machines. *ACS Nanosci. Au* **2022**, *2*, 284–296. [CrossRef]
114. Li, Y.; Fang, B. Neural Stem Cell-Derived Extracellular Vesicles: The Light of Central Nervous System Diseases. *Biomed. Pharmacother.* **2023**, *165*, 115092. [CrossRef]
115. Haider, K.H.; Aramini, B. Mircrining the Injured Heart with Stem Cell-Derived Exosomes: An Emerging Strategy of Cell-Free Therapy. *Stem Cell Res. Ther.* **2020**, *11*, 23. [CrossRef]
116. Lu, J.; Zhang, Y.; Yang, X.; Zhao, H. Harnessing Exosomes as Cutting-Edge Drug Delivery Systems for Revolutionary Osteoarthritis Therapy. *Biomed. Pharmacother.* **2023**, *165*, 115135. [CrossRef]
117. Han, C.; Sun, X.; Liu, L.; Jiang, H.; Shen, Y.; Xu, X.; Li, J.; Zhang, G.; Huang, J.; Lin, Z.; et al. Exosomes and Their Therapeutic Potentials of Stem Cells. *Stem Cells Int.* **2016**, *2016*, 7653489. [CrossRef]
118. Bu, H.; He, D.; He, X.; Wang, K. Exosomes: Isolation, Analysis, and Applications in Cancer Detection and Therapy. *ChemBioChem* **2019**, *20*, 451–461. [CrossRef]
119. Woith, E.; Guerriero, G.; Hausman, J.-F.; Renaut, J.; Leclercq, C.C.; Weise, C.; Legay, S.; Weng, A.; Melzig, M.F. Plant Extracellular Vesicles and Nanovesicles: Focus on Secondary Metabolites, Proteins and Lipids with Perspectives on Their Potential and Sources. *Int. J. Mol. Sci.* **2021**, *22*, 3719. [CrossRef] [PubMed]
120. Cho, J.H.; Hong, Y.D.; Kim, D.; Park, S.J.; Kim, J.S.; Kim, H.-M.; Yoon, E.J.; Cho, J.-S. Confirmation of Plant-Derived Exosomes as Bioactive Substances for Skin Application through Comparative Analysis of Keratinocyte Transcriptome. *Appl. Biol. Chem.* **2022**, *65*, 8. [CrossRef]
121. Hessvik, N.P.; Llorente, A. Current Knowledge on Exosome Biogenesis and Release. *Cell. Mol. Life Sci.* **2018**, *75*, 193–208. [CrossRef] [PubMed]
122. Schorey, J.S.; Bhatnagar, S. Exosome Function: From Tumor Immunology to Pathogen Biology. *Traffic* **2008**, *9*, 871–881. [CrossRef]
123. Hansen, L.L.; Nielsen, M.E. Plant Exosomes: Using an Unconventional Exit to Prevent Pathogen Entry? *J. Exp. Bot.* **2018**, *69*, 59–68. [CrossRef]
124. De Robertis, M.; Sarra, A.; D'Oria, V.; Mura, F.; Bordi, F.; Postorino, P.; Fratantonio, D. Blueberry-Derived Exosome-Like Nanoparticles Counter the Response to TNF-α-Induced Change on Gene Expression in EA.Hy926 Cells. *Biomolecules* **2020**, *10*, 742. [CrossRef]
125. Perut, F.; Roncuzzi, L.; Avnet, S.; Massa, A.; Zini, N.; Sabbadini, S.; Giampieri, F.; Mezzetti, B.; Baldini, N. Strawberry-Derived Exosome-Like Nanoparticles Prevent Oxidative Stress in Human Mesenchymal Stromal Cells. *Biomolecules* **2021**, *11*, 87. [CrossRef]
126. Mu, J.; Zhuang, X.; Wang, Q.; Jiang, H.; Deng, Z.; Wang, B.; Zhang, L.; Kakar, S.; Jun, Y.; Miller, D.; et al. Interspecies Communication between Plant and Mouse Gut Host Cells through Edible Plant Derived Exosome-like Nanoparticles. *Mol. Nutr. Food Res.* **2014**, *58*, 1561–1573. [CrossRef] [PubMed]
127. Tulkens, J.; Vergauwen, G.; Van Deun, J.; Geeurickx, E.; Dhondt, B.; Lippens, L.; De Scheerder, M.-A.; Miinalainen, I.; Rappu, P.; De Geest, B.G.; et al. Increased Levels of Systemic LPS-Positive Bacterial Extracellular Vesicles in Patients with Intestinal Barrier Dysfunction. *Gut* **2020**, *69*, 191–193. [CrossRef] [PubMed]
128. Matsuguchi, T.; Takagi, A.; Matsuzaki, T.; Nagaoka, M.; Ishikawa, K.; Yokokura, T.; Yoshikai, Y. Lipoteichoic Acids from *Lactobacillus* Strains Elicit Strong Tumor Necrosis Factor Alpha-Inducing Activities in Macrophages through Toll-Like Receptor 2. *Clin. Vaccine Immunol.* **2003**, *10*, 259–266. [CrossRef]
129. Jo, C.S.; Myung, C.H.; Yoon, Y.C.; Ahn, B.H.; Min, J.W.; Seo, W.S.; Lee, D.H.; Kang, H.C.; Heo, Y.H.; Choi, H.; et al. The Effect of *Lactobacillus plantarum* Extracellular Vesicles from Korean Women in Their 20s on Skin Aging. *Curr. Issues Mol. Biol.* **2022**, *44*, 526–540. [CrossRef]
130. Schaar, V.; Uddback, I.; Nordstrom, T.; Riesbeck, K. Group A Streptococci Are Protected from Amoxicillin-Mediated Killing by Vesicles Containing β—Lactamase Derived from Haemophilus Influenzae. *J. Antimicrob. Chemother.* **2014**, *69*, 117–120. [CrossRef]
131. Saint-Pol, J.; Gosselet, F.; Duban-Deweer, S.; Pottiez, G.; Karamanos, Y. Targeting and Crossing the Blood-Brain Barrier with Extracellular Vesicles. *Cells* **2020**, *9*, 851. [CrossRef]

132. Surman, M.; Drożdż, A.; Stępień, E.; Przybyło, M. Extracellular Vesicles as Drug Delivery Systems—Methods of Production and Potential Therapeutic Applications. *Curr. Pharm. Des.* **2019**, *25*, 132–154. [CrossRef]
133. de Jong, B.; Barros, E.R.; Hoenderop, J.G.J.; Rigalli, J.P. Recent Advances in Extracellular Vesicles as Drug Delivery Systems and Their Potential in Precision Medicine. *Pharmaceutics* **2020**, *12*, 1006. [CrossRef]
134. Walker, S.; Busatto, S.; Pham, A.; Tian, M.; Suh, A.; Carson, K.; Quintero, A.; Lafrence, M.; Malik, H.; Santana, M.X.; et al. Extracellular Vesicle-Based Drug Delivery Systems for Cancer Treatment. *Theranostics* **2019**, *9*, 8001–8017. [CrossRef]
135. Edem, E.E.; Nathaniel, B.U.; Nebo, K.E.; Obisesan, A.O.; Olabiyi, A.A.; Akinluyi, E.T.; Ishola, A.O. *Lactobacillus plantarum* Mitigates Sexual-Reproductive Deficits by Modulating Insulin Receptor Expression in the Hypothalamic-Pituitary-Testicular Axis of Hyperinsulinemic Mice. *Drug Metab. Pers. Ther.* **2021**, *36*, 321–336. [CrossRef]
136. Nguyen, T.D.T.; Kang, J.H.; Lee, M.S. Characterization of *Lactobacillus plantarum* PH04, a Potential Probiotic Bacterium with Cholesterol-Lowering Effects. *Int. J. Food Microbiol.* **2007**, *113*, 358–361. [CrossRef]
137. Zheng, Z.; Cao, F.-W.; Wang, W.; Yu, J.; Chen, C.; Chen, B.; Liu, J.; Firrman, J.; Renye, J.; Ren, D. Probiotic Characteristics of *Lactobacillus plantarum* E680 and Its Effect on Hypercholesterolemic Mice. *BMC Microbiol.* **2020**, *20*, 239. [CrossRef]
138. Prakoeswa, C.R.S.; Herwanto, N.; Prameswari, R.; Astari, L.; Sawitri, S.; Hidayati, A.N.; Indramaya, D.M.; Kusumowidagdo, E.R.; Surono, I.S. *Lactobacillus plantarum* IS-10506 Supplementation Reduced SCORAD in Children with Atopic Dermatitis. *Benef. Microbes* **2017**, *8*, 833–840. [CrossRef]
139. Nagata, Y.; Yoshida, M.; Kitazawa, H.; Araki, E.; Gomyo, T. Improvements in Seasonal Allergic Disease with *Lactobacillus plantarum* No. 14. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 1869–1877. [CrossRef] [PubMed]
140. Wang, J.; Zeng, Y.; Wang, S.; Liu, H.; Zhang, D.; Zhang, W.; Wang, Y.; Ji, H. Swine-Derived Probiotic *Lactobacillus plantarum* Inhibits Growth and Adhesion of Enterotoxigenic Escherichia Coli and Mediates Host Defense. *Front. Microbiol.* **2018**, *9*, 1364. [CrossRef] [PubMed]
141. Dinev, T.; Beev, G.; Tzanova, M.; Denev, S.; Dermendzhieva, D.; Stoyanova, A. Antimicrobial Activity of *Lactobacillus plantarum* against Pathogenic and Food Spoilage Microorganisms: A Review. *Bulg. J. Vet. Med.* **2018**, *21*, 253–268. [CrossRef]
142. Valdéz, J.C.; Peral, M.C.; Rachid, M.; Santana, M.; Perdigón, G. Interference of *Lactobacillus plantarum* with Pseudomonas Aeruginosa in Vitro and in Infected Burns: The Potential Use of Probiotics in Wound Treatment. *Clin. Microbiol. Infect.* **2005**, *11*, 472–479. [CrossRef]
143. Chen, Y.E.; Fischbach, M.A.; Belkaid, Y. Skin Microbiota–Host Interactions. *Nature* **2018**, *553*, 427–436. [CrossRef]
144. Kurata, A.; Kiyohara, S.; Imai, T.; Yamasaki-Yashiki, S.; Zaima, N.; Moriyama, T.; Kishimoto, N.; Uegaki, K. Characterization of Extracellular Vesicles from *Lactiplantibacillus plantarum*. *Sci. Rep.* **2022**, *12*, 13330. [CrossRef]
145. Gong, S.; Zeng, R.; Liu, L.; Wang, R.; Xue, M.; Dong, H.; Wu, Z.; Zhang, Y. Extracellular Vesicles from a Novel *Lactiplantibacillus plantarum* Strain Suppress Inflammation and Promote M2 Macrophage Polarization. *Front. Immunol.* **2024**, *15*, 1459213. [CrossRef]
146. Kang, S.; Jeon, S.; Baek, H.; Hwang, S.; Kim, S.; Youn, S.H.; Kim, J.W.; Jun, S.-H.; Kang, N.-G. Lactobacillus-Derived Artificial Extracellular Vesicles for Skin Rejuvenation and Prevention of Photo-Aging. *Biomater. Sci.* **2025**, *13*, 2026–2035. [CrossRef]
147. Rajendran Venkataswamy, K. Perspective Chapter: Exosome-Mediated Pathogen Transmission. In *Exosomes—Recent Advances From Bench to Bedside*; Intech Open: London, UK, 2023.
148. Hazrati, A.; Soudi, S.; Malekpour, K.; Mahmoudi, M.; Rahimi, A.; Hashemi, S.M.; Varma, R.S. Immune Cells-Derived Exosomes Function as a Double-Edged Sword: Role in Disease Progression and Their Therapeutic Applications. *Biomark. Res.* **2022**, *10*, 30. [CrossRef] [PubMed]
149. Rai, A.; Fang, H.; Fatmous, M.; Claridge, B.; Poh, Q.H.; Simpson, R.J.; Greening, D.W. A Protocol for Isolation, Purification, Characterization, and Functional Dissection of Exosomes. *Methods Mol Biol.* **2021**, *2261*, 105–149. [PubMed]
150. Chen, Y.; Qi, W.; Wang, Z.; Niu, F. Exosome Source Matters: A Comprehensive Review from the Perspective of Diverse Cellular Origins. *Pharmaceutics* **2025**, *17*, 147. [CrossRef]
151. Andriolo, G.; Provasi, E.; Lo Cicero, V.; Brambilla, A.; Soncin, S.; Torre, T.; Milano, G.; Biemmi, V.; Vassalli, G.; Turchetto, L.; et al. Exosomes From Human Cardiac Progenitor Cells for Therapeutic Applications: Development of a GMP-Grade Manufacturing Method. *Front. Physiol.* **2018**, *9*, 1169. [CrossRef]
152. Langellotto, M.D.; Rassu, G.; Serri, C.; Demartis, S.; Giunchedi, P.; Gavini, E. Plant-Derived Extracellular Vesicles: A Synergetic Combination of a Drug Delivery System and a Source of Natural Bioactive Compounds. *Drug Deliv. Transl. Res.* **2025**, *15*, 831–845. [CrossRef]
153. Yazdanpanah, S.; Romano, S.; Valentino, A.; Galderisi, U.; Peluso, G.; Calarco, A. Plant-Derived Exosomes: Carriers and Cargo of Natural Bioactive Compounds: Emerging Functions and Applications in Human Health. *Nanomaterials* **2025**, *15*, 1005. [CrossRef]
154. Majewski, G.; Craw, J.; Falla, T. Accelerated Barrier Repair in Human Skin Explants Induced with a Plant-Derived PPAR-α Activating Complex via Cooperative Interactions. *Clin. Cosmet. Investig. Dermatol.* **2021**, *14*, 1271–1293. [CrossRef]
155. Yang, G.H.; Lee, Y.B.; Kang, D.; Choi, E.; Nam, Y.; Lee, K.H.; You, H.-J.; Kang, H.J.; An, S.H.; Jeon, H. Overcome the Barriers of the Skin: Exosome Therapy. *Biomater. Res.* **2021**, *25*, 22. [CrossRef]

156. Zingl, F.G.; Leitner, D.R.; Thapa, H.B.; Schild, S. Outer Membrane Vesicles as Versatile Tools for Therapeutic Approaches. *microLife* **2021**, *2*, uqab006. [CrossRef]
157. Xue, K.; Wang, L.; Liu, J. Bacterial Outer Membrane Vesicles and Their Functionalization as Vehicles for Bioimaging, Diagnosis and Therapy. *Mater. Adv.* **2022**, *3*, 7185–7197. [CrossRef]
158. Effah, C.Y.; Ding, X.; Drokow, E.K.; Li, X.; Tong, R.; Sun, T. Bacteria-Derived Extracellular Vesicles: Endogenous Roles, Therapeutic Potentials and Their Biomimetics for the Treatment and Prevention of Sepsis. *Front. Immunol.* **2024**, *15*, 1296061. [CrossRef]
159. Lieberman, L.A. Outer Membrane Vesicles: A Bacterial-Derived Vaccination System. *Front. Microbiol.* **2022**, *13*, 1029146. [CrossRef] [PubMed]
160. Zhao, L.; Chen, J.; Bai, B.; Song, G.; Zhang, J.; Yu, H.; Huang, S.; Wang, Z.; Lu, G. Topical Drug Delivery Strategies for Enhancing Drug Effectiveness by Skin Barriers, Drug Delivery Systems and Individualized Dosing. *Front. Pharmacol.* **2024**, *14*, 1333986. [CrossRef] [PubMed]
161. Chamoun, G.; Forsyth, A.; Kazemeini, S.; Ma, J.; Lam, K.; Kasiri, N.; Frasier, K.M. Systemic Risks of Topical Anesthetics in Barrier-Compromised Dermatologic Patients. *Cureus* **2025**, *17*, e84157. [CrossRef] [PubMed]
162. Akbar, A.; Malekian, F.; Baghban, N.; Kodam, S.P.; Ullah, M. Methodologies to Isolate and Purify Clinical Grade Extracellular Vesicles for Medical Applications. *Cells* **2022**, *11*, 186. [CrossRef]
163. Li, P.; Kaslan, M.; Lee, S.H.; Yao, J.; Gao, Z. Progress in Exosome Isolation Techniques. *Theranostics* **2017**, *7*, 789–804. [CrossRef]
164. Doyle, L.; Wang, M. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. *Cells* **2019**, *8*, 727. [CrossRef]
165. Zaborowski, M.P.; Balaj, L.; Breakefield, X.O.; Lai, C.P. Extracellular Vesicles: Composition, Biological Relevance, and Methods of Study. *Bioscience* **2015**, *65*, 783–797. [CrossRef]
166. Zarovni, N.; Corrado, A.; Guazzi, P.; Zocco, D.; Lari, E.; Radano, G.; Muhhina, J.; Fondelli, C.; Gavrilova, J.; Chiesi, A. Integrated Isolation and Quantitative Analysis of Exosome Shuttled Proteins and Nucleic Acids Using Immunocapture Approaches. *Methods* **2015**, *87*, 46–58. [CrossRef]
167. Zhang, M.; Jin, K.; Gao, L.; Zhang, Z.; Li, F.; Zhou, F.; Zhang, L. Methods and Technologies for Exosome Isolation and Characterization. *Small Methods* **2018**, *2*, 1800021. [CrossRef]
168. Muller, L.; Hong, C.-S.; Stolz, D.B.; Watkins, S.C.; Whiteside, T.L. Isolation of Biologically-Active Exosomes from Human Plasma. *J. Immunol. Methods* **2014**, *411*, 55–65. [CrossRef]
169. Hiemstra, T.F.; Charles, P.D.; Gracia, T.; Hester, S.S.; Gatto, L.; Al-Lamki, R.; Floto, R.A.; Su, Y.; Skepper, J.N.; Lilley, K.S.; et al. Human Urinary Exosomes as Innate Immune Effectors. *J. Am. Soc. Nephrol.* **2014**, *25*, 2017–2027. [CrossRef]
170. Baranyai, T.; Herczeg, K.; Onódi, Z.; Voszka, I.; Módos, K.; Marton, N.; Nagy, G.; Mäger, I.; Wood, M.J.; El Andaloussi, S.; et al. Isolation of Exosomes from Blood Plasma: Qualitative and Quantitative Comparison of Ultracentrifugation and Size Exclusion Chromatography Methods. *PLoS ONE* **2015**, *10*, e0145686. [CrossRef]
171. Ullah, M.; Kodam, S.P.; Mu, Q.; Akbar, A. Microbubbles versus Extracellular Vesicles as Therapeutic Cargo for Targeting Drug Delivery. *ACS Nano* **2021**, *15*, 3612–3620. [CrossRef]
172. Martins, T.S.; Catita, J.; Rosa, I.M.; Da Cruz e Silva, O.A.B.; Henriques, A.G. Exosome Isolation from Distinct Biofluids Using Precipitation and Column-Based Approaches. *PLoS ONE* **2018**, *13*, 1–16. [CrossRef] [PubMed]
173. Serrano-Pertierra, E.; Oliveira-Rodríguez, M.; Rivas, M.; Oliva, P.; Villafani, J.; Navarro, A.; Blanco-López, M.C.; Cernuda-Morollón, E. Characterization of Plasma-Derived Extracellular Vesicles Isolated by Different Methods: A Comparison Study. *Bioengineering* **2019**, *6*, 8. [CrossRef] [PubMed]
174. Livshits, M.A.; Khomyakova, E.; Evtushenko, E.G.; Lazarev, V.N.; Kulemin, N.A.; Semina, S.E.; Generozov, E.V.; Govorun, V.M. Isolation of Exosomes by Differential Centrifugation: Theoretical Analysis of a Commonly Used Protocol. *Sci. Rep.* **2015**, *5*, 17319. [CrossRef] [PubMed]
175. Taylor, D.D.; Shah, S. Methods of Isolating Extracellular Vesicles Impact Down-Stream Analyses of Their Cargoes. *Methods* **2015**, *87*, 3–10. [CrossRef]
176. Salih, M.; Zietse, R.; Hoorn, E.J. Urinary Extracellular Vesicles and the Kidney: Biomarkers and Beyond. *Am. J. Physiol. Ren. Physiol.* **2014**, *306*, F1251–F1259. [CrossRef]
177. Van Deun, J.; Mestdagh, P.; Sormunen, R.; Cocquyt, V.; Vermaelen, K.; Vandesompele, J.; Bracke, M.; De Wever, O.; Hendrix, A. The Impact of Disparate Isolation Methods for Extracellular Vesicles on Downstream RNA Profiling. *J. Extracell. Vesicles* **2014**, *3*, 24858. [CrossRef]
178. Rikkert, L.G.; Engelaer, M.; Hau, C.M.; Terstappen, L.W.M.M.; Nieuwland, R.; Coumans, F.A.W. Rate Zonal Centrifugation Can Partially Separate Platelets from Platelet-derived Vesicles. *Res. Pr. Thromb. Haemost.* **2020**, *4*, 1053–1059. [CrossRef] [PubMed]
179. Ullah, A.; Mabood, N.; Maqbool, M.; Khan, L.; Khan, M.; Ullah, M. SAR-CoV-2 Infection, Emerging New Variants and the Role of Activation Induced Cytidine Deaminase (AID) in Lasting Immunity. *Saudi Pharm. J.* **2021**, *29*, 1181–1184. [CrossRef] [PubMed]
180. Carnino, J.M.; Lee, H.; Jin, Y. Isolation and Characterization of Extracellular Vesicles from Broncho-Alveolar Lavage Fluid: A Review and Comparison of Different Methods. *Respir. Res.* **2019**, *20*, 240. [CrossRef] [PubMed]

181. Deregibus, M.C.; Figliolini, F.; D'antico, S.; Manzini, P.M.; Pasquino, C.; De Lena, M.; Tetta, C.; Brizzi, M.F.; Camussi, G. Charge-Based Precipitation of Extracellular Vesicles. *Int. J. Mol. Med.* **2016**, *38*, 1359–1366. [CrossRef]
182. Liga, A.; Vliegenthart, A.D.B.; Oosthuyzen, W.; Dear, J.W.; Kersaudy-Kerhoas, M. Exosome Isolation: A Microfluidic Road-Map. *Lab. Chip* **2015**, *15*, 2388–2394. [CrossRef]
183. Yang, D.; Zhang, W.; Zhang, H.; Zhang, F.; Chen, L.; Ma, L.; Larcher, L.M.; Chen, S.; Liu, N.; Zhao, Q.; et al. Progress, Opportunity, and Perspective on Exosome Isolation—Efforts for Efficient Exosome-Based Theranostics. *Theranostics* **2020**, *10*, 3684–3707. [CrossRef]
184. Lobb, R.J.; Becker, M.; Wen Wen, S.; Wong, C.S.F.; Wiegmans, A.P.; Leimgruber, A.; Möller, A. Optimized Exosome Isolation Protocol for Cell Culture Supernatant and Human Plasma. *J. Extracell. Vesicles* **2015**, *4*, 27031. [CrossRef]
185. Visan, K.S.; Lobb, R.J.; Ham, S.; Lima, L.G.; Palma, C.; Edna, C.P.Z.; Wu, L.; Gowda, H.; Datta, K.K.; Hartel, G.; et al. Comparative Analysis of Tangential Flow Filtration and Ultracentrifugation, Both Combined with Subsequent Size Exclusion Chromatography, for the Isolation of Small Extracellular Vesicles. *J. Extracell. Vesicles* **2022**, *11*, e12266. [CrossRef]
186. Soda, N.; Rehm, B.H.A.; Sonar, P.; Nguyen, N.-T.; Shiddiky, M.J.A. Advanced Liquid Biopsy Technologies for Circulating Biomarker Detection. *J. Mater. Chem. B* **2019**, *7*, 6670–6704. [CrossRef] [PubMed]
187. Peterson, M.F.; Otoc, N.; Sethi, J.K.; Gupta, A.; Antes, T.J. Integrated Systems for Exosome Investigation. *Methods* **2015**, *87*, 31–45. [CrossRef] [PubMed]
188. Thomas, S.; Kaur, J.; Kamboj, R.; Thangariyal, S.; Yadav, R.; Kumar, K.; Dhania, N.K. Investigate the Efficacy of Size Exclusion Chromatography for the Isolation of Extracellular Vesicles from C. *Elegans*. *J. Chromatogr. B* **2024**, *1233*, 123982. [CrossRef] [PubMed]
189. Stranska, R.; Gysbrechts, L.; Wouters, J.; Vermeersch, P.; Bloch, K.; Dierickx, D.; Andrei, G.; Snoeck, R. Comparison of Membrane Affinity-Based Method with Size-Exclusion Chromatography for Isolation of Exosome-like Vesicles from Human Plasma. *J. Transl. Med.* **2018**, *16*, 1. [CrossRef]
190. Cui, Y.; Gao, J.; He, Y.; Jiang, L. Plant Extracellular Vesicles. *Protoplasma* **2020**, *257*, 3–12. [CrossRef]
191. Hong, C.S.; Muller, L.; Boyiadzis, M.; Whiteside, T.L. Isolation and Characterization of CD34+ Blast-Derived Exosomes in Acute Myeloid Leukemia. *PLoS ONE* **2014**, *9*, e103310. [CrossRef]
192. Lee, K.; Shao, H.; Weissleder, R.; Lee, H. Acoustic Purification of Extracellular Microvesicles. *ACS Nano* **2015**, *9*, 2321–2327. [CrossRef]
193. Pinto, H.; Sánchez-Vizcaíno Mengual, E. Exosomes in the Real World of Medical Aesthetics: A Review. *Aesthetic Plast. Surg.* **2024**, *48*, 2513–2527. [CrossRef]
194. Cho, B.S.; Kim, J.O.; Ha, D.H.; Yi, Y.W. Exosomes Derived from Human Adipose Tissue-Derived Mesenchymal Stem Cells Alleviate Atopic Dermatitis. *Stem Cell Res. Ther.* **2018**, *9*, 187. [CrossRef]
195. Matte, B.F.; Medeiros, H.R.; Dal-Col, V. Exosome-Based Compound Activates Skin's Keratinocytes and Fibroblasts. *Curr. Cosmet. Sci.* **2025**, *29*, 148.