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Customized Ratio Formulation of Human–Plant Extracellular Vesicles (EVs) for Modular, Needs-Based Skincare: A Research Framework

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ABSTRACT

Background: Human mesenchymal stem cell–derived EVs (hEVs) promote dermal repair, while plant-derived exosome-like nanoparticles (pEVs/PELNs) provide antioxidant and photoprotective support. Translating both into safe, personalizableskincare requires standardized quantification, blending rules, and quality controls.

Objective:We propose a Customized Ratio Formulationstrategy that uses filtration-based EV quantification—nanoparticle tracking analysis (NTA)and orthogonal protein/RNA assays—to define three ratio presets: 70:30 (hEV:pEV)for anti-aging repair, 50:50for balanced repair/antioxidation, and 30:70for sensitive-skin antioxidant emphasis.

Methods/Significance:Methods align with MISEV2023guidance for EV production, separation, characterization, and reporting; NTA-anchored particle counts are normalized by purity indices (particle:protein, particle:RNA). The approach is implemented in modular serumsthat let customers (under professional guidance) choose a ratio suited to their skin needs.

Expected outcomes:Improved clinical signals (recovery time, texture, radiance) with strong safety governance (endotoxin screening for hEVs; pesticide panels for pEVs) and transparent documentation for regulatory review.

1. Introduction

Extracellular vesicles are nanoscale (≈50–150 nm) lipid bilayer particles that shuttle proteins, lipids, and regulatory RNAs, modulating inflammation, angiogenesis, and extracellular-matrix (ECM) remodeling in skin. hEVs show consistent signals for wound repair and dermal regeneration, whereas pEVs contribute antioxidant/anti-UVeffects and can enhance barrier homeostasis. Yet, consumer-facing cosmeceuticals rarely provide quantifiedEV

doses or rational blend ratios. We address this by defining a ratio-based formulation framework, grounded in MISEV-compliant analytics and skin-relevant endpoints. ScienceDirect +2 Frontiers +2

2. Scientific Rationale

※Repair axis (hEVs):Reviews and meta/umbrella syntheses report hEV-mediated fibroblast migration, collagen I/III upregulation, angiogenesis, and anti-inflammatory effects in cutaneous models—key mechanisms for anti-aging and post-procedure recovery. ScienceDirect +1

※Protection axis (pEVs):Botanical vesicles (e.g., ginseng, citrus/tea) carry polyphenols and lipids that mitigate UV/ROS stress and support barrier function; recent studies show UV-photoprotectionand oxidative-stress reduction in skin models. BioMed Central +1

※Personalization need:Skin phenotypes vary (photoaging vs sensitivity vs mixed), suggesting benefit from tunable hEV:pEV ratiosrather than one fixed composition. NTA-basedparticle counting—supplemented by protein/RNA metrics—enables reproducible, label-ready dosing. PMC +1

3. Methods

3.1 Upstream production & purification

Human source:serum-free hMSC cultures (mycoplasma-free, early passages). Pre-clear (0.45→0.22 μm), tangential-flow concentration, polish by size-exclusion or charge-aware cleanup per MISEV best practice. Endotoxin-screenedinputs.

Plant source:HACCP/GACP botanicals (e.g., Camellia sinensis, ginseng). Cold-press/juice → pre-clear → membrane size selection. Pesticide-screenedinputs. MDPI

3.2 Quantification & purity indexing

※Primary:NTAfor mode size and particle concentration (target 50–150 nm).

※Orthogonal purity:BCA (protein), RiboGreen (RNA) to compute particle:proteinand particle:RNAindices; optional ApoB/lipoprotein depletion index. Report per MISEV2023(inputs, yields, fraction IDs, negative controls). PMC +1

3.3 Release testing (safety/identity)

hEVs:endotoxin by LAL with low-endotoxin-recovery(LER) controls; TLR4-block in bioassays when indicated.

pEVs:targeted LC–MS/MS pesticidepanel (release = non-detect); bioburden/sterility on both streams.

Markers & morphology:CD9/CD63/CD81 for hEVs; pEV signatures per literature; TEM/cryo-TEM for intact vesicles.

3.4 Ratio presets & formulation

We propose three quantified presets, expressed on a particle-count basis(after purity normalization), with protein/RNA indices retained on the COA:

70:30 hEV:pEV (Anti-aging focus):maximizes repair(collagen/angiogenesis) while retaining oxidative buffering.

50:50 Blend (Balanced):harmonizes repair and antioxidant/anti-UV action for general maintenance.

30:70 hEV:pEV (Sensitive-skin focus):prioritizes low-reactivity protectionfor redness-prone or post-procedure sensitivity.

Vehicle: isotonic, nuclease-managed aqueous serum (pH 6.0–7.0), oxygen-barrier packaging. (No surfactants that disrupt vesicles.) MDPI

4. Evaluation Plan

4.1 In-vitro potency mapping (ratio–response)

Repair readouts:fibroblast scratch closure; COL1A1/COL3A1 and elastin mRNA; pro-collagen ELISA.

Protection readouts:keratinocyte UV-A/B model (ROS, AP-1, IL-1α/IL-8).

Benchmarking:compare each ratio vs single-source controls at matched particle counts; normalize to purity indices. (NTA protocol papers provide reproducibility guidance.) PMC

4.2 3D skin equivalents

TEER recovery after barrier insult; histology (H&E/Masson); OCT microvasculature; cytokine tape-strip panels—stratified by ratio.

4.3 Early clinical (cosmetic endpoints)

Randomized, split-face study (n≈30) in photoaged adults: downtime after fractional laser, profilometry (Ra/Rz), ultrasound dermal density, radiance/evenness scores, subject-reported irritation. Safety includes HRIPT and diary-based tolerability. hEV use must respect regional regulationsfor human-origin biologics in cosmetics. MDPI

5. Anticipated Results & Interpretation

70:30 (repair-weighted):Expect faster re-epithelialization, higher dermal echogenicity, and improved wrinkle metrics—consistent with hEV literature on wound/dermal remodeling. ScienceDirect +1

50:50 (balanced):Expect synergistic ROS suppression with meaningful gains in texture and tone via concurrent ECM and antioxidant pathways. MDPI

30:70 (sensitivity-weighted):Expect lower irritation scores and improved redness/TEWL recovery in sensitive cohorts, aligning with pEV anti-UV/anti-inflammatory signals. BioMed Central

Because outputs are particle-normalizedand purity-indexed, clinical differences can be attributed to biological ratiorather than analytic variability—meeting MISEV goals for transparent, reproducible EV work.

6. Safety, Ethics & Regulatory Notes

Terminology:Use “extracellular vesicles (EVs)” per MISEV2023; avoid definitive “exosome” biogenesis claims unless shown experimentally.

Human-origin policy:Jurisdictions differ on human EVs in cosmetics(e.g., restrictions reported in the UK/EU); ensure market-specific compliance or route via medical device/drug pathways if making therapeutic claims. The Guardian

Documentation:COAs should include NTA counts, mode size, particle:protein and particle:RNA indices, endotoxin (EU/mL), pesticide panel (nd), sterility/bioburden, and stability data.

7. Commercialization Path: Modular Serums

The modularconcept lets clinics or consumers (with professional guidance) select ratio presetsmatching skin state and seasonality. Packaging can include QR-linked COAsand a ratio-selectorguide (e.g., “Repair-Max 70:30,” “Balance 50:50,” “Sensitive 30:70”). Over time, real-world data can refine ratios by phenotype and Fitzpatrick type, informing evidence-based personalization.

8. Conclusion

A Customized Ratio Formulationanchored in NTA-based quantificationand MISEV-aligned purity indicesprovides a rigorous, transparent path to personalizable, medical-grade cosmeceutical serums. By tuning the hEV:pEV balance (70:30, 50:50, 30:70), brands can address distinct needs—anti-aging repair, balanced

maintenance, and sensitive-skin protection—while meeting modern expectations for scientific credibility and safety governance.

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