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"Biomimetic Vegan Exosomes: A Breakthrough in Skincare Innovation, Replicating the Structure and Function of Natural Exosomes Using Advanced Microalgae Biotechnology. A Sustainable, Ethical, and Scalable Alternative to Animal-Derived Exosomes for Targeted Deep Skin Cell Regeneration."

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1. Introduction

Exosomes are nanosized extracellular vesicles, typically ranging from 30 to 200 nm in diameter, enclosed by a lipid bilayer. They transport bioactive molecules such as lipids, proteins, and nucleic acids from cell to cell. To deliver their contents, exosomes express specific proteins and molecules on their membranes that selectively recognize recipient cells, thereby facilitating intercellular communication [1,2]. Exosomes can be secreted by various cell types (e.g., macrophages, epithelial cells, keratinocytes, and fibroblasts), and through the release of their contents to neighboring cells, they can influence cellular behavior, modulate immune responses, and promote tissue repair and regeneration [3].

In recent years, exosomes have emerged as a key tool in regenerative medicine, providing unparalleled repair and renewal at the cellular level. Their application in skin health and rejuvenation is also garnering significant attention, as they target their regenerative effects directly to the skin to address aging, hyperpigmentation, inflammation, and wound healing. Most exosomes used in therapeutics today are animal-derived from cow's milk, animal stem cells, or even human donors. However, their use in skincare faces significant ethical concerns, traceability challenges, high costs, and major regulatory limitations [4]. To overcome these issues, vegan alternatives have emerged, offering a plant-based way to deliver the power of exosomes such as natural vegan exosomes and exosome-like vegan products [5,6].

Natural vegan exosomes are extracellular vesicles directly produced by plants, seaweed or microalgae. These exosomes are naturally secreted by plant cells and often carry a diverse range of bioactive compounds that can benefit skin regeneration, hydration, and protection. However, the concentration of exosomes produced naturally by these organisms is relatively low, making large-scale extraction and purification difficult [6]. Despite the scientific promise of natural vegan exosomes, challenges related to scalability, consistency, and sustainability limit their feasibility for industrial skincare applications [7].

Another type of exosomes are exosome-like vesicles (ELVs), a broad group of extracellular vesicles similar to mammalian-derived exosomes, though they may differ in origin or

characteristics. Some ELVs are isolated from sources like plants (PELVs) and microalgae (MELVs) [8,9]. These vesicles are structurally and functionally similar to mammalian exosomes but may form through different pathways or have distinct compositions. Their size typically ranges from 50 to 200 nanometers [10], consistent with mammalian exosomes, which supports their potential in therapeutic use and cellular uptake. Commercial ELV products are often made with lecithin or phospholipid-based materials. While these can mimic exosome morphology and size, they do not replicate the full biological complexity or membrane structure of natural extracellular vesicles. Their use often stems from current limitations in exosome yield and scalability, leading companies to adopt structural analogues for production feasibility.

A parallel approach for obtaining PELVs or vesicle-like structures rely on methods such as juice extraction, infusion, or aqueous maceration. While these techniques may yield extracellular components, they typically involve the processing of large volumes of plant material and result in substantial residual biomass, contributing to significant waste generation and variable composition depending on the raw material and harvest conditions.

Therefore, there is a growing need for a more efficient, sustainable, and scalable strategy for exosome production, particularly for cosmetic applications. In this regard, as indicated in Table 1, vegan biomimetic exosomes offer a promising alternative to conventional exosomes, which are often limited by their complex composition and low isolation yields.

Table 1. Comparative overview of natural exosomes and exosome-mimetic strategies.

	Animal-derived Exosomes	**Natural Vegan Exosomes**	**"False" Vegan Exosomes**	**Vegan Biomimetic Exosomes**
100% Vegan and Cruelty-free	✗ (Human/Animal Derived)	✓	✓	✓
Sustainability and Ethically Sourced	✗ (Ethical concerns)	✗ (Limited yield)	✓	✓
True Exosomal Structure and Functional	✓	✓	✗ ("Naked" liposomes)	✓
Self-assembled (no lecithin needed)	✓	✓	✗ (Artificially assembled by adding lecithins)	✓
Scalable and Consistent Production	✗ (High cost and variability)	✗ (Low scalability and high variability)	✓	✓

In this context, the aim of the present study is to develop a patented biotechnology platform enabling the sustainable and scalable production of microalgae-derived biomimetic exosomes (MBEs). Although exosomes from plant and microalgae sources offer a vegan and eco-friendly alternative for skincare, their distinct lipid and protein compositions have been shown to limit their ability to effectively interact with human skin cells [11, 12]. To overcome this limitation, we apply a biohacking-inspired strategy, modifying the composition of isolated exosome fractions to closely replicate the lipid architecture and signaling characteristics of human-derived exosomes. This biomimetic adaptation enhances cellular recognition and uptake, enabling regenerative effects comparable to those of native human exosomes.

The present study introduces a novel biotechnology platform for the production of exosome-like vesicles that retain the essential structural and functional properties of natural

extracellular vesicles, specifically optimized for skincare applications. Importantly, the process minimizes formulation waste and eliminates the need for lecithin, supporting both efficacy and sustainability. Inspired by the biological sophistication of natural exosomes, this technology provides a robust foundation for next-generation delivery systems, combining biocompatibility, stability, and efficient skin cell communication in a vegan, sustainable format.

2. Materials and Methods

2.1 Exosome preparation

Microalgae (*Chlamydomonas reinhardtii*, *Spirulina maxima* and *Dunaliella salina*) were suspended in a buffer and gently mixed using a mechanical stirrer to ensure even dispersion. Cell concentration was standardized to approximately 10^8 cells/mL, measured with a Neubauer chamber. A controlled processing sequence was applied to direct the assembling of vesicles enriched in desired bioactive components. Following a stepwise centrifugation sequence, unwanted cellular material and debris were removed. An additional centrifugation helped eliminate larger vesicles, enriching the fraction of interest. A mild surfactant was introduced to influence membrane behavior and encourage the release of specific vesicle populations. The final mixture was diluted with a buffer to adjust vesicle concentration and stability.

2.2 Nano Tracking Analysis (NTA)

Nanoparticle Tracking Analysis (NTA) was performed using the NanoSight NS300 system (Malvern Panalytical, UK) to determine the size distribution and concentration of isolated exosomes. Samples were diluted appropriately in filtered PBS to achieve optimal particle concentration for analysis, and measurements were conducted at room temperature following standard operating procedures.

2.3 Transmission electron microscopy (TEM)

The morphology of the prepared exosomes was characterized by transmission electron microscopy (TEM) using a JEOL 1010 microscope equipped with an Orius CCD camera (Gatan). Samples were negatively stained with 1% uranyl acetate to enhance contrast prior to imaging.

2.4 Lipidomics Sample Preparation and Analysis

Lipid extraction from samples was performed using a modified methyl tert-butyl ether (MTBE) protocol. Briefly, samples were extracted in MTBE containing an internal standard, and the mixture was vigorously shaken. Samples were then centrifuged to separate the organic and aqueous phases. The upper organic phase, containing the extracted lipids, was collected, evaporated to dryness, and reconstituted in methanol supplemented with an internal standard. After vortexing and centrifugation, the supernatant was subjected to LC-MS analysis.

Chromatographic separation was carried out on a Waters ACQUITY UPLC BEH C18 column maintained at 65 °C, using a ZenoTOF 7600 mass spectrometer (SCIEX). A 5 µL injection volume was used per sample, and analyses were performed in both electrospray ionization (ESI) positive and negative modes. Lipid species were identified and quantified using a software platform for multi-omics data visualization and interpretation.

2.5 Proteomics Sample Preparation and Analysis

Protein extraction from samples was performed using the PreOmics iST sample preparation kit, following the manufacturer's protocol. Digested peptides were separated on a Kinetex 2.6 µm XB-C18 100 Å LC column (150 × 0.3 mm) maintained at 40 °C, using a microLC M5 system (SCIEX) coupled to a ZenoTOF 7600 mass spectrometer. Data acquisition was conducted in Zeno SWATH MS mode to enable high-throughput of proteomic profiling.

Proteomic data was processed and analyzed using DIA-NN, a neural network-enhanced software tailored for data-independent acquisition (DIA) workflows, providing accurate identification of peptide features.

2.6 In vitro wound healing assay

Human fibroblasts (LGC Standards Ltd., Teddington, UK) were cultured in well plates with Dulbecco's modification of Eagle medium (DMEM, VWR, Pennsylvania, USA) supplemented with 10% Fetal Bovine Serum. Cells were incubated in a humidified incubator at 37°C and 5% CO_2 with vehicle (Ctl) or MBEs at 0.5% and 1% (Chlamydomonas-derived biomimetic exosomes, CBE; Spirulina-derived biomimetic exosomes, SBE; Dunaliella-derived biomimetic exosomes, DBE) until full confluence. Then, an artificial wound was mechanically created in the cell monolayer by sliding the tip of a pipette on the cell monolayer. Wound healing was monitored at 40x under the Optika optical microscope at 0, 2, 4, 6 and 8 hours after the wound creation by acquisition of photographic images with a camera (Primo Cam HD5). The distance between the wound margins for each picture was measured in µm using ImageJ software. For each experimental condition 3 replicates were performed. The statistical variation on wound margins was analyzed by T-test.

2.7 Clinical efficacy study

Forty healthy female volunteers aged between 35 and 55 years old with normal to dry skin, showing mild to moderate signs of chrono/photoaging such as light to moderate dark spots, fine lines/wrinkles and loss of skin face elasticity were enrolled in a randomized controlled clinical-instrumental study. Subjects were asked to apply twice a day a cream containing 2% CBE on one side of the face and placebo on the contralateral. Evaluations were performed at baseline (T0), after 14 (T14), 28 (T28) and 56 (T56) days of product use. Different skin parameters were evaluated such as wrinkles, smoothness, dark spots, elasticity, firmness, and radiance. For Wrinkles and surface roughness evaluation, pictures were made by skin profilometry (Primos-CR SF, (Canfield Scientific Europe, Utrecht, Netherlands) in the periocular area. Firmness and elasticity were assessed by the mean of three measurements in the jawline area captured via VISIA-CR. Relative skin radiance was measured by the gloss parameter using the CM-700D colorimeter. Relative hyperpigmentation was measured by colorimeter (CM-700D, Konica Minolta, Milan, Italy) and digital pictures were made of the cheek's volunteers by VISIA-CR (Canfield Scientific Europe, Utrecht, Netherlands).

3. Results

3.1 Biomimetic exosomes particles size and quantification by Nano Tracking Analysis (NTA)

The size and concentration of our biomimetic exosomes were determined using nanoparticle tracking analysis (NTA), and the results are presented in Table 2 below.

Table 2. Characterization of different exosome samples based on nanoparticle tracking analysis (NTA).

Microalgae species	Type of biomimetic exosome	Particle concentration (particles/ml)	Size (nm)
C. reinhardtii	CBE	1.77e+10 +/- 1.66e+08	149.1
S. maxima	SBE	2.59e+11 +/- 6.79e+09	169.4
D. salina	DBE	1.67e+10 +/- 5.09e+08	187.6

As indicated in Table 2, the sizes and concentrations of all the samples are found to be at similar levels, confirming that the present invention is applicable to different types of microalgae

3.2 TEM microscopy

Representative TEM images (Figure 1) showed that the MEBs samples presented in this study exhibit well-defined, spherical nanovesicle structures ranging from 100 to 200 nm in diameter. Negative staining with uranyl acetate enhances visualization of the membrane boundaries, confirming a bilayered architecture and structural integrity consistent with natural extracellular vesicles. This image serves as an example of the typical morphology observed across multiple samples.

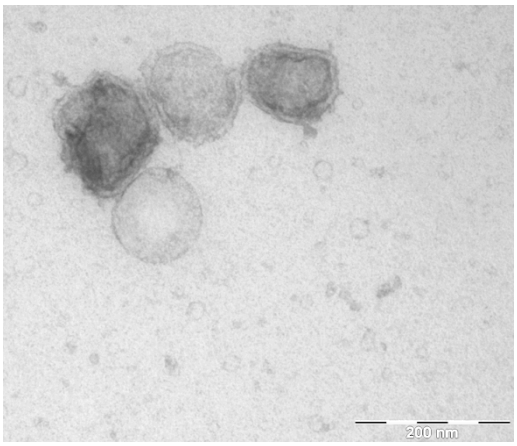

Figure 1. Overview of clustered exosomes displaying characteristic spherical morphology.

3.3 Lipidomics and proteomics analysis

The lipidomics analysis indicates that these new exosomes are enriched in a rich variety of different lipids (Table 3).

Table 3. Selected lipid classes identified in exosome samples and their associated biological functions.

Structural domains	Lipid class	Function in Exosomes
Lipid bilayer membrane	Phosphatidylethanolamine	Membrane curvature and stability.
	Phosphatidylglycerol	Membrane integrity and provides negative charge (vesicle fusion and interactions with target cells).
	Ceramides	Exosome strength and vesicle release.
	Cholesteryl Ester	Membrane rigidity and stability.
	Triacylglycerol	Lipid storage within exosomes.
	N-acyl Ethanolamines	Cell signaling and stress response, mediating anti-inflammatory responses.
Lipid rafts	Sphingolipids	Structural integrity, organization, and functional specialization of the exosomes membrane.

The proteomic analysis detected different proteins with functions that mimic human exosomes (Table 4).

Table 4. Selected proteins and their protein classes identified in exosome samples, and their associated biological functions.

Protein class	Protein	Function in Exosomes
Transmembrane proteins	FAS1	Cell adhesion.
	Transmembrane 9 SF	Vesicle trafficking, protein sorting, and cellular adhesion.
Exosome Biogenesis Proteins	HSP 60, 70 and 90	Protein folding, stress response, and cellular repair.
	Clathrin	Endocytosis and intracellular trafficking.
	RAS-23	Signal transduction.
	ALIX (BRO-1)	Membrane organization, vesicle biogenesis.
	RAB1A, 6 and 18	Vesicular transport and trafficking.
Functional Cargo Proteins	Antioxidant enzymes (thioredoxin, GPX, Peroxiredoxin, Catalase, Superoxide Dismutase)	Protection against oxidative damage.
	Growth Factors (EGF-containing proteins)	Cell proliferation and tissue regeneration.
	DNA repair enzymes (8-oxo-dGTP, RNA helicases)	DNA and RNA repair, maintenance of genomic stability.

3.4 In vitro wound healing analysis

In vitro scratch assays revealed an increased repair capacity of fibroblasts treated with both percentages of MBEs compared to untreated cells at T8 ($p<0.05$). After 6 hours, fibroblasts treated with 0.5% or 1% MBEs showed a significantly greater reduction of the distance of the wound margins artificially inducted compared to T0 (Ctl: -7.5%, CBE: -15.5% or -18.4%; SBE: -11.1% or -9.4%; DBE: -17.2% or -16.4%) (Table 5). These results indicate that treatment with MBEs significantly enhances wound repair and increases the regenerative capacity of fibroblasts in a dose-dependent manner.

Table 5. Reported values refer to the % reduction of the distance of the wound margins artificially inducted for each experimental time compared to T0.

	Ctl	CBE		SBE		DBE	
	-	1 %	0.5 %	1 %	0.5 %	1 %	0.5 %
T2	-3.70%	-12.80%	-9.70%*	-6.20%*	-7.90%	-16.90%*	-11.00%*,o
T4	-3.60%	-15.70%	-10.60%*	-7.20%*	-9.60%	-16.20%*,o	-14.30%*,o
T6	-7.50%	-18.40%	-15.50%	-11.10%*	-9.40%	-17.20%	-16.40%
T8	-17.40%	-30.40%*,o	-30.60%*,o	-33.20%*	-26.20%o	-31.90%*,o	-35.70%*,o

"*"$p<0.05$ vs Ctl group and "o"$p<0.05$ vs T0.

3.5 Clinical efficacy analysis

Following 56 days of twice-daily application of the cream containing 2% CBE, significant improvements were observed across multiple skin parameters compared to the placebo-treated side. Treatment with exosomes resulted in -11.5% ($p<0.001$) reduction in periocular wrinkle depth by day 28, with continued improvement observed over the entire study period relative to the placebo (Figure 2).

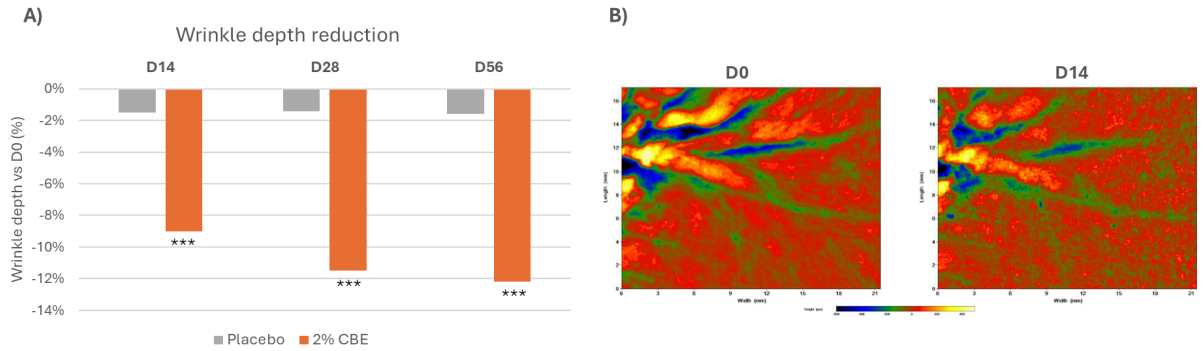

Figure 2. Wrinkle depth evaluation measured by skin profilometry (Primos-CR SF) in the periocular area of healthy volunteers. A) Relative wrinkle depth reduction over time vs D0 in all volunteers included in the clinical study. ***p<0.001. B) Digital pictures of crow's feet of a volunteer over time after treatment with 2% CBE.

A 7.1% improvement in skin smoothness was also observed after 56 days of exosome treatment. Furthermore, Glossmeter analysis showed that skin luminosity and radiance increased by 16.1% (p<0.001) after just 28 days of treatment with exosomes. By day 28, firmness and elasticity increased by 3.7% and 4.6%, respectively, in the exosome-treated skin compared to placebo (Table 6).

Table 6. Skin smoothness, radiance, firmness and elasticity evaluation after treatment with 2% CBE over time in healthy volunteers.

	Smoothness		**Radiance**		**Firmness**		**Elasticity**	
	Ctl	2 % CBE	Ctl	2 % CBE	Ctl	2 % CBE	Ctl	2 % CBE
D14	1.0%	3.9%*	2.7%	9.3%***	1.0%	3.3%***	0.6%	2.0%**
D28	0.9%	4.6%*	3.8%	16.1%***	1.4%	4.6%***	0.9%	3.7%***
D56	1.0%	7.1%***	4.1%	20.0%***	2.9%	7.4%***	1.4%	4.9%***

*p<0.05,**p<0.01 and ***p<0.001 vs Ctl group.

Finally, after 56 days of treatment with exosomes, colorimetric analysis and imaging demonstrated a reduction in dark spots on the cheek area of -22.8% compared to T0 (p<0.001), which was also perceptible to the naked eye (Figure 3). Collectively, these results demonstrate the potent skin rejuvenation potential of microalgae-derived biomimetic exosomes in healthy volunteers.

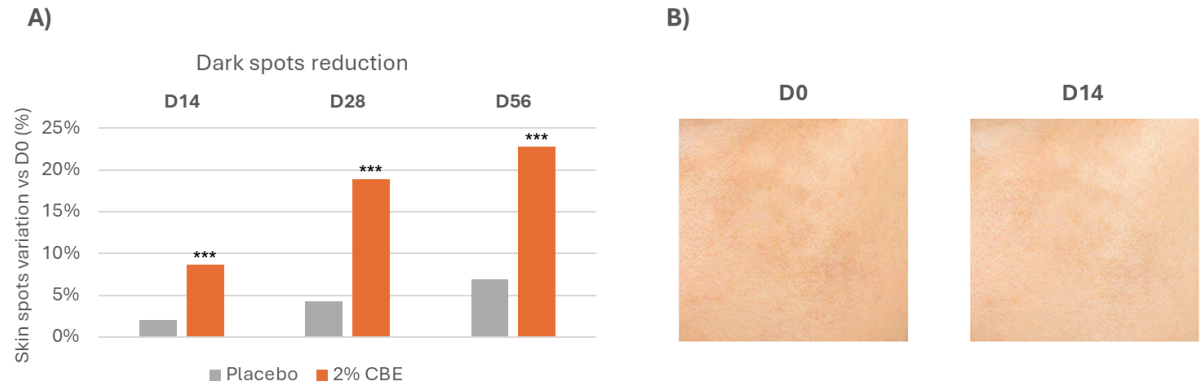

Figure 3. Dark spots evaluation after treatment with 2% CBE over time in healthy volunteers. A) Relative hyperpigmentation reduction vs D0 measured by Colorimeter in all volunteers included in the clinical study. ***p<0.001. B) Digital pictures of cheek's volunteers obtained by VISIA-CR.

4. Discussion

As outlined in the introduction, our objective was to develop vegan biomimetic exosomes (MBEs) derived from microalgae through an innovative biotechnology-driven process. Several unicellular microalgae species were selected with an inherent content of bioactive lipids, proteins, and antioxidants, making them attractive for cosmetic applications. Cultivation in closed photobioreactors under controlled conditions ensures consistent biomass quality, independent of seasonal or environmental fluctuations, supporting reproducibility and sustainable production.

While differential ultracentrifugation and tangential flow filtration are standard for isolating extracellular vesicles, they present scalability challenges due to high costs and operational complexity [13–14]. Although extrusion has been proposed for microalgae-derived exosome analogues [15], its scalability remains limited. To overcome these constraints, we developed a proprietary, patent-pending method based on controlled membrane disruption, followed by purification and refinement steps to isolate vesicle-like structures (~150 nm) while removing cellular debris and non-vesicular components. Notably, the process is free from synthetic phospholipids and organic solvents, employing only minimal COSMOS-certified surfactant for vesicle stabilization and size control.

Characterization by NTA and TEM (Table 2, Figure 1) confirmed vesicle size and morphology consistent with natural extracellular vesicles. To assess their biomimetic potential, we conducted lipidomic and proteomic analyses using *Chlamydomonas reinhardtii* (CBE), a well-characterized model organism in plant biology and photosynthesis research, recognized for its bioactive composition and genomic resources.

Lipidomic profiling (Table 3) revealed the presence of phosphatidylethanolamine (PE), phosphatidylglycerol (PG), ceramides, cholesteryl esters (CE), triacylglycerols (TG), N-acyl ethanolamines (NAE), and sphingolipids—mirroring key lipid classes in human exosomes [16–18]. These lipids are critical for membrane curvature, fusion, stability, and signaling functions relevant to dermal delivery and anti-inflammatory effects.

Proteomic analysis (Table 4) showed strong alignment with human fibroblast-derived exosomes [19–23], including transmembrane proteins (e.g., FAS1), heat shock proteins (e.g., HSP70/90), antioxidants (e.g., superoxide dismutase, thioredoxin), DNA repair enzymes, and calreticulin. These proteins contribute to cellular repair, oxidative stress mitigation, wound healing, and anti-aging pathways.

Collectively, these data confirm the biomimetic nature of MBEs, supporting their functional analogy to human exosomes with simplified, scalable production. While CBE was the primary model, broader omics analyses across additional microalgal strains are warranted to expand the platform. Importantly, these engineered vesicles represent a promising new class of biocompatible delivery systems for active compounds, with potential applications in advanced, ethical, and eco-conscious skincare formulations.

To evaluate biological activity, we performed in vitro and in vivo assessments. In vitro scratch assays (Table 5) demonstrated dose-dependent enhancement of fibroblast migration and wound closure, consistent with literature on exosomal promotion of tissue regeneration via paracrine signaling [24–26]. Clinically, topical application of 2% CBE over 56 days led to significant improvements in wrinkle depth, skin firmness, elasticity, luminosity, and pigmentation, with visible age reduction in the periocular region by day 14 (Figures 2-3, Table 6). These outcomes are comparable to those observed with human-derived exosomes [27–29] and suggest modulation of melanogenesis, in line with effects reported for plant- and stem cell-derived vesicles [30–31].

5. Conclusion

In summary, this study presents an innovative biotechnological platform for the production of biomimetic exosomes derived from microalgae, which replicate the structural and functional properties of natural extracellular vesicles. The developed methodology proves to be biocompatible, sustainable, and efficient, positioning it as a promising foundation for the design of advanced delivery systems with potential applications in skin regeneration and rejuvenation.

6. References

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