EXOSOMES: NATURE'S GIFT TO YOUR SKIN

Dr Rosario Salud Blas explores the applications of exosomes in aesthetic medicine and their role in addressing skin concerns and wound healing

DR. ROSARIO SALUD BLAS is a board-certified dermatologist in the Philippines. She is an International Fellow of the American Academy of Dermatology and a Senior Member of the International Society of Extracellular Vesicles. She is an active consultant in the Department of Dermatology, St. Luke's Medical Center, Global City and the Centre Medical Internationale, Global City, Taguig, Philippines

PERHAPS THE MOST underrated discovery in the last 30 years is the discovery of what exosomes can really do in the human body. Long dismissed as the 'wastebaskets' of cells, exosomes are now being respected for the many important responsibilities they carry out.

Exosomes are small extracellular vesicles produced by almost all living cells, not just human stem cells. These are characteristically:

- nanosize, with a diameter less than 200 nm,
- encapsulated with a lipid bilayer membrane,
- not alive, thus not able to replicate on their own[1].

The main function of an exosome is in cell-to-cell communication. Each of these small extracellular vesicles carries the message of its parent cell and a cargo of needed bioactive macromolecules such as miRNAs and proteins[2]. The lipid bilayer membrane of the vesicle appears to be evolutionarily conserved and is thus not rejected when applied to others, making heterologous sources feasible. The natural sources of exosomes are diverse. These include, for example, adipose tissue and other mesenchymal sources, bacteria and plant-derived exosome-like nanoparticles (PELNs)[3].

At the time of writing, all exosomes used in the specialties of dermatology, aesthetic medicine, and plastic and cosmetic surgery are registered only for topical application. None have been approved as an injectable[4]. Despite this current cosmetic label, reputable exosome manufacturing companies publish their research in respected scientific journals and produce their products in GMP-compliant, pharmaceutical medical-grade facilities. These companies abide by their national MoH regulations and the MISEV 2023 guidelines of the International Society of Extracellular Vesicles.

The current practice of physicians and other health care providers is the synergistic use of exosomes with non-invasive devices such as electrophoresis, iontophoresis, microneedling, radiofrequency, LEDs, lasers and other energy-based technology. The skin and scalp are the most common sites of clinical use. Cosmetic concerns such as hair loss, skin photodamage, atrophic scarring, and medical issues like atopic dermatitis and wound healing are a few of the problems that have been improved with the topical application of exosomes in conjunction with in-clinic procedures.

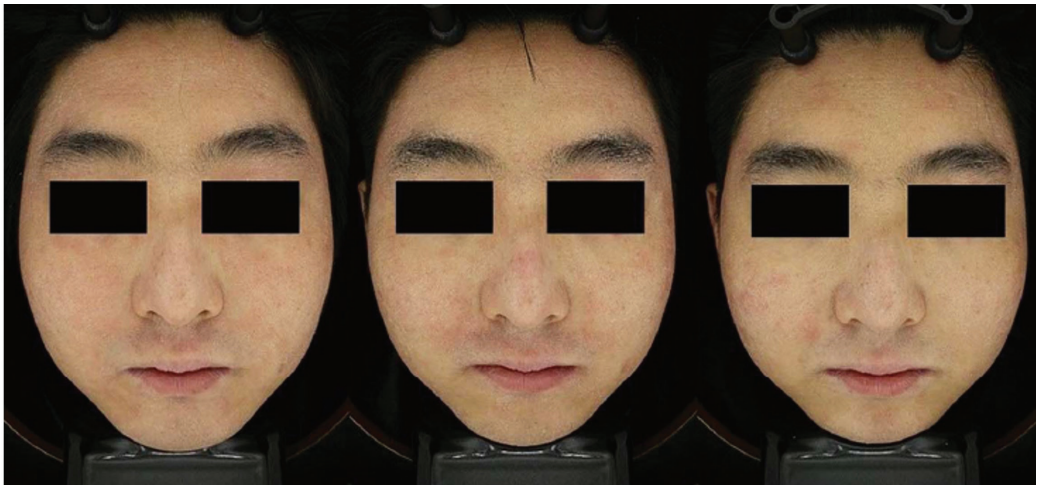

Figure 1 Clinical photographs taken at baseline, at week 2 (after the first treatment), and week 12 (8 weeks after the final treatment). After exosome treatment, clinical improvement of erythema on both cheeks, forehead and chin were noted.

Clinical applications for topical exosomes

Adipose stem cell-derived exosomes (ASC-Exos) are anti-inflammatory and known to have roles in all stages of skin wound healing, such as promoting thrombin activity and angiogenesis[5,6]. Topically applied commercially available ASC-Exo with a hyaluronic acid carrier increases collagen type III and extracellular matrix (ECM) remodelling, resulting in accelerated wound healing rates by 10%[7]. To visibly appreciate this swift healing, one must be sure to address patient variables such as controlling comorbidities like diabetes, preventing any secondary infection in the wound,

"Cosmetic concerns such as hair loss, skin photodamage, atrophic scarring, and medical issues like atopic dermatitis and wound healing are a few of the problems that have been improved with the topical application of exosomes in conjunction with in-clinic procedures."

and encouraging lifestyle changes such as quitting cigarette smoking and the use of e-cigarettes and vaping.

Exosomes also help patients with atopic dermatitis by restoring the skin barrier function. Topically applied ASC-Exos have an effect on the salvage pathway by activating the enzyme sphingosine kinase 1 (Sphk1) and inhibiting S1P lyase (S1PL), resulting in the *de novo* production of ceramides[8]. The anti-inflammatory property of ASC-Exos also helps decrease the erythema associated with dupilumab treatment by decreasing cytokine IL-1α (*Figure 1*)[9]. The relief of chronic seborrheic dermatitis has also been recently documented[10].

Post-inflammatory hyperpigmentation may also be improved by the topical application of PELNs from different plants[11]. These PELNs can transport bioactive materials to inhibit tyrosinase and improve skin hyperpigmentation (*Figure 2*). The ASC-Exos have also been shown to decrease intracellular melanin[12]. These effects are often seen as early as 4 weeks of application, with visibly significant improvement at 8 weeks.

ASC-Exos are also used with microneedling and other energy-based devices to shorten patient downtime and improve clinical results. In post-acne atrophic scarring treated with fractional carbon dioxide laser resurfacing, the addition of ASC-Exos significantly hastened wound healing and skin barrier restoration[13].

These are only a few examples of what these small extracellular vesicles can do for the skin. It is frankly amazing how a registered cosmetic product can swiftly address chronic problems such as skin wound healing and atopic dermatitis in the appropriate patients. We excitedly anticipate more randomised, controlled, double-blind, placebo-controlled trials on this novel product being published soon.

Figure 2 (A) Two months history of post-inflammatory hyperpigmentation due to irritant contact dermatitis. No meds applied. Treatment: 1 session of microneedling plus ASCEplus. Proper use of sunscreen emphasized. (B) Two months after 1 session of microneedling and ASCEplus and sunscreen use. Photo courtesy of Dr Blas.

Five key points to take home

- Exosomes are a novel, cell-free product that is topically applied to improve skin and scalp concerns
- Exosomes are not alive and function primarily in cell-to-cell communication
- Exosomes are only as good as their parent cell and must be produced, isolated, purified, characterised and packaged in GMP-compliant, pharmaceutical medical-grade facilities that follow the MISEV 2023 guidelines and should be registered in the MoH in their country of origin
- At present, exosomes are used synergistically with different devices to improve the results of such treatments and hasten the healing of patients
- At the time of writing, all exosomes are registered as cosmetics. There are none approved as injectables.

References

1. Welsh J, Goberdhan D, O'Driscoll L, et al. Minimal information for studies of extracellular vesicles (MISEV 2023): From basic to advanced approaches. J Extracell Vesicles. 2024; 13: e12404
2. YiQ, Xu Z, Thakur A et al. Current understanding of plant-derived exosome-like nanoparticles in regulating the inflammatory response and immune system microenvironment. Pharmacy Res 2023; 190:106733
3. Flemmin J, Wermuth P, Mahoney M. Extracellular vesicles in the skin microenvironment: Emerging roles as biomarkers and therapeutic tools in dermatologic health and disease. J Invest Dermatol. 2024; 144: 225-233
4. Tawanwongsri W, Vachiramon V. Skin necrosis after intradermal injection of lyophilized exosome: A case report and a review of the literature. J Cosmet Dermatol. 2024 May; 23(5); 1597-1603.
5. Chance T, Rathbone C, Kamucheka R et al. The effects of cell type and culture condition on the procoagulant activity of human mesenchymal stromal cell-derived extracellular vesicles. J Trauma Acute Care Surg. 2019; 87:574-82.
6. Pomatto M, Gai C, Negro F et al. Differential therapeutic effect of extracellular vesicles derived by bone marrow and adipose mesenchymal stem cells on wound healing of diabetic ulcers and correlation to their cargoes. Int J Mol Sci. 2021; 22: 3851.
7. Lee J, Won Y, Kim H et al. Adipose tissue-derived mesenchymal stem-cell derived exosomes promote wound healing and tissue regeneration. Int J Mol Sci 2023 June; 24(13): 10434
8. Shin K, Ha D, Kim J et al. Exosomes from human adipose tissue-derived mesenchymal stem cells promote epidermal barrier repair by inducing de novo synthesis of ceramides in atopic dermatitis. Cells 2020, 9(3):680
9. Han H, Koh Y, Hong J et al. Adipose-derived stem cell exosomes for treatment of dupilumab-related facial redness in patients with atopic-dermatitis. J Dermatol Treat 2023; 34(1): 2220444.
10. Luengarun S, Cho B, Tempark T. Topical moisturizer with rose stem-cell derived exosomes (RSCEs) for recalcitrant seborrheic dermatitis: A case report with 6 months of follow-up. J Cosmet Derm 2024 June 3. doi. org/10.1111/jocd.16389
11. Lee R, Ko H, Kim K et al. Anti-melanogenic effects of extracellular vesicles derived from plant leaves and stems in mouse melanoma cells and human healthy skin. J Extracell Vesicles 2019; 9(1): 1703480
12. Cho S, Lee J, Won Y et al. Skin brightening efficacy of exosomes derived from human adipose tissue-derived stem/stromal cells: A prospective, split-face, randomized placebo-controlled study. Cosmetics 2020; 7(4):90
13. Kwon H, Yang S, Lee J et al. Combination treatment with human adipose tissue stem cell-derived exosomes and fractional CO2 laser for acne scars: A 12-week prospective, double-blind, randomized, split-face study. Acta Derm Venereol 2020;100:adv00310