Plant-Derived Exosomes from Upcycled *Citrus Reticulata* Peel: A Sustainable AI-Driven Cosmetic Innovation

Tuğba Sağır[1,#], Ramazan Kaşmer[2,#], Ezgi Özkan[2], Mehmet Kenar[3], Ebru Işık Alturfan[4], İsmail Tuncer Değim[5], Nihal Karakaş [2, 6*]

[1]*Pim Grup Consultancy, Göktürk, İstanbul, Türkiye*
[2]*Regenerative and Restorative Medicine Research Center, Research Institute for Health Sciences and Technologies (SABITA), İstanbul Medipol University, İstanbul, Türkiye*
[3]*Biomesi Bioagrotechnology R&D, Adana, Türkiye*
[4]*Marmara University, Faculty of Dentistry, Basic Medical Sciences Department, İstanbul, Türkiye*
[5] *Faculty of Pharmacy, Biruni University, İstanbul, Türkiye*
[6]*Department of Medical Biology, International School of Medicine, İstanbul* Medipol University, İstanbul, Türkiye.
[#] equally contributed
*corresponding, nkarakas@medipol.edu.tr

ABSTRACT

Introduction: Upcycling agricultural waste into high-value products supports sustainable innovation in the cosmetic industry. Plant-derived exosomes have recently attracted interest for their regenerative and therapeutic potential in skincare. *Citrus reticulata* (mandarin) peel, a by-product of citrus processing, is particularly rich in bioactive compounds with antioxidant, anti-aging, and skin-brightening properties, making it a promising source of exosomes from otherwise discarded materials. **Methods:** In accordance with green chemistry principles and artificial intelligence (AI) modeling, mandarin peel extract was prepared at 50°C for 4 hours and filtered. Exosomes were isolated through ultracentrifugation at 150,000×g for 70 minutes. Characterization was performed using Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Nanoparticle Tracking Analysis (NTA), including zeta potential assessment. Antioxidant capacity was determined via DPPH assay, and antimicrobial activity was tested using the disc diffusion method. Biological efficacy was evaluated by the exosome treatment on human mesenchymal stem cells (hMSCs) for proliferation analysis. A zebrafish embryo toxicity test assessed developmental safety. **Results:** TEM and SEM imaging confirmed the presence of spherical exosomes with diameters ranging from 120 to 380 nm. Zeta potential ranged from -18 to -25 mV. The exosomes exhibited strong antioxidant activity and a broader antimicrobial spectrum than the crude extract. They significantly promoted hMSC proliferation and showed no adverse effects on zebrafish embryonic development compared to controls. **Conclusion:** Exosomes derived from mandarin peel, optimized through artificial intelligence, serve as an effective and sustainable bioactive ingredient for cosmeceutical formulations when applied at appropriate concentrations.

Key words: Plant-derived Exosome, Artificial Intelligance (AI), Upcycle, *Citrus Reticulata* Peel Extract, Cosmetics

1.INTRODUCTION

In recent years, the cosmetics industry has increasingly turned its attention to exosomes due to their multifaceted therapeutic and aesthetic benefits [1–3]. When incorporated into topical formulations such as creams, serums, and masks, exosomes

demonstrate significant potential in skin repair and rejuvenation. These nanosized vesicles, rich in proteins, lipids, and various signaling molecules, contribute to skin regeneration by enhancing collagen synthesis, reducing inflammation, and protecting against environmental stressors. Furthermore, they improve the performance of other active ingredients such as hyaluronic acid, peptides, and antioxidants [2].

Exosomes, originally identified in the extracellular space in the late 1980s, are nanovesicles derived from endosomal pathways and secreted by nearly all cell types [4–7]. Typically ranging between 30 and 500 nm in diameter, they carry a diverse cargo including DNA, RNA, proteins, lipids, and enzymes. Their biological composition allows them to function as messengers in intercellular communication, playing critical roles in physiological and pathological processes.

While mammalian exosomes have been widely studied, recent attention has also been directed toward plant-derived exosomes. These vesicles, like their animal counterparts, are composed of proteins, lipids, mRNAs, microRNAs, and plant-specific bioactive substances [8–13]. Importantly, they participate in innate plant immunity and intracellular signaling. Due to their abundance, biocompatibility, and biodegradable nature, plant-derived exosomes hold promise as novel, cell-free therapeutic agents for cosmetic and medical applications.

One notable plant source in this context is *Citrus reticulata* (mandarin). The peel extract of this fruit is frequently utilized in cosmetic formulations for its potent antioxidant and brightening properties [14–16]. It is especially rich in flavonoids, vitamin C, and essential oils, which help improve skin tone, reduce hyperpigmentation, and provide an astringent effect that refines pores and refreshes the skin. Additionally, the natural citrus aroma enhances the sensory experience of cosmetic products while supporting skin rejuvenation.

To better understand and optimize the impact of these biologically active agents, computational modeling techniques such as artificial neural networks (ANNs) are increasingly being utilized. ANNs are machine learning tools inspired by the structure and functioning of the human brain. By analyzing complex datasets, they are capable of predicting outcomes and uncovering hidden relationships among variables [17]. Pythia®, a specialized ANN-based software, identifies the most suitable network structure based on available data and trains the model using the least squares method. Once training is complete, it calculates the underlying equations within each neuron to predict outcomes from new input values. This modeling approach significantly reduces the need for exhaustive experimental studies while delivering highly accurate predictive insights [18].

Lastly, human mesenchymal stem cells (hMSCs) have emerged as a preferred in vitro model for studying tissue regeneration processes. These multipotent, non-hematopoietic stem cells can differentiate into a variety of cell types including osteocytes, adipocytes, chondrocytes, neurons, and hepatocytes [19]. Owing to their regenerative capabilities and ease of isolation from tissues such as bone marrow, adipose tissue, and dental pulp, hMSCs are widely employed in therapeutic research [20]. In the current study, hMSCs were selected as the model system due to their inherent relevance in tissue repair and regeneration, thus providing a physiologically meaningful platform for evaluating bioactive compounds.

2. MATERIALS AND METHODS

2.1 *Citrus reticulata* Peel Extraction Optimized by Artificial Intelligance (AI)

Based on different extraction conditions (temperature, solid-liquid ratio, duration, solvent type), the parameters to be used in developing extracts with the total flavonoid content via artificial neural network modeling have been determined through literature studies. After collecting the data, all values were entered into the Excel program. All parameters were accepted as inputs, and the total amount of flavonoids obtained from each extraction study was entered. The Pythia® computer program accepts copy/paste operations from Excel columns. After copying the inputs and outputs, the future function called "Evolutionary Optimization" in the Pythia program was selected and the program was run. Finally, the program provided the best neural network model showing the number of neurons in the layer, taking into account the smallest sum of the squares of deviations from the actual data. The program was trained to use a

specific neural model for the actual data. After the training, the program's calculations for predictions were taken into account. These predicted values were then compared with the actual data.

2.2 Exosome Isolation by Ultracentrifugation

Citrus Reticulata Peel Extract that optimized by AI were centrifuged at 4°C for theree times to remove cell debris, fibers, and large particles. After the final centrifugation, supernatants were collected and transferred to ultracentrifuge tubes. Then, the volume was brought to 30 ml with sterile PBS. To isolate exosomes, SW32 Ti rotor, OptimaXE-100 (Beckman Coulter, USA) was used and samples were centrifuged at 135,000 g for 70 minutes at +4 °C.

2.3 Characterization of the *Citrus Reticulata* Peel Derived Exosomes

2.3.1 Electron Microscopy

2.3.1.1 Imaging of Exosomes by Scanning Electron Microscopy

A drop of the *Citrus Reticulata* Peel derived exosome suspension was deposited for overnight drying and imaged the following day in a Gemini SEM 360 SEM microscope (ZEISS) after sputter-coating the samples with gold.

2.3.1.2 Imaging of Exosomes by Transmission Electron Microscopy

For TEM analysis, the sample was incubated for 10 minutes by dropping it onto a formvar/carbon supported copper grid (Ted Pella 0180 formvar/Carbon 200mesh copper grid). At the end of the incubation period, without allowing the sample to dry, the grid was placed on 25 µL of 2% Uranyl acetate alternative solution (Ted Pella 19485 Uranyl acetate altetnative (Gadolinium acetate tetrahydrate)) on parafilm for 1 minute for staining. After the staining period, the sample-loaded grid was left to dry at room temperature and then examined with a Jeol JEM-2100Plus transmission electron microscope at an accelerating voltage of 200 kV.

2.3.2 Nanoparticle Tracking Assay (NTA)

NTA measurements were performed with a NanoSight NS300. The system consists of a camera system, a syringe pump, and a computer system to process the obtained data. The software used for capturing and analyzing the data was the NTA 3.4 Build 3.4.003. The laser beam was passed through the sample chamber, and the scattered light from the particles in the suspension was observed by a video camera placed in its path. All measurements were performed at 21.9 °C. The mean size and SD values obtained by the NTA software.

2.3.3 Particle Size and Zeta Potential Measurement

Particle size and Zeta potential of the samples suspended in particle-free water were measured with the Zetasizer Ultra (Malvern Panalytical) device (Exosomes; refractive index (n =1.38); absorption (k = 0.01). The ZP of Mandarin extract derived exosomes were measured at 25 °C.

2.4 Disc Diffusion Anti-microbial Activity Test

Pseudomonas aeruginosa (ATCC 9027), Staphylococcusaureus (ATCC 6538), Escherichia coli (ATCC 8739), Candida albicans (ATCC 10231) were used. The test was performed according to the Kirby BauerDisc Diffusion Method.

2.5 DPPH Radical Scavenging Assay

For the assay, a 0.1 mM DPPH solution is prepared by dissolving DPPH in methanol. The solution is kept in the dark to prevent photodegradation. Various concentrations of the test sample are prepared by dissolving the compound or extract in methanol, typically ranging from 10 µg/mL to 100 µg/mL. To initiate the reaction, 1 mL of the DPPH solution is added to each sample solution. The mixtures are then thoroughly mixed and incubated in the dark at room

temperature for 30 minutes to allow the reaction to occur. After the incubation period, the absorbance of each solution is measured at 515 nm using a spectrophotometer. The absorbance of the DPPH solution alone is measured as a control for baseline comparison.

2.6 Cell Viability Assay

Human mesenchymal Stem Cells (UE7T-13 cells, no. RBRC-RCB2161; RIKEN, Japan) were plated at 5000 cells/well into 96 black well plates (3603, Corning) and cultured in DMEM, low glucose (Gibco) containing 10% FBS at 37 °C in 5% CO_2. Cells were cultured overnight and exosomes were added to the cells at diluted concentrations. The cells were incubated under standard culture conditions for 24 hr. To measure the activity of dehydrogenases, which increases in parallel with the increase in the number of living cells, cell proliferation was measured using Cell Titer Glo (Promega) according to the manufacturer's instructions. The values obtained from the exosome-treated cells were normalized against the signal for DMEM-only (control) treated cells.

2.7 Zebra Fish Embryo Toxicity Test

Male and female (2:1) zebrafish were kept in an aquarium rack system at 28°C under a 14/10 light/dark cycle.Fertilized eggs were collected and embryos were rinsed under water several times before used. Embryos were exposed to diluted solutions of mandarin derived exosome. E3 Medium solution was placed in well plates for the control group. Each exposure group was prepared as triplicates in 24-well plates having 20 embryos in each of them. They were monitored to evaluate their development and the images of malformations were recorded by using a stereomicroscope (Zeiss Discovery V8) for 72 hours post-fertilisation (hpf). Hatching rate is defined as the ratio of hatched embryos to the whole number of alive embryos in each well. Accordingly, hatching and mortality analyses were carried out every 24 h.

3. RESULTS

3.1. Exosomes from AI guided mandarin peel extract were collected and characterized

The morphology of exosomes isolated from *Citrus reticulata (mandarin)* peel extract was analyzed through scanning and transmission electron microscopy (SEM, TEM).

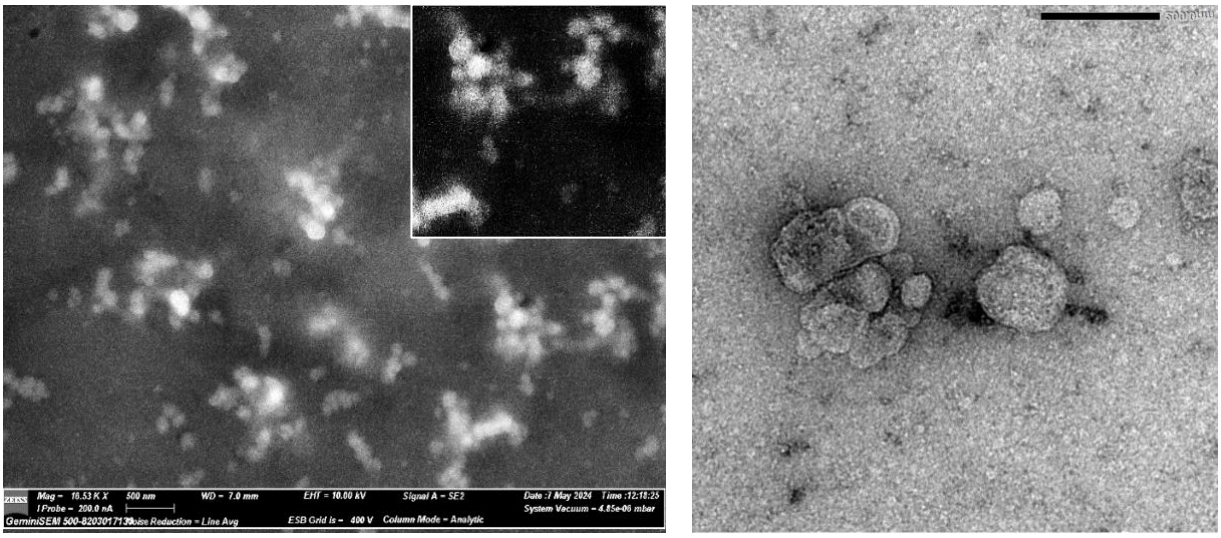

Figure 1: Morphology of mandarin peel derived exosomes. The exosomes were observed using SEM (left panel) and TEM (right panel). Scale bars are 200 nm for both the panels.

In order to investigate plant exosomes, we conducted nanoparticle tracking analysis that allows us to measure the number of exosome particles per ml. Nanoparticle-tracking analysis showed

that the average size of the mandarin derived exosomes were approximately 125.3nm and the total number of exosome was $1.57x10^9$ +/- $2.09x10^8$ particles/ml (Figure 2).

295.

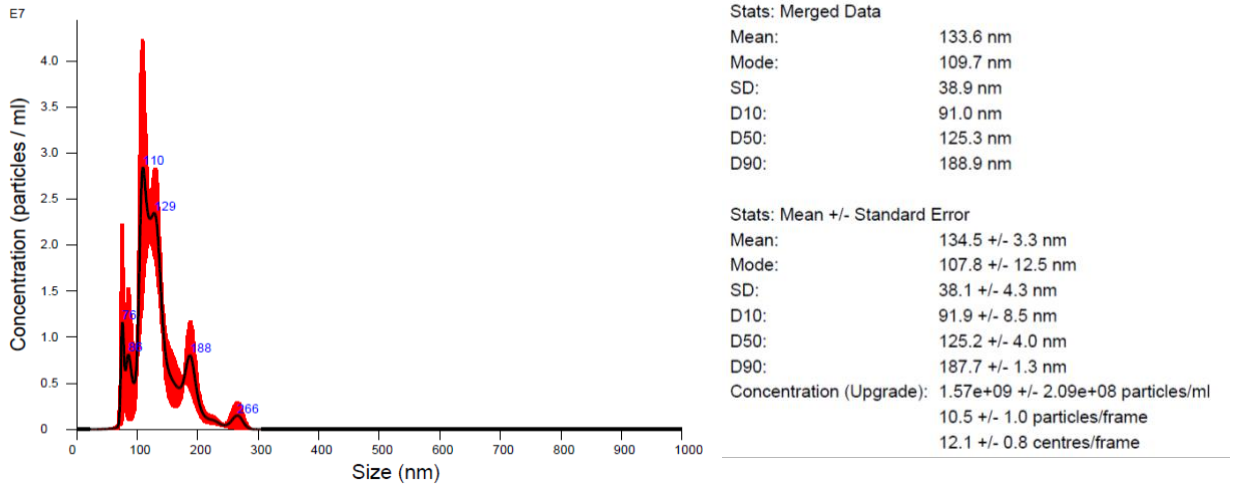

Figure 2. The size and concentration of mandarin peel derived exosomes determined by NTA.: Nanoparticule tracking assay indicates the size range of exosomes is approximately 125nm and the concentration was measured as $1.57x10^{10}$ particules/ml. dilution factor—1:10; laser—red laser; camera level—16; detection threshold—18; slider shutter—1300; slider gain—295.

To further investigate the characteristics of mandarin peel derived exosomes, the size distribution and zeta potential of the exosomes was measured and zeta potential of the exosomes was found -19 mV. The results were analyzed using the zeta sizer device, and it was detected that both the zeta potential of the exosomes and the stability of the working environment were rated as good (Figure 3).

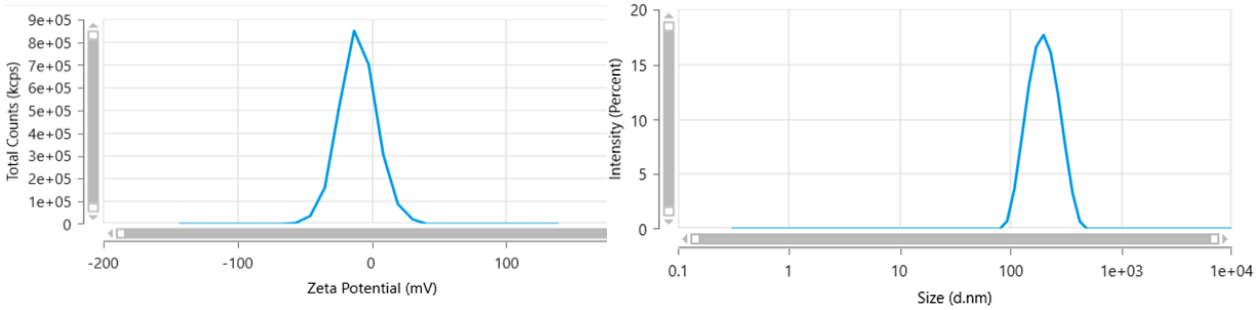

Figure 3. Zeta potential and size distributions of mandarin derived exosomes.

3.2. Mandarin peel derived exosomes showed antimicrobial activity and high antioxidan capacity

The antimicrobial activity of mandarin-derived exosomes was evaluated using the disc diffusion method against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*. The diameters of the inhibition zones were compared with standard antimicrobial agents including Gentamicin (CN 10 µg), Vancomycin (VA 30 µg), Streptomycin (S 10 µg), and Amphotericin B (AMB 20 µg). Mandarin-derived exosomes possess broad-spectrum antimicrobial properties with significant efficacy against both bacterial and fungal

pathogens (Figure 4). Their bioactivity, especially against *S. aureus* and *C. albicans*, supports their potential use as natural antimicrobial agents in dermatological and cosmetic applications.

	Diamater of Inhibition Zone (mm)				
TEST ORGANISIMS	Mandarin Derived Exosome	Gentamicin CN 10 µg	Vancomycin VA 30 µg	Streptomycin S 10 µg	Amphotericin B AMB 20 µg
Staphylococcus aureus	20	20	18	-	-
Pseudeumonas aeruginosa	12	15	-	-	-
Escherichia coli	16	22	-	16	-
Candida albicans	20	-	-	-	28

Figure 4. Antimicrobial activity of mandarin-derived exosomes against selected microorganisms, expressed as the diameter of inhibition zones (mm).

The antioxidant potential of mandarin-derived exosomes was evaluated through the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay and compared against ascorbic acid. As illustrated in Figure 5, the mandarin exosome exhibited a DPPH inhibition activity of approximately 80%, while ascorbic acid showed a slightly higher inhibition of around 82%.

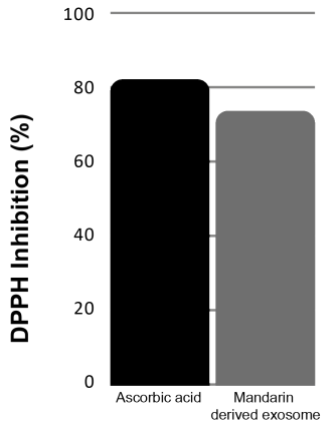

Figure 5. DPPH scavenging activity of mandarin-derived exosomes compared to ascorbic acid.

The slightly lower scavenging effect compared to pure ascorbic acid is reasonable given that exosomes are complex biological structures rather than isolated antioxidant molecules. However, their ability to maintain a high level of radical neutralization suggests a potential synergistic or stabilizing effect from the encapsulated constituents, which may be beneficial in targeted delivery or sustained antioxidant action. From a cosmetic and dermatological perspective, the antioxidant performance of mandarin-derived exosomes presents valuable implications. Oxidative stress is a key contributor to skin aging, inflammation, and damage caused by environmental factors such as UV exposure. Therefore, integrating exosome-based antioxidants into topical formulations may offer enhanced skin protection and rejuvenation effects.

Overall, the results demonstrate that mandarin exosomes possess considerable antioxidant activity, approaching that of pure ascorbic acid, and may serve as promising natural agents for use in functional cosmetic or therapeutic applications.

3.3. The exosomes were functionally active on stem cell proliferation.

The exosomes showed statistically significant proliferative effects on human mesenchymal stem cells (hMSCs). Cell viability increased 20% treated with 1E+08 (particles/ml) exosomes (Figure 6).

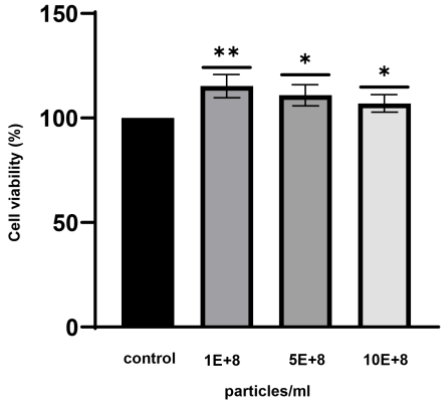

Figure 6. Functional effects of mandarin peel derived exosomes on stem cells. % Cell viability graph of the mandarin derived exosome treated hMSCs after 24 hours of exposure at the concentration ranging from 1E+8, 5E+8, 10E+8 particles/ml. Statistical significance was determined by student's t test ($P < 0.05$: *, $P < 0.01$: **).

3.4. Zebra fish embryo toxicity test demonstrated that mandarin peel derived exosomes are biocompatible

At an average temperature of 28.5°C, zebrafish embryos can hatch 48 to 72 hours after fertilization (hpf). During this time, the zebrafish develop and differentiate their pectoral fins. Growing zebrafish are referred to as "embryos" until 72 hpf, regardless of whether they have hatched, because spontaneously hatching embryos are not developmentally more advanced than those that stay in the chorion. However, embryos can alter their morphological and behavioral traits and lessen the likelihood that hatchlings will be preyed upon by postponing hatching. In our study, mandarin peel derived exosome treatment did not cause a significant difference in the hatching rates at 72 hpf.

Representative images of the zebrafish embryos in the mandarin peel derived exosome treated groups at 24, 48 and 72 hpf are given in Figure 7.

Figure 7. Representative images of mandarin peel derived exosome exposed zebrafish embryos at 24, 48 and 72 hpf.

The safety profile of substances is ascertained using the zebrafish embryo mortality rate assay. Off-target toxicity may be indicated by a high fatality rate. Developmental defects, which can be brought on by environmental, chemical, or genetic factors, may also be linked to increased mortality. The mortality rates of plant derived exosome treated embryos in our study were comparable with the control group. This implies that the mandarin peel derived exosomes are non-toxic and biocompatible at the specified concentrations.

DISCUSSION

In this study, *Citrus reticulata* peel, an agro-industrial by-product, was successfully upcycled into bioactive cosmetic ingredients. The extract and exosome fractions demonstrated significant antioxidant capacity, antimicrobial effects, and proliferative activity on human mesenchymal stem cells (hMSCs), aligning with previous reports that citrus peels contain high levels of flavonoids, vitamin C, and essential oils with dermatological benefits [25, 26]. Our findings support the use of citrus peel not only as a natural active ingredient but also as a sustainable solution that contributes to circular bioeconomy models.

The isolated exosomes exhibited typical size distribution (120–380 nm) and negative zeta potential (-18 to -25 mV), which are consistent with plant-derived exosome characteristics as described in prior studies [27, 28]. Notably, the antimicrobial activity of the exosome fraction was broader than that of the crude peel extract, suggesting that membrane-bound bioactive molecules in exosomes may enhance delivery or stability of antimicrobial agents.

Moreover, exosomes supported hMSC proliferation, indicating potential roles in skin regeneration. However, determination of optimized safe concentrations is essential when using exosomes in end products since over dose may cause harmful side effects. The fish embryo toxicity test confirmed that citrus-derived exosomes do not interfere with early vertebrate development, reinforcing their safety profile for topical applications.

Artificial neural network (ANN) modeling via Pythia® provided predictive insights and demonstrated how AI can optimize natural product extraction processes. AI-based modeling has gained traction in cosmetics R&D due to its ability to simulate biological outcomes and reduce experimental burden [29].

Together, these results indicate that upcycled mandarin (*Citrus reticulata)* peel deriived exosomes are not only effective but also sustainable ingredients for future cosmeceutical formulations.

ACKNOWLEDGMENTS

Exosome isolation & characterization studies were conducted in Nihal Karakaş's lab and financially supported by Nihal Karakaş. Zebrafish toxicity tests were supported by Ebru Işık Alturfan.

CONFLICT OF INTEREST STATEMENT

All authors declare that Nihal Karakaş holds the rights for exosome production and characterization of this study.

REFERENCES

1. Thakur, A., Shah, D., Rai, D., Parra, D. C., Pathikonda, S., Kurilova, S., & Cili, A. (2023). Therapeutic values of exosomes in cosmetics, skin care, tissue regeneration, and dermatological diseases. *Cosmetics, 10*(65). https://doi.org/10.3390/cosmetics10030065
2. Zhang, B., Gong, J., He, L., Khan, A., Xiong, T., Shen, H., & Li, Z. (2022). Exosomes based advancements for application in medical aesthetics. *Frontiers in Bioengineering and Biotechnology, 10*, 1083640. https://doi.org/10.3389/fbioe.2022.1083640
3. Bai, G., Truong, T. M., Pathak, G. N., Benoit, L., & Rao, B. (2024). Clinical applications of exosomes in cosmetic dermatology. *Skin Health and Disease, e348*. https://doi.org/10.1002/ski2.348

4. Kalluri, R., & LeBleu, V. S. (2020). The biology, function, and biomedical applications of exosomes. *Science, 367*(6478), eaau6977. https://doi.org/10.1126/science.aau6977
5. Cho, J. H., Hong, Y. D., Kim, D., et al. (2022). Confirmation of plant-derived exosomes as bioactive substances for skin application through comparative analysis of keratinocyte transcriptome. *Applied Biological Chemistry, 65*, 8. https://doi.org/10.1007/s13765-022-00593-z
6. Zhang, Y., Liu, Y., Liu, H., et al. (2019). Exosomes: Biogenesis, biologic function and clinical potential. *Cell Bioscience, 9*, 19. https://doi.org/10.1186/s13578-019-0283-x
7. Di Bella, M. A. (2022). Overview and update on extracellular vesicles: Considerations on exosomes and their application in modern medicine. *Biology (Basel), 11*(6), 804. https://doi.org/10.3390/biology11060804
8. Dai, J., Su, Y., Zhong, S., et al. (2020). Exosomes: Key players in cancer and potential therapeutic strategy. *Signal Transduction and Targeted Therapy, 5*, 145. https://doi.org/10.1038/s41392-020-00213-3
9. Nemati, M., Singh, B., Mir, R. A., Nemati, M., Babaei, A., Ahmadi, M., Rasmi, Y., Golezani, A. G., & Rezaie, J. (2022). Plant-derived extracellular vesicles: A novel nanomedicine approach with advantages and challenges. *Cell Communication and Signaling, 20*(1), 69. https://doi.org/10.1186/s12964-022-00934-7
10. Yi, Q., Xu, Z., Thakur, K., Zhang, K., Liang, Q., Liu, Y., & Yan, Y. (2023). Current understanding of plant-derived exosome-like nanoparticles in regulating the inflammatory response and immune system microenvironment. *Pharmacological Research*. https://doi.org/10.1016/j.phrs.2023.106866
11. Wei, X., Li, X., Zhang, Y., Wang, J., & Shen, S. (2023). Advances in the therapeutic applications of plant-derived exosomes in the treatment of inflammatory diseases. *Biomedicines, 11*, 1554. https://doi.org/10.3390/biomedicines11101554
12. Sarasati, A., Syahruddin, M. H., Nuryanti, A., Ana, I. D., Barlian, A., Wijaya, C. H., Ratnadewi, D., Wungu, T. D. K., & Takemori, H. (2023). Plant-derived exosome-like nanoparticles for biomedical applications and regenerative therapy. *Biomedicines, 11*, 1053. https://doi.org/10.3390/biomedicines11051053
13. Lian, M. Q., Chng, W. H., Liang, J., Yeo, H. Q., Lee, C. K., Belaid, M., Tollemeto, M., Wacker, M. G., Czarny, B., & Pastorin, G. (2022). Plant-derived extracellular vesicles: Recent advancements and current challenges on their use for biomedical applications. *Journal of Extracellular Vesicles, 11*, e12283. https://doi.org/10.1002/jev2.12283
14. Apraj, V. D., & Pandita, N. S. (2016). Evaluation of skin anti-aging potential of *Citrus reticulata* Blanco peel. *Pharmacognosy Research, 8*(3), 160-168. https://doi.org/10.4103/0974-8490.187247
15. Yang, J., Lee, S. Y., Jang, S. K., Kim, K. J., & Park, M. J. (2023). Inhibition of melanogenesis by essential oils from the citrus cultivars peels. *International Journal of Molecular Sciences, 24*(4), 4207. https://doi.org/10.3390/ijms24044207
16. Sriarumtias, F., Framesti, & Auliasari, N. (2020). Splash mask formulation of tangerine (*Citrus reticulata* Blanco.) peel extract and turmeric (*Curcuma longa* L) extract as a whitening agent. *International Journal of Research in Dermatology, 6*, 341. https://doi.org/10.18203/issn.2455-5518
17. Zou, J., Han, Y., & So, S. S. (2008). Overview of artificial neural networks. *Methods in Molecular Biology, 458*, 15-23. https://doi.org/10.1007/978-1-60327-249-7_2
18. Goel, A., Goel, A. K., & Kumar, A. (2023). The role of artificial neural network and machine learning in utilizing spatial information. *Spatial Information Research, 31*(3), 275–285. https://doi.org/10.1007/s41324-023-00497-x
19. Ullah, I., Subbarao, R. B., & Rho, G. J. (2015). Human mesenchymal stem cells - Current trends and future prospective. *Bioscience Reports, 35*(2), e00191. https://doi.org/10.1042/BSR20150191
20. Vasanthan, J., Gurusamy, N., Rajasingh, S., Sigamani, V., Kirankumar, S., Thomas, E. L., & Rajasingh, J. (2021). Role of human mesenchymal stem cells in regenerative therapy. *Cells, 10*, 54. https://doi.org/10.3390/cells10010054

21. Mu, N., Li, J., Zeng, L., You, J., Li, R., Qin, A., Liu, X., Yan, F., Zhou, Z. (2020). Plant-derived exosome-like nanovesicles: Current progress and prospects. *International Journal of Nanomedicine*. https://doi.org/10.2147/IJN.S285324
22. Zhu, M. Z., Xu, H. M., Liang, Y. J., Xu, J., Yue, N. N., Zhang, Y., Tian, C. M., Yao, J., Wang, L. S., Nie, Y. Q., & Li, D. F. (2023). Edible exosome-like nanoparticles from *Portulaca oleracea* L mitigate DSS-induced colitis via facilitating double-positive CD4+CD8+T cells expansion. *Journal of Nanobiotechnology, 21*(1), 309. https://doi.org/10.1186/s12951-023-02235-w
23. Jaiswal, G. (2018). Purslane in cosmetics: A review. *International Journal of Scientific Research, 7*(4), 32-35. https://doi.org/10.15373/22778179
24. Hegde, S., Elias, S., Arora, S., Adlakha, S., Garg, N., & Kant, T. (2023). A study on the use of AI (artificial intelligence) in the beauty industry in India. *International Journal of Research Publication and Reviews, 4*, 2936–2941.
25. Li, Y., Zhang, J., & Zhang, C. (2020). Citrus flavonoids and their antioxidant, anti-inflammatory, and anti-cancer activities. *Food Chemistry, 326*, 126953. https://doi.org/10.1016/j.foodchem.2020.126953
26. Singh, B., Singh, J. P., Kaur, A., & Yadav, M. P. (2021). Insights into the extraction, functional, and health benefits of citrus peel bioactives. *Food Chemistry, 355*, 129702. https://doi.org/10.1016/j.foodchem.2021.129702
27. Raimondo, S., et al. (2015). *Citrus limon*-derived nanovesicles inhibit cancer cell proliferation and suppress CML xenograft growth by inducing TRAIL-mediated cell death. *Oncotarget, 6*(23), 19514–19527. https://doi.org/10.18632/oncotarget.3841
28. Mu, J., et al. (2014). Interspecies communication between plant and mouse gut host cells through edible plant-derived exosome-like nanoparticles. *Molecular Nutrition & Food Research, 58*(7), 1561–1573. https://doi.org/10.1002/mnfr.201400091
29. López-García, G., et al. (2022). Applications of artificial intelligence in cosmetic dermatology. *Journal of Cosmetic Dermatology, 21*(4), 1361–1369. https://doi.org/10.1111/jocd.14673