International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

The Role of Exosome Intradermal Injection in Stimulating Neocollagenesis: A Systematic Literature Review

Oktavian Tamon

Doctoral Study Program, Faculty of Medicine, Udayana University, Denpasar 80232, Indonesia
Email: *dokter.tamon[at]gmail.com*

Abstract: ***The aim of this research is to investigate the potential of exosomes in promoting the synthesis of new collagen in the skin, specifically focusing on their applications in anti - aging therapy. This study adopts a systematic review approach to gather and analyze data from various studies that examine the effects of intradermal exosome injections on neocollagenesis. Exosomes, nano - sized vesicles released from various types of cells, including stem cells, are known to play a role in intercellular communication and are involved in numerous biological processes, including tissue repair and modulation of the immune system. The research results indicate that the most commonly used method is a review. The primary factors stimulating neocollagenesis include dermal remodeling, activation of the TGF - ß/Smad pathway, mRNA, the use of Calcium Hydroxyapatite (CaHA), TGF - β, regulation of TNF - α, MMP - 1 inhibition, anti - inflammatory effects, reduction of oxidative stress, the use of exosomes derived from placental mesenchymal stem cells, high - intensity LED therapy, the use of fillers containing EGF (Epidermal Growth Factor), exosomes from Mesenchymal Stem Cells (MSCs), and UVB. The role of intradermal exosome injections in stimulating neocollagenesis is to treat photoaged skin.***

Keywords: exosomes, collagen synthesis, anti - aging therapy, skin rejuvenation, intradermal injections

1. Introduction

The skin, comprising approximately 15% of the total adult body weight, is the largest organ in the human body. It is twice as heavy as the brain, weighing around 3 - 5 kg. The skin is composed of two primary layers, namely the epidermis and dermis, with the subcutaneous layer beneath the dermis not classified as part of the skin (1). The epidermis, the outermost layer of the skin, is composed of a specific group of cells called keratinocytes. These cells are responsible for producing a protein called keratin, which plays a crucial role in providing protection. Situated beneath the epidermis is the dermis, which primarily consists of collagen, a type of structural protein. Below the dermis lies the subcutaneous tissue, also known as the hypodermis layer or panniculus, which contains small clusters of fat cells called lipocytes. The thickness of the skin layer varies depending on its location on the body. For instance, the eyelids have a thin epidermal layer measuring less than 0.1 mm, whereas the palms of the hands and soles of the feet possess the thickest epidermal layer, approximately 1.5 mm in thickness (2).

Chondrocyte - derived exosomes (CC - exos) have been used to provide cartilage signaling for efficient regeneration of ectopic cartilage (3) . This CC - EXO promotes collagen deposition and minimizes blood vessel growth, resulting in stable ectopic chondrogenesis (4) . Exosomes derived from three - dimensionally cultured human dermal fibroblast spheroids (3D HDF - XOS) have skin anti - aging properties and the potential to prevent and treat skin aging (5) . They induce collagen synthesis, decrease matrix metalloproteinase - 1 (MMP - 1) expression, and increase dermal collagen deposition. (6) Exosomes isolated from adipose - derived stem cells (ADSCs) downregulated pro - inflammatory markers and upregulated anti - inflammatory cytokines, suggesting their potential in reducing chronic inflammation. In addition, exosome treatment promoted chondrogenesis and increased chondrogenic markers, suggesting their potential for chondrogenic regeneration in osteoarthritis.

Exosomes, which are tiny vesicles enclosed by a membrane and measure around 30 - 100 nm in size, are released by viable cells. Initially discovered in the 1980s, they were initially believed to serve as a means for cells to eliminate undesirable materials. (7–10) However, recent studies have revealed that exosomes play an important role in intercellular communication, involved in normal physiological processes and pathophysiological conditions. These processes include lactation (11) , immune response (12) , neuronal function (11) , and the development and progression of diseases such as liver disease (13) , neurodegenerative diseases (14) , and cancer (15, 16) . Exosomes play a crucial role in biological processes by carrying various substances such as proteins, lipids, RNAs, and small RNAs between cells. These substances reflect the origin of the exosomes and their ability to move between donor and recipient cells. The diverse functions of exosomes, which can have both positive and negative effects, make them important entities in biological mechanisms and potential targets for diagnostic and therapeutic interventions.

The administration of exosomes through a jet injector resulted in the suppression of miR196a and the enhancement of miR - 133a and miR - 223, which play a significant role in the healing of the skin. These exosomes effectively hindered the expression of MMP1 induced by UVB radiation, reinstated type I procollagen, and activated the TGF - β signaling pathways. Furthermore, the exosomes exhibited the ability to alleviate skin inflammation and senescence by reducing the levels of TNF - α. (5) MiR - 223 has been identified as a regulator of multiple cytokines, including the upregulation of IL - 8 and IL - 10 expression and the downregulation of TNF - α levels. Conversely, the upregulation of miR - 133a has been found to reduce the production of pro - inflammatory

cytokines. (17) Hence, exosomes exert their influence on skin tissue via diverse signaling pathways, transmitting distinct messages to dermal fibroblasts, as well as other cells like keratinocytes (18, 19) and macrophages (20) .

2. Research Methods

The method in this research has several process flows, namely:

Figure 1: Research Stages

Figure 1 represents a research process that encompasses several stages. The first stage is the planning stage, which serves as the initial step in implementing a Systematic Literature Review (SLR). Following the planning stage, the implementation stage of the SLR begins. Lastly, the Reporting stage involves the composition of a comprehensive report summarizing the findings of the SLR.

Research question
At this stage, questions are determined according to the research topic. The following are the research questions in this study:
1) RQ1: Which methods were employed to gather data regarding the intradermal injection of exosomes in promoting neocolagenesis?
2) RQ2: What are the elements that trigger the process of neocolagenesis?
3) RQ3: How does the intradermal injection of exosomes contribute to the stimulation of neocolagenesis?

Search Process
The search process is a stage of inquiry aimed at finding sources relevant to the research question. The source search process is conducted at the website address https: //scholar. google. co. id/.

Inclusion and Exclusion Criteria
At this stage, the criteria for the found data are determined, assessing whether the data is suitable to be considered as a source for research or not. The criteria for data to be deemed suitable as a research data source are as follows:
1) The obtained data has a time range from the year 2013 to 2023.
2) The data is sourced from https: //scholar. google. co. id/.
3) Only journal papers related to intradermal exosome injections in stimulating neocollagenesis are considered for data inclusion.

Quality Assessment
At this stage the data that has been found will be evaluated based on the following questions:
1) QA1: Was the journal article released between 2013 and 2023?
2) QA2: Is the journal paper focused on the use of intradermal exosome injections to promote neocollagenesis?
3) QA3: Does the journal article cover the topic of neocollagenesis?

And each paper will be assigned a value based on the questions above.
1) Yes: for journal papers that align with the quality assessment questions.
2) No: for journal papers that do not align with the quality assessment questions.

Data collection
At this stage, the data needed in the research is collected for further analysis. The following are the steps of data collection:
1) Visit the website https: //scholar. google. co. id/.
2) Enter the keywords "intradermal injection of exosomes in stimulating neocolagenesi"
3) Under "Custom range", enter 2013 in the first box and 2023 in the second box. This indicates that the range of journal papers selected is 2013 - 2023.

Data analysis
The data that has been collected in the previous stage will be analyzed at this stage. The results that have been analyzed will answer all research questions that have been determined previously.

Documentation
The data that has been collected in the previous stages will be analyzed at this stage. The results that have been analyzed will answer all research questions that have been determined previously.

3. Results

Search Process Results and Inclusion and Exclusion Criteria
Only six journal papers were found that met the inclusion and exclusion criteria during the search process. These criteria specified that the papers had to be published between 2013 and 2023 and discuss topics related to "intradermal injection of exosomes" and "neocolagenesis". The obtained information was subsequently classified into different types of journals. The types of journals successfully obtained are as follows:

Table 1: Grouping by Journal Type

No	Journal Type	Years	total
1	Cells	2023	1
2	Georgian Medical News	2022	1
3	Frontiers in Endocrinology	2023	1
4	Frontiers in Physiology	2023	1
5	International Journal of Nanomedicine	2023	1
6	Journal of Cosmetic Dermatology	2023	1
7	Military Medical Research	2023	1
8	Nature Biomedical Engineering	2023	1
9	Stem cell research & therapy	2020	1

Quality Assessment Results
The following are the results of the quality assessment written in table form:

Table 2: Quality Assessment Results

No	Authors	Years	QA1	QA2	QA3	Result
1	Mengna Duan, Yan Zhang, Haiyang Zhang, Yupeng Meng, Ming Qian and Guokun Zhang (21)	2020	Yes	Yes	Yes	accepted
2	Uwe Wollina, Alberto Goldman (22)	2022	Yes	Yes	Yes	accepted
3	Chan - Sheng Cai, Gui - Juan He & Fa - Wei Xu (23)	2023	Yes	Yes	Yes	accepted
4	Greg Chernoff BSc, MD, FRCS (C) (24)	2023	Yes	Yes	Yes	accepted
5	Jia-Yi Ding, Min-Jiang Chen, Ling-Feng Wu, Gao-Feng Shu, Shi-Ji Fang, Zhao-Yu Li, Xu-Ran Chu, Xiao-Kun Li, Zhou-Guang Wang and Jian-Song Ji (25)	2023	Yes	Yes	Yes	accepted
6	Jia Dong, Bin Wu and Weidong Tian (26)	2023				
7	Mario Adrián Tienda - Vázquez, Juan Manuel Hanel, Elsa Margarita Márquez - Arteaga, Ana Paola Salgado - Álvarez, Christian Quintus Scheckhuber, José Rafael Alanis - Gómez, Janette Ivone Espinoza - Silva, Manuel Ramos - Kuri, Fabiola Hernández - Rosas, Elda M. Melchor - Martínez, and Roberto Parra - Saldívar (27)	2023	Yes	Yes	Yes	accepted
8	Sun Hye Shin, Yoon Hwan Lee, Nark - Kyoung Rho and Kui Young Park (28)	2023	Yes	Yes	Yes	accepted
9	Yi You, Yu Tian, Zhaogang Yang, Junfeng Shi, Kwang Joo Kwak, Yuhao Tong, Andreanne Poppy Estania, Jianhong Cao, Wei - Hsiang Hsu, Yutong Liu, Chi - Ling Chiang, Benjamin R. Schran, Kristin Huntoon, DaeYong Lee, Ziwei Li, Yarong Zhao, Huan Zhang, Thomas D. Gallup, JongHoon Ha, Shiyan Dong, Xuefeng Li, Yifan Wang, Wen - Jing Lu, Eman Bahrani, Ly James Lee, Lesheng Teng, Wen Jiang, Feng Lan, Betty Y. S. Kim & Andrew S. Lee (29)	2023	Yes	Yes	Yes	accepted

4. Data Analysis

At this stage the data is analyzed and the results will answer the Research Question (RQ) that has been determined previously and will discuss the role of intradermal injection of exosomes in stimulating neocolagenesis that often appears from 2013 - 2023.

Outcome of RQ1: Methods used for data collection

Based on Research Question 1 or RQ1 regarding the results of RQ1: Methods used to collect data on the role of intradermal injection of exosomes in stimulating neocolagenesis, the results obtained are the categories of papers based on research methods. From the results shown in table 3, it shows that the most widely used method is review, then experiment, then quantitative.

Table 3: Research method categories

No	Research method	Research Paper	Result
1	Experiment	(21) (23) , (29)	3
2	Quantitative	(24) , (27)	2
3	Review	(22) , (26) , (25) , (28)	4

Result of RQ2: Factors that stimulate Neocolagenesis

Based on Research Question 2 or RQ2 regarding the factors that cause aging, paper categories based on factors that cause aging were generated. From the results shown in table 4, it shows that the factors that stimulate Neocolagenesis are Dermal Remodeling, Activation of TGF - β/Smad Pathway, mRNA, Use of Calcium Hydroxyapatite (CaHA), TGF - β, TNF - α Regulation, MMP - 1 Inhibition, Anti - inflammatory Effects, Oxidative Stress Reduction, Use of exosomes derived from placental mesenchymal stem cells, Use of high intensity LED therapy, Use of fillers containing EGF (Epidermal Growth Factor), Exosomes from Mesenchymal Stem Cells (MSCs), and UVB.

Table 4: Factors that stimulate Neocolagenesis

No	Contributing factors	Research Paper	Result
1	Activation of TGF - β/Smad Pathway	(21), (23)	2
2	mRNA	(21), (25), (29)	3
3	Dermal Remodeling	(22), (23), (29)	3
4	Use of Calcium Hydroxyapatite (CaHA)	(22), (24)	2
5	TNF - α Regulation	(23)	1
6	TGF - β	(23), (27)	2
7	Inhibition of MMP - 1	(23)	1
8	Anti - inflammatory Effects	(23)	1
9	Oxidative Stress Reduction	(23), (26)	2
10	Use of exosomes derived from placental mesenchymal stem cells	(24)	1
11	Use of high - intensity LED therapy	(24)	1
12	Use of near infrared light (930 nm)	(24)	1
13	Exosomes from *Mesenchymal Stem Cells* (MSCs)	(25)	1
14	UVB	(27)	1
15	Use of fillers containing EGF (Epidermal Growth Factor)	(28)	1

Results From RQ3: The Role of Intradermal Injection of Exosomes

Based on Research Question 3 or RQ3 regarding the role of intradermal injection of exosomes in stimulating neocolagenesis, the results were obtained in the form of paper categories based on the role of intradermal injection of exosomes. The results are shown in table 5.

Table 5: Role of Intradermal Injection of Exosomes

No	Role of Intradermal Injection of Exosomes	Research Paper	Result
1.	Treating skin undergoing photoaging	(21) , (22) , (23) , (26) , (27) , (28) , (29)	7
2	Tissue regeneration	(21) , (22) , (24) , (25)	4

Summary of Data Analysis Results

From the results of each Research Question or RQ, information was obtained regarding research methods, factors that stimulate neocollagenesis, and the role of intradermal injection of exosomes in stimulating neocollagenesis which has been studied by many researchers from 2013 to 2023.

Table 6: Frequency Categories of the Most RQ

RQ	Aspects	Most Frequency Category
1	Research Methods Category	Review
2	Factors that stimulate Neocolagenesis	Dermal Remodeling and mRNA
3	Role of Intradermal Injection of Exosomes	Treating skin undergoing photoaging

5. Discussion

Exosomes, which are small extracellular vesicles, have been proven to play a role in stimulating neocollagenesis, a process involving the synthesis and deposition of new collagen in the skin. Exosomes can originate from various sources, including adipose tissue, mesenchymal stem cells, and platelets. They contain bioactive molecules such as growth factors, cytokines, and microRNAs, which can exert paracrine effects on target cells and modulate cellular processes. This process involves the synthesis and deposition of new collagen in the skin, crucial for maintaining skin elasticity and reducing the appearance of wrinkles. The mechanism by which exosomes stimulate neocollagenesis involves a decrease in the expression of tumor necrosis factor - alpha (TNF - α) while concurrently increasing the expression of transforming growth factor - beta (TGF - β). (30) . This leads to increased production of matrix metalloproteinase - 1 (MMP - 1) and pro - collagen type I, ultimately increasing collagen synthesis in the skin. In addition, exosomes have been shown to be beneficial for skin care, promoting healing, hydration, and skin protection, further supporting their role in stimulating collagen production and improving skin appearance. (30)
Intradermal exosome injection is a method of delivering these vesicles directly into the skin. This approach has been explored for various applications, including skin aging treatment and wound healing. For example, exosomes derived from human adipose tissue - derived stem cells have been injected into the skin of mice, leading to increased collagen synthesis and skin rejuvenation. Similarly, exosomes from mesenchymal stem cells have been used to treat skin wounds in mice, resulting in faster wound healing.

Neocollagenesis refers to the process of forming new collagen in the body. Collagen is a crucial protein for the structure, strength, and elasticity of the skin, as well as other connective tissues. In the context of aesthetics and skin care, neocollagenesis often becomes the target of various interventions and treatments to improve skin appearance, reduce wrinkles, and enhance skin firmness and elasticity. This process can be triggered by various treatments, including the use of fillers, laser therapy, microneedling, and others, aiming to stimulate skin cells to produce more collagen. In the context of filler use, such as hyaluronic acid or poly - L - lactic acid, the goal is not only to fill the spaces under the skin that have lost volume but also to stimulate the neocollagenesis process. This means that in addition to the direct effects of the filler itself, there are also long - term benefits from the production of new collagen that can help improve the structure and quality of the skin from within. (31)

Intradermal exosome injections have been proven to stimulate neocollagenesis and enhance skin regeneration. (32) The intradermal exosome injection in stimulating neocollagenesis is crucial as it promotes the proliferation and migration of fibroblasts, which is a key process in the formation of new collagen. Exosomes can stimulate cell migration, proliferation, and collagen synthesis in a dose - dependent manner, including the upregulation of collagen type I and III gene regulation. This indicates that exosomes, especially those derived from adipose stem cells (ASC), when injected intradermally, can enhance the wound healing process by facilitating the production of new collagen, thereby contributing to skin improvement and rejuvenation. (33)

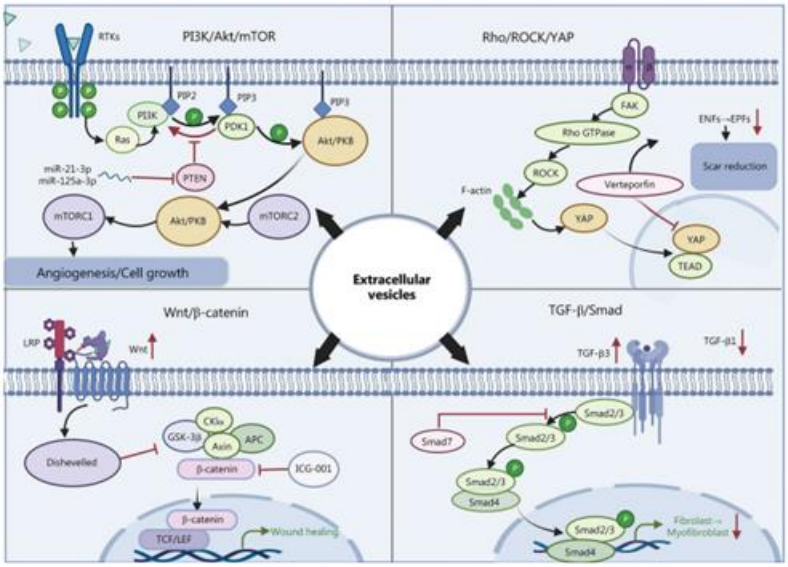

Figure 3: Schematic of Signaling Pathway in skin related to Intradermal Injection of Exosome (25)

The signaling pathway scheme in the skin associated with intradermal exosome injection involves several main pathways. First, the PI3K/Akt/mTOR pathway is activated by exosomes, contributing to the wound healing process, promoting fibroblast proliferation and migration, as well as collagen synthesis. Second, the TGF - β/Smad pathway is involved in inflammation and fibrosis modulation, where exosomes can regulate the transition of fibroblasts into myofibroblasts, crucial for wound healing and skin regeneration. Third, the Wnt/β - catenin pathway plays a significant role in skin regeneration and wound healing. Exosomes mediate the proliferation of hair follicle stem cells through this pathway, supporting hair regeneration and growth. Finally, the Rho/ROCK/YAP Axis pathway is involved in cytoskeleton reorganization and cell migration, crucial for wound healing, and exosomes can also influence this pathway to support the skin healing process. (25)

Intradermal exosome injections play a role in stimulating neocollagenesis through several mechanisms. Firstly, exosomes isolated from three - dimensional spheroids of human dermal fibroblasts (3D HDF - XOs) demonstrate the ability to enhance the expression of pro - collagen type I, a crucial component of the extracellular matrix, while significantly reducing the expression of MMP - 1, an enzyme associated with collagen degradation. This effect is primarily associated with the downregulation of tumor necrosis factor - alpha (TNF - α) expression and the upregulation of transforming growth factor - beta (TGF - β) expression mediated by 3D HDF - XOs. Secondly, exosomes overexpressing miR - 1246 (OE - EX) generated through lentivirus infection show a significant decrease in MMP - 1 expression by inhibiting the MAPK/AP - 1 signaling pathway and increasing the secretion of pro - collagen type I by activating the TGF - β/Smad pathway. OE - EX also exhibits anti - inflammatory effects by preventing UVB - induced IκB - α degradation and inhibiting NF - κB overexpression. This suggests that intradermal exosome injections can stimulate neocollagenesis and have therapeutic potential in addressing photoaging. (23)

The mechanism by which intradermal exosome injections promote neocollagenesis can be comprehended by their ability to augment the synthesis of collagen and elastin. Specifically, exosomes derived from adipose - derived stem cells (ADSC) have demonstrated the capability to upregulate the expression of the TGF - β1 gene, a pivotal factor in facilitating the synthesis of collagen and elastin. This process plays a critical role in the restoration and rejuvenation of skin tissues, including the stimulation of neocollagenesis, which entails the formation of fresh collagen within the skin. The heightened expression of TGF - β1, facilitated by exosomes, results in an increased production of collagen and elastin, thereby contributing to the enhancement of skin structure and function subsequent to damage, such as that induced by UVB - induced photoaging. (27)

6. Conclusion

Based on the previous review, exosomes demonstrate significant therapeutic potential in the field of tissue regeneration and wound healing, including applications in anti - aging therapy. Exosomes, as small extracellular vesicles, play a key role in intercellular communication and have the ability to influence the proliferation and migration of crucial cells such as fibroblasts and keratinocytes, which are essential in the skin healing and regeneration processes. Furthermore, exosomes have been proven to enhance the production of new collagen in the skin, essential for maintaining skin strength, firmness, and elasticity, indicating their considerable potential in anti - aging applications.

Exosomes from various sources, including stem cells and adipose cells, have been shown to be effective in stimulating collagen synthesis and accelerating wound healing, demonstrating their ability to improve skin appearance and support skin regeneration. Additionally, the potential of exosomes in treating other medical conditions such as heart disease, by reducing scar tissue and promoting myocardial regeneration, as well as their ability to reduce inflammation, indicates the broad therapeutic applications of exosomes beyond dermatology.

References

[1] Tortora GJ, Derrickson B. *Organization, Support and Movement, and Control Systems of the Human Body*. Vol 1. Hoboken, NJ: Wiley; 2009.

[2] James WD, Berger TG, Elston DM. Andrews' Diseases of the Skin. *Clin Dermatology, 10th ed Philadelphia, PA Saunders/Elsevier Inc*. Published online 2006: 231 - 250.

[3] Pegas ES, dos Santos FBC, Abdalla BMZ. Introduction: Chemical Substances for Injectable Cosmetic Neocollagenesis. *Minim Invasive Aesthetic Proced A Guid Dermatologists Plast Surg*. Published online 2020: 467 - 474. doi: 10.1007/978 - 3 - 319 - 78265 - 2_66

[4] Tutuianu R, Rosca AM, Iacomi DM, Simionescu M, Titorencu I. Human mesenchymal stromal cell - derived exosomes promote in vitro wound healing by modulating the biological properties of skin keratinocytes and fibroblasts and stimulating angiogenesis. *Int J Mol Sci*.2021; 22 (12): 6239. doi: 10.3390/ijms22126239

[5] Hu S, Li Z, Cores J, et al. Needle - free injection of exosomes derived from human dermal fibroblast spheroids ameliorates skin photoaging. *ACS Nano*.2019; 13 (10): 11273 - 11282. doi: 10.1021/acsnano.9b04384

[6] Zhao C, Chen J, Peng W, Yuan B, Bi Q, Xu Y. Exosomes from adipose-derived stem cells promote chondrogenesis and suppress inflammation by upregulating miR-145 and miR-221. *Mol Med Rep*.2020; 21 (4): 1881 - 1889. doi: 10.3892/mmr.2020.10982

[7] Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). *J Biol Chem*.1987; 262 (19): 9412 - 9420. doi: 10.1016/S0021 - 9258 (18) 48095 - 7

[8] Pan BT, Teng K, Wu C, Adam M, Johnstone RM. Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. *J Cell Biol*.1985; 101 (3): 942 - 948. doi:

10.1083/jcb.101.3.942

[9] Trams EG, Lauter CJ, Salem JN, Heine U. Exfoliation of membrane ecto - enzymes in the form of micro - vesicles. *Biochim Biophys Acta (BBA) - Biomembranes*.1981; 645 (1): 63 - 70. doi: 10.1016/0005 - 2736 (81) 90512 - 5

[10] Johnstone RM, Bianchini A, Teng K. Reticulocyte maturation and exosome release: transferrin receptor containing exosomes shows multiple plasma membrane functions. Published online 1989. doi: 10.1182/blood. V74.5.1844.1844

[11] 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 (2): 329 - 339. doi: 10.1083/jcb.97.2.329

[12] Admyre C, Johansson SM, Qazi KR, et al. Exosomes with immune modulatory features are present in human breast milk. *J Immunol*.2007; 179 (3): 1969 - 1978. doi: 10.4049/jimmunol.179.3.1969

[13] Masyuk AI, Masyuk T V, LaRusso NF. Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. *J Hepatol*.2013; 59 (3): 621 - 625. doi: 10.1016/j. jhep.2013.03.028

[14] Vella LJ, Sharples RA, Nisbet RM, Cappai R, Hill AF. The role of exosomes in the processing of proteins associated with neurodegenerative diseases. *Eur Biophys J*.2008; 37: 323 - 332. doi: 10.1007/s00249 - 007 - 0246 - z

[15] Bard MP, Hegmans JP, Hemmes A, et al. Proteomic analysis of exosomes isolated from human malignant pleural effusions. *Am J Respir Cell Mol Biol*.2004; 31 (1): 114 - 121. doi: 10.1165/rcmb.2003 - 0238OC

[16] Schorey JS, Bhatnagar S. Exosome function: from tumor immunology to pathogen biology. *Traffic*.2008; 9 (6): 871 - 881. doi: 10.1111/j.1600 - 0854.2008.00734. x

[17] Tahamtan A, Teymoori - Rad M, Nakstad B, Salimi V. Anti - inflammatory microRNAs and their potential for inflammatory diseases treatment. *Front Immunol*.2018; 9: 1377. doi: 10.3389/fimmu.2018.01377

[18] Espada J, Matabuena M, Salazar N, et al. Cryptomphalus aspersa mollusc eggs extract promotes migration and prevents cutaneous ageing in keratinocytes and dermal fibroblasts in vitro. *Int J Cosmet Sci*.2015; 37 (1): 41 - 55. doi: 10.1111/ics.12167

[19] Huang P, Bi J, Owen GR, et al. Keratinocyte microvesicles regulate the expression of multiple genes in dermal fibroblasts. *J Invest Dermatol*.2015; 135 (12): 3051 - 3059. doi: 10.1038/jid.2015.320

[20] Zhao J, Hu L, Gong N, Tang Q, Du L, Chen L. The effects of macrophage - stimulating protein on the migration, proliferation, and collagen synthesis of skin fibroblasts in vitro and in vivo. *Tissue Eng Part A*.2015; 21 (5 - 6): 982 - 991. doi: 10.1089/ten. tea.2013.0726

[21] Duan M, Zhang Y, Zhang H, Meng Y, Qian M, Zhang G. Epidermal stem cell - derived exosomes promote skin regeneration by downregulating transforming growth factor - β1 in wound healing. *Stem Cell Res Ther*.2020; 11: 1 - 11. doi: 10.1186/s13287 - 020 - 01971 - 6

[22] Wollina U, Goldman A. UPPER ARM CONTOURING–A NARRATIVE REVIEW. *Georgian Med News*.2022; 11 (332): 29 - 35.

[23] Cai CS, He GJ, Xu FW. Advances in the applications of extracellular vesicle for the treatment of skin photoaging: a comprehensive review. *Int J Nanomedicine*. Published online 2023: 6411 - 6423. doi: 10.2147/IJN. S433611

[24] Chernoff G. Combining topical dermal infused exosomes with injected calcium hydroxylapatite for enhanced tissue biostimulation. *J Cosmet Dermatol*.2023; 22: 15 - 27. doi: 10.1111/jocd.15695

[25] Ding JY, Chen MJ, Wu LF, et al. Mesenchymal stem cell - derived extracellular vesicles in skin wound healing: roles, opportunities and challenges. *Mil Med Res*.2023; 10 (1): 36. doi: 10.1186/s40779 - 023 - 00472 - w

[26] Dong J, Wu B, Tian W. How to maximize the therapeutic effect of exosomes on skin wounds in diabetes mellitus: review and discussion. *Front Endocrinol (Lausanne)*.2023; 14: 1146991. doi: 10.3389/fendo.2023.1146991

[27] Tienda - Vázquez MA, Hanel JM, Márquez - Arteaga EM, et al. Exosomes: A Promising Strategy for Repair, Regeneration and Treatment of Skin Disorders. *Cells*.2023; 12 (12): 1625. doi: 10.3390/cells12121625

[28] Shin SH, Lee YH, Rho NK, Park KY. Skin aging from mechanisms to interventions: focusing on dermal aging. *Front Physiol*.2023; 14: 1195272. doi: 10.3389/fphys.2023.1195272

[29] You Y, Tian Y, Yang Z, et al. Intradermally delivered mRNA - encapsulating extracellular vesicles for collagen - replacement therapy. *Nat Biomed Eng*.2023; 7: 887–900. doi: 10.1038/s41551 - 022 - 00989 - w

[30] Thakur A, Shah D, Rai D, et al. Therapeutic Values of Exosomes in Cosmetics, Skin Care, Tissue Regeneration, and Dermatological Diseases. *Cosmetics*.2023; 10 (2): 65. doi: 10.3390/ cosmetics10020065

[31] Corduff N. Introducing aesthetic regenerative scaffolds: An immunological perspective. *J Cosmet Dermatol*.2023; 22: 8 - 14. doi: 10.1007/978 - 3 - 319 - 78265 - 2_66

[32] Chen Y, Xue K, Zhang X, Zheng Z, Liu K. Exosomes derived from mature chondrocytes facilitate subcutaneous stable ectopic chondrogenesis of cartilage progenitor cells. *Stem Cell Res Ther*.2018; 9 (1): 1 - 14. doi: 10.1186/s13287 - 018 - 1047 - 2

[33] Prasai A, Jay JW, Jupiter D, Wolf SE, El Ayadi A. Role of exosomes in dermal wound healing: a systematic review. *J Invest Dermatol*.2022; 142 (3): 662 - 678. doi: 10.1016/j. jid.2021.07.167