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Review

Exosomes derived stem cells as a modern therapeutic approach for skin rejuvenation and hair regrowth

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ABSTRACT

Background: The skin covers the surface of the body and acts as the first defense barrier against environmental damage. Exposure of the skin to environmental physical and chemical factors such as mechanical injuries, UV rays, air pollution, chemicals, etc. Leads to numerous damages to skin cells such as fibroblasts, keratinocytes, melanocytes, etc. The harmful effects of environmental factors on skin cells could lead to various skin diseases, chronic wounds, wrinkles, and skin aging. Hair is an essential part of the body, serving multiple functions such as regulating body temperature and protecting against external factors like dust (through eyelashes and eyebrows). It also reflects an individual's personality. Therefore, the need for new treatment methods for skin diseases and lesions and at the same time preserving the youth, freshness, and beauty of the skin has been highly noticed by experts. Exosomes are nanovesicles derived from cells that contain various biological compounds such as lipids, proteins, nucleic acids, and carbohydrates. They are secreted by a variety of mammalian cells and even different plants. Exosomes are of great interest as a new therapeutic approach due to their stability, ability to be transported throughout the body, paracrine and endocrine effects, as well as the ability to carry various compounds and drugs to target cells.

Aim: In this review, we have discussed the characteristics of exosomes, their cellular sources, and their therapeutic effects on wrinkles, skin aging, and rejuvenation and hair regrowth.

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1. Introduction

1.1. Skin damage

The skin is the covering layer of the body and consists of four main parts: the outermost layer or stratum, the second layer or the epidermis, the third layer or the dermis, and the innermost or fourth layer which is the subcutaneous or hypodermis [1]. The epidermis is one of the most important layers of the skin, which contains key elements such as keratinocytes, fibroblasts, macrophages, adipose cells, extracellular matrix (ECM), and many growth factors [2,3]. Skin is exposed to several environmental factors that lead to various damages during human life. Skin is the first defense barrier against physical factors such as sunlight (UVA, UVB), chemical agents such as air pollution and smoking, and microbial factors like bacteria, fungi, and other infectious factors [4,5]. Aging does not happen only with the passing of life, but also many environmental elements are effective in the aging process. For example, exposure to excess amounts of UV causes many health risks, including atrophy, hyperpigmentation, malignancies, and acceleration of the aging process which causes skin wrinkles [6]. Treatment of skin disorders is performed in various ways such as surgery, transplantation, using medicines, and new methods such as cell and exosome therapy [7]. Hair is an essential part of the body, serving multiple functions such as regulating body temperature and protecting against external factors like dust (through eyelashes and eyebrows). It also reflects an individual's personality [8]. Each strand of hair consists of a root and a shaft. The hair root is located in the innermost layer of the skin and is surrounded by hair follicles, which are connected to sebaceous glands. On the other hand, the shaft is the visible part of the hair. Additionally, each hair follicle is connected to a muscle that provides support, and numerous nerves lead to the follicle. However, the hair root is connected to a hair bulb. The hair bulb contains the hair papilla, which feeds the hair root with blood. New cells are constantly produced in the hair bulb, close to the papilla [9].

1.2. Hair loss

The hair growth cycle consists of three phases: the anagen phase, in which 90 % of a person's hair is in this phase. At the end of the growth phase, the hair root separates from the papilla, and a transitional phase called the catagen phase begins, lasting between 2 and 4 weeks [10]. In the third phase, known as the telogen phase, the hair bulb is completely separated from the papilla due to the interruption of blood flow during the resting phase (Table 1). Hair loss occurs when the hair remains in a prolonged resting phase. A healthy adult typically loses 70 to 100 hairs per day, but these are replaced by new hair growth. However, if the root becomes damaged and multiple hairs enter the resting phase simultaneously, without being replaced by new hair, baldness occurs. hair loss is a natural part of the aging process. As we age, our hair follicles undergo changes, resulting in thinner and less abundant hair. This phenomenon affects both men and women and is influenced by genetic and hormonal factors [11]. Hair loss is a widespread condition that affects millions of people worldwide. It can be caused by various factors [12–14], including Various diseases and drugs are included, as fully explained in Table 2.

1.3. Cell therapy: a novel approach for treating hair loss

In recent years, cell therapy has emerged as a promising treatment method for combating hair loss. By harnessing the power of cells, this innovative approach offers new hope for individuals struggling with hair loss. Cell therapy involves the use of specialized cells to stimulate hair growth and restore the natural hair cycle. These cells, derived from various sources such as the patient's own body or laboratory-grown cultures, are carefully injected into the scalp in targeted areas. For hair regrowth, researchers have primarily focused on two types of stem cells: mesenchymal stem cells (MSCs) and dermal papilla cells (DPCs) [15]. Once introduced, they work to rejuvenate dormant hair follicles and promote the growth of new, healthy strands. What sets cell therapy apart from other treatments is its ability to address the root cause of hair loss. Rather than simply covering up the problem or temporarily stimulating hair growth, this method aims to revive the hair follicles themselves. By revitalizing these follicles, cell therapy not only promotes the growth of new hair but also enhances the quality and thickness of existing strands [16]. In addition to its efficacy, cell therapy also offers several other advantages. Firstly, it is a safe and minimally invasive procedure, with minimal side effects reported. Secondly, it is a versatile treatment method that can be tailored to

Table 1
Stages of hair growth.

		Gene	Function
Anagen	Anagen 1	β-catenin, Wnt, TGF- β, TGF-α, Stat3, Stat1	Start of anagen
	Anagen II	PPRad, IGF-1, FGF-G	Epithelial signal to dermal papilla
	Anagen V/IV	Notch, sx2, KRTs, KAPs	Differentiation to inner root sheath and hair shaft
	Anagen IV	Msx2, Activin, IGF-1, FGF5	Anagen maintenance
Catagen		BDNF, BMP, VDR, IL-1, ER, ERRG, Barx	Catagen inducer
Telogen		VDR, RAR, Desmoglin3	Telogen Inducer and maintenance

Table 2
Factors that influence hair loss.

Autoimmune diseases associated with alopecia areata	Category of drugs causing hair loss	Drugs causing hair loss
Hashimoto thyroiditis	Cholesterol lowering drugs	Clofibrate and gemfiprozil
Vitiligo	Parkinson medications	Levodopa
Systemic lupus erythematosus	Agents for gout	Allopurinol
Autoimmune thrombocytopenic purpura	Ulcer drugs	Cimetidine, ranitidine, famotidine
Type I (insulin-dependent) diabetes	Anticoagulants	Coumarine and heparin
Myasthenia gravis	Agents for gout	Allopurinol
Celiac disease	Anti arithritis	Penicillamine, indomethacin, naproxen, sulindac
Allergic asthma	Trimethadione	
Epilepsy	Drugs derived from Vitamin A	Isotretinoin, etretinate
Graves' disease	Antidepressants	Tricyclics, amphetamines
	Beta blocker drugs	Atenolol, Nadolol, timolol, propranolol,
	Anticonvulsant for epilepsy	Trimethadione
	Others	Male hormone (anabolic hormones), antineoplastics

each individual's unique needs. Whether the cause of hair loss is genetic, hormonal, or due to other factors, cell therapy can be customized accordingly. Furthermore, cell therapy is a long-lasting solution. Unlike temporary treatments such as topical medications or hairpieces, this method aims to provide enduring results. Once the cells are injected and hair growth is stimulated, the effects can persist for an extended period, reducing the need for frequent follow-up treatments. In conclusion, cell therapy represents a groundbreaking advancement in the field of hair loss treatment. By harnessing the potential of specialized cells, this innovative approach offers a safe, effective, and long-lasting solution for individuals seeking to combat hair loss. With further research and advancements, cell therapy holds the potential to revolutionize that treat this common condition [13].

Procedure for Stem Cell Therapy for Hair Loss:

Harvesting: Stem cells are extracted from the patient's body.

Cultivation: The extracted stem cells are then cultured to develop healthy hair follicles.

Regenerative Treatments for Hair Regrowth:

Although stem cell-based therapies for hair regrowth are still in the experimental stage, several treatments have emerged as viable options [17].

1.4. Exosome

Exosomes are double-membrane particles produced in most mammalian cells with a size of about 30–150 nanometers (nm) that are smaller than the other Extracellular vesicles (EV) [18]. Since exosomes can easily pass through the stratum corneum barrier and be absorbed into the dermis layer, they could be a suitable carrier to deliver substances to skin cells. Furthermore, they can cross the blood brain barrier. The endothelial cells of cerebrospinal capillaries are tightly connected, allowing only molecules that are smaller than 500 KD and highly lipophilic to pass through the blood-brain barrier. Consequently, exosomes that are less than 150 nm in size and weigh less than 500 KD can easily cross this barrier [19]. The interaction between exosomes and intercellular junction molecules, specifically ICAM-1, on the endothelial cells of cerebral microvessels, leads to the formation of the cerebral blood barrier and facilitates the penetration of exosomes into the brain and spinal tissue. Exosomes induce communication and transport materials between cells [20,21]. They contain proteins, DNA, RNA, miRNA, heat shock proteins, enzymes, growth factors, and other compounds and biomarkers [22] (Fig. 1). Studies have shown that exosomes could be extracted from various sources such as keratinocytes, endothelial cells, immune cells, body fluid, adipose-derived mesenchymal stem cell (ADMSCs) [23], umbilical cord-derived mesenchymal stem cell (UC-DMSC) [6], induced pluripotent stem cells (iPSCs) [24], human umbilical vein endothelial cells (HUVEC) [25], bovine colostrum [26] and plant sources such as Phellinus −linteus and apple (Table 3) [27]. Due to the special ability of exosomes to carry different compounds such as various growth factors, proteins, and drugs, today they are gaining a lot of attention in the treatment of many disorders such as skin problems and wrinkle removal. Exosomes, derived from stem cells such as MSCs and ADSCs, show promise for treating hair loss. These small nano-sized vesicles contain growth factors and bioactive molecules that stimulate hair follicle activity and promote hair growth. Additionally, exosomes from MSCs include IL10, TGF-β (Transforming Growth Factor β) and other anti-inflammatory cytokines, creating a favorable environment for hair growth. Exosomes derived from DPCs activate hair follicle stem cells, encouraging the development of new hair follicles (Fig. 2).

1.5. Platelet-rich plasma (PRP) therapy

Platelet-rich plasma (PRP) therapy involves injecting concentrated platelets from the patient's own blood into the scalp. These platelets contain growth factors that stimulate hair follicle activity, resulting in improved hair growth.

In addition to promoting hair growth, exosomes can also enhance angiogenesis, which improves blood supply to nourish the hair follicles. Furthermore, exosomes can be engineered as drug delivery systems, allowing for targeted delivery of therapeutic molecules to the scalp [28]. The growth factors affecting hair growth and their mechanism of action are shown in Table 4. One

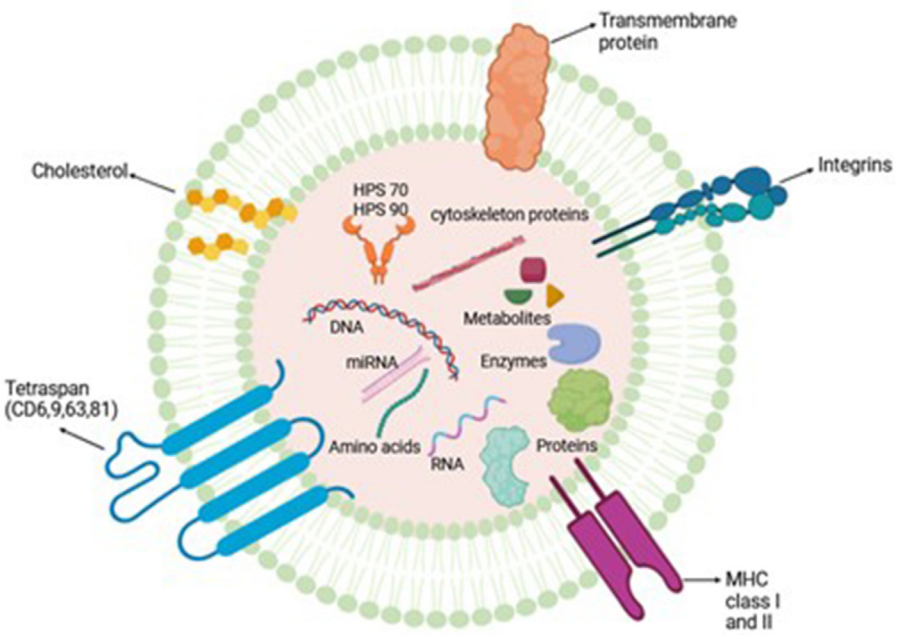

Fig. 1. Exosome structure. Exosomes are double-membrane particles and contain proteins, DNA, RNA, miRNA, heat shock proteins, enzymes, metabolites and other compounds and biomarkers.

brand that appears to effectively deliver on the promise of stem cell exosomes and produce credible clinical results is CALECIM [29]. The Advanced Hair System, a hair serum developed by our brand, contains a proprietary active ingredient called PTT-6. This ingredient is a complex blend of exosomes, growth factors, and proteins that are secreted by ethically derived stem cells. Over a hundred clinical observations have shown a success rate of 95 % in treating mild to moderate hair loss. Users have reported visible regrowth within 6 weeks of use, making the Advanced Hair System a popular choice in hair clinics worldwide. It can also be used at home with

Table 3
Studies in cell therapy of skin diseases and hair loss and its mechanism of action.

Source	Mechanism of action	Function	References
Mesenchymal stem cell exosomes	miR-223 coated by MSCS-exos regulates M2 polarization of macrophages by targeting Pknox1	Wound healing	He et al. (2019)
Keratinocyte-derived exosomes	Carrying miR-330-5p inhibits melanin production by targeting TYR	Hyperpigmentation	Liu et al. (2019)
Exosomes derived from human amniotic stem cells	miR-181a-5p and miR-199a, respectively, inhibit melanin production By reducing MITF expression	Hyperpigmentation	Wang et al. (2021)
Milk exosomes	miR-2478 directly targets rap1a via the Akt-GSK3 β pathway as a Regulator of Melanin production, which reduces Melanin content in melanocytes and inhibits Melanin formation<	Hyperpigmentation	Bae and Kim, (2021), Han et al. (2022)
Fat mesenchymal stem cell exosomes	By regulatingmiR-22, Wnt/β-catenin signal pathway and TNF-α signal pathway, the proliferation and migration of DPCs and expression of ALP, versican and Alpha-smooth muscle actin (α-SMA) proteins were promoted	Control hair loss	Nilforoushzadeh et al. (2020), Li et al. (2022b)
Human-induced potent stem cell derived exosomes	It decreased the activity of SA-β-gal and inhibited the expression of P53 and P21 in HDFs	Anti-aging	Lee et al. (2020a)
Blood exosomes	NAMPT carried in exosomes increases the biosynthesis of NAD	Anti-aging	Yoshida et al. (2019)
Endothelial progenitor cells exosomes	Activation of ERK1/2 signal pathway enhances the ability of human endothelium to proliferate, migrate and become tube	Wound healing	Zhang et al. (2016b)
Exosomes derived from human umbilical mesenchymal stem cell	Activation of ERK pathway significantly inhibits Melanin synthesis during MITF degradation	Hyperpigmentation	Kim et al. (2015)
Exosomes derived from dermal papilla cells	Down-regulation of relevant hair follicle inhibitory signal proteins by genes involved in the key pathways of β-catenin, WNT, BMP2 and BMP4 promotes the proliferation of hair follicle stem cells	Control hair loss	Zhou et al. (2018), Zhang et al. (2022)
Fat mesenchymal stem cell exosomes	Inhibit the over-expression of MMP-1, MMP-2, MMP-3 and MMP-9 induced by UV irradiation, and enhance the expression of Collagen Type I and III and elastin	Anti-aging	Choi et al. (2019)
Exosomes derived from human Mesenchymal stem cell	Activation of hair inductivity of DPCs, AKT phosphorylation, Bcl-2 in dermal papilla, and regulation of proliferation of DPCs	Control hair loss	Rajendran et al. (2017), Taghiabadi et al. (2020)

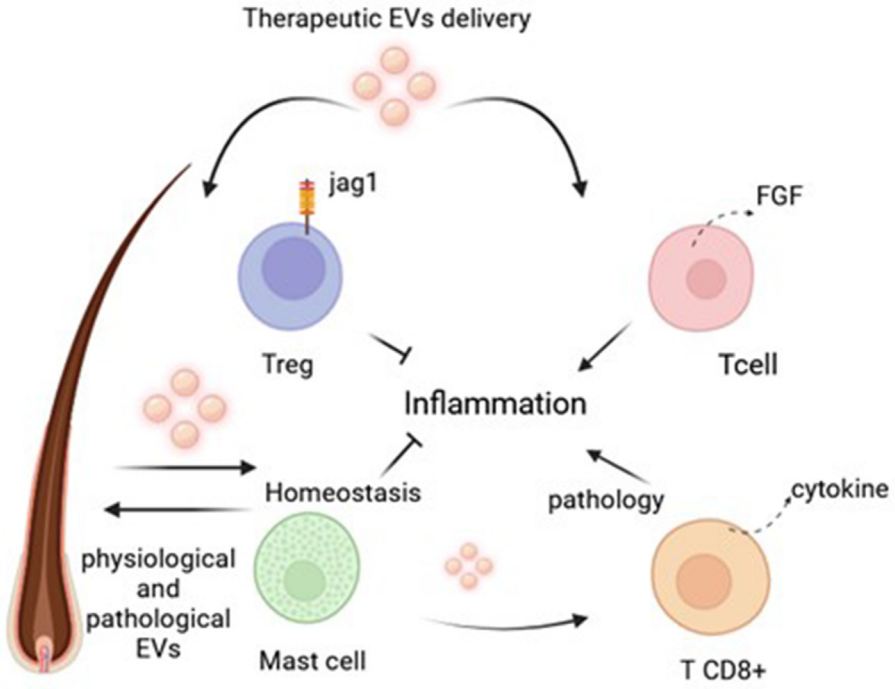

Fig. 2. Extracellular-vesicle-mediated conversation between immune cells and hair follicles. Vesicles can affect the function of hair follicle stem cells directly or indirectly by affecting the immune cells of this area. Skin-resident regulatory T (Treg) cells, which express high levels of the Notch ligand Jagged-1 (Jag1), play a crucial role in promoting hair follicle stem cell function and contributing to hair follicle regeneration. Normally, skin resident mast cells are responsible for maintaining the immune privilege of hair follicles. However, in cases of alopecia areata, these mast cells can become proinflammatory. This occurs when mast cells have reduced levels of TGF-β1 and release exosomes that stimulate T lymphocytes to multiply and release cytokines. The γδ-T cell population in mouse skin secretes FGF-9, which helps regulate the formation of new hair follicles after skin injuries. Moreover, both epithelial and dermal hair follicle cells have the ability to release extracellular vesicles (EVs), which can potentially target other cell populations within the hair follicle or skin resident immune cells. This contributes to the modulation of local inflammation. In the diagram, purple arrows indicate the movement of EVs, red arrows represent proinflammatory stimuli, and green T bars indicate anti-inflammatory stimuli.

the provided derma stamper. Dr. Munir Somji, a leading expert in hair restoration, explains the science behind the product in a recent interview, stating that the growth factors and exosomes derived from stem cells can activate a person's own stem cells within the hair follicles. This leads to reduced inflammation, a common cause of various types of hair loss, and promotes faster growth for longer and fuller hair [30,31]. But the use of exosomes for hair loss treatment is still in the early stages of research and development, promising results have been shown in preclinical and early clinical studies. These studies have demonstrated that exosomes can stimulate hair growth, improve the function of hair follicles, and reduce inflammation associated with specific types of hair loss.

1.6. Low-level laser therapy (LLLT)

LLLT, or low-level laser therapy, is a non-invasive treatment that is gaining popularity. It involves using red light to stimulate blood flow to the scalp, which helps promote hair growth. Research has shown that LLLT can help slow down hair loss and encourage hair regrowth in individuals with androgenetic alopecia. The potential of stem cells and other emerging treatments is truly exciting. These innovative approaches to hair regrowth represent a significant advancement in addressing the persistent problem of hair loss. While these therapies are still in the experimental stage, they offer hope to millions of people who desire a fuller and healthier head of

Table 4
Growth factors and their mechanism of action on hair growth.

Paracrine factor	Activity on hair growth
VEGF	Improves perifollicular angiogenesis, resulting in increased size of HFs and shafts
HGF	Activators enhance the proliferation of follicular epithelial cells
EGF	Improves the activity and growth of follicle outer-root sheath cells by activating Wnt/β-catenin flagging
PDGF and receptor	Induces and maintains anagen phase of hair cycle.
IL-6	Is involved in wound-induced hair neogenesis through STAT3 activation
IGF-I	Improves the migration, survival, and proliferation of HF cells
IGFBP1e6	Manage the effect of IGF-1 and its connection with ECM proteins at the HF level
TGF-β	Stimulates the signaling pathways that manage the hair cycle
KGF (FGF-10)	Stimulates proliferation and differentiation of early progenitor cells within HFs. Induces anagen phase in resting HFs.
FGF-1, FGF-2	Induces anagen phase in resting HFs
bFGF	Improves the advancement of HFs
BMP	Maintains the DPC phenotype
BMPR1a	Maintains the proper identity of DPCs
M-CSF and receptor	Is involved in wound-induced hair growth
Wnt3a	Is involved in HF advancement through b-catenin flagging
PGE2	Stimulates anagen in HFs
PGF2a and analogs	Enhance the change from telogen to anagen

hair [32]. The common side effects such as itching, red spots, congestion in the deep external auditory canal wall, and mild allergic manifestation Low-Level Laser Therapy in Patients with Complaints of Tinnitus: A Clinical Study. Available from: https://www.researchgate.net/publication/236978820_Low-Level_Laser_Therapy_in_Patients_with_Complaints_of_Tinnitus_A_Clinical_Study [accessed May 11, 2024]. Mechanism of LLLT therapy is described in Table 5.

2. Importance of rejuvenation

With the development and progress of societies and changes in the comprehensive view of aesthetics and its effect on self-confidence, researchers are looking for new treatment methods such as the use of biological and cellular products to deal with skin aging.

3. Skin wrinkle, aging characterization, and mechanisms

In the aging process of the skin, the structure of the extracellular matrix significantly changes. As mentioned earlier, the dermis is located between the subcutaneous and the epidermis layers and contains ECM and fibroblasts. Fibroblast (subsets including ACTA2+ myofibroblasts, WISP2+, MFAP5+, APCDD1+, COL18A1+, APCDD1+, COL18A1+, COL1A1+, COL1A2, +POSTN+ and MMP2+) originate from mesenchymal cells that are responsible for building connective tissue and secreting ECM [33]. ECM consists of elastin, collagen, glycosaminoglycan (GAGs), and proteoglycans (PGs). One of the main components of the ECM (Extra Cellular Matrix) is collagen, which is destroyed and reduced during the aging process due to the reduction of the TGF-β signaling pathway, pyro ptosis (Fig. 4), an increase of TNF-α expression (Fig. 5), and the increased activity of matrix metalloproteinase1,2 (MMP1,2) [34]. The decrease in the amount of collagen synthesis prevents the mechanical connection between fibroblast cells and the ECM, and as a result, this will lead to a decrease in the function of fibroblasts and collagen synthesis. Elastic fibers are one of the other important components of the ECM, which decrease drastically in aging and accumulate abnormally in the skin. Collagen makes up 75 % of the dry weight of the skin and is responsible for elasticity, strength, and resistance. The dermis layer of the skin consists of 3 types of collagen type 1, 3, and 4. Collagen type 1 is 80–90 %, collagen type 3 is 8–12 %, and collagen type 4 is less than 5 % of collagen in the ECM of the skin [35]. Different methods are used for the characterization of exosomes, for example, using flow cytometry to identify surface markers such as CD81 and CD36, electron microscopy, and the nanoparticle tracking analysis (NTA) method [36,37]. Factors affecting skin aging are shown in Fig. 3.

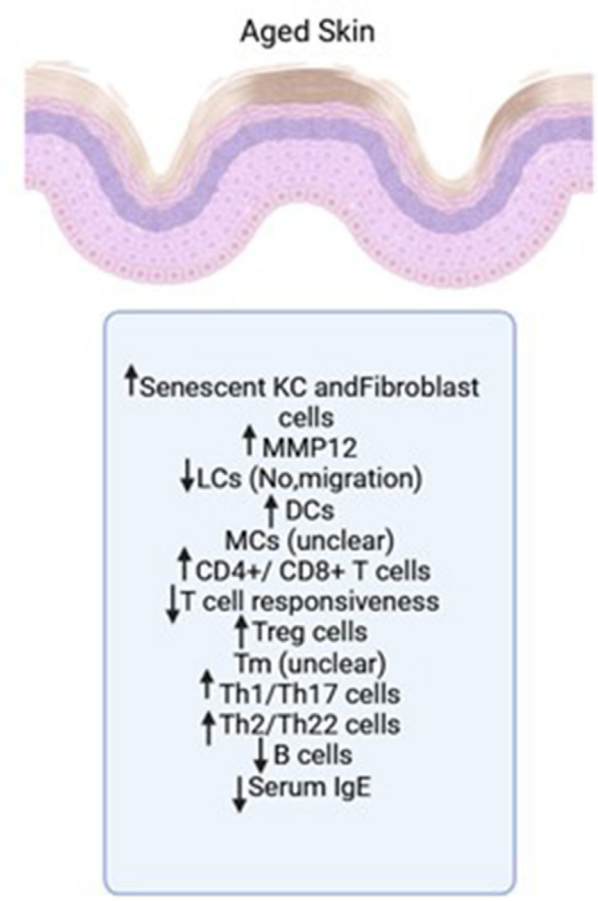

Fig. 3. The various immune cells and factors that affect skin aging.

Table 5
Mechanism of LLLT therapy.

	LLLT therapy						
Cytokines	Transcription factors	Mitochondrial signaling	Growth factors	Ion concentration	Nitric oxide	ATP synthesis	apoptosis
IL-1β↓ TNF-α PGF-2 LTB-4 IFN	NfκB modulation: cell migration, proliferation, inflammatory and stress-induced responses HIFs modification: healing of burn wound, alleviation of neuropathic pain, promotion recovery	Modulation of membrane potential(ΔΨm), MAPK/ERK kinase pathway: cell's growth, development, aging, maintenance of homeostasis, control of metabolic process	TGF-β: immune cell' MMP's, osteoblasts bFGF: tissue repair, tumor growth HGF: Hepatocyte proliferation, mortality, morphogenesis inflammatory process	Permeability of the cell membrane to Ca2+ Increased metabolism and excitability Release of Ca2+ from intracellular stores Growth of Ca2+intracellular level	Angiogenesis Tissue and cell growth Inflammatory process Immune response Vasodilation Wound healing	Recovery of heart cell' resistance of muscles Healing of wounds Tissue regeneration Collagen synthesis Anti-inflammatory effect	Apoptosis induction
IL-10↑							
LPO↓							
GSH↑							

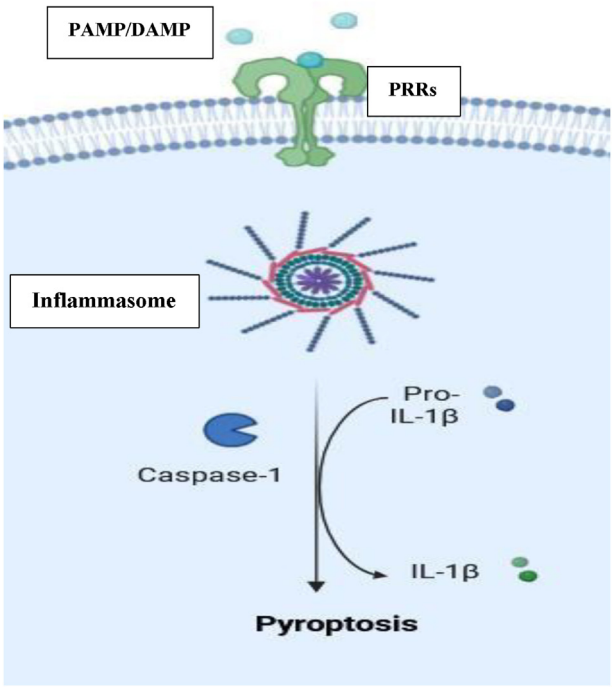

Fig. 4. Pyroptosis: The process involves the binding of PAMP (Pathogen-Associated Molecular Pattern) like virus, bacteria, and DAMP (Damage-Associated Molecular Pattern) like ROS, ATP, ds DNA, …to their respective receptors known as PRR (Pattern Recognition Receptors), such as NLR (NOD-like receptors), TLR (Toll Like Receptors). This binding then triggers the assembly of pro-caspase1 and ASC, leading to the formation of the inflammasome and the activation of caspase1. Once caspase1 is activated, it cleaves IL1 and IL18 precursors (pro- IL1β, pro-IL18), initiating various cellular processes that ultimately result in cell death by pyroptosis.

4. Molecular pathways of aging

4.1. TGF-β signaling pathway and aging

TGF-β is a pleiotropic cytokine that plays an important role in the physiological processes of the body, including stages of fetal development, tissue homeostasis, and the aging process. TGF-β induces fibroblast proliferation through autocrine activation of growth factors like FGF and PDGF. It also plays a role in collagen deposition and ECM remodeling by stimulating fibroblast proliferation and the production of collagen, fibronectin, MMPs, and PEA. Additionally, TGF-β activates Jak2 in fibroblasts, leading to Stat3 phosphorylation. The fibrogenic effects of this gene include increased cell proliferation, myofibroblast differentiation, ECM production, α-SMA (α-Smooth Muscle Actin) expression, and stress fiber production. Studies have shown that aberrant or increased activation of the TGF-β signaling pathway can cause pathological conditions such as reducing the body's ability to regenerate naturally, disrupting metabolic processes, inflammation, tissue fibrosis, Appearance of signs and symptoms of aging such as skin wrinkles, and involving with diseases such as Alzheimer's, muscular atrophy, obesity, and osteoarthritis [38]. In the human body, there are three subgroups of TGF-β, including TGF-β1, TGF-β2, and TGF-β3. TGF pathway signaling plays a very important role in various body processes such as the cell cycle, ROS production, DNA damage repair, regulation of telomerase activity, URS (Unfolded Protein Response) pathway, and autophagy, so it plays an important role in the aging pathways [39]. There are two types of serine-threonine kinase receptors for TGF-β in the body: TGF-β R1 and TGF-β R2. Each of these receptors has several subgroups. TGF-β R1 has 7 subgroups including Activin Receptor Like Kinase1-7 (ALK1-7), and TGF-β R2 has 5 subgroups, including: TβRⅡ, Act RⅡA, Act RⅡB, BMP RⅡ, and AMH RⅡ. After the ligand binds to TGFR, a heterotetrametric complex is formed from TGFR1 and TGFR2, and activation of receptors occurs by serine-threonine kinase enzymes [40] (Fig. 6). The figure below shows the TGF signaling pathway and its relationship with regulating the expression of different genes in inducing the aging process in different cells of the body, including skin fibroblasts, and causing phenotypic changes of aging, including wrinkling of the skin of the body and especially the face [34].

4.2. Telomerase and aging

Telomeres are nucleoprotein complexes with a length of 17–23 Kb at the end of chromosomes. Telomerases are enzymes that add TTAGGG repetitions to the end of chromosomes causing telomere length to increase [41]. In the absence of telomerase in somatic cells such as fibroblast, keratinocyte, epithelial cells, etc., the length of the telomere with each division decreases so much that eventually the cell growth stops, and apoptosis occurs. Therefore, physiologically, the body goes towards aging. Fibroblasts are essential in the dermis layer because they produce fibers and proteins. These cells play a crucial role in repairing skin tissue and preserving its youthful appearance. Therefore, the function of telomerase in fibroblast cells is particularly important because these cells play a crucial role in repairing and maintaining skin health [42]. On the other hand, stem cells present in different tissues, including the skin, like other cells in the body, are affected by various events such as the accumulation of DNA damage, genetic instability, ROS production, etc., and finally, their ability to regenerate is reduced, so the aging process occurs over time.

4.3. Inflammation and aging

With increasing age, increasing contact with pathogenic and chemical environmental factors, as well as changes in cellular metabolism increase the production of free radicals in the body, which is the main cause of functional and structural disorders of cells. During the aging process, old cells accumulate in different layers. These cells cannot divide but are still metabolically active. Aging cells in different body tissues secrete SASP (Senescence Associated Secretory Phenotype) inflammatory cytokines that change the tissue microenvironment. SASP included IL1, IL3, IL6, IL8, IL18, CCL2, TNF-α, INF-ɣ, TGFβ, CXCL1, and CXCL12 [43]. For example, old skin fibroblasts secrete a large amount of SASP compared to young fibroblasts, which by changing the ECM of the skin prevents the normal differentiation of keratinocyte cells, disrupts the normal function of the epidermal skin barrier, aggravates the aging of fibroblast cells, and increases the production of inflammatory cytokines like IL6 in immune cells. These events, by intensifying the inflammatory microenvironment, lead to the creation of chronic systemic inflammation, which ultimately causes the dysfunction of organs, including the skin, and the emergence of appearance phenotypes such as wrinkles and dry skin. As a person becomes older, the number of Treg and T CD8 cells increases, the number of T CD4 cells remains constant, and the expression of immunosuppressive receptor PD1 increases. These changes lead to the suppression of the activity of the specific immune system, and in this way, the lack of cleaning of old and dead cells and inflammatory factors leads to the acceleration of the aging process. Thus, inflammation acts as an endogenous factor for aging [44,45].

5. Exosomes derived from mammalian cell sources for skin wrinkle treatment

5.1. MSC-derived exosomes (MSC-exo)

Mesenchymal stem cells (MSCs) and cell products derived from them such as exosomes are currently being considered as one of the

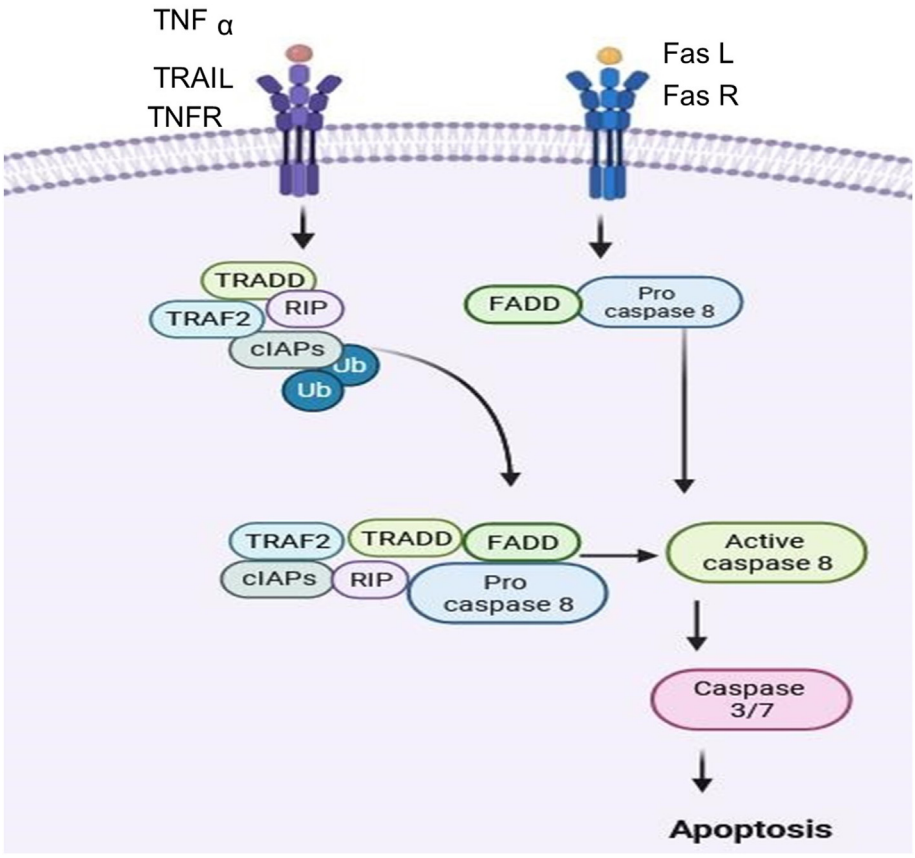

Fig. 5. Apoptosis: Tumor Necrosis Factor (TNF)-Related Apoptosis-Inducing Ligand (TRAIL) initiates cell death through two mechanisms: direct caspase activation or indirect activation via the release of apoptogenic factors from mitochondria. TRAIL-induced apoptosis is mediated by the TRAIL receptors, DR4 and DR5. These receptors recruit adaptor proteins such as Fas-Associated protein with Death Domain (FADD) and apical procaspases like procaspase-8 through death domain (DD) interaction. Together, these components form the Death Inducing Signaling Complex (DISC), which triggers the activation and release of apical caspases. The activated apical caspases then initiate two main pathways of cell death. In the extrinsic pathway, caspase-8 directly activates effector caspase-3, leading to apoptosis. Alternatively, the death receptor pathway (FAS) can activate the intrinsic pathway involving mitochondria. In this pathway, changes in the mitochondrial membranes cause the release of apoptogenic factors such as cytochrome *c*. Once in the cytosol, cytochrome *c* binds to the caspase-activating protein Apaf1, which then binds to procaspase-9, forming the apoptosome and inducing the processing and activation of caspase-9. This activated caspase-9 can then cooperate with caspase-8 in the processing and activation of caspase-3, ultimately resulting in cell death.

best cell therapy options in regenerative medicine. These cells have characteristics such as low immunogenicity, self-renewal, and the ability to differentiate into tissue-specific progenitors, migrate to damaged areas, and function through paracrine and autocrine pathways during cell damage [22]. The immune system produces cytokines and inflammatory mediators against external agents, which is the result of the activation of macrophages. The pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Fig. 2) play important roles in recruiting other cells of the immune system and activating other macrophages [46]. In contrast, anti-inflammatory cytokines that are produced from regulatory T cells, T helper 2, and alternatively activated macrophages and monocytes control immune and anti-inflammatory responses. The main anti-inflammatory cytokines are IL-1 receptor agonist (IL-1RA), IL-4, IL-10, and TGF-β, which inhibit the Th-1 responses and production of pro-inflammatory cytokines [47]. Therefore, regulation of inflammation is an important therapeutic goal for the treatment of inflammatory diseases, and it has been proven that MSC has features such as suppression of immune responses to reduce immune and inflammatory reactions [48]. It has been shown that a variety of miRNAs exist in exosomes such as miR-291a3p. Expression of miR-291a3p by targeting the TGFβ receptor in old mice treated with embryonic mesenchymal stem cells exosome (EMSC-exo) reduces the expression of SA-β-gal (Senescence-associated beta-galactosidase) and increases the proliferation and migration of HDF (human dermal fibroblast) cells [33]. SA-β-gal is a hydrolase enzyme that catalyzes the hydrolysis of β-galactosides into monosaccharides only in senescent cells. So, SA-β-gal is regarded to be a biomarker of cellular senescence [49]. Expression of miR-291a3p in exosomes by reducing the amount of SA-β-gal and increasing the proliferation of fibroblast cells delays skin aging and helps to rejuvenate and reduce wrinkles in murine study [50]. The variety and the functions of miRNAs involved in hair and skin is stated in Table 6.

5.1.1. Role of mesenchymal stem cell-Conditioned medium (MSC-CM) in skin wrinkle treatment

MSCCM has been shown to have anti-aging and anti-wrinkle effects, as well as the potency to treat skin and hair diseases. MSC-CM contains beneficial secretions including growth factors and exosomes. However, MSC-CM also contains unwanted compounds such as components of the culture medium, enhancers, and cellular excretory molecules such as lactate and ammonium, which are prohibited substances in cosmetics. Therefore, keeping exosomes and other therapeutic agents in the condition media while removing harmful substances can be a suitable approach for skin rejuvenation [51].

5.2. Adipose-derived stem cells-derived exosomes (ADSC-exo)

ADSC-exo plays a crucial role in increasing collagen production in skin fibroblast cells, specifically collagen type 1 and type 3, by

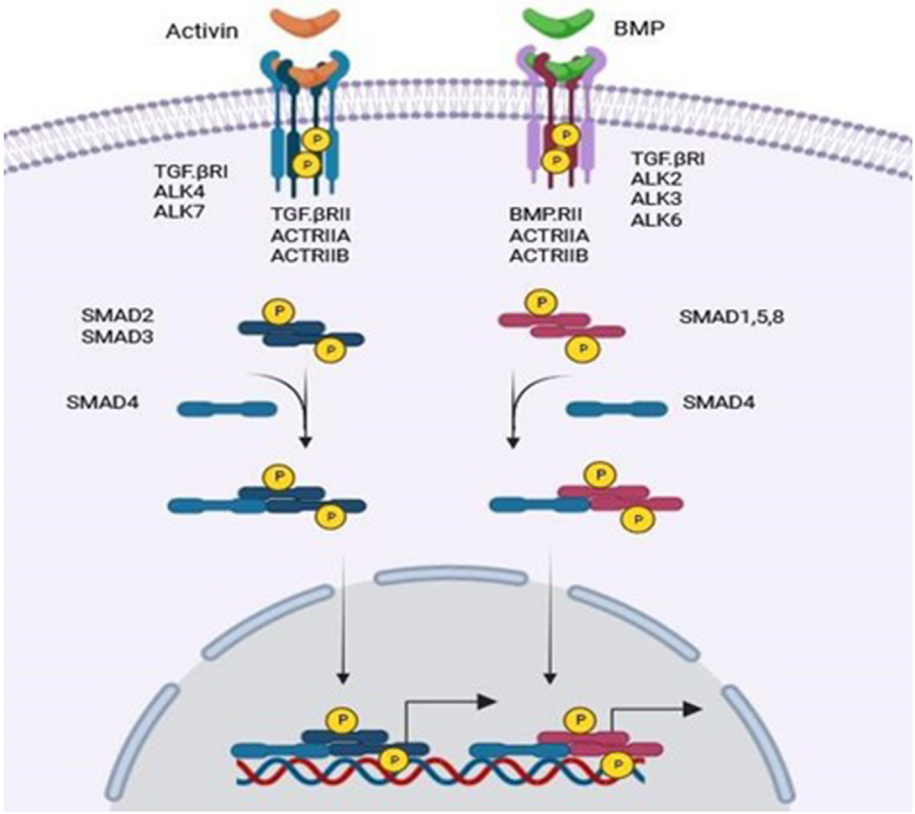

Fig. 6. Activin and BMP signaling pathway. Schematic overview of the canonical BMP and TGF-β signalling pathway, which relies on SMAD proteins. The pathway begins with the binding of BMPR1α, TGF-βR1, ACVRL1, or ACVR1 to a heteromeric complex of type I receptors. These type I receptors are linked with type II receptors such as BMPR2, TGF-βR2, ACTR2A/2B. Inside the cell, the transcription factors SMADs, which respond to BMP or TGF-β, undergo phosphorylation. They then combine with co-SMAD4 and move into the nucleus. The inhibitory SMAD6 regulates this signalling pathway.

activating the PI3K/Akt signaling pathway. Several studies, including Lu et al. and others, have reported that miR-486-5pADSC-exo promotes neoangiogenesis in skin tissue by targeting HDF cells and HMECs. Additionally, Liang et al. and Kang et al. have demonstrated that miR-125a and ADSC-exo miR-31 enhance pro-angiogenic activity through the FIH1 factor in HUVEC cells, leading to increased angiogenesis in skin tissue. Moreover, Cooper et al. and He have shown that the Wnt/β-catenin pathway plays a vital role in HDF cell proliferation and migration by binding to miR-124. This process involves the activity of lncRNA MALAT1 in ADSC-exo. He et al. has also observed that ADSC-exo activates the ERK/MAPK pathway, leading to increased activity and expression of TGF-β3, collagen type 3, and MMP3 in HDF cells. Furthermore, Zhang and Yang (2011) investigated the effects of ADSC-exo miR-21 on the HaCaT strain and demonstrated that this molecule activates keratinocytes and induces MMP-9, ultimately facilitating skin repair [52]. In a study by Hoang et al., ADSC-exos containing surface markers CD9, CD63, and AJO2 were found to induce the expression of VEGF, FGF2, HGF, and PDGF-BB. This induction, along with the conversion of fibroblasts to myofibroblasts, plays a crucial role in promoting skin repair [53]. Jun-xian Liang and colleagues in 2020 studied skin rejuvenation in a mouse model using exosomes isolated from fat tissue [54]. Exosome injection into the skin wrinkles of mice led to an increase in collagen expression and a decrease in MMP expression after 7 days. Histological evaluations of the skin at the injection site showed an increase in the proliferation of fibroblasts in the epidermis 28 days after the injection and an improvement in the condition of wrinkles. Therefore, ADSC-exo can be a potential therapeutic agent to eliminate wrinkles, especially those caused by photoaging [23]. Recently, ADSC-exo has been separated by ExoSCRT technology, which is a method of separating exosomes based on the use of TFF filters (Tangential Flow Filtration) and is one of the most reliable and safe methods for isolating exosomes [55]. The ASCE commercial product (ExoCoBioTM), which was used as the first cosmetic product in the International Commission on Irrigation and Drainage (ICID), has been isolated from ADSC cells using the ExoSCRT method. The advantages of using ADSC-exo isolated using TFF include: 1) Induction of collagen and elastin synthesis in skin fibroblasts, 2) Induction of proliferation of human dermal fibroblast (HDF) and human follicle dermal papilla cells (HFDPC), 3) Reducing inflammation by decreasing the expression level of proinflammatory cytokines, 4) Decreased expression of thymic stromal cytokine lymphopoietin (TSLP), and 5) Increasing the synthesis of ceramide, dihydroceramide, sphingosin and Sphingosine-1-phosphate (S1P) [56,57]. Analysis of secretomes that have been isolated from different cells for the treatment of skin diseases and wounds shows that the safety and efficiency of ADSC-exo is more than the exosomes isolated from BM-MSC in many aspects [58]: 1) Lack of expression of MHC-II molecules on the surface of ADSC, 2) Proof of inhibiting the growth of cancer cells both in vivo and in vitro, and 3) Induction of higher levels of anti-inflammatory M2 macrophages in ADSC-CM compared to BM-MSC-CM. ADSC-exo can be called a preferred regenerative cosmetic material due to its ability to signal to the surrounding cells and induce the differentiation of fibroblast cells, keratinocytes, and active epidermal cells such as hair follicles, which have great effects on the multiple layers of the skin [59,60].

Table 6
The variety and the functions of miRNAs involved in hair and skin-associated exosomes.

miRNA	Source of MSC	Targets or Pathways	Processes and Effects
miR-181c	UC-MSC	TLR4; NF-κB/P65	Lnflammatory cytokine production ↓
miR-146a	MSC	IRAK1, TRAF6, NF-κB	Lnflammatory cytokine production ↓; Inflammatory gene expression ↓
miR-223	BMSC	Pknox1	M2-phenotype macrophage polarization ↑
miR-let-7b	UC-MSC	TLR4/NF-κB/STAT3/AKT	M2-phenotype macrophage polarization ↑; Lnflammatory cytokine production ↓
miR-34a-5p miR-124-3p miR-146a-5p	ADSC	ARG1, CD206, TSG-6, TGF-β1	M2-phenotype macrophage polarization ↑
miR-146a miR-132	ADSC	ROCK1/PTEN	Pro-angiogenic gene expression ↑; Proliferation and tube formation of HUVEC ↑
miR-17-5p	UC-MSC	AKT/HIF-1α/VEGF	Proliferation, migration, and tube formation of HUVEC ↑
miR-221-3p	BMSC	AKT/eNOS	Proliferation, migration, and tube formation of HUVEC ↑; VEGF secretion ↑; Granulation tissue formation ↑
miR-126	BMSC	PIK3R2; PI3K/AKT	Proliferation, migration, and tube formation of HUVEC ↑
miR-126-3p	SMSC	MAPK/ERK; PI3K/AKT	Migration of HMEC ↑; capillary-network formation ↑
	BMSC	SPRED1/Ras/ERK	Proliferation, migration, and tube formation of HUVEC ↑
miR-125a	ADSC	DLL4	Endothelial tip cell formation ↑
miR-486-5p	ADSC	Sp5/CCND2	Proliferation and migration of HSF and HMEC ↑; HMEC angiogenesis ↑
miR-19b↓	ADSC	H19/SOX9/Wnt/β-catenin	Proliferation, migration and invasion of HSF ↑; collagen fibre formation ↑
miR-19b	ADSC	CCL1/TGF-β	Proliferation and migration of HSF and HaCaT cells ↑; HSF, HaCaT and endothelial cell apoptosis ↓
miR-135a	AMSC	LATS2	Proliferation and migration of fibroblasts ↑
miR-93-3p	BMSC	APAF1	Proliferation and migration of HaCaT cells ↑; Cellular apoptosis ↓
miR-150-5p	MSC	PTEN	Proliferation and migration of HaCaT cells ↑
miR-27b	MSC	ITCH	Proliferation and migration of HSF and HaCaT cells ↑; Collagen fiber proliferation ↑; epithelialization ↑
miR-10b	ADSC	PEA15	Proliferation and migration of HaCaT cells ↑; Cellular apoptosis ↓
miR-125b	UC-MSC	TP53INP1	Proliferation and migration of endothelial cells ↑; Cellular apoptosis ↓
miR-141-3p	ADSC	TGF-β2/Smad2/3	Proliferation and migration of hypertrophic scar fibroblasts ↓; myofibroblast transdifferentiation ↓
miR-21, miR-23a, miR-125b, miR-145	UC-MSC	TGF-β2/Smad2	Myofibroblast transdifferentiation ↓; collagen deposition ↓
miR-29a	ADSC	TGF-β2/Smad3	Migrating and proliferating of hypertrophic scar<Fibroblasts ↓; collagen deposition and ECM fibrosis ↓
miR-181a	ADSC	Sirtuin1	Myofibroblast transdifferentiation ↓; collagen deposition ↓
miR-138-5P	MSC	SIRT1	Proliferation, migration and protein expression in human skin fibroblasts ↓
miR-192-5P	ADSC	IL-17RA/Smad	Proliferation and migration of hypertrophic scar fibroblasts ↓; myofibroblast transdifferentiation ↓; collagen deposition ↓
miR-21-5p	BMSC	SPRY2	Migrating and proliferating of hypertrophic scar fibroblasts ↓; collagen deposition ↓
miR-145-5p	PMSC	CDKN1A; ERK/AKT	Proliferation and migration of senescent fibroblasts ↑; cellular senescence ↓; cellular apoptosis ↓
	dMSC	CAMK1D; PTEN	Proliferation and migration of senescent dermal fibroblasts↑; cellular senescence ↓; cellular apoptosis ↓
miR-146a	ADSC	Src kinase; VE-cadherin; Caveolin-1	Angiogenesis ↑; cellular senescence ↓; Migration of senescent endothelial cells ↑
miR-126	BMSC	Spred-1	Angiogenesis ↑; tissue regeneration ↑
miR-29b-3p	BMSC	MMP-2; TGF-β/Smad; MAPK/AP-1	Migration of human dermal fibroblasts ↑; photoaging ↓; matrix metalloproteinase ↓; Procollagen ↑
miR-302b	DPSC	ERK	Cell proliferation ↑; Stemness ↑; cellular senescence ↓
miR-302b	DPSC	ERK	Cell proliferation ↑; Stemness ↑; cellular senescence ↓
miR-493-3p	UC-MSC	TNF-α/NF-κB	Growth and migration of fibroblasts ↑; Procollagen ↑; oxidative stress levels ↓; cellular senescence ↓
miR-196a-5p	UC-MSC	NF-κB	
Hair loss			
miR-22 ↓	ADSC	Wnt/β-catenin; TNF-α	Hair growth ↑; hair regeneration ↑; dermal thickness ↑; Proliferation and migration of DPC ↑; anti-apoptosis ↑
miR-122-5p	ADSC	TGF-β1/Smad3	Hair bulb size ↑; dermal thickness ↑

5.3. Human umbilical cord -MSC derived exosomes (HUCMSC-exo)

Human umbilical cord mesenchymal stem cells (HUCMSC) are one of the best treatment options for tissue engineering and cell therapy. The use of exosomes derived from HUCMSC (HUCMSC-exo) is expanding to treat various diseases in both market and research. Studies show that HUCMSC-exo facilitates skin regeneration and repair. Subcutaneous injection of HUCMSC-exo to UV irradiated mice has been shown to have antioxidant and anti-inflammatory effects against apoptosis and damage. Studies have revealed that the expression level of sirtuin 1 protein (SIRT 1) in a keratinocyte cell line (HaCaT) is increased under the effect of UV rays and hydrogen peroxide to inhibit DNA damage and autophagy [6,25]. SIRT1 is a member of the sirtuin family. SIRT1 leads to deacetylation of lysine amino acid residues of target proteins and plays an important role in the regulation of apoptosis, mitochondrial function, cell cycle regulation, and cell metabolism. In addition, SIRT1 inhibits NFKB signaling and thus reduces inflammation and promotes healing processes [61,62]. Studies conducted by Peipei Wu et al. proved that the 14-3-3ζ protein in Huc-MSC exosomes can be a very effective agent for the treatment of UV-induced skin wrinkles by activating the anti-inflammatory and antioxidant pathway of SIRT1. Similarly, exosomal miR 146a, which is highly expressed in UC-MSC cells, negatively regulates senescence by targeting the NFKβ signaling pathway [6].

5.4. BM-MSC derived exosomes (BM-MSC-exo)

Peroxiredoxins (Prdxs) antioxidant enzymes are highly expressed in exosomes derived from BM-MSC cells. Transfer of the genes expressing this class of enzymes through exosomes has been shown to reduce cell aging phenotype, such as the expression of SA-βgal, p21, p53, IL1α, IL6, and γ-H2AX [22,63]. Researchers observed that the long non-coding RNA (lncRNA) H19 inhibits miR-152-3p by binding to it, leading to increased expression of the phosphatase and PTENA genes. This ultimately suppresses apoptosis and inflammation in fibroblast cells. Other studies have concluded that exosomes derived from bone marrow mesenchymal stem cells (MSC-BM) decrease the expression of TGF-beta1, SMD 2, SMD 3, and SMD 4, while increasing the expression of TGF-beta3 and SMD 7. As a result, the function of HaCaTs human keratinocyte cell lines, human skin fibroblasts, and HDF proliferation is enhanced. Additionally, Xie et al. demonstrated that local injection of BM-MSC-exo can stimulate VEGF gene expression, leading to angiogenesis [64].

5.5. iPSCs derived exosomes (iPSCs-exo)

The iPSCs-exo generally promotes wound healing and combats aging by inducing collagen synthesis and angiogenesis with four mechanisms: 1) effect on HDF cells involved with damage caused by UVB radiation, 2) effect on the mRNA expression level of MMP1 and 3 and collagen types 1 and 3, 3) effect on migration and proliferation of HDF, and 4) reversing aging by changing the expression of gene profiles in HDF cells. To discover the effects of exosomes derived from human induced pluripotent stem cells (iPSCs-exo) on the reconstruction and repair of skin wrinkles and rejuvenation, Myeongsik Oh and colleagues investigated the effects of iPSCs-exo on aged HDFs by UV irradiation. Cell proliferation and viability were determined by an MTT assay and cell migration capacity was shown by a scratch wound assay and a transwell migration assay. The results showed that treatment of aged HDFs with iPSCs-exo leads to a decrease in the expression level of SA-βgal. Exosome injection has a significant effect on the expression of genes related to the structure of the ECM in aged HDF so that MMP1 and 3 are considerably decreased and the expression level of collagen type 1 is increased [24,65].

5.6. HUVEC-derived exosomes (exo-HUVEC)

Human umbilical vein endothelial cells (HUVEC) are one of the sources of endothelial cells that contain large amounts of growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), platelet-derived growth factor-AA (PDGF-AA), placental growth factor (PGF), and transforming growth factor-beta (TGF-β) which increase proliferation, cell migration, and collagen synthesis [66]. Joo et al. observed that exo-HUVECs increased the growth of endothelial and angiogenic cells by upregulating the expression of VEGFR2 [67]. In another study, Jung et al. used immunofluorescent staining to demonstrate that the number of CD31-positive cells in the exosome-treated group was significantly higher compared to the control group. Furthermore, these exosomes exhibited a significant effect in enhancing the proliferation rate in the MMT test [68]. Additionally, Zhou et al. reported that exo-HUVECs in a gelma environment promoted collagen deposition and angiogenesis. Moreover, it has been established that exo-HUVECs, when administered in specific concentrations, induce tissue remodeling. In this way, these factors can induce the migration of fibroblasts and keratinocytes from the wound site to the center during the cell proliferation phase, so that these factors induce the formation of ECM by fibroblasts and re-epithelialization of the wound [69]. Photo-aging, especially under the influence of UVB, causes premature aging of the skin. UVB induces ROS production and direct DNA damage. By activating the MAPK (Mitogen Activated Protein Kinases), NFκβ, and AP-1 pathways, ROS increases the activity of MMP1 as a mediator of collagen degradation [70]. Destruction of collagen type 1, the main component of the skin, causes wrinkles. Molecular changes in the skin, due to photo-aging, could generally reduce collagen synthesis, proliferation, and migration of skin fibroblasts, and ultimately reduce angiogenesis and blood vessel production [71]. Angiogenesis is not possible without the help of endothelial cells because these cells are responsible for the formation of capillary networks and blood clots during wound healing [72]. In this way, these factors can induce the migration of fibroblasts and keratinocytes from the wound site to the center during the cell proliferation phase, so that these factors induce the formation of ECM by fibroblasts and re-epithelialization.

5.7. Bovine colostrum-derived exosomes (Col M-exos)

Damage and induction of aging with UV occurs in three types of skin cells including keratinocytes, melanocytes, and fibroblasts. Treatment with exosomes inhibits ROS production in epidermal keratinocytes. Also, exosomes decrease the production of MMPs and increase collagen synthesis. In low concentrations, ROS acts as a necessary signal for normal physiological regulation of cellular functions such as regulation of cell cycle, growth, and development [73,74]. However, excess amounts of ROS by damaging macromolecules could activate cell death. In one study, UVC rays (the most harmful UV rays) were used to check the severity of cell damage. HaCaTs cell line was used to investigate the effect of exosomes on the level of expression of ROS in keratinocytes. Treatment of HaCaTs with exosomes and then exposure to UVC decreased intracellular ROS expression level through glutathione (GSH) oxidation and increased glutathione protein expression level in the HaCaTs line. Milk exosomes increased the antioxidant capacity of HaCaTs by reducing ROS through the glutathione oxidation pathway. The results obtained from the studies suggest that exosomes increase the resistance of cells to ROS and maintain the potency to reproduce by inducing the proliferation of damaged cells. Col M-exo increases skin elasticity by affecting fibroblasts. Fibroblasts balance the environment of the skin through the synthesis of collagen and extracellular matrix; therefore, they are very important cells in maintaining the elasticity of the skin. The expression levels of MMP2 and collagen type 1 in cells treated with Col M-exos, especially fibroblasts that were affected by UV rays, were significantly decreased, and increased, respectively. According to previous studies, it was found that cow's milk induces collagen type 1 expression through the STAT6 pathway in human fibroblasts [75]. In addition, it has been shown that human and donkey milk promote the cell cycle and proliferation of skin fibroblast cells through growth-regulatory kinases, especially the P-ERK pathway. Previous studies have revealed that milk exosomes are structurally strong enough to pass through environments with extreme pH and the digestive tract [76]. Col-*M*-exos effectively cause ECM construction by increasing the vitality of skin fibroblasts and collagen synthesis under the influence of UV rays, which leads to firmness and elasticity of the skin. Col M-exos is used as an ingredient in skin treatments and cosmetics [77].

6. Exosomes derived from plant cell sources for skin wrinkle treatment

6.1. Fruits

Nanovesicles (NVs) have been successfully isolated from plants such as lemon [78], strawberry [79], grapes [80], ginger [81] and

broccoli [82]. Several studies have shown how NVs derived from plants could affect mammalian cells. It has also been proven that these particles have anti-inflammatory and antioxidant effects. NVs derived from lemon have been proven to inhibit inflammation, and oxidative stress of MSCs in vitro, and protect mice against colitis [83]. Also, these vesicles in vivo inhibit the proliferation and decrease the survival of cancer cells by activating apoptosis by TRAIL (tumor necrosis factor (TNF)-related apoptosis-inducing ligand) (Fig. 3) and cytokines such as IL-6 and IL-8 and pro-angiogenesis [84]. Apples are rich in polyphenols, which have many uses such as anti-cancer and antiinflammation due to anti-oxidant molecules. Apple-derived nanovesicles (ADNV) have now been isolated and characterized, and these particles have been shown to have anti-inflammatory properties. These particles have been studied in aging and skin repair and cosmetic delivery systems [27].

6.2. *Phellinus –linteus (PL)*

PL is a mushroom with medical uses that contains many compounds such as polysaccharides, polyphenols, and flavones, and has important regulatory roles such as anti-tumor, reducing inflammation, and blood sugar control. For example, PL polysaccharides inhibit the pathway of MAPK and inflammatory factors in the cell. PL water-soluble extracts have immunomodulatory effects in atopic dermatitis [85]. Also, the extract of this mushroom is used in the formulation of skincare and cosmetic products. Following the discovery of exosomes derived from mammalian cells, much evidence showed that FELNVs (fungi exosome-like nanovesicles) also have therapeutic uses such as anti-tumor and regenerative effects [86,87]. EVs derived from fungi play an important role in cell metabolism and signal transduction. Researchers aim to discover and identify the nanoparticles that are secreted from PL to determine the anti-aging molecular mechanisms of these particles. The results obtained from studies have shown that these exosomes have beneficial effects in improving the volunteers' skin texture, and the PL extract name is mentioned as an ingredient in the catalog of cosmetic products. These compounds significantly reduce skin spots caused by UV, wrinkles, moles, and red areas, which shows that the particles are useful and effective in delaying aging and reducing the inflammatory reactions of volunteers' skin. Production of high amounts of ROS under the influence of UV rays increases the damage caused by oxidative stress such as lipid oxidation. Oxidation of lipids through the production of MDA (malondialdehyde) causes skin aging and is used to determine oxidative stress [88]. Superoxide dismutase (SOD) is an antioxidant metalloenzyme that scavenges oxygen radicals [89]. In addition, aging cells are larger and produce large amounts of SA-β-gal, which are determined as skin aging biomarkers. The effects of FELNV on ROS production, MDA level, SOD enzyme activity, and SA-β-gal expression level have been measured. Results have shown that these compounds decrease MDA, ROS, and SA and increase SOD enzyme activity in the HaCaT cell line. It was also found that FELNV-derived RNAs play an anti-aging role by affecting the growth and proliferation of HaCaT cells that were exposed to UV. FELNVderived RNAs significantly decrease SA-β-gal and increase SOD activity compared to the control group and have anti-aging properties [90]. Exosomes have a high level of miRNA molecules that play an important role in regulating gene expression and pathophysiological processes [91,92]. In PL, five different miRNAs named miR-CM-1 to miR-CM-5 were identified. It has been proven that 2-*O*-methyl changes in plant miRNAs increase resistance to aging [27]. The miR-CM-1, 3 with pro-protective effects inhibits the decrease in the viability of HaCaT cells under the influence of UV. miR-CM-1 decreases the expression of SA-β gal, MMP1, ROS, and MDA, and increases the activity of SOD (Super Oxide Dismutase), the expression level of COL1A 2 in UV-induced cell line, and ultimately delays aging. The effect of miR-CM-1 on the expression level of MICAL2 (molecules interacting with CasL) is very intense. MICAL2 is a monooxygenase that directly binds to F-actin depolymerase, which is responsible for the production of ROS in the regulation of actin microfilaments. Overexpression of MICAL2 increases ROS, MMP, SA-β gal and decreases COL1A and SOD expression, and finally accelerates senescence [93]. The miR-CM-1 encapsulated in artificial exosomes can reduce UV-induced senescence in mouse models. miR-CM-1 has better effects than FELNV in reducing abnormal epidermal hyperplasia. The loss of dense collagen in the dermal layer of the skin was significantly observed in the control groups induced by UV, while the amount of collagen increased significantly in the groups treated with FELNV and miR-exo [27]. The microenvironment of the skin consists of collagen fibers, elastin, decorin, gelatin, fibronectin, and various proteoglycans with a three-dimensional structure. ECM is a dynamic environment that has different amounts of components with different proportions in different stages of development from embryo to adulthood and under different environmental conditions and in diseases. The dynamic structure of the skin occurs due to changes in the expression of specific proteases called MMP (zinc-dependent endopeptidase Matrix Metalloproteinase) [94], ADAM (A Disintegrin and Metalloproteinase) and ADAMTS (ADAM with Thrombospondin motive) and the regulation of their expression by 4 types of proteins called TIMP1-4 (Tissue Inhibitors of Matrix metalloproteinase1-4). Skin aging is a natural process that is caused by the disruption of the natural balance of synthesis and destruction of ECM components due to the disruption of the natural ratio of MMP/TIMP: 1/1. With age, the amount of collagen synthesis decreases by 1.5 % per year, as well as the synthesis of elasticity fibers and hyaluronic acid in the skin [95]. With age, telomere length decreases, and under the influence of environmental factors, UV, hormonal, and epigenetic changes, the amount of ROS production increases. ROS by activating NFKB and MAP kinase inflammatory pathways leads to the expression of AP1 transcription factor, which can lead to an increase in the expression of MMP1, 3, 9, and 12 in dermis fibroblasts. Therefore, the balance of MMP/TIMP is disrupted and the level of destruction of collagen, fibronectin, laminin-332 and other ECM components increases. These changes lead to a decrease in skin elasticity, dryness and dehydration, and the appearance of wrinkles [96].

7. Conclusion

Exosomes are nanovesicles that are produced from almost all mammalian body cells and many plant sources. They are present everywhere in the body, such as fluids (amniotic, milk, saliva, etc.) and interstitial fluids, and they can cross the blood-brain barrier. They carry different types of compounds such as DNA, RNA, miRNA, different lipids, proteins, and large amounts of several types of growth factors such as PDGF, VEGF, and even different cytokines such as anti-inflammatory cytokines IL10, TGF, etc. Therefore, exosomes have properties of angiogenesis, repair and modulation, regulation of the immune system, and anti-inflammatory effects [97]. Several studies have shown that exosomes can be a suitable treatment option for regenerative medicine and cosmetics. Recently, it has been proven that the plasma EVs of young mice increase the half-life of old mice and slow down the aging process through exosomal nicotinamide phosphoribosyl transferase (eNAMPT) [98]. Another study showed that exosomes from young mice can be transferred to the tissues of old mice and inhibit the expression of aging-related molecules such as mTOR, p16, and telomerase-related genes such as Men1, M11a, Tep1, Terf2, Tert, and

Tnks in old mice [99]. Another report showed that serum Evs from young mice attenuate inflammation in old mice with a relative rejuvenation of old T-cell immunotolerance. The injection of hucMSC-exo into aged mice treated with 2H2O and D-galactose inhibits the aging process in HqC 2 cardiomyocytes through the expression of the MALAT1 gene [100]. It is important to mention here that despite all the potential therapeutic properties of exosomes in skin regeneration, there is still a need for more research and studies to determine the best method of extracting and purifying exosomes, the appropriate dose for treatment, the best source of exosomes, and the modifications required for maximum efficiency.

Ethics approval statement

This study was approved by the ethical committee of Tehran University of Medical Sciences.

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Declaration of competing interest

None.

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