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Aplicação de Exossomas em Cosméticos para Regeneração e Rejuvenescimento Cutâneo

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Ananda Riede Ferreira

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Este Trabalho de Conclusão de Curso foi julgado adequado para obtenção do título de Bacharela em Farmácia e aprovado em sua forma final pelo Curso de Graduação em Farmácia

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RESUMO

O envelhecimento da pele é um fenômeno biológico inevitável. Os sinais aparecem principalmente nas áreas fotoexpostas e as pessoas estão cada vez mais atentas ao autocuidado. Sendo assim, o interesse no desenvolvimento de terapias inovadoras para o tratamento cutâneo têm aumentado. Recentemente, os exossomas (exos) ganharam grande destaque na área médica e, apesar da escassez de dados, algumas empresas já fornecem produtos cosméticos contendo exossomas entre os ingredientes. Existem poucos ensaios clínicos envolvendo sua aplicação para regeneração e rejuvenescimento da pele, mas os resultados de estudos in vitro e in vivo foram positivos. Eles demonstraram, por exemplo, que os exossomas promovem angiogênese, aumento da proliferação e migração de células da pele, aumento de proteínas da matriz extracelular (MEC) e, consequentemente, melhoram a aparência da pele, favorecem a cicatrização de feridas e reduzem a formação de cicatrizes. Considerando os avanços sobre o potencial de aplicação dos exossomas na regeneração e rejuvenescimento da pele, este artigo visa realizar um levantamento bibliográfico sobre o estado atual de seu uso em cosméticos, incluindo estudos, ensaios clínicos, benefícios, limitações e produtos encontrados no mercado.

Palavras-chave: Exossomos; Rejuvenescimento cutâneo; Regeneração cutânea.

ABSTRACT

Skin aging is an inevitable biological phenomenon. The signs appear mainly in the photo exposed areas and people are increasingly attentive to self-care, so, there has been heightened interest in the development of innovative therapeutic approaches for these cases. Recently, exosomes (exos) have become a major focus in the medical field and despite the lack of data, some companies already offer exosome-based interventions. There are not many clinical trials on its application for skin regeneration and rejuvenation, but the results of in vitro and in vivo studies have been positive. They demonstrated, for example, that exosomes promote angiogenesis, increased proliferation and migration of skin cells, increased extracellular matrix (ECM) proteins and, consequently, favor wound closure and reduced scar formation. Considering the advances on the potential application of exosomes in the regeneration and rejuvenation of the skin, this review aims to carry out a bibliographical survey on the current status of its use in cosmetics, including studies, clinical trials, benefits, limitations and products found on the market.

Keywords: Exosomes. Skin rejuvenation. Skin regeneration.

SUMÁRIO

1 INTRODUÇÃO

A pele é considerada o maior órgão e barreira do corpo humano, com aproximadamente $2m^2$. Ele cobre toda a superfície do corpo e desempenha um papel importante na termorregulação, vigilância imunológica e produção de vitamina D. Além disso, devido às suas propriedades de barreira, protege os tecidos e órgãos internos do meio externo, ela evita a perda de água e eletrólitos, controla a penetração de agentes químicos, a entrada de microorganismos e protege da radiação ultravioleta (UV) (KHAVKIN; ELLIS, 2011; ZHAO et al., 2020).

Anatomicamente, é dividida em três camadas, a epiderme, a derme e a hipoderme. A epiderme é a camada mais superficial, é constituída por queratinócitos que formam o epitélio escamoso estratificado queratinizado, e subdivide-se em estrato basal, estrato espinhoso, estrato granuloso, estrato lúcido e estrato córneo. Sendo que em alguns locais onde a pele é mais fina, não se verifica a presença do estrato lúcido. As células do estrato basal multiplicam-se continuamente e, à medida que se aproximam da superfície, diferenciam-se, tornam-se achatadas e começam a produzir e acumular queratina. Vários outros tipos de células também são encontrados na epiderme, além dos queratinócitos, tais como melanócitos e as células de Langerhans. Como a epiderme não possui vasos sanguíneos, nutrientes e oxigênio chegam até ela por difusão passiva, a partir dos vasos da derme (CESTARI, 2018; RAJESH; WISE; HIBMA, 2019). A derme é um tecido de sustentação da epiderme, seus principais componentes incluem colágeno, fibras elásticas, proteoglicanos, vasos sanguíneos, nervos, folículos pilosos, glândulas sudoríparas e sebáceas e abundante matriz celular. A derme é composta por duas regiões compostas por duas regiões: região papilar mais superficial, localizada logo abaixo das papilas dérmicas e fixada por tecido conjuntivo frouxo, e a região reticular, mais profunda e fixada por tecido conjuntivo denso irregular. Por fim, a camada mais profunda, a hipoderme, é envolta por células-tronco mesenquimais, tecido conjuntivo e adipócitos, que são células armazenadoras de gordura, o que faz com que essa camada atue como isolante térmico, amortecedor e reserva energética (RAJESH; WISE; HIBMA, 2019; VOLPATO, FREITAS, STORPIRTIS, 2009).

A Matriz Extracelular (MEC) é essencial para a morfologia e funções da pele e é constituída por um complexo de numerosas proteínas e polissacarídeos

formando uma organização em rede (FULOP; KHALIL; LARBI, 2012; JUNQUEIRA; CARNEIRO, 2000). O colágeno é uma das principais proteínas da MEC, compreendendo cerca de 77% em peso da pele humana livre de gordura. Trata-se de uma proteína fibrosa responsável pela proteção mecânica, elasticidade, firmeza, minimização de rugas e prevenção da desidratação. Outras proteínas presentes na MEC incluem a fibrina, fibronectina, vitronectina e elastina. A elastina, fornece força, elasticidade e ajuda na reparação dos tecidos, enquanto a fibrina, fibronectina e vitronectina são mediadores chave na homeostasia e migração celular na cicatrização de feridas. Glicoproteínas como lamininas, presentes na membrana basal, e integrinas, as quais agem como receptores de membranas, também são proteínas estruturais que facilitam a adesão e migração celular (BYRON; HUMPHRIES, 2013, TRACY; MINASIAN; CATERSON, 2016; UDOMPATAIKUL; SRIPIROJ; PALUNGWACHIRA, 2009).

O envelhecimento da pele é um fenômeno biológico inevitável e pode ser resultado da diminuição da função celular como consequência do processo normal de envelhecimento ou devido à exposição a fatores externos nocivos. Fatores intrínsecos e extrínsecos atuam sinergicamente para induzir alterações na pele, que se manifestam clinicamente como queimaduras, eritema, hiperpigmentação, telangiectasias, pele seca, rugas profundas, perda do tônus natural ou câncer de pele (MESA-ARANGO; FLOREZ-MUNOZ; SANCLEMENTE, 2017).

O envelhecimento cutâneo intrínseco ou cronológico é aquele decorrente da passagem do tempo, determinado principalmente por fatores genéticos, estado hormonal e reações metabólicas, como o estresse oxidativo. (LIMA, 2019). O estresse oxidativo ocorre quando há um desequilíbrio entre a produção e a remoção de espécies reativas de oxigênio (EROs). As EROs são moléculas instáveis com número ímpar de elétrons que, em busca do elétron de que necessitam, reagem com outras moléculas, o que leva a uma reação em cadeia que causa a destruição celular, pois a célula antes estável, ao ter seu elétron retirado, torna-se outra radicais livres (VANZIN; CAMARGO, 2008; STEINER; ADDOR, 2014).

Especificamente, o dano oxidativo às proteínas tem sido considerado central para as mudanças nos processos celulares e é alimentado pela geração excessiva de EROs da auto-oxidação da glicose. A glicação é a reação espontânea realizada pela associação de açúcares redutores livres com grupos amino livres de proteínas e lipídios, formando produtos finais de glicação avançada (AGEs, do inglês

advanced glycation end-products). Como resultado, a glicação afeta o suporte do tecido da pele, pois danifica as fibras de colágeno e elastina, e a oxidação prejudica o metabolismo e a função das células epiteliais (LIMA, 2019).

Além do envelhecimento natural, fatores externos como poluição, exposição solar, tabagismo, má alimentação, poucas horas de sono e estresse podem estar relacionados a produção de espécies reativas de oxigênio (ROS) e envelhecimento cutâneo (MESA-ARANGO; FLOREZ-MUNOZ; SANCLEMENTE, 2017). A radiação ultravioleta do sol ou de fontes artificiais tem um efeito deletério sobre as funções da pele e sobrevida dos queratinócitos, um processo conhecido como fotoenvelhecimento. Adicionalmente, a luz visível e a radiação infravermelha também mostraram levar ao dano cutâneo (LIEBEL et al., 2012).

Como consequência do processo de envelhecimento intrínseco e extrínseco, a pele sofre alterações fisiológicas e perde inevitavelmente as suas características estruturais e funcionais (TODOROVA; MANDINOVA, 2020). O envelhecimento da pele diminui a proliferação de fibroblastos dérmicos humanos, a síntese de colágeno e acelera a degradação da matriz extracelular através das metaloproteinases da matriz (MMPs, do inglês *matrix metalloproteínases*). A renovação celular, a matriz extracelular e a vascularização são reduzidas e as junções dermo-epidérmicas ficam mais fracas. Isso leva à desorganização, fragmentação e redução das fibras colágenas e afeta a barreira cutânea, as propriedades elásticas e mecânicas da pele e a sua reatividade vascular (ALDAG; NOGUEIRA TEIXEIRA; LEVENTHAL, 2016; RORTEAU et al., 2020). Além disso, o tecido adiposo da hipoderme se atrofia por mecanismos de senescência, lipólise e redistribuição visceral. Esses fenômenos, juntamente com a atrofia de massa muscular levam à flacidez, pois causam um afinamento da pele e um enfraquecimento de seu suporte adipo-muscular (BELLU et al., 2021).

Sinais de envelhecimento cutâneo aparecem principalmente nas áreas fotoexpostas e levam muitas pessoas a procurarem alternativas que melhorem o aspecto da pele. Os tratamentos tópicos convencionais para combater o envelhecimento cutâneo envolvem o uso de antioxidantes como os polifenóis e as vitaminas C, B3 e E, que melhoram a elasticidade e reduzem o eritema e problemas de pigmentação, e da Vitamina A (ou retinol) e seus derivados (retinaldeido e tretinoína) que estimulam a síntese de colágeno e de fibras elásticas e reduzem a síntese de metaloproteinases (MMPs) (BOISMAL et al., 2020; MASAKI, 2010;

RATTANAWIWATPONG et al., 2020). Como tratamento sistêmico podem ser administrados por via oral a coenzima Q10 e antioxidantes como vitamina C e E, que neutralizam as espécies reativas de oxigênio e assim, também reduzem a síntese de MMPs (CZAJKA et al., 2018).

A pele também está sujeita a sofrer agressões que causam alterações na sua integridade como, por exemplo, as lesões ou feridas cutâneas, que podem levar à incapacidade funcional. As feridas cutâneas podem ocorrer devido a traumas, queimaduras ou úlceras diabéticas (BLAKYTNY; JUDE, 2006). É um tipo de lesão dos tecidos moles e sua cicatrização envolve múltiplos processos, incluindo hemostasia, inflamação, proliferação e remodelação (GAO et al., 2019; RODRIGUEZ-MENOCAL et al., 2012). Esses processos são prejudicados pelo envelhecimento, pois o envelhecimento afeta a diferenciação, migração, proliferação e apoptose das células da pele que são essenciais na cicatrização (LEWIS et al., 2014).

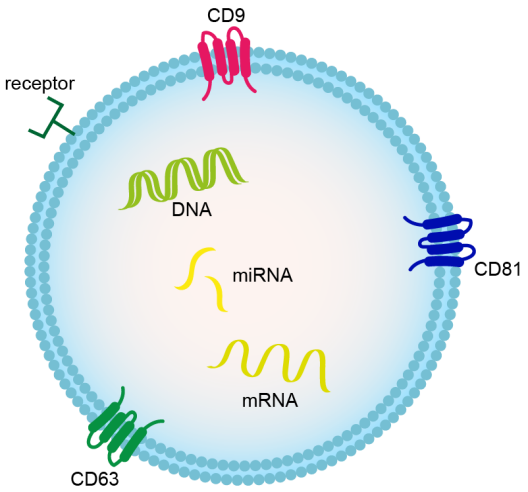
A proliferação e reepitelização das células da pele são importantes para a regeneração da pele (AN et al., 2021). O processo começa na camada basal e tem como objetivo substituir as células epidérmicas por células mais jovens. Na cicatrização de feridas, as principais células envolvidas na reepitelização e construção do tecido de granulação são os queratinócitos, células endoteliais e fibroblastos (BELVEDERE et al., 2020).

Os métodos convencionais de tratamento para cicatrização de feridas podem causar cicatrizes atróficas e anormalidades pigmentares e incluem enxerto de pele, transplante de retalho de pele e terapia a laser. Outro método inclui o uso de *scaffolds* bioativos, mas eles são caros e inadequados para feridas em grandes escalas (TURNER; BADYLAK, 2015; REZA VAGHARDOOST et al., 2018). Existe também a opção de aplicação local de fatores de crescimento específicos e terapia celular, porém, os fatores de crescimento são facilmente degradados nos fluidos corporais, e a dosagem não é facilmente controlada no local da ferida (BERNUZZI et al., 2014; MAREK KUCHARZEWSKI et al., 2019).

O desenvolvimento de produtos dermocosméticos contendo exossomas para o cuidado da pele tem recebido especial interesse nos últimos anos, sendo atualmente encontrados em cremes, séruns e máscaras com uma variedade de benefícios terapêuticos e anti-envelhecimento (THAKUR et al., 2023). Exossomas são vesículas constituídas de fosfolipídeos de tamanho nanométrico (30 a 200 nm)

secretados por células eucarióticas como fibroblastos, macrófagos e células-tronco mesenquimais e podem ser encontrados em vários fluidos biológicos, incluindo saliva, esperma, plasma, urina e leite materno. Estas estruturas são originadas de corpos multivesiculares contendo vesículas intraluminais, as quais são liberadas para o meio extracelular pela via endolisossomal (LÄSSER et al., 2011; SHEN et al., 2021; SULLIVAN et al., 2005). Os exossomas carregam várias biomoléculas como proteínas, ácidos nucléicos e lipídios e estão envolvidos em vários processos biológicos, incluindo a comunicação célula-célula, reparação tecidual e modulação do sistema imune. Na pele, essa comunicação é essencial para manter as funções celulares e a homeostase tecidual (BORGES; REIS; SCHOR, 2013; THAKUR et al., 2023, XIONG et al., 2021). Ao serem capturados pela célula receptora, os exossomas conseguem reprogramá-la, pois transportam proteínas, fatores de crescimento, lipídios, RNA bioativos, que podem alterar o fenótipo e a função da célula (BANG; THUM, 2012). O mecanismo pelo qual eles são capturados pode variar, eles possuem proteínas de membrana como CD9, CD63 e CD81 que possuem afinidade por ligantes nas membranas das células receptoras, o que permite que sejam direcionados para um tecido ou microambiente específico. A captura também pode ocorrer pela fusão direta do exossomo com a membrana da célula receptora, seguida da transferência do conteúdo do exossomo, como mRNAs, miRNAs, proteínas e moléculas sinalizadoras, ou também pode ocorrer por endocitose (MATHIVANAN; SIMPSON, 2009). A estrutura e composição dos exossomos pode ser melhor compreendida através da representação da figura 2.

Figura 2 – Representação da Estrutura e Composição dos Exossomas



Fonte: elaborado pelo autor

Exossomos endógenos são essenciais para o desenvolvimento fisiológico e patológico da pele (XIONG et al., 2021) e participam de mecanismos moleculares complexos de doenças inflamatórias crônicas, servindo como potenciais biomarcadores para o diagnóstico e tratamento de doenças de pele (YANG et al.; 2021). Alguns estudos observaram que os exossomos exógenos são opções terapêuticas em estética e medicina regenerativa, principalmente na prevenção e redução de cicatrizes, rejuvenescimento da pele, regulação da pigmentação e crescimento capilar. (YANG et al.; 2021). Eles podem melhorar a função dos queratinócitos e fibroblastos, aumentar a camada de gordura e aumentar a síntese de colágeno e elastina (XIONG et al., 2021).

Considerando o exposto acima, este trabalho teve como realizar um levantamento bibliográfico sobre a aplicação dos exossomas em cosméticos para regeneração e rejuvenescimento cutâneo, incluindo os mecanismos envolvidos nos efeitos anti-envelhecimento e de regeneração cutânea, quando aplicados topicamente. Este Trabalho de Conclusão de Curso foi escrito na forma de artigo para ser publicado na revista *International Journal of Cosmetic Science*.

2 OBJETIVOS

2.1 OBJETIVO GERAL

Realizar levantamento bibliográfico sobre a aplicação dos exossomas em cosméticos para regeneração e rejuvenescimento cutâneo.

2.2 OBJETIVOS ESPECÍFICOS

a) Descrever os mecanismos envolvidos no envelhecimento cutâneo
b) Descrever os avanços referentes aos benefícios do uso dos exossomas para regeneração cutânea e combate ao envelhecimento cutâneo.
c) Levantar quais produtos atualmente comercializados que contém exossomas em sua composição;
d) Identificar quais os resultados já observados com o uso de exossomas.

3 METODOLOGIA

Neste trabalho foi realizada uma revisão sobre o potencial emprego de exossomas na regeneração e rejuvenescimento cutâneo, usando as bases de dados informatizadas do Portal da Capes e Google Acadêmico. Para refinamento da busca no Portal da Capes e Google Acadêmico foram empregadas as seguintes palavras chaves: “exosomes”, “skin care”, “skin aging”, “marketed”, “clinical trial”, "cosmetics" intercalados com o operador booleano AND. Não foram incluídas citações. O período da busca foi de 2013 a 2023. A partir da leitura e análises dos resumos, foram selecionadas as publicações mais relevantes para o trabalho seguindo os critérios de inclusão. Após essa pré-seleção, os trabalhos que se encaixaram no tema da revisão foram lidos na íntegra, e foi feita a extração de dados. Estes dados foram compilados na forma de um artigo científico a ser submetido, que será apresentado a seguir.

4 RESULTADOS E DISCUSSÃO

Os resultados e discussão deste trabalho foram compilados no artigo Potential Application of Exosomes in Skin Anti-aging and Regenerative Dermocosmetics.

Potential Application of Exosomes in Skin Anti-aging and Regenerative Dermocosmetics

Ananda Riede Ferreira[1]*, Elenara Maria Teixeira Lemos Senna [2]*

Abstract

Skin aging is an inevitable biological phenomenon and in addition to the signs appearing mainly in the photo exposed areas, skin aging also affects skin regeneration. People are increasingly attentive to self-care and there has been an increase in the number of elderly people in the world, so, there has been heightened interest in the development of innovative therapeutic approaches for these case. Recently, exosomes (exos) have become a major focus in the medicinal field and studies on their application for skin regeneration and rejuvenation have started to be done. The results were positive, demonstrating, for example, that exosomes promote angiogenesis, increased proliferation and migration of skin cells, increased extracellular matrix (ECM) proteins and, consequently, favored wound closure and reduced scar formation. Considering the advances on the potential application of exosomes in skin regeneration and rejuvenation, this review aims to carry out a bibliographical survey on the current state of its use in cosmetics, including studies, clinical trials, benefits, limitations and products found on the market.

Keyword: Exosomes. Skin rejuvenation. Skin regeneration.

Introduction

The skin is considered the largest organ of the human body, with approximately 2m^2. It covers the entire body surface and plays an important role in thermoregulation, immune surveillance, and vitamin D production. Furthermore, due to its barrier properties, it protects internal tissues and organs from the external environment and thus prevents the loss of water and electrolytes, controls the penetration of chemical agents and the entry of microorganisms, and protects from ultraviolet radiation [1][2].

Anatomically, the skin is divided into the epidermis, the dermis, and the hypodermis (Figure 1). The epidermis is the skin's most superficial layer,

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predominantly constituted by keratinocytes, forming the keratinized stratified squamous epithelium. The epidermis is subdivided into stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. But in some places, where the skin is thinner, there is no stratum lucidum. Cells in the stratum basale continuously multiply and, as they approach the surface, differentiate, become flattened, and begin to produce and accumulate keratin [3]. In addition to the keratinocytes, melanocytes, and Langerhans cells are also found in the epidermis [4]. The dermis is the second layer of the skin, and it is constituted by highly vascularized and innervated connective tissue whose primary function is to provide support and nutrition to the epidermis. The main components of the dermis include collagen, elastic fibers, proteoglycans, blood vessels, nerves, hair follicles, sweat and sebaceous glands, and an abundant cellular matrix. Finally, the deepest layer, hypodermis, is encompassed by mesenchymal stem cells, connective tissue, and adipocytes, which are cells that store fat, which makes this layer act as a thermal insulator, shock absorber, and energy reserve [3][5].

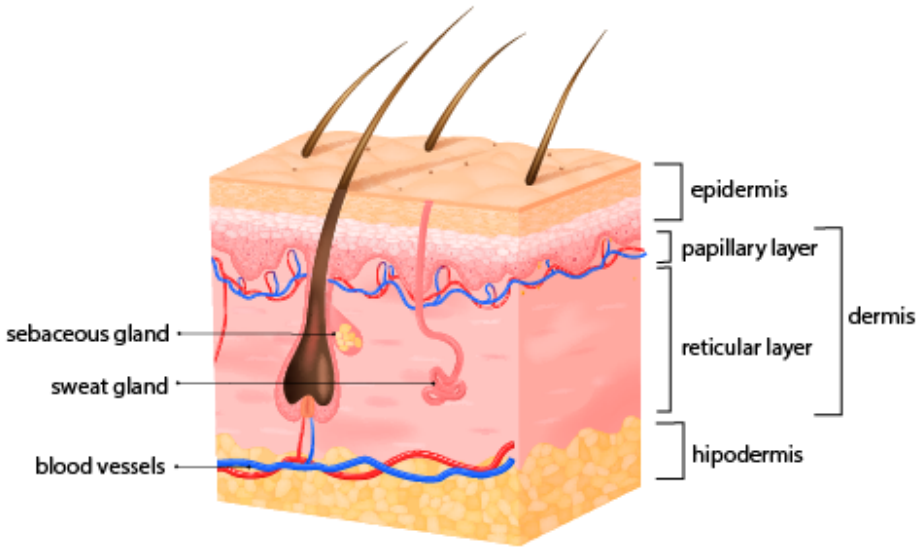

Fig. 1 Representation of the skin structure

Extracellular Matrix (ECM) is essential for skin morphology and functions [6]. It comprises a complex of numerous proteins and polysaccharides forming a network-like organization [7][8]. Collagen is one of the main proteins of the ECM, comprising about 77% by weight of fat-free human skin. It is a fibrous protein responsible for mechanical protection, elasticity, firmness, minimization of wrinkles,

and prevention of dehydration. Other proteins present in the ECM include fibrin, fibronectin, vitronectin, and elastin. Elastin provides strength and elasticity and aids tissue repair, while fibrin, fibronectin, and vitronectin are key mediators of homeostasis and cell migration in wound healing. The laminins in the basement membrane, and integrins, which act as membrane receptors, are also structural glycoproteins facilitating cell adhesion and migration [9][10][11].

Skin Aging

Skin aging is an inevitable biological phenomenon resulting from decreased cellular function due to the normal aging process or exposure to harmful external factors. Intrinsic and extrinsic factors act synergistically to induce changes in the skin, which clinically manifest as burns, erythema, hyperpigmentation, telangiectasias, dry skin, deep wrinkles, loss of natural tone, or skin cancer [12]. Intrinsic or chronological skin aging is mainly determined by genetic factors, hormonal status, and metabolic reactions. Specifically, oxidative damage has been considered central to changes in cellular processes and is fueled by the generation of excessive ROS from glucose autoxidation. Glycation is the spontaneous reaction caused by the association of free reducing sugars with free amino groups of proteins and lipids, forming advanced glycation end products (AGEs). As a result, glycation affects skin tissue support as it damages collagen and elastin fibers, and oxidation impairs epithelial cell metabolism and function [13][14]. In addition to natural aging, external factors such as pollution, sun exposure, smoking, poor diet, few hours of sleep, and stress may be related to the production of reactive oxygen species (ROS) and skin aging [12][15]. Ultraviolet radiation from the sun or artificial sources has a deleterious effect on skin function and keratinocyte survival, a process known as photoaging. Additionally, visible light and infrared radiation have also been shown to lead to skin damage [16].

Due to the intrinsic and extrinsic aging process, the skin undergoes physiological changes and inevitably loses its structural and functional characteristics [15]. Skin aging decreases the proliferation of human dermal fibroblasts (HDFs) and collagen synthesis and accelerates the degradation of the extracellular matrix through matrix metalloproteinase (MMPs) [17]. Cell renewal, extracellular matrix, and vascularity are reduced, and the dermal-epidermal junctions weaken, leading to the disorganization, fragmentation, and reduction of collagen fibers, which in turn, affects

the skin barrier, the elastic and mechanical properties of the skin, and its vascular reactivity [18][19]. Consequently, the appearance of wrinkles, changes in pigmentation, and loss of vigor and luminosity occur. An increase in flaccidity is also observed as the adipose tissue of the hypodermis atrophies by mechanisms of senescence, lipolysis, and visceral redistribution. These phenomena, together with the atrophy of the muscular mass, cause a thinning of the skin and a weakening of its adipose and muscular tissue support [20].

Signs of skin aging appear mainly in photo-exposed areas and lead many people to search for alternatives that improve the appearance of the skin [21]. Conventional topical treatments to combat skin aging involve the use of antioxidants such as polyphenols and vitamins C, B3, and E, which improve elasticity and reduce erythema and pigmentation problems, and Vitamin A and its derivatives, retinaldehyde, and tretinoin that stimulate the synthesis of collagen and elastic fibers and reduce the synthesis of metalloproteinases (MMPs) [22][23][24]. As a systemic treatment, coenzyme Q10 and antioxidants such as vitamin C and E can be administered orally, neutralizing reactive oxygen species and thus also reducing the synthesis of MMPs [25].

The skin is also subject to aggressions that cause changes in its integrity and can lead to functional disability. Cutaneous wounds are a type of soft tissue injury that can occur from trauma, burns, or diabetic ulcers [26]. Its healing involves multiple processes, including hemostasis, inflammation, proliferation, and remodeling, which are hampered by aging since it affects differentiation, migration, proliferation, and apoptosis of skin cells essential in healing [27-29].

Proliferation and re-epithelialization of skin cells are important for skin regeneration [30]. The process begins in the basal layer and aims to replace epidermal cells with younger cells. In wound healing, the main cells involved in the re-epithelialization and construction of granulation tissue are keratinocytes, endothelial cells, and fibroblasts [31].

Conventional wound healing treatment carries a risk of the development of atrophic scars and abnormal pigmentations and includes skin grafting, skin flap transplantation, and laser therapy on large scales. In addition, engineered bioactive scaffolds can be used for skin regeneration, but they are expensive and inadequate for application in large wound areas [32][33]. There is also the option of local application of specific growth factors and cell therapy. However, growth factors are

quickly degraded in body fluids, and the dosage is not easily controlled at the wound site [34][35].

The development of dermo-cosmetic products containing exosomes for skin care has received special interest in recent years [36]. Exosomes are nanometric vesicles made up of phospholipids (30 to 200 nm) secreted by eukaryotic cells such as fibroblasts, macrophages, and mesenchymal stem cells. They can be found in various biological fluids, including saliva, sperm, plasma, urine, and breast milk. These structures originate from multivesicular bodies containing intraluminal vesicles, which are released into the extracellular environment by the endo-lysosomal pathway [37-39]. Exosomes carry various biomolecules such as proteins, nucleic acids, and lipids and are involved in several biological processes, including cell-cell communication, tissue repair, and immune system modulation. In the skin, this communication is essential to maintain cellular functions and tissue homeostasis [36][40][41]. The structure and composition of exosomes can be better understood through the representation of Figure 2.

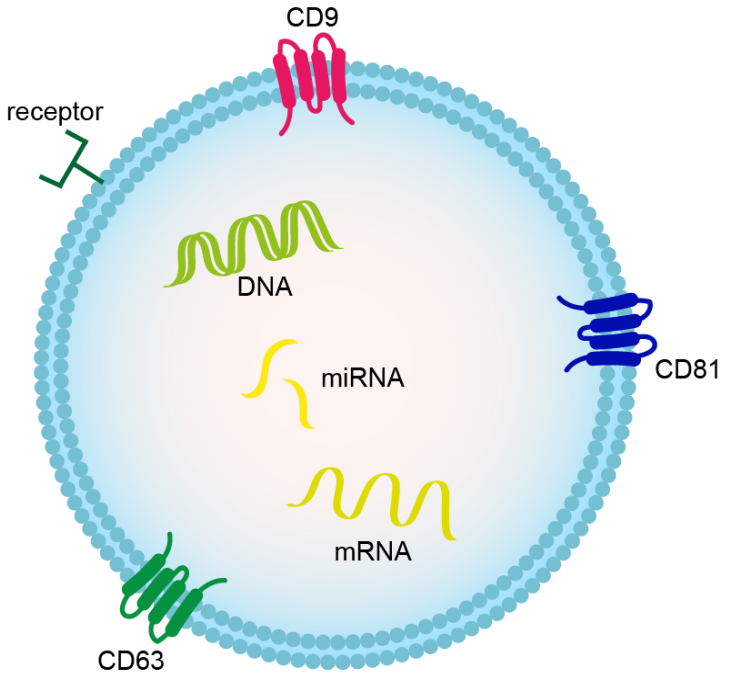

Fig. 2 Representation of the Structure and Composition of Exosomes

Endogenous exosomes are essential for the physiological and pathological development of the skin and participate in complex molecular mechanisms of chronic

inflammatory diseases, serving as potential biomarkers for the diagnosis and treatment of skin diseases [41][42].

Some studies have demonstrated that exogenous exosomes are therapeutic options in aesthetics and regenerative medicine, especially in the prevention and reduction of scars, skin rejuvenation, regulation of pigmentation, and hair growth [42]. They can improve the function of keratinocytes and fibroblasts, increase the fat layer and increase collagen and elastin synthesis [41]. (Figure 3). In the next topic, we describe the application of exosomes in cosmetics for skin regeneration and rejuvenation, including the mechanisms involved in the anti-aging and skin regeneration effects when applied topically.

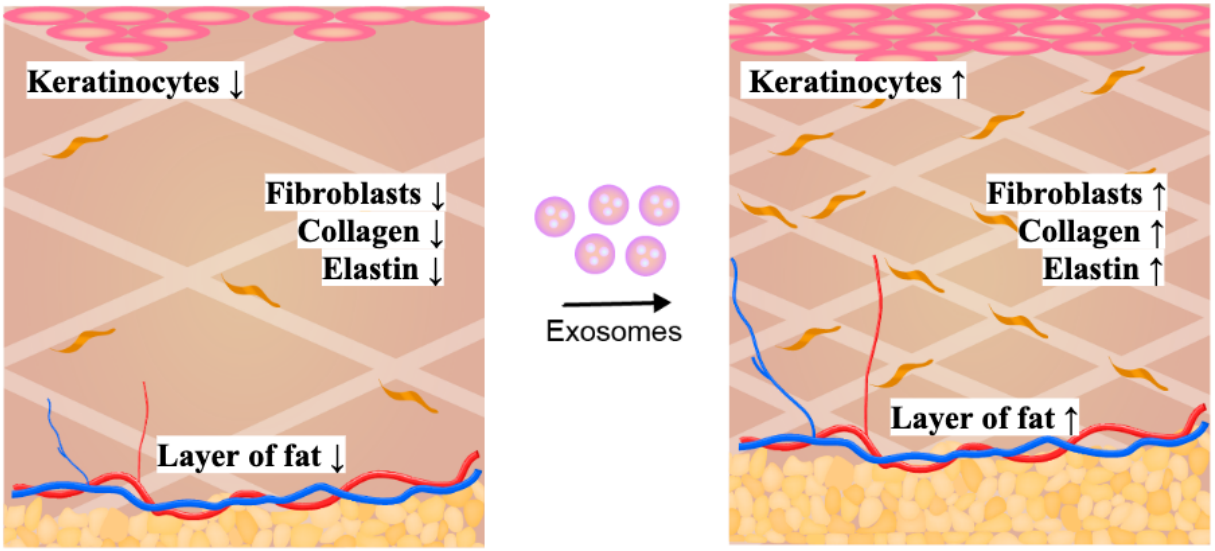

Fig. 3 Effect of exosomes on the skin function improvement. Exosomes have the potential to enhance the function of keratinocytes and fibroblasts, boost the synthesis of collagen and elastin, and augment dermal fat, thereby effectively promoting the regenerative and restorative capabilities to combat skin aging.

Exosomes in dermocosmetic products

In the last century, we have verified the population aging with the reduction of fertility and life expectancy increase. The increasing median age in the population has demanded the development of new skincare products that reduce the signs of aging and improve the appearance of the skin [43][44]. In this sense, the use of exosomes has gained attention and seems to be a great strategy for promoting skin regeneration, repair, and rejuvenation. Its interest is based on its property to carry

high concentrations of bioactive molecules and its ability to penetrate the skin and interact with skin cells [42][45]. Endogenous exosomes are involved in cell-cell communication. When captured by the receiving cell, exosomes manage to reprogram it as they transport proteins, growth factors, lipids, and bioactive RNA, which can alter the phenotype and function of the cell [46]. The mechanism by which they are captured can vary, they have membrane proteins such as CD9, CD63, and CD81 that have an affinity for ligands on the membranes of recipient cells, which allows them to be targeted to a specific tissue or microenvironment. Capture can also occur by direct fusion of the exosome with the recipient cell membrane followed by the transfer of exosome contents such as mRNAs, miRNAs, proteins, and signaling molecules, or it can also occur by endocytosis [47]. (Figure 4).

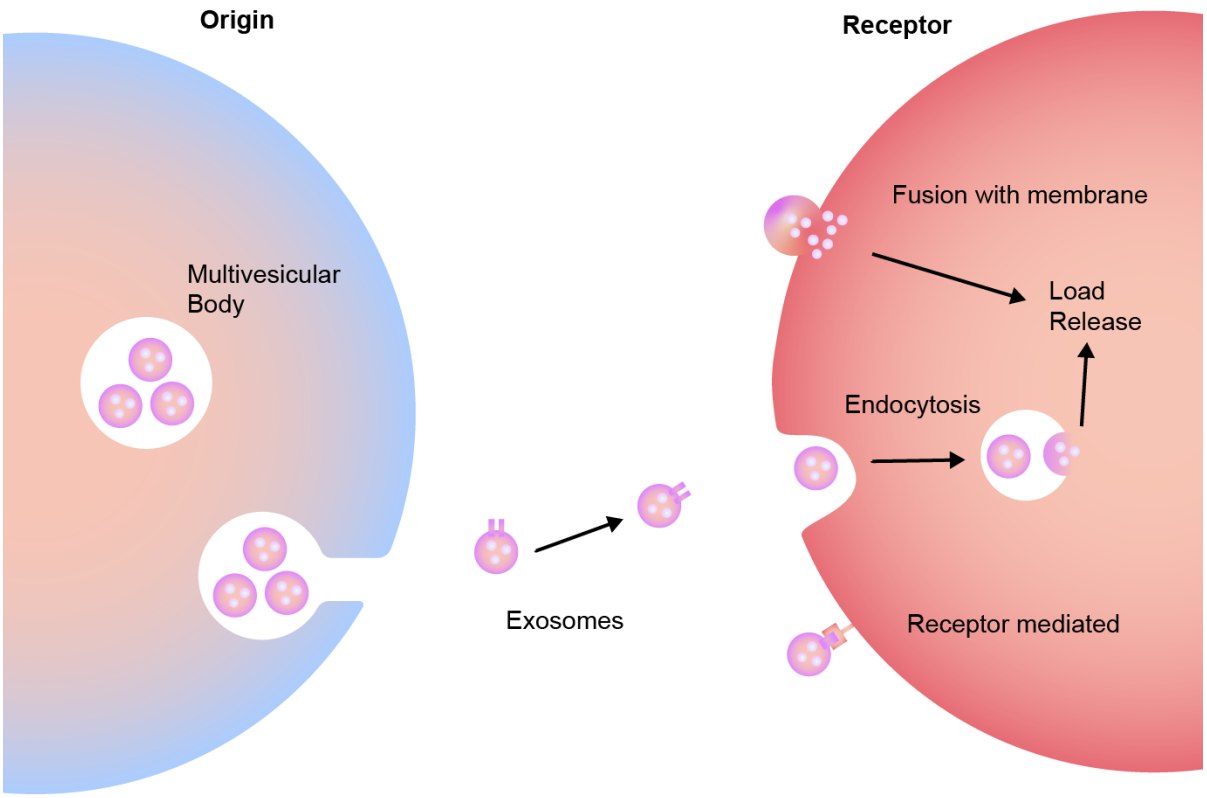

Fig. 4 Mechanism of Interaction of Extracellular Vesicles and Target Cell

In recent years, using exogenous exosomes to treat skin damage has been extensively explored. The key benefits of exosomes are high stability, non-immune rejection, and direct stimulation of target cells. For obtaining high-quality exosomes for commercial use, isolation techniques are applied, and the choice of the cell from which the exosomes will be obtained is essential since the composition will determine

its function, direction, and charge protection. For example, using plants has the advantages of a safety profile, lower cost, and the possibility of large-scale production [48]. The high mass production of high-quality exosomes is also crucial. 2D and 3D cell culture manufacturing processes have been employed to achieve this (49). In addition, isolation techniques such as differential centrifugation, size exclusion chromatography, field flow fractionation, microfluidic filtration, polymer precipitation, or immunoaffinity capture should be applied to obtain high-quality exosomes [50]. The methods employed in the exosome characterization include super-resolution microscopy, fluorescence microscopy, transmission electron microscopy, cryogenic electron microscopy, nanoparticle tracking analysis, tunable resistive pulse sensing, dynamic light scattering, single-particle interferometric reflectance and high-resolution flow cytometry [51]. Standard methods for detecting exosomes-labeled proteins include Western blotting, ELISA, mass spectrometry nanoplasmonic Exo sensor, integrated magnetic-electrochemical Exo sensor, and ExoScreen [30].

Exosomes in Skin Regeneration and Rejuvenation

In the early 2000s, mesenchymal stem cell (MSC) therapy emerged as an alternative treatment for several disorders. MSCs are multipotent, easy to access and cultivate, and can be isolated from different tissues such as skin, placenta, and bone marrow. However, recent studies have shown that mesenchymal stem cells' therapeutic efficacy occurs through exosome release [42]. Exosomes have proteins, lipids, and other molecules that help promote healing, hydration, and skin protection, as they increase collagen production, reduce inflammation, protect the skin from environmental stressors, and may enhance the effectiveness of other active ingredients, such as hyaluronic acid, peptides and antioxidants [52]. Furthermore, their dosage can be easily controlled, stable, easily stored, and evade the immune response, with no risk of hypersensitivity reactions [30]. Taking into account its recent discovery and its numerous advantages, several preclinical studies have been carried out with exosomes, and it has been documented that they can induce skin regeneration and rejuvenation. Some of them are described in Table I.

Table I Preclinical studies enclosing the application of exosomes in skin regeneration and rejuvenation.

Type of study	Exosome source	Type of exosome	Experimental model	Results	Refs
In vitro	Umbilical cord	HucMSC exos	Dermal fibroblasts	Increased HDFs proliferation and migration; Increased collagen I, fibronectin and elastin gene expression; Increased protein levels of procollagen type 1 C-peptide; Decreased metalloproteinase-1 expression.	[53]
In vitro	Umbilical cord	HucMSC exos	HaCat and dermal fibroblasts	Inhibited heat stress-induced apoptosis in HaCAT; Promoted proliferation of HaCAT and DFL; Increased b-catenin and its downstream genes expression in DFL; Increased phosphorylated form of AKT in HaCAT and DFL.	[54]
In vitro	Umbilical cord	HucMSC exos	HaCaT	Increased cell proliferation and migration; Suppressed apoptosis.	[55]
In vitro	Umbilical cord	HucMSC exos	HUVECs	Induced proliferation, migration, and angiogenesis.	[56]
In vitro	Umbilical cord	AGWJ exos	Dermal fibroblasts	Increased cell viability and migration.	[57]
In vitro	Adipose tissue	ADSC exos	HaCaT	Increased cell migration and β-catenin expression; Inhibited apoptosis; Inhibited the increment of Bax and the reduction of Bcl-2.	[58]
In vitro	Adipose tissue	ADSC exos	HUVEC	Promoted the proliferation and migration; Promoted angiogenesis.	[59]
In vitro	Adipose tissue	ADSC exos	HUVEC and dermal fibroblasts	Increased proliferation and migration of HDFs; Promoted proliferation and tube formation of HUVEC.	[60]
In vitro	Bone Marrow	Macrophage exos	Mouse fibroblasts	Reprogrammed classically activated M1 macrophages into M2 macrophages.	[61]
In vitro	Bone Marrow	DFO exos	HUVEC	Increased phosphorylated form of AKT and proliferation cell; Upregulated the migration of HUVEC.	[62]
In vitro	Skin	HUVECs exos	HaCaT and dermal fibroblasts	Promoted the proliferation and migration of HaCaT and hFBs.	[2]
In vitro	Umbilical cord	HUVECs exos	Dermal fibroblasts	Increased cell proliferation and collagen type-1 synthesis.	[63]
In vitro	Skin	FDMSCs exos	Dermal fibroblasts	Increased coll I and III, elastin, fibronectin mRNA production and the expression of active Notch1, Jagged 1, and Hes 1; Promoted proliferation and migration.	[64]
In vitro	Culture of Human amniotic epithelial cells	hAECs exos	Dermal fibroblasts	Promoted proliferation and migration.	[65]

Table I (Continued).

Type of study	Exosome source	Type of exosome	Experimental model	Results	Refs
In vitro	Saliva	Saliva exos	HUVEC	Induced proliferation, migration, and angiogenesis.	[66]
In vitro	Blood serum	BS exos	HaCAT and fibroblasts	Induced fibroblasts proliferation and migration; Induced HaCAT migration and Inhibited heat stress-induced apoptosis in HaCAT.	[67]
In vitro	*Beta vulgaris* extract	BEX	HUVEC and Fibroblasts	Induced angiogenesis in HUVEC; Enhanced the expression of the hyaluronan synthase enzyme 2 in fibroblasts.	[68]
Ex vivo	Umbilical cord	HucMSC exos	Human abdominal skin	Increased collagen I and elastin expression; Decreased matrix metalloproteinase-1 expression.	[53]
In vivo	Umbilical Cord	HucMSC exos	Rat	Increased levels of CK19 and PCNA.	[54]
In vivo	Umbilical Cord	HucMSC exos	Mice	Increased wound closure, re-epithelialization, and neovascularization; Reduced scar formation.	[55]
In vivo	Umbilical Cord	HucMSC exos	Rat	Accelerated skin wound healing and angiogenesis; increased expression of CD31 and Angiopoietin-2 protein.	[56]
In vivo	Umbilical Cord	AGWJ exos	Mice	Increased collagen deposition.	[57]
In vivo	Adipose tissue	ADSC exos	Rat	Reduced infiltration of inflammatory mediators; Increased bulky and neatly organized collagen deposition; More newly formed vessel; Increased miR-126-3p and decreased PIK3R2 expression.	[59]
In vivo	Bone marrow	DFO exos	Rat	Longer newly formed epidermis and dermis; Reduced scar formation; Increased amounts of wavy collagen fibers and density of blood vessels.	[62]
In vivo	Skin	FDMSCs exos	Mice	Promoted proliferation, ECM deposition and re-epithelization.	[64]
In vivo	Menstrual blood	MenSC exos	Mice	Increased wound closure, microvessel density, coll I synthesis; Reduced the granulation tissue cellularity.	[70]
In vivo	Culture of Human amniotic epithelial cells	hAECs exos	Rat	Increased wound closure; Reduced scar formation.	[65]

Exosome abbreviations: ADSC exos: adipose-derived stem cell exosome; AGWJ exos: exosome from acellular gelatinous Wharton's jelly; BEX: exosomes from Beta vulgaris extract; DFO exos: exosomes originated from bone marrow-derived MSCs (BMSCs) preconditioned by deferoxamine; EPC exos: exosomes from endothelial progenitor cells; FDMSC exos: exosome from fetal dermal mesenchymal stem cells; hAEC exos: exosomes from human amniotic epithelial cells; HUVECs exos: exosome derived from Human umbilical vein endothelial cells; HucMSC: exosome from umbilical cord blood-derived mesenchymal stem cells; MenSC exos: exosome from menstrual blood-derived mesenchymal stem cells.
Cell culture abbreviations: DFL: Dermal fibroblast; HaCaT: Human immortalized keratinocytes; HDF: Human dermal fibroblasts; HUVEC: Human umbilical vein endothelial cells.

As indicated in Table I, in vitro studies carried out in cell culture have demonstrated that exosomes increase collagen, fibronectin, and elastin gene expression and decrease the MMP-1 expression [56][64][65]. As previously mentioned, collagen, fibronectin, and elastin are responsible for the ECM structure, and MMP-1 breaks down type I, II, and III interstitial collagens (10). In addition, the culture cell studies have demonstrated an increase in the proliferation and migration of HaCAT, HDFs, and HUVECs and an increase in angiogenesis in HUVECs [2, 55-58, 60, 62, 63, 65-68]. The fibroblasts are the primary cell type to synthesize collagen and elastic fibers of the ECM, cytokines, and growth factors [71]. The keratinocytes accelerate the re-epithelialization process. The endothelial cells play a crucial role in controlling vascular homeostasis and angiogenesis, providing a blood supply for wound healing, and facilitating the transport of nutrients [72]. Furthermore, an increase of b-catenin in DFL and HaCAT was demonstrated. B-catenin plays an important role in adhesion protein and is involved in signaling pathways, mainly those related to Wnt. The Wnt/beta-catenin pathway is implicated in the modulation of cell migration in epithelial healing processes [54][58]. In DFL, HaCAT and HUVEC, an increase in the phosphorylated form of AKT was observed and the activation of the AKT pathway is associated with the reduction of heat stress apoptosis [54][62][54]. Studies with adipose-derived stem cell exosome (ADSC exos) detected the inhibition of apoptosis induced by H_2O_2, increased proapoptotic protein Bax, and decreased antiapoptotic protein Bcl-2 expression [58].

As well, the reprogramming of classically activated M1 macrophages into M2 macrophages, increased levels of procollagen type 1 C-peptide protein, and an increase in expression of active Notch1, Jagged 1 and Hes 1 was also observed in fibroblasts [53][61][64]. M1 and M2 macrophages are proinflammatory and anti-inflammatory cells, so switching from M1 to M2 macrophages accelerates wound healing [61]. Notch is important in the maintenance, development, regulation of

homeostasis, and decisions about the fate of stem cells [73]. Jagged 1 activates Notch signaling regulating the maturation of the human epidermis, and Hes 1 is a transcriptional regulator of Notch signaling [74].

The roles of human umbilical cord blood-derived mesenchymal stem cells-derived exosomes (HUC-MSCs exos) in cutaneous collagen synthesis and human skin permeation were investigated by Kim et al. Results showed that Exo-Green labeled HUC-MSCs exos approached the outermost layer of the epidermis after 3 hours and gradually approached the epidermis after 18 hours. Moreover, increased Collagen I and Elastin expressions were found after 3 days of treatment on human skin, evidencing the potential application of HUC-MSCs exos in skin rejuvenation [53].

Mass spectrometry analysis carried out by Bahtyar et al. revealed that exosomes of Wharton's jelly umbilical cord contain a large amount of alpha-2-macroglobulin, a protein that mimics the effect of acellular gelatinous Wharton's jelly exosomes (AGWJ exos) on wound healing. The authors also evidenced that AGWJ exosomes enhance cell viability and cell migration in vitro and enhance skin wound healing in mice's punch biopsy wound model [57].

Xu et al. demonstrated that endothelial progenitor cell-derived exosomes (EPC exos) significantly enhance skin wound healing in control and diabetic mice. High-throughput sequencing showed that miRNA-221-3p was highly expressed in EPC exos, increasing protein expression levels of the angiogenesis-related factors VEGF, CD31, and cell proliferation marker Ki67 [69]. The effects of exosomes from menstrual blood-derived mesenchymal stem cells (MenSC exos) on the wound-healing process in diabetic mice were investigated by Dalifardouei et al. The authors found that MenSC exos reduce inflammation through induced polarization of M1-M2 macrophages, enhance neoangiogenesis through vascular endothelial growth factor A upregulation, and accelerate re-epithelialization through NF-κB p65 subunit upregulation and activation of the NF-κB signaling pathway. Also, the authors suggest that MenSC exos reduce scar formation by decreasing the Col1:Col3 ratio [70].

Regarding exosome administration, a study involving local and intravenous injections showed that the intravenous route was superior in wound healing to local injection [75]. Another study demonstrated that the topical absorption of exosomes could be improved by performing microdermabrasion, which causes exfoliation of the

stratum corneum and creates an inflammatory environment [76]. Using exosomes through simple dermal infusion after a topical nitric oxide generator serum application, exfoliation with sea salt, and LED treatment was also investigated to optimize exosome function [76]. Also, exosomes can be introduced in regenerative therapies, mixed with hydrogels, or used to coat scaffolds using fibrin gels [77].

A survey on ClinicalTrials.gov by the term "exosomes" returned 158 results. Among these, those involving rejuvenation, skin regeneration, and wound healing were selected [78]. So, only five clinical trials remained, and all of them are relatively recent. They are summarized in Table II.

Table II Clinical trials enclosing the application of exosomes in skin regeneration and rejuvenation.

Study Title	Status	Conditions	Interventions	Phase	NCT Number	Study Start	Locations
Mesenchymal Stem Cells Derived Exosomes in Skin Rejuvenation	Recruiting	Anti Aging	Combination Product: exosome injection	Phase 1 Phase 2	NCT05813379	Feb. 1, 2022	Iran, Islamic Republic of
Pilot Study of Human Adipose Tissue Derived Exosomes Promoting Wound Healing	Not yet recruiting	Wounds and Injuries	Procedure: Adipose tissue derived exosomes	Not Applicable	NCT05475418	Aug. 5, 2022	-
Evaluation of Personalized Nutritional Intervention on Wound Healing of Cutaneous Ulcers in Diabetics	Not yet recruiting	Foot, Diabetic	Dietary Supplement: Personalized Nutritional Intervention	Not Applicable	NCT05243368	May 1, 2023	Córdoba, Andalucía, Spain
Therapeutic Potential of Stem Cell Conditioned Medium on Chronic Ulcer Wounds	Completed	Chronic Ulcer	Drug: Conditioned Media	Phase 1	NCT04134676	June 1, 2019	Tangerang, Banten, Indonesia
Effect of Plasma Derived Exosomes on Cutaneous Wound Healing	Unknown	Ulcer	Other: plasma-derived exosomes	Early Phase 1	NCT02565264	Sept. 2015	Kumamoto, Japan

With their ability to help improve skin tone, texture, and appearance, early evidence suggests that applying exosomes could transform the approach to skincare and be the big news in the cosmetics market [36]. A survey on Google Patents by the terms "exosomes AND skin rejuvenation" returned 746 results, and by the terms "exosomes AND skin regeneration" came up 14752 results and a survey on Google of what is already on the market found the results described in Table III. The skincare benefits of using exosomes are assigned to their properties of increasing collagen synthesis, improving elasticity, and reducing wrinkles, resulting in effective anti-aging therapy. Besides, exosomes can contribute to skin repair of damage caused by the sun and promote skin hydration, improving skin texture. Exosomes' cargos, such as cytokines, nucleic acids, proteins, and other bioactive compounds, help to protect the skin from environmental stressors and reduce the appearance of dark spots and other discoloration [36]. Considering the properties mentioned above, the development of exosome-containing dermo-cosmetic products still has much to be explored.

Table III Cosmetics with exosomes on the market.

Brand	Cosmetic Form	Source	Skin care benefits	Country of manufacture	Refs
Dermaline (PDX^2)	Skin booster	Asian centella	Regenerates and soothes skin, provides whitening, moisturizing, brightening and firming	Korea	[79]
Neogen	Cream	Asian centella	Revitalizes, hydrates and firms	Korea	[80]
Tonymoly	Ampoule mask	Asian centella	Provides elasticity	Malaysia	[81]
St. Lawrence	Serum (needle application)	Umbilical cord	Rejuvenates	China	[82]
Infinivive	Serum	Umbilical cord	Hydrates and reduces the appearance of fine lines and wrinkles	United States	[83]
Dermaceuticals	Serum	Umbilical cord	Repair, regenerates and reduces signs of aging skin	United States	[84]
Exoreju	Powder	Cord blood	Revitalizes, hydrates, firms and illuminates	-	[85]
Hitokan	Serum	Adipose tissue	Hydrates and rejuvenates	Japan	[86]
Eelhoe	Suspension water light	-	Hydrates, firms and illuminates	Malaysia	[87]
ASCEplus	Gel mask	Damask rose stem cell	Regenerates, illuminates and is anti-inflammatory	Korea	[88]
DDS	Booster gel	MSC	-	Japan	[89]

Conclusions

As presented, exosomes are promising for application in cosmetics in the search for skin regeneration and rejuvenation, as reinforced by the positive results found in both in vitro and in vivo studies. In addition to their therapeutic potential, they maintain high long-term stability, have high targeting capacity, and promote low immunogenicity when they are autogenous exosomes. However, more research, improved protocols, and standardized procedures are needed to well establish the use of exosomes in dermocosmetic products.

Abbreviations: ADSC: adipose-derived stem cells; AGEs: Advanced glycation end products; AGWJ: acellular gelat- inous Wharton's jelly; AT: Adipose tissue; BEX: exosomes from Beta vulgaris extract; BM: Bone marrow; BS: blood serum; Coll: Collagen; DFL: Dermal fibroblast; DFO exos: exosomes originated from bone marrow-derived MSCs (BMSCs) preconditioned by deferoxamine; ECs: Endothelial cells; ECM: Extracellular matrix; EVs: extracellular vesicles; Exos: Exossomes; HaCaT: Human immortalized keratinocytes; hAECs: Human amniotic epithelial cells; HDFs: Human dermal fibroblasts; HucMSC: Umbilical cord blood-derived mesenchymal stem cells; HUVEC: Human umbilical vein endothelial cells; MenSCs: Menstrual blood‐derived mesenchymal stem cells; MMPs: matrix metalloproteinase; MSCs: Mesenchymal stem/stromal cells; ROS: Reactive oxygen species; UC: Umbilical cord; UN: United Nations.

Conflicts of Interest: The authors declare that there are no conflicts of interests.

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5 CONSIDERAÇÕES FINAIS

A proposta deste trabalho de conclusão de curso consistiu em realizar um levantamento bibliográfico sobre a aplicação de exossomas em cosméticos para regeneração e rejuvenescimento cutâneo. O estudo foi bem sucedido e os objetivos foram alcançados. Embora seja um tema relativamente novo, foi possível constatar a existência de uma quantidade significativa de artigos que abordam o assunto, principalmente em relação à regeneração.

Os estudos pré-clínicos analisados evidenciaram que os exossomas possuem um grande potencial de emprego nessa área, os resultados revelaram que essas estruturas favorecem por exemplo, a síntese de células e proteínas essenciais para a regeneração e rejuvenescimento cutâneo. No entanto, o levantamento bibliográfico também demonstrou que a quantidade de ensaios clínicos realizados até o momento ainda é limitada. Isso destaca a necessidade de mais pesquisas clínicas para validar os resultados promissores observados nas pesquisas pré-clínicas. Apesar dessa limitação, é interessante observar que produtos contendo exossomas já estão sendo comercializados. Essa rápida incorporação no mercado pode ser atribuída à demanda crescente por soluções inovadoras no campo dos cosméticos e à busca por alternativas mais eficazes. No entanto, é fundamental que esses produtos sejam rigorosamente testados e regulamentados para garantir a segurança e eficácia para as pessoas.

Sendo assim, espera-se que futuras pesquisas continuem a explorar essa área, buscando desenvolver produtos cosméticos cada vez mais seguros e eficazes, a fim de atender às demandas dos consumidores por soluções inovadoras de cuidados com a pele.

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