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The Targeted Regulation of Extracellular Vesicles by Natural Active Ingredients for Skin Repair

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Abstract. Extracellular vesicles (EVs), as natural nano EVs, not only have high biocompatibility and strong penetration, but also can achieve targeted delivery, making them an ideal natural drug carrier. Natural active substances have advantages such as multi-target, anti-inflammatory and antioxidant properties, and have good application prospects in the field of skin repair. In recent years, studies have shown that the combination of EVs and natural active ingredients can form significant synergistic effects. This article analyzes the limitations and challenges of a single EV mechanism, summarizes the roles and deficiencies of different natural active ingredients, points out the problems of insufficient standardized preparation in current research, and concludes that natural active ingredients complement EVs when combined. The combined application of natural active ingredients and EVs provides new research directions and theoretical basis for safe and efficient skin repair and natural drug delivery strategies. This provides a reference for targeted regulation of EVs by natural active ingredients and a theoretical basis for subsequent research on the combination therapy of natural drugs and EVs.

Keywords: Extracellular vesicles; Natural active ingredients; Mesenchymal stem cell; Skin repair; Flavonoids; Polysaccharides; Saponins; Polyphenols.

1. Introduction

The skin is the largest protective barrier in the human body, playing an important role in resisting foreign substances and maintaining body stability. The human skin is mainly divided into three layers from the outside to the inside, namely the epidermis, dermis, and subcutaneous tissue. They each perform their respective duties and play an important role in an orderly manner, but they are susceptible to various factors such as acute trauma, ultraviolet radiation, and environmental pollutants, which can lead to core injury problems such as wound healing, photoaging, scar hyperplasia, and environmental pollutant induced damage.

Adult skin has two main mechanisms for repairing wounds: regeneration and repair. Skin regeneration refers to the self repairing function of the skin, replacing damaged or old cells with new ones without leaving obvious scars; Skin repair refers to the use of targeted care or medical methods to help damaged skin recover. During the repair process, scars are formed due to the inability of tissues to produce normal cells[1]. The normal process of skin repair is dynamic and highly continuous, consisting of four stages: hemostasis, inflammation, proliferation, and remodeling. Epithelial stem cells, fibroblasts, keratinocytes, and immune cells play important roles in it. At present, there are also some problems with stem cells in wound healing. Adult stem cells are easily damaged again by inflammatory immune cells when they are within the attack range of strong inflammation [2,3]. Extracellular vesicles (EVs), as a type of EV with a diameter of 30-200 nm, mediate intercellular communication by carrying different biomolecules such as proteins, lipids, and nucleic acids (RNA and DNA). Therefore, EVs play an important role in tissue repair and drug delivery [1,4]. However, the low targeted delivery efficiency and insufficient specificity of single exosome therapy in vivo, as well as the inconsistent therapeutic effects caused by the heterogeneity of exosome sources, limit its clinical application [1,2,4].

At present, some medicinal plants have clear active ingredients, such as carotenoids, flavonoids, green tea extract Epigallocatechin gallate(EGCG), Astragalus polysaccharides (APS), wolfberry

polysaccharides, ginsenosides, etc. Medicinal plant derived exosomes have attracted much attention in skin repair due to their wide sources, minimal side effects, and multi-target regulation [5]. However, most natural active ingredients have poor water solubility, low transdermal efficiency, insufficient stability, are easily affected by the environment, and tend to overlook the synergistic effects of multi-component interactions in medicinal plants [5]. Therefore, this review aims to combine the single repair mechanism of EVs with the skin repair effect of natural drugs. EVs, as efficient transport carriers, can enhance the stability and targeting of natural active substances[4]; And natural active substances can further enhance the anti-inflammatory and antioxidant abilities of EVs, and the two combine and interact with each other. Therefore, this review combines recent advances in research and focuses on the targeted regulation of EVs by natural active ingredients to achieve skin repair.

2. Overview of Exosomes and Skin Repair

2.1. Biological Characteristics and Functions of EVs

EVs are nanoscale vesicles actively secreted by cells, with a lipid bilayer structure that can effectively prevent the degradation of transported goods [6]. During the process of intracellular invagination and formation of small vesicles, they actively encapsulate bioactive substances such as proteins, lipids, and nucleic acids in the cytoplasm. Therefore, from the perspective of formation mechanism, EVs are naturally capable of encapsulation, and their generation process itself determines that they can serve as containers for drug loading. In addition, intercellular information exchange also relies on the help of EVs, which serve as carriers of intercellular communication, delivering mRNA, microRNAs (miRNAs), transcription factors, etc. to target cells, promoting wound healing [7]. Moreover, due to its stable transport in body fluids, high biocompatibility and stability, low immunogenicity, and ability to directly deliver drugs to cells, EVs are often regarded as effective carriers for drug delivery [4,6].

2.2. Research Progress of EVs from Different Sources in Skin Repair

EVs from different cell sources have varying regenerative potentials. Its unique properties and functions enable EVs to have diverse applications in different situations. Therefore, it is important to explore in depth how EVs from different sources can promote tissue recovery [8].

2.2.1. Mesenchymal stem cell (MSC) derived exosomes.

MSCs are a diverse class of adult pluripotent stem cells with the ability to self renew and produce exosomes with different functions. At present, the main research sources of EVs derived from MSCs include umbilical cord MSCs (UCMSCs), adipose derived MSCs (ADSCs), and bone marrow MSCs (BMSCs) [8].

In recent years, there has been an increasing amount of research on the therapeutic potential of human UCMSC derived exosomes (hUCMSC Exos). Because the collection of hUCMSCS has advantages such as non invasiveness and low immunogenicity, making it the most ideal source of EVs [8]. EVs derived from bone marrow MSCs have strong regenerative ability and can also promote angiogenesis, but the process of obtaining BMSCs is invasive and painful, which may reduce donor willingness and bring limitations [8]. EVs derived from adipose tissue MSCs play a crucial role in immune regulation, characterized by high blood lipid levels and anti fibrotic effects, with significant efficacy in treating keloids [8]. EVs derived from umbilical cord MSCs have outstanding performance in tissue injury repair. hUCMSC derived extracellular cells can significantly accelerate wound healing by reducing inflammation, stimulating angiogenesis, and promoting extracellular matrix formation, such as rapid recovery of the skin barrier at the injured site [7,9,10]. Despite their specific targeting abilities and involvement in different pathological states, there are still issues with the immunogenicity and safety of mammalian derived exosomes [11].

2.2.2. Plant-derived extracellular vesicles (PDEVs).

With the emergence of safety and scalability issues associated with the use of mammalian derived EVs, it has gradually been discovered that PDEVs can effectively circumvent these inherent limitations. Therefore, in recent years, EVs have received significant attention in related research [11]. PDEVs are nanoscale vesicles extracted from plant EVs that are similar to mammalian derived EVs. So far, research on EVs has mainly focused on mammals, and PDEV like nanovesicles are still in their early stages [12]. PDEVs contain lipids, proteins miRNA, Secondary metabolites and other substances have low immunogenicity and high stability, can transmit signals across species, and have anti-inflammatory effects. For example, EVs from scallions can alleviate inflammation of microglia [11]. In addition, PDEVs also have strong antioxidant properties. Nanovesicles that can be isolated from organic mixtures of fruits and vegetables have extremely strong antioxidant capacity, comparable to superoxide dismutase 1 (SOD1) [12]. Because PDEVs are safe, stable, widely available, and possess anti-inflammatory, antioxidant, and immune regulatory activities, they have broad prospects in skin wound repair, natural drug delivery, and other fields.

2.3. Limitations and Challenges of Single Exosome Therapy

At present, there is still a long way to go before EVs can be truly applied on a large scale in clinical practice. There is currently no unified industry standard for how to quickly and efficiently extract high-quality MSC EVs. Moreover, the content of MSC itself in the body is low, and even if it can be amplified in vitro, it is still not enough to make up for it. Moreover, EVs are influenced by factors such as the source and culture environment of MSCs, making it even more difficult to standardize [2]. The quality of PDEVs is unstable, with large batch differences, and their composition and yield are affected by planting methods, growth environments, and other factors. The number of PDEVs in organically grown apples is 100 times that of traditionally grown apples [12]. Moreover, the route of administration affects toxicity. Intravenous injection of PDEVs derived from tea/camellia can cause liver and kidney toxicity, but oral administration is not a problem [6]. PDEVs still suffer from poor targeting and are prone to accumulate in non target areas. For example, PDEVs injected intravenously are trapped in the lungs [12]. In addition, PDEVs also have problems such as short action time, rapid clearance in the body, difficult storage, and easy inactivation [12]. Overall, there are many challenges in a single exosome related therapy.

3. Research Progress on the Use of 3 Natural Active Ingredients for Skin Injury Repair

3.1. Flavonoids

Common flavonoid compounds include Myricetin (Myr), Quercetin, etc. Myricetin is commonly found in fruits and can promote wound healing. It has multiple biological activities such as antioxidant, anti allergic, anti-inflammatory, and immune regulation. However, its water solubility is extremely poor, resulting in low bioavailability. Currently, it needs to be combined with other compounds or biomaterials to enhance the solubility of Myr in water [13].

Quercetin is commonly found in the stems, leaves, flowers, skins, seeds, and fruits of plants. It mainly has anti-inflammatory and antioxidant functions, and can also enhance the body's immunity. Quercetin mainly exerts anti-inflammatory effects by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX), regulating the NF - κ B/peroxisome proliferator activated receptor C (PPAR - γ) pathway; It can also bind with collagen, enhance the synthesis of collagen in granulation tissue, and promote wound healing [14]. However, it still has the problem of poor water solubility, and although the current nano formulation technology can improve its permeability and stability to some extent, there is still a time limit [14].

3.2. Polysaccharides/Saponins

With air pollution, PM2.5 easily adheres to the skin and enters the keratinocytes (HaCaT cells), leading to skin inflammation, aging, and even skin cancer. Fortunately, researchers have demonstrated that Lycium Barbarum Polysaccharides (LBP) can protect skin cells and combat the damage caused by P M2.5 [15]. PM2.5 can cause a decrease in HaCaT cell viability, morphological damage, and significant apoptosis. So they treated the cells with LBP in advance and found that it could significantly reverse this phenomenon. Therefore, LBP has a clear protective effect against PM2.5 induced skin cell damage [15]. In addition, LBP also has antioxidant properties by inhibiting the endoplasmic reticulum stress apoptosis pathway, effectively clearing ROS (oxygen activity), and reducing wound oxidative stress damage [15].

APS is the main active ingredient of traditional Chinese medicine Huangqi, and the active ingredients that play a major role in wound healing are mostly polysaccharides and saponins. APS has anti-inflammatory and cell cycle regulating effects and can effectively improve microcirculation. In addition, APS gel can also accelerate the healing and skin regeneration of mouse back wounds [14]. The safety of Astragalus membranaceus extract (APS and astragaloside saponins) is relatively high, and there are no significant toxic side effects within the safe dose range for rats/dogs [14].

Ginseng is known as the king of herbs, and ginsenosides are the core active ingredient of ginseng. Ginsenoside Rb1 belongs to a class of saponin compounds, which are diverse compounds widely distributed in the plant kingdom [14]. Ginsenoside, one of which is Rb1, has the functions of accelerating wound epithelialization, promoting angiogenesis, and combating skin damage caused by Ultraviolet B (UVB) [14,15]. Ginsenoside has been used as a supplement since ancient times, and modern research has also proven its benefits for multiple systemic diseases in the body, which is sufficient to demonstrate its overall safety [14]. However, due to the numerous subtypes of ginsenosides, the activity of different subtypes varies greatly, sometimes exhibiting unexpected toxicity or side effects [15]. Therefore, more precise research is needed before clinical application to optimize usage and avoid potential risks.

3.3. Polyphenols

Table 1. The roles of EGCG and its wound dressings in the biophysiological events at different wound healing stages.

Wound Healing Stage	Role of EGCG and Its Wound Dressings
Hemostasis	Increasing hemadsorption
Inflammation	Limiting the infiltration of neutrophils
	Inhibiting the migration and adhesion of monocytes
Proliferation	Advancing re-epithelialization
	Accelerating angiogenesis
	Altering collagen synthesis
	Reducing ECM formation
Remodeling	No reference about the effect of EGCG on collagen remodeling, vascular maturation and regression

Plant polyphenols, as natural multifunctional active substances, are not only an economic alternative to existing drug treatments, but also have the effect of promoting skin repair and maintenance [16]. Curcumin is a polyphenolic compound extracted from turmeric, which has strong anti-inflammatory, antioxidant, and antibacterial effects. It promotes skin wound healing from multiple links by regulating key pathways such as TGF β 1 and ERK [14]. Therefore, curcumin is not only a safe and effective natural ingredient, but also a potential raw material for developing new wound healing preparations. EGCG is the core, most active, and highest content tea polyphenol in green tea. It is a classic antioxidant, anti-inflammatory, and antibacterial skin protectant. However, its oral bioavailability is extremely low, and direct injection can hardly promote wound healing, so using topical application (skin dressing) is the most ideal way [16]. Table 1 lists the roles of EGCG and its wound dressings in the biophysical events during wound healing [16].

Both cell experiments and animal models have confirmed that EGCG and its dressings can effectively promote skin wound healing. In addition, EGCG can significantly increase the level of HO-1 protein, which is associated with wound closure and neovascularization. Therefore, EGCG has the potential for scar treatment, but there is a lack of sufficient clinical experimental evidence [16].

3.4. Other Natural Active Ingredients

Table 2. Sources and functions of different natural active ingredients

Ingredient Name	Source	Primary Functions	Key Mechanisms / Advantages	Notes
Honey extract	Natural honey	Promote wound healing	Reduces wound healing time (by an average of 5.32 days); inhibits COX1/COX2 activity to reduce inflammation, edema and pain; promotes angiogenesis by inducing macrophages to release VEGF	May contain toxic components depending on the source; not considered completely safe
Comfrey extract	Leaves/roots of Symphytum officinale	Accelerate wound closure	Topical application significantly shortens healing time; 10% concentration formulation shows better efficacy than 1% in children	Associated with hepatotoxicity and carcinogenic potential; clinical use is limited
Chamomile extract	Flowers/leaves of Matricaria chamomilla	Anti-inflammatory, antioxidant, wound healing	Exerts anti-inflammatory effects via the COX-2 pathway; promotes re-epithelialization and collagen formation; compatible with hydrogels for wound dressings	Classified as a flavonoid; well-studied mechanism
Resina Draconis (Dragon's blood)	Red resin from Dracaena cochinchinensis	Promote healing, anti-infection	Shortens re-epithelialization time; significantly upregulates TGF-β1 and VEGF; forms a polyphenol protective layer to reduce inflammation	Also has antithrombotic, antioxidant and antiseptic properties

In addition to natural active ingredients such as flavonoids, polysaccharides/saponins, and polyphenols, there are also many other natural active ingredients in nature. This article selects and summarizes four different natural active ingredients based on the research of Liu et al. (Table 2) [14]. Therefore, the active ingredients of different medicinal plants have specific functions. By incorporating the active ingredients of medicinal plants into EVs derived from mesenchymal stem cells, the anti-inflammatory and antibacterial effects of medicinal plants can be combined with the tissue repair and healing promoting properties of stem cell EVs, which can significantly improve the therapeutic effect. However, due to the limited source of MSC EVs and the potential for immune rejection in allogeneic transplantation, this method also has significant limitations [5].

4. The Synergistic Effect of Natural Ingredients and Evs

Table 3. Comparison of loading of active ingredients in extracellular vesicles

Project	Passive Loading	Active Loading
Core principle	Active ingredients are co cultured with donor cells, and exosomes carrying active ingredients are naturally secreted by cells	Using manual methods to directly introduce active ingredients into extracellular vesicle vesicles
Technical method	Co-incubation of active ingredients with donor cells	Electroporation, Co- incubation, Freeze-thaw cycles, Sonication
Advantages	The operation is relatively gentle, which can better preserve the natural structure of extracellular vesicles	Significantly improve the stability and bioavailability of active ingredients, without being limited by donor cell types
Application value	Suitable for active ingredients that are easily taken up by cells and non-toxic to cells	Provided key technical support for the modern delivery of active ingredients from medicinal plants

The combination of natural active ingredients and EVs can break through the limitations of a single mechanism and enhance the comprehensive efficacy of skin injury repair. The two complement each other's strengths and weaknesses. EVs rely on their own vesicle structure to build a safe carrier

structure for natural active ingredients, avoiding the problems of easy loss and poor stability of small molecules. Natural active ingredients supplement the shortcomings of EVs in anti-inflammatory and antioxidant activities. The bidirectional interaction between the two forms an EV natural component co delivery system.

There are two types of EVs related to medicinal plants, one is directly isolated from medicinal plants, and the other is EVs loaded with plant active ingredients. This article summarizes the EV loading techniques based on the research of Zhao C et al. (Table 3) [5].

Human derived EVs carry a large amount of growth factors, functional miRNAs, and other repair core substances, which play an important role in keratinocyte proliferation and wound tissue regeneration [7]. By incorporating the active ingredients of medicinal plants into EVs derived from MSCs, the repair limit is higher, and it can simultaneously regulate oxidative stress and inflammatory pathways, minimizing scar formation and promoting skin repair [5]. However, there are still shortcomings due to its high preparation cost and potential safety hazards in immune recognition, making it more suitable for laboratory mechanism exploration and difficult to popularize.

5. Conclusion

This article first elaborates on the current research progress of different EVs, then reviews the research progress of using different natural active ingredients for skin injury repair, and finally analyzes the synergistic effect of natural ingredients and EVs. Intended to provide a new approach for developing safe and efficient natural medicine delivery strategies. However, current research still has limitations, such as the lack of unified standards for preparation processes and insufficient research on molecular mechanisms of action. In the future, it is necessary to further improve the extraction technology of EVs, optimize the method of combining EVs with natural active substances, establish standardized processes and quality control systems, and promote the transformation from laboratory research to clinical practice.

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