

Potential Application of Plant-Derived Extracellular Vesicles in Treatment of Burn Wounds

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Abstract: Burns are triggered by exposure of skin to heat sources, chemicals, electric currents, or radiation. Due to the cross-interaction of multiple factors, the healing mechanism of burns is complex. In recent years, plant-derived extracellular vesicles (P-EVs) have been found to possess characteristics such as anti-inflammatory, antioxidant, antibacterial, and promotion of angiogenic, owing to their rich content of proteins, nucleic acids, and secondary metabolites, which make P-EVs have great application prospects in the field of tissue regeneration. This article, based on the specificities of healing mechanisms of burn wounds compared to general wounds, systematically reviews the extraction techniques of P-EVs, their bioactive components, and the molecular mechanisms in repair of burn wounds. Moreover, P-EVs have certain advantages in biocompatibility and promoting cell proliferation for repair, providing innovative strategies for the treatment of burn wounds directly or as a complement for the existing therapeutics. However, their clinical application still faces challenges such as the lack of standardized extraction processes, unclear targeting mechanisms, and long-term safety assessment. Future research can combine multidisciplinary technologies to further optimize the extraction and targeting of P-EVs, promoting their translational application in regenerative medicine. This article aims to provide theoretical references for the basic research and clinical practice of P-EVs in repair of burn wounds and to envision their development prospects as a new treatment method for burn wounds.

Keywords: Burns, burn wounds healing, exosomes, plant-derived extracellular vesicles

Introduction

The skin, the largest organ in the human body, performs a wide range of vital functions.¹ It serves as a protective barrier, shielding the body from bacteria, viruses, and other harmful substances.¹ Beyond protection, the skin plays a key role in regulating body temperature and facilitates the perception of touch, temperature changes, and pain.¹ Burns, which are injuries to the tissue, can result from exposure to heat (flames, hot liquids, or heated objects), chemicals, electrical currents, or radiation. These injuries often lead to tissue necrosis and functional impairment, making burns a significant and challenging category of clinical trauma.² Among the various types of burns, thermal burns, which are caused by flames or wet sources and categorized according to the depth of tissue damage, are the most prevalent.³ Burn wounds healing is a complex physiological process that involves several stages, including inflammation, cell proliferation, neovascularization, extracellular matrix remodeling, and re-epithelialization.^{4,5} For optimal recovery, these processes must occur in precise coordination to restore the skin's functionality.^{6,7} Burns are a global public health problem, which causing approximately 180, 000 deaths annually, according to the estimation of WHO.⁸ Critically, more than two-thirds of these fatalities occur in low- and middle-income countries (LMICs), with the highest burden concentrated in the African and South-East Asian regions.⁸ Additionally, non-fatal



burns result in significant morbidity, including prolonged hospitalization, permanent disfigurement, and disability, which often lead to stigma and rejection.⁸ While direct medical costs vary by region, they universally impose substantial economic burdens.^{9,10} In South Africa, it is estimated that 26 million US dollars is spent each year on treating burns caused by kerosene (paraffin) stove accidents.⁸ Burn wounds healing, however, poses unique challenges. Patients often encounter complications, including insufficient autologous skin for grafts and the risk of immune rejection when using allografts. These barriers complicate the treatment process and contribute to the broader public health burden.^{11,12} Consequently, it is necessary to develop innovative and effective strategies to enhance the treatment of burn wounds.

For skin wounds, a variety of promising intervention strategies have been developed, including peptides and hydrogel.^{13–15} While bandages and gauze are effective in stopping bleeding, they are non-degradable, susceptible to infection, and incapable of maintaining the moist environment crucial for optimal healing.^{16,17} Hydrogels are commonly used in burn wounds care to absorb exudate and retain moisture. However, hydrogels lack targeted anti-inflammatory and antioxidant properties, which significantly limits their therapeutic potential.¹⁸ Peptides have the ability to fight bacteria and act as antioxidants, but they have poor cell penetration ability and are difficult to target diseased tissues.^{19–22}

These restrictions have prompted people to explore new treatment strategies. In this case, P-EVs have attracted attention. Exosomes are membranous vesicles composed of lipid membranes with a phospholipid bilayer structure, which play a vital role in both intercellular and interspecies communication.²³ Exosomes exhibit favorable characteristics for potential applications, persisting stably in various body fluids such as ascites, plasma, serum, urine, breast milk, and tears.²⁴ They also demonstrate high biocompatibility, low immunogenicity, low cytotoxicity, and a relatively long circulation half-life.²⁴ Researchers have found that P-EVs have a similar structure to exosomes.²⁵ P-EVs contain a variety of bioactive substances, including proteins, nucleic acids, and lipids.²⁶ These bioactive components can regulate key cellular processes of burn wounds healing such as proliferation, migration, differentiation, and angiogenesis.^{27–29} Furthermore, P-EVs can effectively deliver DNA and proteins, functional siRNAs, and various other therapeutic drugs to target cells without altering their biological activity.³⁰ Thus, P-EVs are expected to become complementary therapies for clinical treatment of burn wounds. For example, P-EVs derived from bitter melon were found to enhance vascular endothelial cell synthesis and promote the recovery of damaged cells, highlighting their considerable potential in burn wounds repair.³¹ Therefore, P-EVs have broad application prospects in management of burn wounds. This article reviews the potential application of P-EVs in healing of burn wounds and analyzes its mechanism of action. Additionally, the challenges and prospects of P-EVs in clinical applications were discussed, which aimed to bridge the gap between basic research and practical application of P-EVs.

Physiological Characteristics and Repair Mechanisms of Burn Wounds

Physiological Characteristics of Burn Wounds

Burns are severe traumatic injuries that can cause extensive bodily harm and often result in long-term consequences, such as functional impairments and changes in physical appearance.³² For patients, the prolonged treatment process is frequently accompanied by intense pain and significant psychological distress.³² For their families, the high cost of medical care and the demands of long-term recovery can pose substantial financial challenges.³² Additionally, the expenses associated with burn wounds treatment and rehabilitation place a considerable strain on the broader healthcare system.³² Therefore, effective management of initial tissue damage and timely interventions during the healing process are critical components of early burn wounds treatment.³³ Thermal injuries to the skin lead to a marked increase in vascular permeability, which is the primary cause of post-burn edema and hypovolemic shock.³⁴ This phenomenon is marked by a significant increase in vascular wall permeability, leading to the leakage of large volumes of plasma-like fluid, extensive exudation from the burn wounds, and fluid accumulation in both tissue interstitial spaces and potential third-spacing compartments.³⁴ Such fluid shifts affect not only the burn site but also surrounding uninjured tissues, causing pronounced edema.³⁴ In severe cases, generalized edema can give rise to life-threatening complications, including cerebral edema due to increased intracranial pressure, elevated abdominal pressure, and fascial compartment syndrome.³⁴ If left untreated, these conditions can lead to irreversible organ damage or prove fatal.³⁴

Clinical Heterogeneity of Burns

The clinical manifestations and pathophysiological responses of burns show significant heterogeneity, which is mainly attributed to the causes, the systemic reactions, and the long-term outcomes.² Different injury causes usually lead to different patterns of tissue damage. For instance, alkaline chemical injuries may cause liquefactive necrosis, while acidic burns may result in coagulative necrosis.^{2,35} Frostbite may involve cellular crystallization and ischemia-reperfusion injury.^{2,35} Severe burns can trigger a unique and complex systemic response, including a prolonged state of high metabolism lasting for several year and immune dysfunction which increases the patient's susceptibility to infections^{36,37} The intensity and duration of this response vary from patient to patient, and the effects of burns are long-lasting.² The recovery of patients will not only be involved in scar issues, but their mental health, quality of life, and the ability of return to work will also be continuously affected.^{38,39}

Based on the severity, burns can be classified into different degrees that are superficial thickness (first degree), superficial partial thickness (second degree), deep partial thickness (second degree), full thickness (third degree) and fourth degree.² The clinical characteristics and treatment methods vary according to the different degrees of burn (Table 1).² Grasping the complexities of these burn wounds is essential for creating effective treatment strategies and enhancing the healing process.³³ Targeted treatments should be carried out based on the actual clinical situation. The reason why first-degree and second-degree burn wounds can heal spontaneously lies in the fact that they retain the source of cells for epithelial regeneration.⁴⁰ These remaining epithelial cells form the basis for re-epithelialization and drive the wound to be repaired through the natural healing process.^{40,41} However, the healing dynamics of third-degree and fourth-degree full-thickness skin burn wounds have undergone fundamental changes.⁴⁰ Due to the thermal injury, the entire layer of dermis and all its epidermal appendages were damaged, and the wounds completely lost its endogenous epithelial regeneration ability.⁴⁰ The current gold standard treatment is early escharotomy and skin grafting, aiming to replace the necrotic tissue with autologous skin through transplantation, thereby achieving wound coverage and fundamentally altering the healing trajectory.^{40,42} Therefore, accurate evaluation of the depth of burn wounds involves determination of their inherent potential for healing essentially. This is of crucial importance for making the right decisions regarding treatment ranging from conservative therapy to surgical intervention.

Mechanisms of Burn Wounds Repair

General Mechanisms of Natural Wound Healing

The natural wound healing stage is the foundation for understanding the healing process of burn wounds.² Wound healing is a highly intricate repair process involving the precise coordination and integration of various biomolecules.⁴³ This process encompasses the regulation of cellular activity, the reconstruction of the vascular system, and the reorganization of tissue structure.⁴³ Together, these interdependent and closely interconnected mechanisms form a well-organized wound repair network, which is essential for ensuring complete and effective healing.⁴³ Wound healing phases include hemostasis, inflammation, proliferation, and remodeling of the extracellular matrix (ECM) (Figure 1).⁴⁴ Far from being

Table 1 The Clinical Characteristics and Therapeutic Methods of Different Degrees of Burns²

Depth Classification	Level of Tissue Damage	Clinical Characteristics	Therapeutic Methods
Superficial thickness (first degree)	Epidermis	Pain, no blistering, no scarring, and no surgery required.	Analgesia and self-healing.
Superficial partial thickness (second degree)	Epidermis and superficial dermis	More painful, blisters, and potential for scarring.	Debridement, dressings, and infection prevention.
Deep partial thickness (second degree)	Deep dermis	Pain alleviation, dryness, requiring surgical intervention, and forming more scars.	Surgical excision and grafting.
Full thickness (third degree)	Entire dermis	Demonstrating loss of sensation to light touch and pinprick, dryness, small areas will heal with substantial scar or contracture, large areas require skin grafting, and high risk of infection.	Mandatory surgical excision and grafting.
Fourth degree	Injury to deeper tissues (muscle and bone)	Leading to loss of the burned part, almost no pain, tendency to darken, and requiring surgical intervention.	Extensive debridement and complex reconstruction.

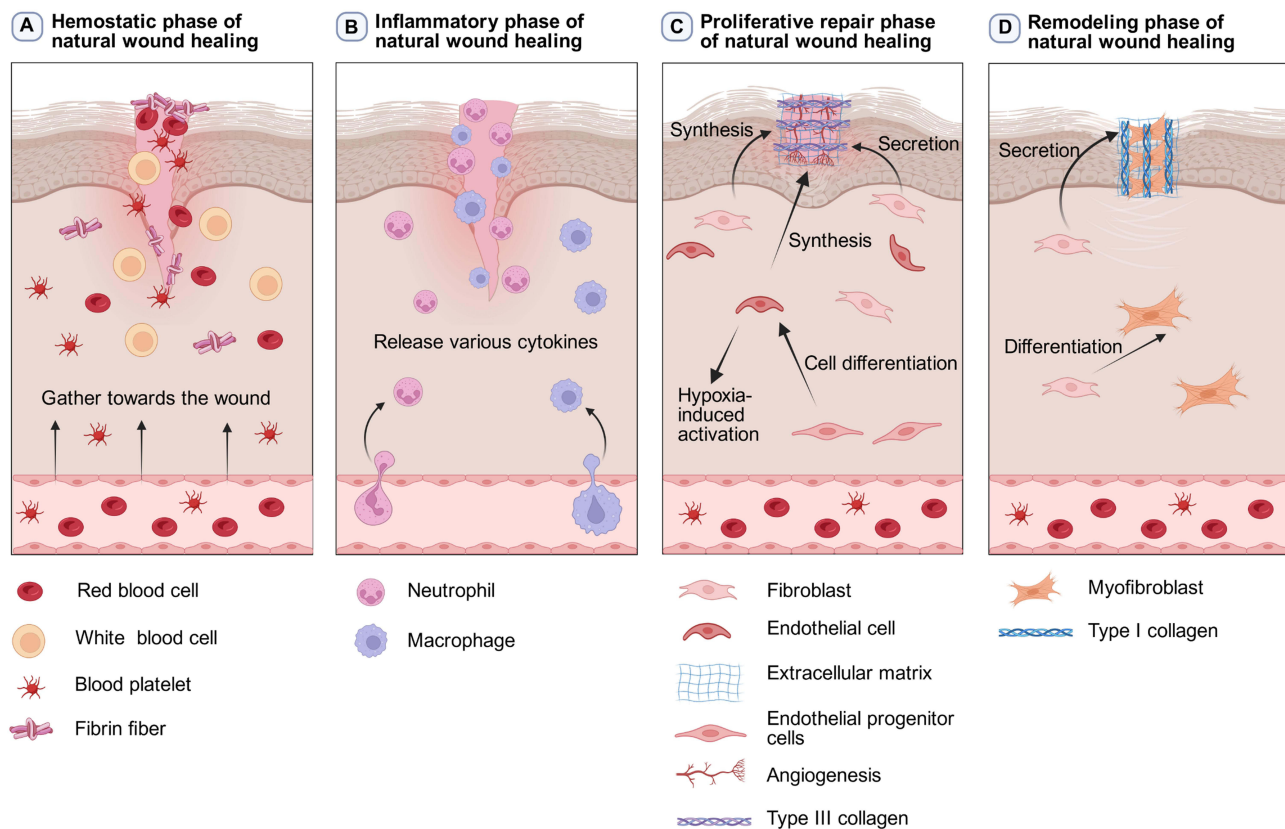


Figure 1 The general healing process of natural wound healing. Natural wound healing involves multiple stages, including hemostasis, inflammation, proliferation, and remodeling. **(A)** During the hemostasis period, platelets, red blood cells, white blood cells, and fibrin fibers among other blood components will gather at the injured area to form a blood clot, which will seal the wound and limit blood loss. **(B)** During the inflammatory period, neutrophils and macrophages gradually infiltrate the wound and release various cytokines. **(C)** During the proliferation and repair period, endothelial progenitor cells undergo cell differentiation to become vascular endothelial cells. These vascular endothelial cells will be activated in the hypoxic environment of burn wounds, thereby initiating angiogenesis. Activated fibroblasts and vascular synthetic cells secrete extracellular matrix and attach to the wound site. At this stage, the activated fibroblasts mainly secrete type III collagen, forming a temporary matrix. **(D)** During the remodeling period, fibroblasts differentiate into myofibroblasts which can promote contraction and closure of wounds, and the type III collagen will be remodeled into more the resilient type I collagen.

linear or independent, these stages are dynamic, continuous, and intricately linked, maintaining the integrity and progression of the wound repair process.^{45,46} Critical participants in this process include skin cells, immune cells, ECM components, cytokines, and chemokines, all of which play pivotal roles in modulating and orchestrating the intricate cascade of events.^{45,46}

The Special Pathological and Physiological Mechanisms of Burn Wounds Repair

Hemostatic Phase of Wound Healing

After a skin injury, the body swiftly activates hemostatic mechanisms to prevent further blood loss.⁴⁷ In the early stages, blood components such as platelets, red blood cells, white blood cells, and fibrin fibers accumulate at the injury site, forming a blood clot that seals the wound and minimizes blood loss.⁴⁷ Concurrently, platelets and damaged tissues release specific cytokines that guide fibrin to the wound surface, creating a cellular scaffold that supports immune cell activity and prepares them for the next phase of healing.⁴⁷ Both normal wounds and burn wounds exhibit vasoconstriction responses.⁴⁸ The early vasoconstriction in normal wounds is to achieve local hemostasis, but in severe burn wounds, the early vasoconstriction is part of the systemic stress response and shock, which can lead to reduced tissue perfusion.^{48,49}

Inflammatory Phase of Burn Wounds Healing

The inflammatory phase is a critical stage in wound healing, serving to prevent infection and prepare the tissue for subsequent repair.⁵⁰ Neutrophils act as the first responders during this phase, playing an essential role in eliminating debris and pathogens.⁵⁰ Beyond their antimicrobial functions, neutrophils release various cytokines and chemokines that

amplify the immune response by attracting additional immune cells to the wound site.⁵⁰ Their population peaks within 1 to 2 days after injury.⁵⁰ As neutrophil numbers diminish, macrophages begin to infiltrate the wound, with their activity peaking around day 5. By day 14, macrophage levels gradually decline and stabilize.⁵⁰ Macrophages release various growth factors and cytokines, including platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), fibroblast growth factor (FGF), and interleukin-6 (IL-6).^{51,52} They also produce pro-inflammatory mediators such as interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α), which are crucial for maintaining the inflammatory phase.^{51,52} In addition to driving the immune response, macrophages facilitate the resolution of inflammation by clearing residual neutrophils and cellular debris.^{53,54} They also release cytokines and growth factors that stimulate the differentiation, proliferation, and migration of endothelial cells, keratinocytes, and fibroblasts.^{53,54} These processes are vital for neovascularization (the formation of new blood vessels), re-epithelialization (the regeneration of skin cells), and ECM deposition.^{53,54} Together, these activities not only contribute to wound closure but also lay the foundation for tissue remodeling during the proliferative phase.^{53,54}

During the inflammatory phase, burn wounds share the basic biological process mediated by immune cells, which aims to eliminate damage and resist infection, with ordinary wounds.^{2,48} However, severe burn wounds amplify this localized, controllable response into a severe, prolonged and systemic pathological storm.² Its characteristics include systemic capillary leakage and shock, an overactive unique mediator system (such as the kinin system), and contradictory systemic immunosuppression.^{2,48} This uncontrolled inflammatory response is not only the main cause of life-threatening issues during the acute phase of burn wounds, but also lays the groundwork for long-term complications such as delayed healing, extremely high metabolism and pathological scarring.² Due to the excessive inflammation of the burn wounds that leads to systemic immunosuppression, and the damage caused by heat to the skin's protective barrier, one of the main challenges faced by burn wounds is their susceptibility to infection.⁵⁵ This damage compromises the barrier's natural defense mechanisms, leading to a nutrient-rich exudate buildup.⁵⁵ This microenvironment, in turn, becomes a fertile breeding ground for pathogenic microorganisms, which can quickly colonize and proliferate within the wound, dramatically increasing the risk of infection.⁵⁵

Proliferative Repair Phase of Burn Wounds Healing

During the proliferation and repair phase, activated fibroblasts play a central role in the formation of granulation tissue and the synthesis of key ECM components.^{56,57} In this stage, fibroblasts mainly secrete type III collagen which transform into type I collagen during the ECM remodeling phase.⁵⁸ This collagen serves as a structural scaffold, supporting neovascularization (the formation of new blood vessels) and the recruitment of inflammatory cells.^{56,57} Meanwhile, the hypoxic environment at the wound site stimulates the activation of vascular endothelial cells (EC), thereby triggering angiogenesis.⁵⁹ Simultaneously, endothelial progenitor cells (EPCs) are mobilized, migrating from the bone marrow into the circulatory system.⁵⁹ These progenitor cells differentiate into endothelial cells, which contribute to the formation of new blood vessels at the injury site.⁵⁹ The activities of fibroblasts and capillarogenesis are intricately coordinated.⁶⁰ Together, they promote the synthesis of ECM and granulation tissue, contributing to re-epithelialization.⁶⁰ As the newly deposited ECM accumulates, it undergoes continuous degradation and remodeling by enzymes such as collagenase and elastase.⁶¹ This remodeling process persists until the ECM achieves equilibrium, establishing the structural foundation required for normal wound closure.⁶¹ During the proliferative phase, burn wounds and normal wounds share the basic biological processes mediated by fibroblasts and keratinocytes, which aim to close the wound through the formation of granulation tissue, angiogenesis, and re-epithelialization.^{2,48} However, the proliferative phase of severe burn wounds initiates in an extremely unfavorable internal environment: the continuous extremely high metabolic rate consumes a large amount of energy and substrates necessary for repair, while the uncontrolled inflammation disrupted the normal repair signals.^{62,63} Furthermore, deep burn wounds destroy the basal layer of the re-epithelializing epidermis, forcing the healing process to start from the deeper skin appendages with great difficulty.⁶⁴ These factors collectively lead to the often-abnormal proliferation and repair of burn wounds, and the final outcome is highly dependent on the depth of the injury and is prone to developing into hypertrophic scars and contractures.^{65,66}

Remodeling Phase of Burn Wound Healing

The remodeling phase represents the final stage of wound healing, following the proliferation phase.^{56,57,67} During this critical stage, fibroblasts transform into myofibroblasts, which possess contractile properties that facilitate wound contraction and closure.^{56,57,67} Simultaneously, the ECM undergoes structural alterations. Macrophages release various enzymes that further remodel the ECM, reshape the wound architecture, and support tissue maturation.^{56,57,67} Gradually, granulation tissue is replaced by connective tissue, allowing the wound to heal and ultimately close.⁵⁷

While the human body demonstrates an innate capacity to repair epidermal burn wounds, severe burn wounds often lead to long-term complications, including impaired wound healing, metabolic imbalances, immune dysfunction, cardiovascular problems, and psychological trauma.² These complications may result in chronic pain, diminished quality of life, reduced work productivity, and an elevated risk of mortality.^{39,40,68} Together, they impose lifelong physical and mental health challenges on patients.^{39,40,68} During the remodeling period, both burn wounds and ordinary wounds undergo collagen remodeling and scar maturation, including the conversion of collagen types and the remodeling of the matrix mediated by myofibroblasts.⁴⁸ However, the remodeling process of burn wounds is severely pathologically deviated under the drive of continuous inflammation and extremely high metabolism.^{62,63} Its core feature is a significant imbalance in collagen metabolism, leading to the formation of hypertrophic scars.^{62,63} The clinical outcome of this kind of abnormal repair is devastating, often resulting in functional impairments such as scar contractures and long-term abnormal pigmentation.^{69,70} Therefore, the re-formation period of burn wounds is not merely a local repair endpoint, but rather a long and challenging stage that is closely linked to the patient's overall pathophysiology and determines their long-term quality of life.

Other Factors Affecting Burn Wound Healing

The severity of a burn wound, the risk of infection, and individual patient characteristics are pivotal in determining the healing trajectory of burn wounds.^{71–74} Burn depth and severity are primary factors influencing the extent of tissue damage and the corresponding healing mechanisms.⁷¹ For example, superficial burns, such as first-degree burns, affect only the outermost layers of the skin, causing redness and mild discomfort.⁷² These burns generally require minimal treatment and heal relatively quickly.⁷² Conversely, deeper burn wounds, like third-degree burns, extend into the subcutaneous fat, muscle, and even bone in severe cases.⁷² Such injuries heal slowly, often necessitate surgical interventions like skin grafting, and frequently result in permanent scarring.⁷² Infection poses a critical threat to the healing of burn wounds, as pathogens can exacerbate the inflammatory response, prolong inflammation, and impede the healing process.⁷³ Therefore, to mitigate infection and support optimal healing, maintaining a sterile environment and utilizing antimicrobial therapies are indispensable.

Reducing local inflammation and optimizing the wound microenvironment are vital strategies for promoting healing and minimizing scar formation.^{75,76} The normal restoration of skin barrier function depends on maintaining specific physiological conditions over a sustained period.⁷⁷ Any disruption in this process can impair wound healing, resulting in chronic or poorly healing wounds.⁷⁷ Chronic wounds are often characterized by dysfunctional and delayed cellular activity, triggering a pathological inflammatory response that culminates in persistent ulcers.⁷⁷ Common underlying causes of chronic wounds include diabetes, ischemia, venous stasis, and pressure ulcers.⁷⁷ Additionally, comorbidities and the overall health of the patient significantly influence the healing process. Conditions such as malnutrition and diabetes can obstruct the body's natural healing mechanisms, leading to delays or incomplete recovery.⁷⁴ For instance, deficiencies in essential micronutrients can hinder the healing process by impairing cellular repair, immune function, and tissue regeneration.⁷⁴ In diabetic patients, wound healing is often impaired due to abnormal inflammatory responses, impaired granulation tissue formation, insufficient angiogenesis, and poor epithelialization.⁷⁸ These challenges are partly from disruptions in epidermal intercellular junctions and disconnections between basal cells and basement membranes, which hinder the activation of normal skin repair.⁷⁸

In short, due to the unique pathological and physiological characteristics of burn wounds, such as excessive inflammatory response, blocked cell proliferation, and abnormal tissue remodeling. Traditional gauze and bandages, although helpful in stopping bleeding, often fail to provide a moist environment and increase the risk of infection. Hydrogels can absorb exudate, but lack targeted anti-inflammatory or antioxidant functions. Although antimicrobial peptides have the potential for antibacterial and antioxidant properties, their poor cell permeability and limited targeting to tissues limit their efficacy. P-EVs carry a variety of bioactive molecules and can regulate key cellular processes, such as proliferation, migration, differentiation,

and angiogenesis. P-EVs can also transport proteins and DNA to target cells without affecting their activity. Therefore, P-EVs are expected to become a supplementary strategy for burn treatment.

Biological Characterization of P-EVs

Composition and Origin of P-EVs

Exosomes are small membrane vesicles composed of lipid bilayers, usually between 30 ~150 nm in diameter.^{23,79} These vesicles are usually “saucer-like” or “cup-shaped” and are formed by the fusion of intracellular multivesicular bodies with the cell membrane, and then released into the extracellular space.^{23,79} Exosomes play an important role in intercellular and interspecies communication by delivering various bioactive molecules.^{23,79} Exosome membranes are rich in proteins, while vesicle contents typically include lipids, RNA (such as mRNA and microRNA), DNA, and other molecules capable of regulating a variety of physiological and pathological processes.^{23,79} Recently, researchers have found that P-EVs have a similar structure to exosomes.^{25,26} These vesicles are secreted by plant cells and are naturally non-toxic.⁸⁰

P-EVs are mainly composed of lipid bilayers, and the biological active molecules such as proteins, nucleic acids, and secondary metabolites were encapsulated within or embedded in the lipid bilayers (Figure 2).⁸⁰ The lipid composition of membrane is mainly composed of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), and digalactosyldiacylglycerol (DGDG) et.al^{81,82} In terms of protein composition, P-EVs contain a variety of functional proteins. Annexins, heat shock proteins (HSPs), and aquaporins have been widely identified to play crucial roles in vesicle biogenesis, membrane fusion, and immune regulation processes.^{83,84} For instance, heat shock protein 70 (HSP70) can be successfully delivered to human cells as functional exogenous proteins.⁸⁵ Tetraspanin 8 (TET8) and tetraspanin 9 (TET9), which are members of the tetraspanin family, are involved in the formation and secretion of P-EVs, the transmission of small RNAs, and the immune response of plant.⁸⁶ Additionally, actions have been identified in various P-EVs, which suggests that P-EVs may play an important role in active processes related to the cell skeleton, such as organelle movement and vesicle transport.⁸⁷ Among the components of nucleic acids in P-EVs, plant-specific microRNAs (miRNAs) play a crucial role in mediating their core functions.⁸⁰ For instance, miR18a derived from grapefruit-derived extracellular vesicles (Gf-EVs) can inhibit the growth

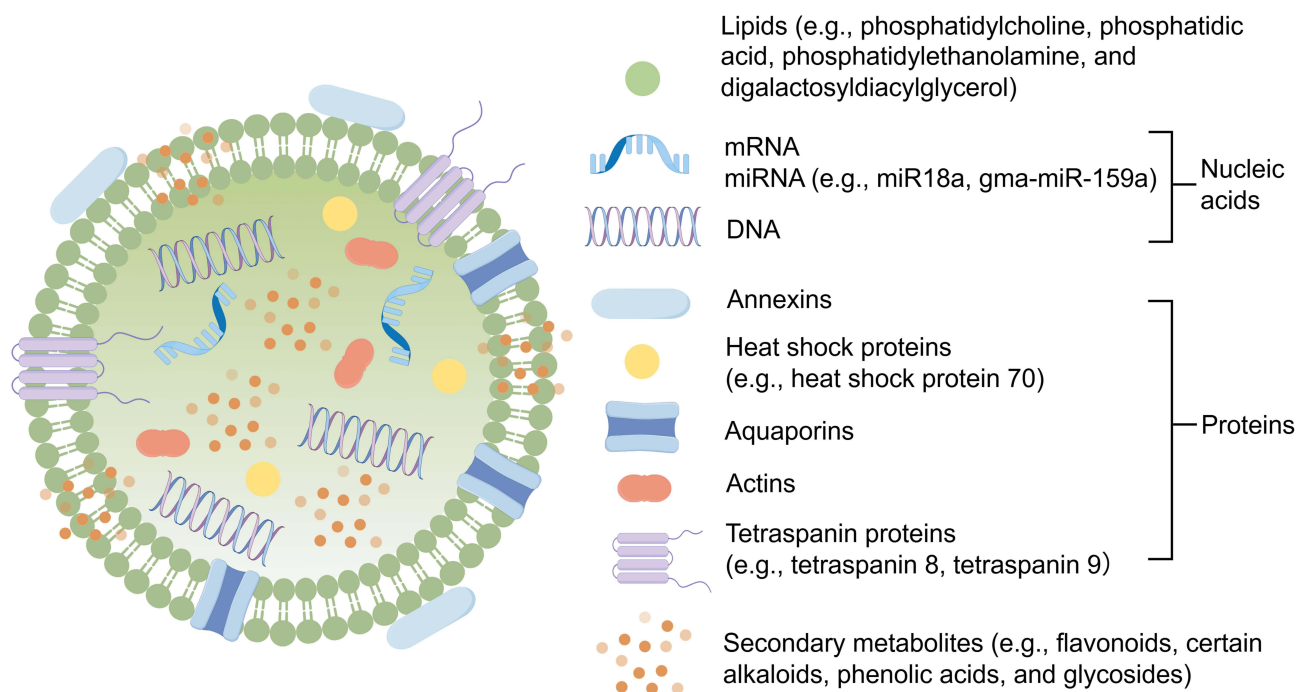


Figure 2 The generalized composition of P-EVs. P-EVs are mainly composed of lipid bilayers, and the bioactive substances such as proteins, nucleic acids, and secondary metabolites are encapsulated within or embedded in the lipid bilayers. Bioactive substances are present within P-EVs, embedded in the lipid bilayer, or adsorbed on their surface.

of colon tumors and liver metastasis by regulating the β -catenin and IFN- γ /IRF2 axis in macrophages.³⁰ The gma-miR-159a of soybean-derived extracellular vesicles (Sb-EVs) can induce apoptosis in human colon cancer cells through the TCF7 inhibition mechanism.^{88,89} Ginger-derived extracellular vesicles (G-EVs) contain miRNAs such as csi-miR396e-5p and bdi-miR5179, which exhibit significant anti-inflammatory effects in human intestinal cells.⁹⁰ In addition, messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), siRNAs, and piRNAs were also identified in P-EVs.^{25,91–93} Moreover, P-EVs also contain a wide variety of plant-specific secondary metabolites, including flavonoids, phenolic acids, and alkaloids, etc.^{94,95} These compounds were reported to possess strong anti-inflammatory and antioxidant activities.^{94,95} They can work in synergy with nucleic acids and proteins to form the comprehensive pharmacological basis of PELNs for promoting wound healing and regulating the inflammatory microenvironment.^{94,95} The secondary metabolites are distributed within the membranes and cavities of P-EVs based on their chemical properties.^{96,97} Hydrophobic metabolites such as flavonoids and hydrophilic metabolites such as certain alkaloids tend to be embedded in the lipid bilayer, but hydrophilic metabolites such as phenolic acids and glycosides are dissolved in the aqueous phase within the cavity.^{96,97}

Comparison of P-EVs with Mammalian Exosomes and Artificial Nanoparticles

Exosomes are a specific subtype of extracellular vesicles which are derived from endosomes of mammalian cells. They form in multivesicular bodies within the cell and are subsequently released into the extracellular space through the fusion of multivesicular bodies with the cell membrane.⁹⁸ P-EVs is a broad term that encompasses all types of lipid-coated nanoparticles secreted from plant cells. Unlike the mammalian system, the exact biogenesis pathways of many P-EVs have not been fully elucidated.^{98,99} Therefore, in accordance with the principle of using operational terms for EVs with less studies as recommended by the MISEV guidelines, the general term “P-EVs” was used to refer to these vesicles. P-EVs are typically isolated from plant extracellular fluids or culture supernatants and have similar sizes (50 ~ 200 nanometers) and bilayer membrane structures to mammalian EVs.^{98,99} Artificial nanoparticles are synthetic nano-delivery vehicles, such as liposomes, polymer nanoparticles, and solid lipid nanoparticles, whose formation is driven by physical or chemical methods rather than biological processes.¹⁰⁰

P-EVs are nano-sized vesicles in form, which are similar to mammalian exosomes, both functionally play significant roles in a non-cell-autonomous manner, and even participate in inter-species information exchange.^{101,102} P-EVs originate from plants, while exosomes were initially discovered and studied in mammalian cells.¹⁰² Furthermore, P-EVs can be isolated from a diverse array of plants, making them a readily available and potentially cost-effective resource.²⁹ There are more clinical studies on exosomes, and some of them have entered the clinical trial stage, while the clinical research on P-EVs is relatively less.¹⁰² In addition, P-EVs pose no risk of being human pathogens and can be easily produced on a large scale.¹⁰⁰ Mammalian exosomes may carry dangerous molecules, such as tumor substances and viruses.¹⁰⁰ Large-scale production of exosomes relies on cell culture, which is costly and has limited output.¹⁰⁰

Both P-EVs and artificial nanoparticles can be used as nano-scale carriers for drug delivery.¹⁰⁰ P-EVs do not require chemical synthesis and possess natural lipid membrane structures with high stability. They are derived from food and exhibit low immunogenicity. However, their content is limited by plant types, thus requiring modification.¹⁰⁰ However, artificial nanoparticles need to be synthesized artificially, which lead to their stability being affected by the preparation process, and lead to them having a risk of triggering immune reactions.¹⁰⁰ Artificial nanoparticles can flexibly carry multiple drugs, but the preparation process is complex and the cost for large-scale production is high.¹⁰⁰

Separation and Extraction Methods for P-EVs

Collectively, the isolation and extraction of P-EVs from plant material can be achieved using several techniques.

- (1) Ultracentrifugation is a commonly method which gradually removes cellular debris and larger vesicles through stepwise centrifugation (Figure 3).^{103,104} First, setting the centrifuge at $3000 \times g$ for 20 minutes to remove dead cells and large cell fragments.^{105–107} Then, setting the centrifuge at $10000 \times g$ for 40 minutes to remove cell debris and most of the fibers.^{105–107} Next, collecting the supernatant and filtrating through a $0.22 \mu m$ filter to remove pectin, small fibers, and other large molecular polymers.^{105–107} Finally, through an ultracentrifuge at $120,000 \times g$ for 90 minutes, collecting the precipitate as P-EVs.^{105–107} During this process, particles with different densities

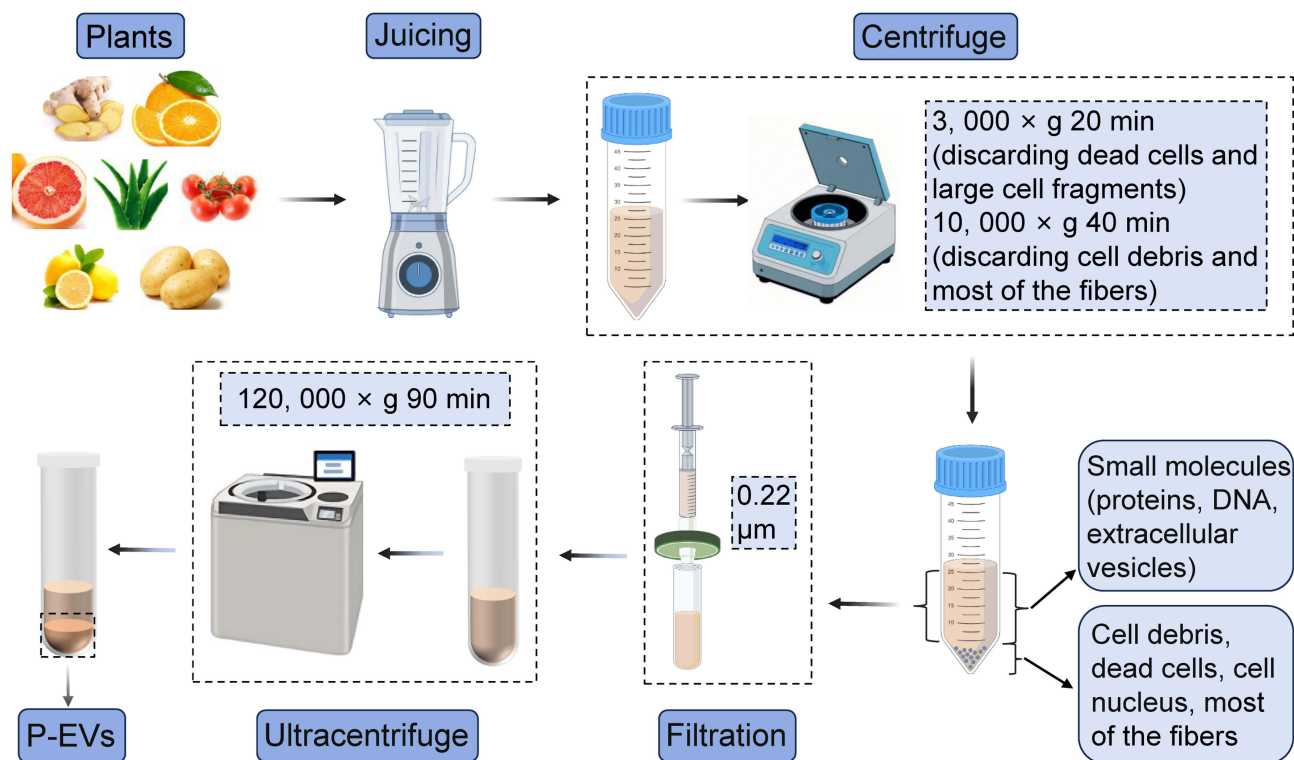


Figure 3 Isolation of P-EVs based on ultracentrifugation. First, various plants juice is obtained through extraction. Then, the juice is centrifuged in a low-speed to obtain the supernatant which contains small molecules such as proteins, DNA and extracellular vesicles, and the precipitate which contains cell debris, dead cells, most of the fibers, and cell nuclei will be discarded. Next, the supernatant is collected and filtered with a 0.22 μm filter membrane to remove pectin, small fibers, and other large molecular polymers. Finally, ultracentrifugation is performed on the supernatant, and the precipitate is collected and saved as P-EVs.

and sizes settle at distinctive rates under centrifugal force, ultimately yielding P-EVs.^{103,104} However, this method carries the risk of damaging P-EVs and may lead to reduced purity.^{103,104}

- (2) Sucrose density gradient centrifugation serves as an alternative method for the isolation and purification of P-EVs. Although this approach yields higher purity, it shares certain limitations with ultracentrifugation, including the potential for P-EVs damage and a time-intensive process.¹⁰⁸
- (3) Ultrafiltration and polymer precipitation: Ultrafiltration employs filter membranes with varying pore sizes to isolate P-EVs from particles of differing sizes. Polymer precipitation involves the use of polymers, such as polyethylene glycol, which interact with surface proteins on P-EVs to promote their precipitation.¹⁰³ These techniques are widely utilized for P-EVs purification, but they tend to yield low recovery rates.¹⁰³
- (4) Immunoaffinity, volumetric exclusion chromatography, and microfluidics are emerging technologies that enable more precise separations and demonstrate relatively improved results.^{103,109} However, they continue to face limitations in efficiency and optimization.^{103,109}
- (5) Tangential flow filtration (TFF). The TFF system consists of two filters with different pore sizes, connected to a power pump that circulates the fluid continuously.¹¹⁰ This continuous circulation enhances the separation of specific size ranges through double filtration.¹¹⁰ Some researchers combined TFF with other exosome extraction methods and demonstrated this approach could increase the yield of exosomes effectively.^{111,112}

In Summary, the choice of extraction and isolation methods for P-EVs largely depends on the unique characteristics of the sample and the intended application. Each method offers distinct advantages, but also comes with specific challenges, such as the risk of P-EVs damage, purity reduction, and time-consuming operation processes which can impede efficiency, particularly in large-scale applications. However, recent advancements in microfluidics, as well as electrical, acoustic, and force-based separation techniques, show great promise for enhancing both the efficiency and the delicacy of vesicle extraction processes.

Identification of P-EVs

The identification of P-EVs depends on the shape, size, and surface charge. Commonly, characterization is carried out using electron microscopes. Scanning electron microscopes (SEM) is suitable for observing the surface morphology and three-dimensional structure of P-EVs, but its resolution is lower than that of transmission electron microscopes (TEM)^{113,114} TEM has high resolution and can provide detailed morphological information of P-EVs.^{115,116} However, TEM assay needs to be operated in a vacuum environment and the samples need to undergo complex processes, which may damage the structure of P-EVs.^{115,116} Atomic force microscopes (AFM) can non-destructively capture and detect P-EVs, and display the morphology and structure of P-EVs clearly.¹¹⁷ However, the operation is rather complex, and strict requirements are imposed on the sample surface.¹¹⁷

The size and Zeta potential of P-EVs are important parameters that affect their biological functions such as intracellular uptake and drug delivery.¹¹⁸ The size and Zeta potential of P-EVs are typically characterized using Dynamic Light Scattering (DLS) and Nanoparticle Tracking Analysis (NTA). DLS has the advantages of simple operation and high efficiency but is prone to be affected by large particles during particle size analysis.^{119,120} Therefore, the measurement results in a single dispersion system are relatively accurate.¹¹⁹ NTA can capture and analyze the movement trajectories of individual particle, which can reduce the interference from large particles, improve measurement accuracy, and provide concentration data of P-EVs.^{119,120}

Role and Advantages of P-EVs

P-EVs, which are similar to animal-derived exosomes, can be internalized by both plant and animal cells, thereby facilitating intercellular communication.⁸⁵ Enriched with plant-specific active ingredients, P-EVs held significant promise as tools for disease treatment and drug delivery.^{29,121} Unlike vesicles derived from mammalian sources, P-EVs were inherently non-pathogenic and free from risks associated with infection or biological contamination due to their natural origin.^{122,123} This quality makes P-EVs a safer and more reliable alternative for applications in human therapeutic and drug delivery.^{122,123} P-EVs can deliver exogenous proteins to human cells efficiently, and the delivered proteins remain functionally active.⁸⁵ The use of Citrus limon-derived EVs as carriers for doxorubicin (DOX) did not affect the pharmacotoxicity of DOX. Studies on HeLa and HEK293T cell lines showed that Citrus limon-derived EVs do not exhibit cytotoxic effects and can be considered as safe drug carriers.¹²⁴ P-EVs can effectively transport therapeutic drugs across cellular barriers, which represents a significant advantage in drug delivery. Furthermore, pharmacological studies have underscored the anti-inflammatory, anti-tumor, and immunomodulatory properties of P-EVs. Gf-EVs could efficiently deliver biotinylated DNA and proteins, functional siRNAs, and various other therapeutic agents to target cells without altering their biological activity.²⁹ G-EVs were mainly taken up by intestinal epithelial cells (IECs) and macrophages.¹⁰⁷ Although G-EVs can be taken up by intestinal epithelial cells and macrophages, the precise molecular mechanism of their targeted delivery has not yet been clarified.¹⁰⁷ The targeting ability of P-EVs may stem from their complex surface molecular composition. Taking G-EVs as an example, their membranes are rich in specific lipids such as phosphatidic acid and monogalactosyldiacylglycerol, as well as carry a small amount of membrane proteins such as aquaporins and chloride ion channels.¹⁰⁷ A large amount of negatively charged phospholipids (such as phosphatidylcholine), which present on the surface of P-EVs, may interact through charges or act as ligands to bind to the receptors (such as integrin family members or other adhesion molecules) of target cells, thereby mediating specific recognition and uptake.¹²⁵ In addition, G-EVs could alleviate acute colitis, enhance intestinal repair, and prevent chronic colitis and colitis-associated cancer (CAC).¹⁰⁷ Thus, the medicinal properties of P-EVs, which are combined with high efficiency of cellular uptake, exceptional biocompatibility, and stability, highlights their immense potential in treatment of a wide range of diseases, such as inflammatory bowel disease, colitis-associated cancer, acute liver failure, and nonalcoholic fatty liver disease.^{29,107}

P-EVs exhibit a range of distinctive biological functions, including immune modulation, cellular repair, and tissue regeneration.^{29,107} Their remarkable potential in wound healing and anti-inflammatory therapies stems from their capacity to enhance tissue repair and inflammation regulation, making them highly advantageous in such applications.^{29,107} Furthermore, P-EVs were notable for their high production yield, ease of extraction, cost-efficiency,

eco-friendly manufacturing processes, and inherent safety.^{29,121} In conclusion, P-EVs represent an emerging and innovative class of nanomedicine. Their plant-based composition ensures safe, effective, and biocompatible therapeutic versatility, particularly in the domains of drug delivery, wound care, and anti-inflammatory treatments. The affordability, high yield, and natural origin of P-EVs make them unparalleled candidates for advancing nanomedicine and biopharmaceutical applications. Additionally, G-EVs could ameliorate dextran sulfate sodium (DSS)-induced murine colitis by upregulating expression of heme oxygenase-1 (HO-1) and inhibiting production of interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) in intestinal macrophages.¹²⁶ And *Brucea javanica*-derived extracellular vesicles (BJ-EVs) could suppress tumor progression and metastasis by delivering 10 distinct miRNAs into 4T1 cells, which could significantly retard the growth and metastasis of 4T1 cells by regulating the PI3K/Akt/mTOR signaling pathway.¹²⁷ Thus, P-EVs ability to facilitate cross-species cellular communication and deliver therapeutic outcomes suggests a promising potential for advancing phytotherapy.

Mechanisms of Burn Wound Repair by P-EVs

P-EVs exhibit a multimodal therapeutic profile in burn wound management, including enhanced cellular regeneration and proliferation, anti-inflammatory modulation, pro-angiogenic stimulation, regulation of redox homeostasis, and antimicrobial activity (Figure 4 and Table 2).

Promoting Repair and Proliferation of Cells for Burn Wound Healing

Burn wounds typically progress through four stages: hemostasis, inflammatory response, tissue proliferation, and remodeling.⁴⁴ The early inflammatory phase plays a critical role in determining the extent and development of scarring during later stages.⁵⁰ As the largest organ in the body, the skin generally retains its function during the healing of minor wounds.¹ However, severe trauma or an abnormal inflammatory response could result in excessive tissue repair, leading to the formation of scar tissue, which not only negatively impacts appearance but also may increase the risk of cancer in extreme cases.^{128,129} P-EVs have demonstrated promising potential in enhancing burn wound healing due to their diverse biological effects, including anti-inflammatory, pro-angiogenic, and antioxidant properties. Furthermore, P-EVs are rich

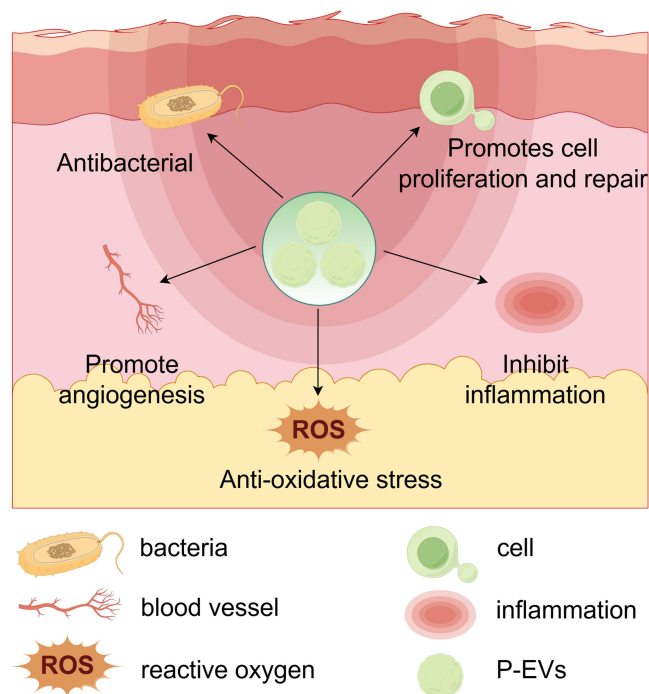


Figure 4 The regulatory mechanism of P-EVs in burn wounds healing process. P-EVs exhibit a multimodal therapeutic profile in burn wounds management, including enhanced cellular regeneration and proliferation, anti-inflammatory modulation, pro-angiogenic stimulation, regulation of redox homeostasis, and antimicrobial activity.

in bioactive molecules such as proteins, lipids, and nucleic acids, which aid in cell repair, proliferation, and migration, making them highly effective for wound recovery.

For instance, P-EVs have been shown to enhance the proliferation of human dermal fibroblasts and keratinocytes, which are involved in tissue regeneration and repair.^{130,131} Their activation facilitates the formation and restoration of new tissue in burn wounds, significantly expediting the healing process.^{130,131} P-EVs of *physalis peruviana* fruit were demonstrated to have therapeutical bioactivities, including regeneration of dermis, induction of actin cytoskeletal rearrangement, stimulation of type I collagen biosynthesis, and downregulation of matrix metalloproteinase-1 (MMP-1) secretion.¹³² Although these functional studies provide experimental evidence for the role of P-EVs in promoting cell repair and proliferation, the underlying deeper signaling pathways still need to be further elucidated. P-EVs, which were isolated from cabbage (Cabex) and red cabbage (Rabex), showed potent cytoprotective properties, by inhibiting the activation of Caspase-3, they alleviate the apoptosis of human keratinocytes and dermal fibroblasts, which highlight their potential in burn wound healing.²⁷

Additionally, P-EVs derived from *Aloe vera* peel showed excellent cytocompatibility with human skin cells, which enhanced the proliferation and migration of keratinocytes and fibroblasts.¹³³ *Wheat grass*-derived extracellular vesicles (Wg-EVs) not only upregulated the gene expression of type I collagen (COL1A) significantly, which provided a crucial matrix environment for cell migration and tissue reconstruction, but also significantly promoted the proliferation and migration of human dermal fibroblasts, keratinocytes, and endothelial cells.¹³⁴ Similarly, P-EVs derived from tomato (*Solanum lycopersicum*) were found to promote the migration of human keratinocytes and mouse fibroblasts, further highlighting their therapeutic potential for burn wound healing.²⁸ Lemon-derived extracellular vesicles (L-EVs) could promote fibroblasts to migrate to the scratch area at a higher speed and a greater migration rate.¹³⁵ Collectively, these findings suggest that P-EVs can accelerate the wound healing process by fostering cell repair, inhibiting cell apoptosis, enhancing migration, and promoting tissue regeneration.

Anti-Inflammatory Effects

Following a burn wound, the acute inflammatory response occurs locally at the wound site.⁵⁰ Pro-inflammatory cytokines also have a positive effect on wound healing. For instance, pro-inflammatory cytokines initiate wound healing by recruiting immune cells and promoting proliferation, but excessive inflammation can impair healing and lead to scarring.^{136,137} Therefore, balanced regulation of these cytokines is crucial for optimal wound repair. However, an excessive inflammatory reaction not only delays the healing process but also may lead to secondary injuries.⁵⁰ P-EVs exhibit remarkable anti-inflammatory properties by regulating immune cell activity and suppressing excessive inflammatory responses, which play a crucial role in the effective healing of burn wounds. Various P-EVs-based strategies have been proven to be effective in mitigating excessive inflammation, preventing infections, and accelerating tissue regeneration.

P-EVs derived from *Aloe vera* peel, through the key proteins they carry such as glutathione S-transferase P and phosphoenolpyruvate carboxykinase, effectively inhibited the secretion of TNF- α , IL-1 β and IL-6 in macrophages and keratinocytes.¹³⁸ This indicates that targeting these inflammatory regulatory proteins may be an effective strategy for suppressing excessive inflammatory responses at the wound site. P-EVs derived from cabbage exhibit dose-dependent inhibition of the expression of key pro-inflammatory mediators (such as IL-6, IL-1 β and COX-2).²⁷ Through comparing the differences in mRNA and protein levels, the study found that the inhibition of COX-2 by it might involve post-transcriptional regulatory mechanisms.²⁷ In addition, garlic-derived extracellular vesicles (Ga-EVs) were shown to inhibit the NF- κ B/NLRP3 signaling and block the CCR2/CCR5-mediated immune cell infiltration, which could form a powerful synergistic anti-inflammatory network.¹³⁹ Although this result comes from a liver model, the NF- κ B pathway has been regarded as a typical pro-inflammatory signaling pathway.¹⁴⁰ These results suggest that P-EVs have the potential to regulate the excessive inflammatory response of burn wounds.

Similarly, another study assessed the anti-inflammatory effects of *Allium tuberosum*-derived extracellular vesicles (At-EVs) in RAW264.7 cells and mice with colitis. Results showed that At-EVs inhibit the activation of NF- κ B, down-regulate the mRNA and protein levels of TNF- α , IL-1 β , and IL-6, and up-regulate the protein level of the anti-inflammatory factor IL-10, thereby exerting an anti-inflammatory effect.¹⁴¹ G-EVs significantly reduced the mRNA and protein levels of TNF- α , IL-6, and IL-1 β , and increased the expression of IL-10 and IL-22.¹⁰⁷ Lemon-derived

Table 2 Functions of Different Plant-Derived Extracellular Vesicles (P-EVs)

Functions	In vitro Experiments	In vivo Experiments	Discovery	Plants-Derived P-EVs
Promoting repair and proliferation of cells	HDFs		Promoting dermal regeneration, inducing actin cytoskeleton rearrangement, stimulating type I collagen biosynthesis, and downregulating MMP-1 secretion	<i>Physalis peruviana</i> fruit
	Immune cells, HaCaT cells, HDFs, and RAW264.7 cells	BALB/c mice	Inhibition of the apoptosis of human keratinocytes and fibroblasts.	Cabbage (Cabex) and red cabbage (Rabex)
	HaCaT cells and HDFs		Enhancing the proliferation and migration of keratinocytes and fibroblasts.	<i>Aloe vera</i> peel
	Endothelial cells, epithelial cells and dermal fibroblasts		Enhancement of cell viability and migration efficiency.	<i>Wheat grass</i>
	Human keratinocytes and mouse fibroblasts.		Promoting the migration of human keratinocytes and mouse fibroblasts.	Tomato (<i>Solanum lycopersicum</i>)
Anti-inflammatory effects	RAW 264.7, L929 cells, and HDFa	Sprague Dawley rats	Promoting the migration of fibroblasts.	Lemon
	RAW264.7 cells, THP-1 M0 cells, and HaCaT cells		Reducing the secretion of pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6.	<i>Aloe vera</i> peel
	Immune cells, HaCaT cells, HDFs, and RAW264.7 cells	BALB/c mice	Inhibiting the expression of key pro-inflammatory mediators, such as IL-6, IL-1 β , and COX-2, in a dose-dependent manner.	Cabbage (Cabex) and red cabbage (Rabex)
		BALB/c mice	Suppression of the LPS/D-GalN-induced inflammatory response.	Garli
	RAW 264.7 cells	C57BL/6 mice	Reducing the levels of inflammatory factors, including IL-1 β , IL-6, TNF- α , and NF- κ B pathway-associated proteins.	<i>Allium tuberosum</i>
Promotion of angiogenesis	RAW 264.7 cells, Caco-2BBE, and Colon-26 cells	C57BL/6 mice and FVB/NJ mice	Promoting the healing of injured Caco2-BBE monolayer cells.	Ginger
	HDFs	Zebrafish embryos	Inhibiting the recruitment of macrophages and exerting anti-inflammatory effects.	Lemon
	HUVECs		Enhancing the tube-forming ability of HUVECs and stimulating angiogenesis.	Grapefruit
	HUVECs		Promoting the formation of tube-like structure.	<i>Wheat grass</i>
	RAW 264.7 cells, L929 cells, and HDFs	Sprague Dawley rats	Upregulating the expression of vascular biomarkers CD31 and VEGF.	Lemon
Antioxidant effects	MSCs		Preventing oxidative stress in a dose-dependent manner.	Strawberry of <i>Fragaria x ananassa</i> (cv. Romina)
	Human hepatoblastoma HepG2 cells	C57BL/6 mice	Inhibiting the production of ROS induced by rotenone.	Blueberry
	HDFs	Zebrafish embryos	Reducing ROS levels in fibroblasts stimulated with H ₂ O ₂ and UVB.	Lemon
	RAW 264.7 cells, L929 cells, and HDFa	Sprague Dawley rats	Activating the AhR/Nrf2 signaling pathway and thereby upregulating the cellular antioxidant defense system to eliminate ROS.	Lemon
Antimicrobial effects	HaCaT cells and HDFs		Reducing reactive ROS levels in keratinocytes.	<i>Aloe vera</i> peel
	<i>Micrococcus luteus</i> and <i>Escherichia coli</i>	Wistar mice	Anti- <i>Escherichia coli</i> activity and stimulating the proliferation of beneficial probiotic bacteria.	Peppermint
	<i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Aspergillus niger</i> , and <i>Candida albicans</i>		Notable antibacterial efficacy.	Banana

Abbreviations: HDFs, Human Dermal Fibroblasts; MMP-1, matrix metalloproteinase-1; HaCaT, Human adult low Calcium high Temperature keratinocytes; RAW264.7, Abelson murine leukemia virus-induced tumor cell line 264.7; THP-1, Human acute monocytic leukemia cell line; L929 cells, Mouse fibroblast cell line L929; HUVECs, Human Umbilical Vein Endothelial Cells; MSCs, Mesenchymal Stem Cells; UVB, Ultraviolet B; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; TNF- α , tumor necrosis factor-alpha; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; UVB, Ultraviolet B.

extracellular vesicles (L-EVs) possess powerful anti-inflammatory properties.¹⁴² The mechanism is not based on a single target, but rather involves the coordinated inhibition of the ERK and NF- κ B two core inflammatory signaling pathways, exerting effects at multiple levels such as in macrophages and T lymphocytes.¹⁴² These results further highlight the potential of P-EVs in managing inflammation associated with burn wounds.

Promotion of Angiogenesis

Angiogenesis plays a crucial role in wound healing, particularly in burn injuries, where an enhanced blood supply is essential for tissue repair and regeneration.¹⁴³ Research has demonstrated that P-EVs extracted from bitter melon contain key bioactive molecules, including vascular endothelial growth factor (VEGF) and CD31.³¹ These molecules can directly accelerate the healing of burn wounds by stimulating vascular endothelial synthesis and supporting the recovery of damaged cells.³¹ Notably, they had a significant effect in promoting the repair of deep second-degree burn wounds and held promise as a potential therapeutic agent for burn treatment.³¹ Gf-EVs were shown to enhance the tube-forming ability of endothelial cells, upregulate the expression of ECM and cytoskeletal components such as collagen, fibronectin, laminin and vimentin, and regulate the balance of migratory cytokines (such as RANTES, EGF, IGF-1) and inhibitory factors (such as TIMP-1).¹⁴⁴ At the same time, they protect the function of endothelial cells through anti-oxidative stress, and jointly create a microenvironment conducive to angiogenesis.¹⁴⁴ In addition, through in vitro tube formation experiments, it was confirmed that Wg-EVs have the potential to promote angiogenesis. However, the molecular mechanism by which wheat exosomes coordinate the proliferation, migration and lumen formation of endothelial cells remains a problem that needs to be addressed in future research.¹³⁴ L-EVs significantly increased the expression of vascular biomarkers CD31 and VEGF, suggesting therapeutic potential for endothelial cell regeneration.¹³⁵ These studies have demonstrated the ability of P-EVs to promote angiogenesis and have shown great potential in promoting wound healing in burn patients.

Antioxidant Effects

Burn wounds predominantly induce oxidative stress through excessive free radical generation, which can directly compromise tissue integrity and disrupt regenerative pathways.¹⁴⁵ The natural antioxidant components in P-EVs, such as polyphenolic compounds and flavonoids, demonstrate significant antioxidant activity.¹⁴⁶ These components help reduce the production of free radicals, mitigate oxidative damage, and support wound healing.¹⁴⁶ P-EVs, which were isolated from the strawberry juice of *Fragaria x ananassa* (cv. Romina), were enriched with anthocyanins, folic acid, flavonols, and vitamin C, all of which exhibited strong antioxidant properties.¹⁴⁶ Further experiments indicated that mesenchymal stem cells (MSCs) efficiently internalized strawberry-derived extracellular vesicles (S-EVs) without compromising cell viability.¹⁴⁶ Moreover, pretreatment of MSCs with S-EVs effectively inhibited oxidative stress in a dose-dependent manner.¹⁴⁶ Similarly, blueberry-derived extracellular vesicles (B-EVs) could activate the nuclear factor E2-related factor 2 (Nrf2) signaling pathway, thereby directly enhancing the antioxidant defense capacity of cells. This is manifested by a significant reduction in reactive oxygen species (ROS) levels, as well as the restoration of the activities of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione (GSH).¹⁴⁷ Furthermore, L-EVs are rich in various flavonoids, such as chuanxiong sinapine, vicarin-2, and stachyose glycoside, etc., which can activate the AhR/Nrf2 signaling pathway and upregulate the cell's antioxidant defense system, thereby effectively eliminating ROS and promoting tissue repair.¹⁴⁸ Through non-targeted metabolomics analysis, another study revealed that L-EVs were rich in natural antioxidants such as vitamin C, flavonoids, and citric acid, which can neutralize free radicals, alleviate oxidative stress, and protect cells from oxidative damage caused by high sugar environment.¹³⁵ *Aloe vera* peel-derived extracellular vesicles (AV-EVs) can activate the core transcription factor Nrf2, thereby initiating the intrinsic antioxidant defense program of the cells.¹³³ This is manifested by a dose-dependent increase in the activity of key antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), and by significant upregulation of the expressions of Nrf2, HO-1, CAT, and SOD at the genetic level.¹³³ Furthermore, AV-EVs are rich in superoxide dismutase (SOD), thioredoxin-dependent peroxidase oxidoreductase, and ascorbate peroxidase, etc.¹³⁸ These enzymes can form a coordinated antioxidant defense network that can effectively remove excessive ROS and protect cells from oxidative damage.¹³⁸ Notably, the source of P-EVs is important in the future treatment of burn wounds. Plants deriving from organic farming should be the first choice for P-EVs isolation, since those from intensive farming may deliver residual pesticides.¹⁴⁹ The production of P-EVs from organic farming was 22% ~ 49% higher than that from intensive farming, and the total antioxidant capacity of P-EVs from organic fruits and vegetables was also 6% ~ 21% stronger than that from intensive fruits and vegetables.¹⁴⁹ The P-EVs contain various antioxidant molecules, including enzymatic antioxidants such as superoxide dismutase (SOD) and catalase; non-enzymatic antioxidants such as glutathione (GSH), ascorbic acid (vitamin C), citric acid, and energy molecules such as ATP.¹⁴⁹ These components can directly eliminate

ROS and thereby reduce oxidative damage.¹⁴⁹ The antioxidant components of P-EVs from the mixed fruits and vegetables were abundant and had a significant synergistic effect, which also demonstrated strong stability (resistant to decomposition) and high bioavailability.^{149,150} P-EVs exhibit antioxidant properties and are expected to create a favorable microenvironment for the repair of burned tissues.

Antimicrobial Effects

Burn wounds are highly susceptible to bacterial infection, often involving pathogens such as *Escherichia coli*, which can significantly delay the healing process. Therefore, it is of utmost importance to develop effective strategies to control infection of burn wounds.^{73,151} Peppermint leaf-derived extracellular vesicles (PI-EVs) could disrupt the integrity of bacterial cell membrane by carrying internal miRNAs, phospholipids, membrane proteins, and other bioactive molecules, which could increase the permeability of the cell membrane, cause the leakage of intracellular contents, and finally achieve antibacterial effects.¹⁵² Banana-derived extracellular vesicles (B-EVs) exhibit broad-spectrum antibacterial activity, with particularly significant inhibitory effects on Gram-positive bacteria (such as *Staphylococcus aureus* and *Bacillus subtilis*).¹⁵³ B-EVs are rich in key components such as gallic acid, chlorogenic acid, and methyl gallate.¹⁵³ These molecules can induce excessive accumulation of ROS within the bacteria, triggering oxidative stress, which subsequently disrupts the electron transfer chain, interferes with signal transduction, and causes DNA damage, ultimately leading to metabolic disorders and death of the bacteria.¹⁵³ Moreover, these bioactive compounds may also inhibit key enzyme systems related to bacterial energy metabolism and cell wall synthesis.¹⁵³

Prospects and Challenges of P-EVs in Burn Wounds

Prospects

P-EVs offer significant potential as an innovative approach for burn wound repair due to their remarkable biological properties, such as biocompatibility, anti-inflammatory effects, promotion of cell proliferation, and enhancement of angiogenesis. These characteristics make P-EVs promising as drugs that can accelerate the healing process of burn wounds. Composed of natural bioactive molecules such as proteins, lipids, and nucleic acids, P-EVs regulate critical aspects of wound healing, including cell migration, proliferation, and tissue regeneration. A significant advantage of P-EVs lies in their capacity to integrate with traditional therapies or biologics. For instance, using hydrogels enriched with P-EVs could extend the residence time of exosomes at the wound site, thereby prolonging their therapeutic efficacy.^{152,154,155} This synergistic capability enables P-EVs to enhance the effects of existing treatments, offering the potential to achieve better overall wound healing outcomes. Furthermore, the choice of plant sources is also very important. It is advisable to opt for organic crops. Some mixed plants also have synergistic effects.

Challenges

While P-EVs demonstrate significant potential for burn wound repair, several technical and regulatory challenges must be addressed before their widespread clinical application can be realized. (1) Lack of high-yield and standardized extraction methods. The current routine extraction and separation methods in the laboratory are time-consuming and have low yields, as well as may damage the integrity of the P-EVs due to mechanical damage. Therefore, it is necessary to develop a reliable, scalable, and standardized separation scheme for P-EVs. Integrating multiple separation technologies into a single platform may lead to a more efficient, scalable, and cost-effective separation system for P-EVs, while the purity, sterility, and retention of biological activity of the extracted substances should be taken into consideration. (2) Customization for characteristics of burn wounds. The multifunctional hydrogel, which is injectable, can detect wound conditions, and possesses antibacterial properties, has achieved excellent results in burn wounds healing.^{156–158} Regarding the clinical heterogeneity of burn wounds, P-EVs can also be loaded into multifunctional hydrogels, which can enable a synergistic effect, addresses the short half-life issue of P-EVs, and finally achieve a sustained-release effect.¹⁵⁹ (3) Improved targeting and bioactivity. To maximize therapeutic efficacy, the targeting ability of P-EVs must be enhanced, ensuring their precise delivery to damaged cells within burn wounds. Exosomes interact with target cell receptors through their surface proteins such as integrins, transmembrane proteins (e.g., CD63, CD81), and lectins,

thereby achieving organ-specific distribution.¹⁶⁰ This provides a paradigm for analyzing the natural targeting mechanism of P-EVs. For instance, the lipids such as monogalactosyldiacylglycerol (MGDG) and phosphatidic acid, which are abundant in G-EVs, along with their specific membrane proteins (such as aquaporins), are likely to act as natural targeting sites. The initial targeting process is mediated through charge, hydrophobicity, or specific ligand-receptor recognition.¹⁰⁷ Future research can draw on the methods of exosome proteomics to systematically identify the characteristic surface molecules of P-EVs from different sources, and verify their interaction with integrins that are highly expressed at the burn site. Combining the targeted logic of exosomes with the inherent advantages of P-EVs is expected to lead to the development of a new generation of “green” nanomedicines, which can not only be used for treating burn wounds, but also for precise treatment of various diseases such as inflammatory disorders, cancer, and tissue repair. Drawing on the strategies of nanomedicine, specific targeting molecules could be attached to the surface of P-EVs, thereby creating a drug delivery system that can precisely identify and act on specific wound cells.¹⁶¹

(4) Unclear Mechanism of Action. The precise mechanism through which P-EVs exert their therapeutic effects remains inadequately understood. Extensive and in-depth studies are necessary to elucidate the underlying processes, which will guide their optimized clinical application. Multi-omics methods, such as proteomics, lipidomic, and RNA sequencing, can be employed to comprehensively identify the substances which were carried by P-EVs from different plant sources. This will help identify the key active components that are responsible for their therapeutic effects. Subsequently, the specific roles of these components in processes such as angiogenesis and anti-inflammation should be verified.

(5) Ethical and Regulatory Considerations. The therapeutic use of P-EVs faces significant ethical and regulatory challenges, particularly due to varied regulatory frameworks across different countries and regions. The US FDA regulates therapies based on extracellular vesicles as biological products under the Public Health Service Act, requiring an Investigational New Drug (IND) application and subsequent Biologics License Application (BLA).¹⁶² The classification depends on the intended use, mechanism of action, and composition of P-EVs product. If P-EVs are engineered primarily as delivery vehicles for a defined drug (e.g., siRNA), they would be reviewed as a “combination product”.¹⁶² In the European Union (EU), therapies based on extracellular vesicles are predominantly classified as Advanced Therapy Medicinal Products (ATMPs), if their contents are deemed to have a direct therapeutic effect on human physiology, the EVs would be subject to rigorous oversight by the Committee for Advanced Therapies (CAT).¹⁶² The lack of specialized guidelines for P-EVs in different regions pose difficulties in promoting the global clinical application. Developing standardized guidelines for P-EVs use in medical applications is indispensable to addressing these hurdles.

(6) Evaluation of Long-Term Safety and immunogenicity. Comprehensive evaluations of the long-term safety and immunogenicity of P-EVs remain necessary to confirm their reliability for clinical use. Establishment of safe dose range and concentration is crucial for clinical application. Although short-term (7-day) oral administration of P-EVs in healthy mice did not cause pathological changes in the major organs of the mice, the long-term safety of this treatment still requires supplementary data from animal experiments.¹⁰⁷ In addition, the immunogenicity of P-EVs should be paid due attention to. On one hand, their inherent immunomodulatory ability is one of the mechanisms that promote healing of burn wounds. On the other hand, as non-autologous substances, P-EVs may be recognized by the host immune system and trigger unnecessary immune responses.¹³³ To comprehensively assess the long-term biological safety of P-EVs, future studies should include a systematic toxicological evaluation in accordance with Good Laboratory Practice for Nonclinical Laboratory Studies (GLP).

(7) Selection of plant sources. Organic agriculture and non-genetically modified approaches attribute the therapeutic effects entirely to the inherent biological activity of P-EVs, rather than to the interfering variables introduced by genetic engineering. The P-EVs derived from non-genetically modified plants have their components mainly influenced by the variety and growth conditions, and are relatively easy to standardize. Moreover, large-scale cultivation will require a significant number of agricultural resources, which raises concerns about land use, water consumption, and potential impacts.¹⁶³ It is necessary to conduct regular assessments to mitigate environmental impacts and develop sustainable and ethical procurement strategies. Moreover, when selecting the plant sources for P-EVs, plants that have been treated with pesticides should be avoided, preventing the occurrence of pesticide residues. Although P-EVs showed great potential in treatment of burn wounds, their clinical application still faces challenges. Currently, there are no clinical studies on the application of P-EVs in burn wounds. The clinical studies on exosomes derived from mesenchymal stem cells have achieved preliminary positive results for diabetic foot ulcers.¹⁶⁴ This provides a reference clinical development

model for the application of P-EVs in burn wounds treatment. Furthermore, P-EVs production that complies with the Good Manufacturing Practice (GMP) standards is the cornerstone of clinical translation. Thus, the current methods for preparing P-EVs should strictly ensure their sterility, purity, and biological activity.

Summary

Burn wounds pose a substantial medical challenge due to factors such as deep tissue damage, severe inflammation, and an elevated risk of infection. There are certain limitations to the single traditional treatment method. In this context, P-EVs show considerable promise in advancing burn wound healing. The P-EVs derived from different plant sources exhibit unique biological activities in key aspects such as anti-inflammatory, antioxidant, promotion of angiogenesis, antibacterial, and acceleration of re-epithelialization due to the different combinations of miRNAs, proteins, and metabolites. Although P-EVs have potential in the treatment of burn wounds, the therapeutic properties of P-EVs from different sources varies.^{27,28} For the complex pathology of burn wounds, it requires simultaneous control of inflammation, protection from oxidative stress, and promotion of tissue regeneration.² In this context, lemons-derived extracellular vesicles (L-EVs) present certain advantages and become a particularly promising candidate. The significant advantage lies in that L-EVs can not only effectively inhibit pro-inflammatory cytokines and eliminate reactive oxygen species, but also significantly increase the expression of vascular biomarkers CD31 and VEGF, demonstrating the potential for promoting angiogenesis.^{135,142,148} Therefore, although the choice of plant sources may depend on the specific treatment goals, the current evidence establishes L-EVs as the leading candidate for burn treatment owing to their comprehensive and multi-mechanistic mode of action, which is highly compatible with the clinical needs for management of burn wound.

P-EVs inherent functional diversity makes P-EVs potentially a supplementary option for burn treatment. Nevertheless, while P-EVs hold significant promise, their clinical application remains in its infancy. The clinical application of P-EVs still faces numerous challenges, including unclear mechanisms, safety concerns, and regulatory issues. These problems must be addressed in order to fully realize its potential in burn treatment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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