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Regenerative Medicine for Equine Skin Wound Healing: A Review of Zinc Oxide Nanoparticles, Mesenchymal Stem Cell-Derived Microvesicles, and Propolis

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ABSTRACT: Skin wound healing in animals often requires veterinary intervention with mesenchymal stem cell-derived microvesicles (MSC-MVs) emerging as a promising therapeutic avenue. MSC-MVs, minute membrane-bound structures carrying bioactive molecules, play a crucial role in influencing wound-healing processes. They modulate inflammation, which is vital for tissue repair, and stimulate the proliferation and migration of skin cells and fibroblasts, thereby facilitating tissue regeneration. Furthermore, they induce angiogenesis, which is crucial for the delivery of oxygen and nutrients to the wound site. However, realizing their potential in routine veterinary practice entails addressing current challenges. Tailored research on the optimal efficacy in target animal species is imperative because of species specificity. Determining the appropriate dosing and administration frequency for different wound types is crucial to avoid compromising the efficacy or introducing side effects. Developing efficient delivery methods suitable for diverse veterinary applications remains a priority along with standardizing production protocols to ensure consistent quality and therapeutic effects. Although generally safe, further investigation into the potential side effects, especially with prolonged use, is necessary. A cost-effectiveness analysis is essential to ensure accessibility. Future research should focus on comparative clinical trials, exploring combination therapies and targeted delivery systems, and optimizing MSC-MVs and their cargo properties. Long-term safety and effectiveness studies are vital, particularly for chronic wound management. Finally, cost-benefit analysis will determine the feasibility of incorporating MSC-MVs into routine veterinary care, potentially revolutionizing wound healing.

KEYWORDS: Equine, Skin, Wound, Healing, Regeneration, Stem cells, Nano particles, Propolis

1. Introduction

Cutaneous wound healing is a complex process that develops similarly across animal species. This process is categorized into three main stages that go together to repair damage [1, 2]. The first stage is the inflammatory phase, which focuses on stopping bleeding and preventing infection [1, 3]. Vasoconstriction slows blood flow, platelets aggregate to form a clot, the wound is sealed [4, 5], and neutrophils and macrophages move to the injured area[5]. The second stage is the proliferative phase. Fibroblasts start to create a scaffold of collagen fibers and build connective tissues [1, 5]. Simultaneously, skin cells from the edges of the wound start to multiply and distribute toward the center. New blood vessels grow into newly formed tissues, providing vital nutrients and oxygen for healing[1, 5]. The terminal stage is remodeling, in which the repaired area is refined and strengthened. The body reorganizes the collagen fibers laid down earlier, making them more robust and aligned in the direction of stress on the skin. However, this remodeled tissue often contains fewer elastic fibers than healthy cutaneous tissue, leading to scar formation[6]. Although the scar might not be as strong or flexible as the original tissue, it provides a functional patch to close the wound and prevent further damage [2]. The healing process can be stunned in cases of chronic wounds, severe burns, or injuries with significant tissue loss [7]. In such instances, traditional wound care approaches may be inadequate for achieving complete or optimal healing [8, 9]. Regenerative medicine emerges as a promising field offering new and effective therapeutic strategies to address these limitations[9, 10]. Traditional wound care focuses primarily on creating an environment that facilitates the inherent healing cascade of the body. In contrast, regenerative medicine takes a more proactive approach, aiming to directly stimulate the body's regenerative potential [6, 9, 11, 12, 13]. This involves the utilization of stem cells [14, 15], growth factors

[16, 17], bioengineered scaffolds [18, 19], or nanoparticles [20, 21, 22, 23] to actively promote the proliferation and differentiation of new skin cells and underlying tissues. Although regenerative medicine applications in wound healing are still under development and refinement, the potential benefits are undeniable [23]. The objective of this review was to successfully examine recent advancements in regenerative medicine tailored to equine skin wound healing. Specifically, it aimed to assess the efficacy and mechanisms of action of propolis, nanozinc oxide, and mesenchymal stem cell microvesicles in promoting wound healing in horses. We critically evaluated the clinical applications, challenges, and future directions of these modalities in equine practice.

Regenerative Medicine Approaches

Propolis in Skin Wound Healing

Propolis, also known as bee glue, is a complex mixture of resinous bee products with a rich history of medicinal use, as it contains a diverse array of bioactive compounds, including flavonoids, phenolic acids, terpenoids, and aromatic acids [24]. These bioactive constituents are believed to be responsible for its anti-inflammatory, antibacterial, and antioxidant properties[24, 25]. The potential benefits of propolis in skin wound healing can be attributed to its multifaceted biological activities. Studies have shown that propolis promotes tissue regeneration [26, 27]. Propolis extracts have been demonstrated to stimulate the proliferation and migration of fibroblasts, which are responsible for collagen synthesis [28]. Additionally, propolis may enhance the activity of growth factors involved in tissue repair [29]. The anti-inflammatory properties of propolis are believed to be mediated by various bioactive components [25]. Propolis extracts have been shown to suppress the production of proinflammatory mediators and promote the expression of anti-inflammatory markers [30, 31]. The ability to modulate inflammation can contribute to a more efficient healing process. Propolis exhibits broad-spectrum antibacterial activity against various wound pathogens [32, 33, 33, 34, 35]. This property can help prevent wound infections, which are a significant complication that can impede healing. Studies have suggested that propolis may stimulate angiogenesis by promoting the proliferation and migration of endothelial cells, the building blocks of blood vessels [36, 37]. Recent research has shown that the topical application of propolis significantly accelerates wound closure and healing [38, 39, 40]. Despite these encouraging findings, further research is needed to fully elucidate the mechanisms of action of propolis in wound healing and to optimize its delivery methods, especially in equines.

1.0.1. Nanozinc Oxide in Skin Wound Healing

Zinc oxide nanoparticles (nZnO) 1–100 nm in size have emerged as a potential therapeutic tool in the field of skin wound healing through interaction with biological molecules that promote various biological activities essential for wound healing [41]. One of the most crucial properties of nZnO for wound healing is its broad-spectrum antimicrobial activity[42]. nZnO can effectively combat bacteria, fungi, and viruses [43, 44, 45, 46]. This characteristic is vital as it helps prevent wound infections, which is a major roadblock to successful healing. nZnO also exhibits anti-inflammatory effects. Studies have shown its ability to suppress the production of pro-inflammatory mediators, leading to a more efficient healing process by reducing inflammation-mediated tissue damage [47, 48, 49, 50]. Furthermore, nZnO appears to promote angiogenesis and the formation of new blood vessels. This process is vital for delivering oxygen and nutrients to the wound site, thereby accelerating healing [51, 52, 53, 54]. Studies in rabbits have shown that topical application of nZnO ointment significantly accelerates wound closure compared to wounds treated using conventional methods [55]. Animal models have demonstrated the ability of nZnO to reduce inflammation and promote tissue regeneration in wounds, creating an optimal healing environment [48]. There are concerns regarding the potential cytotoxic effects of nZnO at high concentrations [56]. Further research is needed to determine safe and effective dosage ranges for wound-healing applications, especially in horses. In some cases, nZnO nanoparticles may induce unintended inflammatory responses at the application site [57]. Careful design and

characterization of nZnO formulations are crucial to minimize this risk. The potential environmental impact of nZnO nanoparticles released from wound dressings must be evaluated to ensure their responsible development and use. The future of nZnO in wound healing in equine practice is promising, with ongoing research addressing safety concerns and optimizing the delivery methods. Combining nZnO with other wound healing agents may offer synergistic effects, addressing broader aspects of the healing process.

1.0.2. Mesenchymal Stem Cells (MSCs) and microvesicles

MSCs are a population of adult stem cells found in various tissues such as bone marrow, adipose tissue, and umbilical cord blood. These cells have remarkable regenerative potential. They possess the ability to differentiate into various cell types, such as bone, cartilage, and fat cells, and can secrete a plethora of growth factors and cytokines that promote tissue repair [58, 59, 60]. Microvesicles, also known as exosomes, are tiny membrane-bound sacs released by cells. They act as cellular messengers, shuttling various cargo molecules such as proteins, lipids, and RNA between cells [61, 62, 63]. MSC-derived microvesicles (MSC-MVs) contain a rich cocktail of bioactive molecules known to influence various cellular processes that are critical for wound healing [64, 65]. MSC-MVs can modulate the immune response, suppress inflammation, and promote transition to the tissue repair phase of healing [66, 67]. MSC-MVs can stimulate the proliferation and migration of skin cells (keratinocytes) and fibroblasts, which are essential for reepithelialization and collagen deposition, respectively [68, 69]. In addition, MSC-MVs can promote the formation of new blood vessels, which deliver vital oxygen and nutrients to the wound site and accelerate healing [70]. Although MSC-MVs hold promise for veterinary wound healing, certain challenges need to be addressed. MSC-MVs derived from one species may not be as effective as those derived from the other. Veterinary research should focus on species-specific MSC-MVs for optimal efficacy [71]. Determining the optimal dose and frequency of MSC-MV administration for different wound types in animals and especially in equine requires further investigation [72, 73]. In addition, the development of efficient and practical delivery methods for MSC-MVs suitable for veterinary applications, particularly in equine applications, is crucial [74]. Despite these challenges, opportunities for MSC-MVs in veterinary wound healing are promising. MSC-MVs offer a potentially less invasive approach than traditional cell therapy using live MSCs.

1.0.3. How Propolis, Nanozinc Oxide, and MSC-Derived Microvesicles Promote Wound Healing

ropolis contains various bioactive compounds, including flavonoids and phenolic acids, which suppress the production of proinflammatory mediators. This helps regulate the inflammatory response and create a more favorable environment for healing [75]. Propolis extracts have been shown to stimulate the proliferation and migration of fibroblasts, which are responsible for collagen synthesis, a crucial component of the extracellular matrix for tissue repair [39, 76]. Additionally, propolis may enhance the activity of growth factors involved in stimulating the cell proliferation and differentiation necessary for tissue regeneration [39]. Propolis exhibits broad-spectrum antibacterial activities against various wound pathogens. This helps to prevent wound infections, a significant complication that can impede healing [77]. ZnO nanoparticles possess inherent antimicrobial properties that can directly kill bacteria on the wound surface, reducing the risk of infection [78]. Studies have suggested that nZnO can regulate the inflammatory response by suppressing the production of pro-inflammatory cytokines and promoting the expression of anti-inflammatory markers. This helps to create a balanced inflammatory environment conducive to healing[50]. ZnO nano particles may stimulate the formation of new blood vessels by promoting the proliferation and migration of endothelial cells, the building blocks of blood vessels. This improved blood flow facilitates the delivery of oxygen and nutrients, which are essential for wound healing [51]. MSC-MVs contain bioactive molecules that can modulate the immune response. They can suppress excessive inflammation, while promoting the recruitment of immune cells

necessary for tissue repair [79]. MSC-MVs deliver growth factors and other signaling molecules that stimulate the proliferation and migration of skin cells (keratinocytes) and fibroblasts. This facilitates re-epithelialization (closing the wound surface with new skin cells) and collagen deposition, which are essential for rebuilding the damaged tissue [80]. In addition, MSC-MVs can promote the formation of new blood vessels by signaling endothelial cells to proliferate and migrate. This improved blood flow is crucial for delivering oxygen and nutrients to the wound site and accelerating healing [81]. Propolis, nZnO, and MSC-MVs can influence the expression and activity of growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which play key roles in stimulating cell proliferation, migration, and differentiation during wound healing. Propolis and nZnO can modulate the activity of signaling pathways such as NF-KB, which regulates the expression of pro-inflammatory genes. MSC-MVs can also influence these pathways, thereby promoting a more balanced inflammatory response. Propolis and nZnO may stimulate collagen synthesis and deposition in fibroblasts. Additionally, MSC-MVs can deliver factors that regulate the remodeling of the extracellular matrix, creating a supportive environment for tissue regeneration.

1.0.4. Propolis, Nanozinc Oxide, and MSC-MVs in Veterinary Wound Healing

Propolis, nanozinc oxide (nZnO), and mesenchymal stem cell-derived microvesicles (MSC-MVs) have been explored for their potential applications in veterinary wound healing. Propolis extracts incorporated into wound dressings or ointments may promote healing of various wounds, including surgical incisions, pressure sores, and lick granulomas in dogs, cats, and rats [82, 83, 84, 85]. ZnO nanoparticles may be incorporated into wound dressings or gels to promote healing in chronic wounds, diabetic foot ulcers, and burns in animals. One study investigated the use of an nZnO-containing ointment on wounds in horses [86, 87]. The results demonstrated faster wound closure and improved granulation tissue formation compared to conventional treatment. Several studies have explored the use of MSC-MVs in animals with wounds. The results showed significant improvements in wound healing and reduced inflammation [88].

1.0.5. Challenges and Future Directions

Propolis, nanozinc oxide (nZnO), and mesenchymal stem cell-derived microvesicles (MSC-MVs) represent a new wave of potential therapies for veterinary wound healing. However, translating this promise into routine clinical practice necessitates addressing the current challenges and exploring future research directions. Species Specificity: Propolis, nZnO, and MSC-MVs may exhibit varying efficacy across different animal species. Research specific to the target animals is crucial for optimizing their use. Dosage Optimization: Determining the optimal dose and frequency of administration for each therapy and different wound types requires further investigation. Inappropriate dosing can lead to reduced efficacy or unintended side effects. Delivery Methods: Developing efficient and practical delivery methods suitable for veterinary applications is essential. The current methods may not be ideal for all wound types or animal species. Standardization: Standardization of propolis composition, nZnO particle characteristics, and MSC-MV production protocols is necessary to ensure consistent quality and therapeutic effects. Safety Considerations: While generally considered safe, the potential side effects of propolis, nZnO at high concentrations, and long-term use of MSC-MVs require thorough investigation. Cost-effectiveness: The cost of production and administration of these therapies must be evaluated to ensure accessibility for veterinary practices and pet owners.

Conclusions

This review highlights the significance of advances in regenerative medicine for skin wound healing in animals, with an emphasis on equine applications. These collective findings highlight the promising therapeutic potential of propolis, nanozinc oxide, and mesenchymal stem cell (MSC)-derived microvesicles in promoting wound

healing in horses. Propolis demonstrates notable efficacy, attributed to its antimicrobial and anti-inflammatory properties, whereas nanozinc oxide offers a versatile and effective wound dressing material. Additionally, MSC-derived microvesicles represent a novel approach that harnesses the regenerative capabilities of stem cells for tissue repair. However, the significance of these therapies in veterinary practice cannot be understood. They offer promising alternatives to traditional wound management approaches, with the potential to accelerate healing, reduce complications, and improve overall outcomes in equine patients. Moreover, their application extends beyond wound healing to various dermatological conditions and surgical nterventions, thereby further enhancing their clinical relevance. Continued research and development efforts are warranted to optimize the efficacy, safety, and accessibility of regenerative therapies in veterinary medicine. Addressing challenges such as standardization, scalability, and regulatory considerations is paramount to their widespread adoption and integration into routine clinical practice. Ultimately, by harnessing the potential of propolis, nanozinc oxide, and MSC-derived microvesicles, we can not only advance the field of regenerative medicine but also enhance the quality of care and welfare of animals, particularly equines, in need of wound-healing interventions.

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