Resveratrol in Wound Healing Application: Cellular Effects, Mechanisms, and Dressing Innovations

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Abstract

Resveratrol (RSV), a polyphenolic compound found in various plants and fruits, has garnered significant attention for its therapeutic potential in wound healing. Known for its anti-inflammatory, antioxidant, antimicrobial, and anti-aging properties, RSV plays a pivotal role in regulating cellular and molecular processes essential for wound repair. This review explores RSV's effects on different skin cells involved in wound healing, including fibroblasts, keratinocytes, and macrophages. Mechanisms underlying RSV's benefits, such as its modulation of inflammation, promotion of angiogenesis, and enhancement of tissue regeneration, are discussed. Despite challenges like low bioavailability, innovative RSV-loaded wound dressings like hydrogels and nanovesicles show promise in enhancing its efficacy by ensuring sustained release and tissue compatibility. Further research is crucial to optimize RSV delivery systems and establish standardized treatment protocols to maximize its therapeutic benefits in wound care.

Significance | This review discusses the Resveratrol's therapeutic potential in wound healing by reducing inflammation, oxidative stress, and microbial infections, promoting tissue repair.

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1. Introduction

Resveratrol (RSV), a natural compound found in mulberries, *Polygonum cuspidatum*, grapes, and red wine, is classified as a polyphenol and phytoalexin (Kaur, A. et al., 2022; Arslaner, A., 2020). It has been extensively studied for its health benefits, showing significant anti-inflammatory, antioxidant, and anti-aging properties (Zhang, L. X. et al., 2021; Islam et al. 2024). Skin wounds, resulting from damage to the epidermal layer, trigger a well-coordinated healing process involving cellular, humoral, and molecular systems (Abdallah, F., Mijouin, L., & Pichon, C. 2017). RSV's anti-inflammatory properties may accelerate wound healing by regulating angiogenesis activity (Hecker, A. et al., 2022; Pignet, A. L. et al., 2021; Jia, Y. et al., 2022). Additionally, RSV offers antioxidant properties, providing protection against oxidative damage and offering therapeutic benefits for various wound conditions.

2. Enhancing Skin Cell Functionality: RSV's Impact on Diverse Cellular Aspects in Wound Healing

The wound healing process involves several types of cells, including endothelial cells, fibroblasts, keratinocytes, macrophages, and mesenchymal stem cells (Wen, S. et al. 2020). These cells collaborate to facilitate wound repair, each fulfilling critical roles during different stages of healing. Typically, wound healing progresses through three distinct phases: inflammation, proliferation, and remodelling activities (Jia, Y., 2022). During the inflammation phase, the body's immune response triggers the recruitment of

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white blood cells to combat infections and remove debris from the wound site. In the proliferation phase, new tissue is generated to fill the wound and promote its closure. Finally, in the remodelling phase, the newly formed tissue undergoes strengthening and reorganization to restore normal tissue architecture and function. The duration of the healing process varies depending on factors such as the size and severity of the wound, ranging from a few days for minor wounds to several months for more extensive injuries.

2.1 Fibroblasts

Fibroblasts are crucial dermal cells central to wound healing, transitioning from inflammation to tissue remodelling. They express key genes like PDGFR and COL1A (Augustine et al., 2020), secreting growth factors, cytokines, collagen, and other matrix components to aid re-epithelialization. As the predominant dermal cell type, fibroblasts play a fundamental role in wound recovery, progressing through the stages of haemostasis, inflammation, granulation tissue formation, and tissue remodelling. They actively express PDGFR and COL1A genes during their quiescent state. Research indicates that dermal fibroblasts enhance wound healing by releasing growth factors, cytokines, collagen, and ECM components from the inflammatory phase until complete re-epithelialization of the injured tissue (Tao, K., et al. 2015).

2.2 Keratinocytes

Keratinocytes, resilient epidermal cells that defend against pathogens and UV radiation, play a crucial role in healing burn wounds by restoring the skin barrier. Their migration and proliferation are essential for rebuilding this barrier and stimulating fibroblast growth, thereby enhancing wound healing. Known for their resistance to pathogens and their ability to protect deeper skin layers from UV damage, keratinocytes are valuable in burn wound care. They migrate and proliferate towards the wound edge, contributing to the reconstruction of the epidermal barrier. This process is facilitated by keratinocyte growth factor, which also promotes fibroblast proliferation through paracrine signalling (Hecker, A. et al., 2022). Additionally, compounds like RSV aid in skin repair by reducing inflammation and oxidative stress caused. RSV could accelerate wound closure through VEGF-mediated angiogenesis (Schilrreff, P., & Alexiev, U. (2022). Quiet data controller 1 (SIRT1), which plays a crucial part in keeping up vitality adjust within the body, has been distinguished as a potential activator of RES. SIRT1, involved in keratinocyte and fibroblast growth during wound healing, operates via NO-dependent pathways (Prabhakar, P. K., et al. 2020).

2.3 Macrophages

Macrophages, essential immune cells in wound healing, initially release pro-inflammatory cytokines like IL-6, IL-1, and TNF. However, excessive activation can lead to chronic inflammation and impaired healing (Ding et al., 2022; Bártolo, 2022; Resnik et al., 2020). RSV helps regulate macrophage activation, reducing the production of pro-inflammatory proteins and promoting faster healing, especially in diabetic patients. Macrophages play a critical role in combating infections and restoring tissue balance during wound repair. They serve as the first line of defense by engulfing pathogens through phagocytosis. RSV's activation of SIRT1 in macrophages has shown to mitigate inflammatory responses induced by stimuli like lipopolysaccharide (LPS) (López-Hernández & Rodríguez-Bernaldo de Quirós, 2018). Pterostilbene, a derivative of RSV, also aids in reversing epigenetic changes in macrophages and limiting pro-inflammatory protein production, thereby enhancing wound healing, particularly in diabetic conditions.

3 Understanding the Mechanisms Driving RSV's Positive Impact on Wound Healing

3.1 Anti-Inflammatory Effect

Inflammation, driven by macrophages, is a natural response to external challenges, often induced in research by lipopolysaccharide (LPS) (Rafe et al., 2019). RSV has been shown to reduce the production of inflammatory cytokines such as COX-2, PGE2, TNF-α, and IL-1. Studies using a rat burn wound model found that RSV-loaded hydrogels decreased inflammation-related markers (Pignet et al., 2021). RSV's anti-inflammatory properties are crucial for wound healing, with SIRT1 playing a pivotal role. It's noted to reduce APE1/Ref-1 expression, a SIRT1 target, and promote its nuclear translocation in LPS-stimulated monocytes, suggesting SIRT1 activation by RSV may regulate collagen synthesis, accelerate wound closure, and mitigate scarring (Pinheiro et al.; Christovam et al., 2019). Moreover, RSV's effects extend beyond direct antioxidant actions, possibly involving interactions with epidermal growth factor receptor (EGFR) pathways in cell nuclei and cytoplasm (Lee et al., 2022).

3.2 Antimicrobial Effect

Timely intervention is critical in preventing local infections during the initial stages of tissue damage, a vital aspect of wound care. Common pathogens like *S. aureus, P. aeruginosa, and C. albicans* underscore the urgency for prompt administration of antimicrobial agents (Shevelev et al., 2020; Vestergaard & Ingmer, 2019). RSV, a natural plant extract, exhibits antimicrobial properties believed to disrupt cell membrane potential and inhibit DNA synthesis, effective against both bacteria and fungi (Abedini et al., 2021). However, its potency against *C. albicans* appears relatively weaker compared to *S. aureus* and *P. aeruginosa*, possibly due to heightened inflammatory responses in fungal infections. RSV also surpasses other plant extracts in antibacterial efficacy, notably boosting macrophage and fibroblast populations crucial for accelerating wound healing and restoring epidermal and follicular structures (Shevelev et al., 2020). Its effectiveness against *Stenotrophomonas* in burn wounds further underscores RSV's potential as an effective antimicrobial treatment.

3.3 Antioxidant Effect

Oxidative stress and inflammation are closely intertwined and pivotal in wound healing processes. Excessive reactive oxygen species (ROS) can delay healing (Dunnill et al., 2017; Cano et al., 2018). RSV, a potent natural antioxidant, has demonstrated protective effects against various diseases by promoting Nrf2 aggregation in the nucleus and enhancing Mn-SOD production to reduce cellular ROS levels (Farkhondeh et al., 2020). These benefits were evident in a rat model of skin burn injuries. RSV's anti-inflammatory and antioxidant properties are crucial for mitigating inflammation and supporting wound healing. It acts by modulating oxidative stress pathways, underscoring its potential therapeutic role in managing oxidative damage-related conditions and promoting tissue repair.

3.4 Antiageing Effect

As people age, the likelihood of persistent, non-healing skin lesions rises. Research indicates that RSV exhibits anti-aging properties in tissue injury healing (Stacchiotti et al., 2018). Studies in young rats suggest intermittent RSV dosing has minimal impact on wound healing, while continuous therapy in aged rats reduces senescence markers like p16 and p21. This regimen enhances cell proliferation in the epidermis and around hair follicles, highlighting RSV's potential anti-aging role in wound recovery (Zhao et al., 2017). Moreover, RSV promotes angiogenesis and accelerates wound healing by stimulating growth of CD31+ vascular endothelial cells through AMPK activation, as observed in granulation tissue CD31 mapping (Parsamanesh et al., 2021; Huang et al., 2019). Combined with other phytonutrients, RSV further enhances its anti-aging effects in skin damage scenarios.

4 RSV's Potential in Advanced Wound Healing Dressings

RSV holds promise in wound healing applications despite challenges like low bioavailability and water-insolubility. To enhance its effectiveness, various advanced wound dressings have been developed, including hydrogels, platforms, Dermalix, nanovesicles, and wafers, tailored to optimize RSV delivery (Chen et al., 2022). These dressings are designed to address specific delivery challenges and ensure sustained release, compatibility with surrounding tissues, and therapeutic efficacy (Ávila-Salas et al., 2019). Hydrogels, such as those incorporating chitosan, offer biocompatibility, biodegradability, and excellent water absorption properties essential for wound healing (Boominathan & Sivaramakrishna, 2017). They maintain structural integrity while absorbing wound exudates and can be tailored into smart hydrogels responsive to environmental cues like pH and temperature (Dickmeis, Kauth, & Commandeur, 2021). Combining chitosan with sodium hyaluronate and RSV enhances these properties, improving tissue adherence and therapeutic outcomes (Yang et al., 2022).

Innovative approaches also include using gelatin and cyclodextrin molecules to create hydrogels with desirable shear strength and injectability (Zheng et al., 2020). Moreover, polyvinyl alcohol (PVA) cryogel membranes derived from RSV-loaded hydrogels improve scaffold properties, serving as effective carriers for bioactive substances and enhancing wound healing (Poornima & Korrapati, 2017). Traditional wound dressings like gauze and bandages, while widely used, often fall short in terms of moisturization and infection control. They can also adhere to wounds, causing discomfort during changes and potentially damaging new tissue. Advancements in medical technology have spurred the development of these novel dressings to overcome these limitations. RSV’s anti-inflammatory properties are crucial in wound healing, aiding in reducing inflammation and promoting tissue repair (Parsamanesh et al., 2021; Zhao, C.C., et al., et al.2020). By integrating RSV into various forms of advanced wound dressings, researchers aim to harness its full therapeutic potential, enhancing angiogenesis and granulation tissue formation crucial for healing.

To establish RSV as a viable treatment option, ongoing research focuses on refining drug delivery systems for both topical and systemic applications. This includes optimizing RSV’s bioavailability and ensuring its sustained release within wound environments to maximize therapeutic benefits. By meeting stringent criteria such as biocompatibility, moisture management, and infection prevention, these next-generation wound dressings pave the way for more effective wound care strategies. The development of RSV-infused wound dressings represents a significant advancement in wound management. By overcoming RSV’s delivery challenges and leveraging its therapeutic properties, these innovative dressings offer promising avenues for improving outcomes in wound healing, reducing complications, and enhancing patient recovery.

5 Conclusion

RSV emerges as a promising therapeutic agent for enhancing wound healing due to its multifaceted biological effects. By targeting inflammation, oxidative stress, and microbial infections, RSV facilitates the intricate process of tissue repair and regeneration. Its ability to stimulate cell proliferation, modulate cytokine production, and promote angiogenesis underscores its potential in improving clinical outcomes for various wound types. Despite challenges associated with its bioavailability, recent advancements in wound dressing technologies offer innovative solutions to harness RSV's full therapeutic potential. Future research should focus on refining delivery systems, optimizing dosages, and conducting clinical trials to validate RSV's efficacy and safety in diverse wound healing applications. Ultimately, integrating RSV into clinical practice holds promise for revolutionizing wound care strategies and improving patient outcomes worldwide.

Author contributions

N.M. and R.B.S.M.N.M. contributed equally to this work. N.M. conceived the study and designed the experiment. R.B.S.M.N.M. conducted the data analysis and interpretation. N.M. provided critical revisions to the manuscript and assisted with data collection. Both authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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