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Nanoparticle-Based Therapeutics for Enhanced Burn Wound Healing: A Comprehensive Review

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Abstract: Burn wounds pose intricate clinical challenges due to their severity and high risk of complications, demanding advanced therapeutic strategies beyond conventional treatments. This review discusses the application of nanoparticle-based therapies for optimizing burn wound healing. We explore the critical phases of burn wound healing, including inflammation, proliferation, and remodeling, while summarizing key nanoparticle-based strategies that influence these processes to optimize healing. Various nanoparticles, such as metal-based, polymer-based, and extracellular vesicles, are evaluated for their distinctive properties and mechanisms of action, including antimicrobial, anti-inflammatory, and regenerative effects. Future directions are highlighted, focusing on personalized therapies and the integration of sophisticated drug delivery systems, emphasizing the transformative potential of nanoparticles in enhancing burn wound treatment.

Keywords: nanomedicine, burns, wound, regeneration, therapy

Introduction

Burn wounds are among the most severe and complex injuries encountered in clinical practice. Their complexity stems from a multifaceted healing process that requires a precise balance between different stages: hemostasis, inflammation, proliferation, and remodeling.[1] Each of these stages should occur in a coordinated manner to achieve optimal healing. However, the high risk of complications, including infections, hypertrophic scarring, and chronic non-healing wounds, can exacerbate the difficulty of treatment, making wound healing highly unpredictable and patient-dependent.[2] Traditional burn wound treatments, such as surgical debridement, skin grafts, and topical antimicrobial agents, frequently fall short in comprehensively addressing these challenges, highlighting the urgent need for innovative therapeutic strategies.[3,4]

Nanotechnology has emerged as a promising field with the potential to advance burn wound care. Nanoparticles, characterized by their nanoscale size and unique physicochemical properties, offer distinct advantages for medical applications.[5] Their small size allows them to penetrate deeper into tissues and interact closely with cellular components, enhancing their therapeutic potential. These advantages include a high surface area-to-volume ratio, which enhances their reactivity and interaction with biological tissues, and the ability to be functionalized with various therapeutic agents, enabling targeted and controlled delivery. The versatility of nanoparticles makes them particularly well-suited for addressing the specific challenges associated with burn wound management.[6–8]

Nanoparticles can be engineered to deliver therapies that modulate these critical processes.[9] For instance, metal-based nanoparticles, such as silver and titanium dioxide, have demonstrated potent antimicrobial properties, significantly reducing the risk of infection in burn wounds.[10–12] Silver nanoparticles, in particular, are well-known for their broad-spectrum antimicrobial activity against bacteria, fungi, and viruses. These nanoparticles can be incorporated into wound dressings or topical formulations, providing a sustained release of antimicrobial agents directly at the wound site.[11]

In addition to infection control, managing inflammation is another crucial aspect of burn wound healing.[13] Prolonged or excessive inflammation can delay healing and lead to chronic wounds. Polymer-based nanoparticles can be designed to deliver anti-inflammatory agents in a controlled manner, thereby reducing inflammation and promoting a conducive environment for

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healing.[14,15] For example, nanoparticles loaded with corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) can provide sustained anti-inflammatory effects, reducing the need for frequent drug administration and minimizing systemic side effects.[16]

Tissue regeneration is a vital component of the healing process, and nanoparticles can play a significant role in promoting this aspect of wound repair. Growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), are essential for cell proliferation, angiogenesis, and tissue remodeling.[17,18] Nanoparticles can be engineered to deliver these growth factors in a controlled and sustained manner, enhancing their bioavailability and therapeutic efficacy. Moreover, extracellular vesicles (EVs) derived from stem cells have shown promise in promoting cell proliferation and differentiation, further aiding tissue regeneration. These vesicles can be loaded into nanoparticles, providing a targeted delivery system that enhances their regenerative potential.[19–21]

While nanoparticle-based therapies have been explored in various biomedical contexts, this review focuses on their novel applications specifically tailored for burn wound healing. We We aim to elucidate how nanoparticles can target different stages of burn healing, offering enhanced therapeutic outcomes. Metal-based nanoparticles, such as silver and titanium dioxide, are discussed for their antimicrobial properties and role in infection control. Polymer-based nanoparticles are explored for their ability to deliver anti-inflammatory agents and growth factors, promoting a favorable healing environment. Additionally, the potential of EVs-loaded nanoparticles in enhancing tissue regeneration is highlighted. In contrast to traditional treatments, this review explores how recent advances in nanoparticle-based technologies—such as personalized drug delivery systems and innovative combinations of nanoparticles with extracellular vesicles (EVs)—have the potential to significantly improve burn wound healing outcomes.

Pathology of Burn Wounds

Burn wounds present significant clinical challenges due to their complex and multifaceted healing process, which can be divided into three primary stages: inflammation, proliferation, and remodeling.[22,23] Each stage is crucial for the successful recovery of the wound and requires a precise and coordinated sequence of cellular and molecular events (Figure 1).[24] A delay or disruption in any one of these stages can lead to complications, such as infection, delayed healing, or abnormal scar formation.

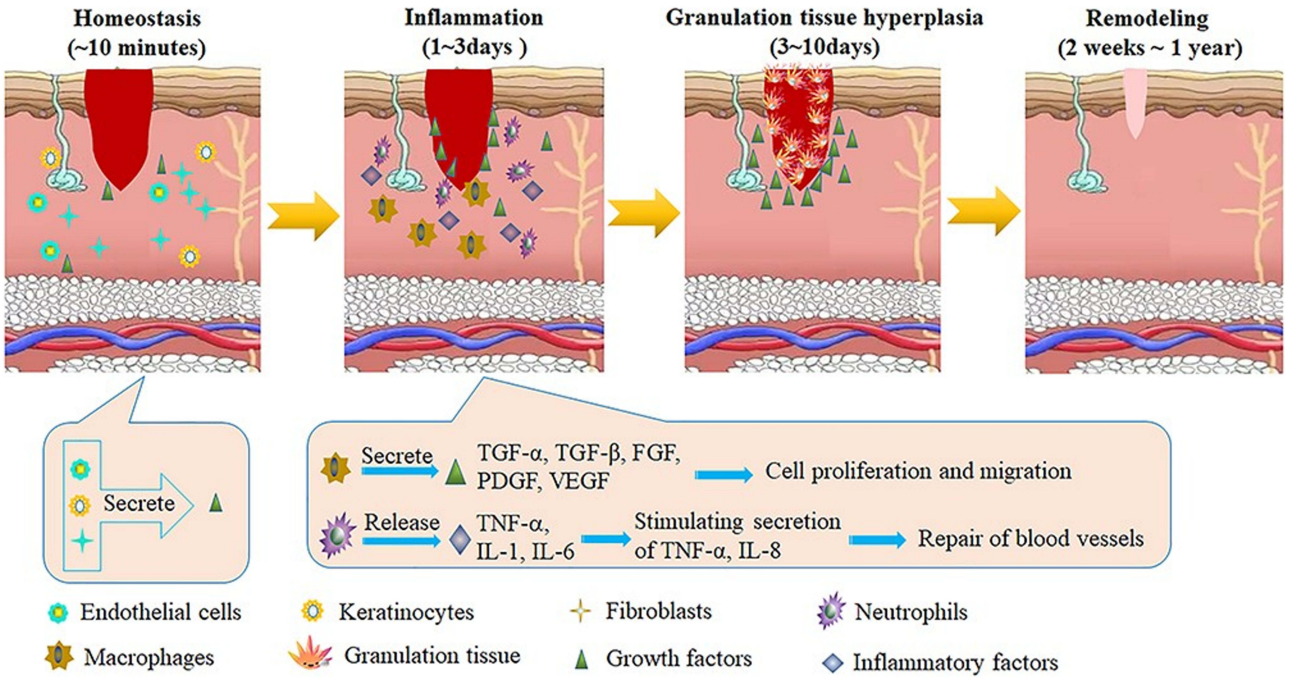

Figure 1 The mechanisms involved in the healing of burn wounds include the actions of various factors: TGF-α (transforming growth factor alpha), FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor), IL-8 (interleukin 8), and TNF-α (tumor necrosis factor alpha). Reproduced from Huang R, Hu J, Qian W, Chen L, Zhang D. Recent advances in nanotherapeutics for the treatment of burn wounds. *Burns Trauma*. 2021;9:tkab026. Creative Commons.[24]

The initial inflammation stage begins immediately after the injury, characterized by the rapid activation of the immune system.[25] This phase involves the recruitment of neutrophils and macrophages to the wound site, where they play a significant role in clearing debris, pathogens, and damaged tissue. The inflammatory response is essential for preventing infection and setting the stage for subsequent healing processes.[26,27] Neutrophils are among the first responders, arriving at the wound site within minutes to hours, where they exert antimicrobial effects and release signals that attract macrophages.[28] Macrophages then take over to phagocytose remaining debris and secrete cytokines and growth factors that promote tissue repair.[29]

Following the inflammation stage, the wound enters the proliferation phase, where new tissue begins to replace the damaged one.[30] This stage is marked by the proliferation of several cell types, including fibroblasts, keratinocytes, and endothelial cells. Fibroblasts are responsible for synthesizing collagen and extracellular matrix components, forming granulation tissue that provides a scaffold for new tissue formation. Keratinocytes proliferate and migrate across the wound bed to re-establish the epidermal barrier in a process known as re-epithelialization.[31] Endothelial cells contribute to angiogenesis, the formation of new blood vessels, which is vital for supplying nutrients and oxygen to the healing tissue.[32] Together, these processes result in the formation of granulation tissue, re-epithelialization, and angiogenesis, collectively promoting wound closure and restoration of skin integrity.

The final stage of burn wound healing is remodeling, which can last for months to years. During this phase, the newly formed tissue undergoes maturation and reorganization to enhance its strength and functionality.[33] Collagen fibers, initially laid down in a haphazard manner, become realigned and cross-linked to form a more structured and resilient matrix.[2] Myofibroblasts, specialized cells within the granulation tissue, facilitate wound contraction by pulling the edges of the wound together, thereby reducing its size.[34] The result is the formation of durable scar tissue that provides structural support and protection. However, excessive remodeling can lead to hypertrophic scarring or keloid formation, which may cause functional and aesthetic impairments.

Several factors influence the healing process of burn wounds, making it a highly individualized and variable process. Multiple factors, including the extent of burn injury, infection, and individual patient characteristics, significantly impact the healing process. The severity and depth of the burn are primary determinants of the extent of tissue damage and the complexity of the repair mechanisms required.[35] Superficial burns, such as first-degree burns, typically heal with minimal intervention, while deeper burns, such as third-degree burns, may require extensive medical intervention, including skin grafts.[22] Infection poses a major threat to the healing process, as pathogens can exacerbate the inflammatory response, leading to prolonged inflammation and delayed healing.[36] Ensuring a sterile environment and using antimicrobial agents are critical for preventing infections in burn wounds.

Patient health and comorbidities also play a significant role in burn wound healing. Conditions such as diabetes, poor nutrition, and immunosuppression can impair the body's natural healing capabilities, leading to delayed or incomplete healing. Chronic conditions may necessitate specialized treatment strategies to promote effective wound closure. Diabetic patients, for instance, often experience impaired blood flow and neuropathy, which can complicate wound healing.[37] Malnutrition can deprive the body of essential nutrients needed for cellular repair and immune function, further hindering the healing process.[38] Immunosuppressed individuals may struggle to mount an effective immune response, increasing their susceptibility to infections and complicating wound management.

Age is another critical factor influencing burn wound healing. Younger patients typically exhibit more robust regenerative abilities and heal faster compared to older patients.[39] In pediatric patients, the skin's higher elasticity and better overall health contribute to more efficient healing. In contrast, older patients may experience slower recovery due to decreased cellular turnover, reduced collagen production, and a general decline in physiological functions.[40] The presence of age-related comorbidities, such as cardiovascular disease and diabetes, can further complicate the healing process in elderly patients.

Types of Nanoparticles Used in Burn Wound Treatment

Metal-Based Nanoparticles

Metal-based nanoparticles have attracted extensive attention for their unique properties and broad applications, particularly in the treatment of burn wounds.[41,42] These nanoparticles offer distinct advantages due to their antimicrobial efficacy, biocompatibility, and ability to enhance the healing process.

Silver Nanoparticles

Silver nanoparticles (AgNPs) have shown substantial promise in burn wound treatment, primarily due to their potent antibacterial properties and ability to promote tissue regeneration.[43] AgNPs are effective against a wide range of bacteria, including multidrug-resistant strains, making them invaluable in preventing and treating infections in burn wounds (Figure 2). One approach is the development of an injectable antibacterial hydrogel that combines asiaticoside-loaded liposomes with ultrafine AgNPs. This hydrogel promotes enhanced healing in infected burn wounds through a sustained

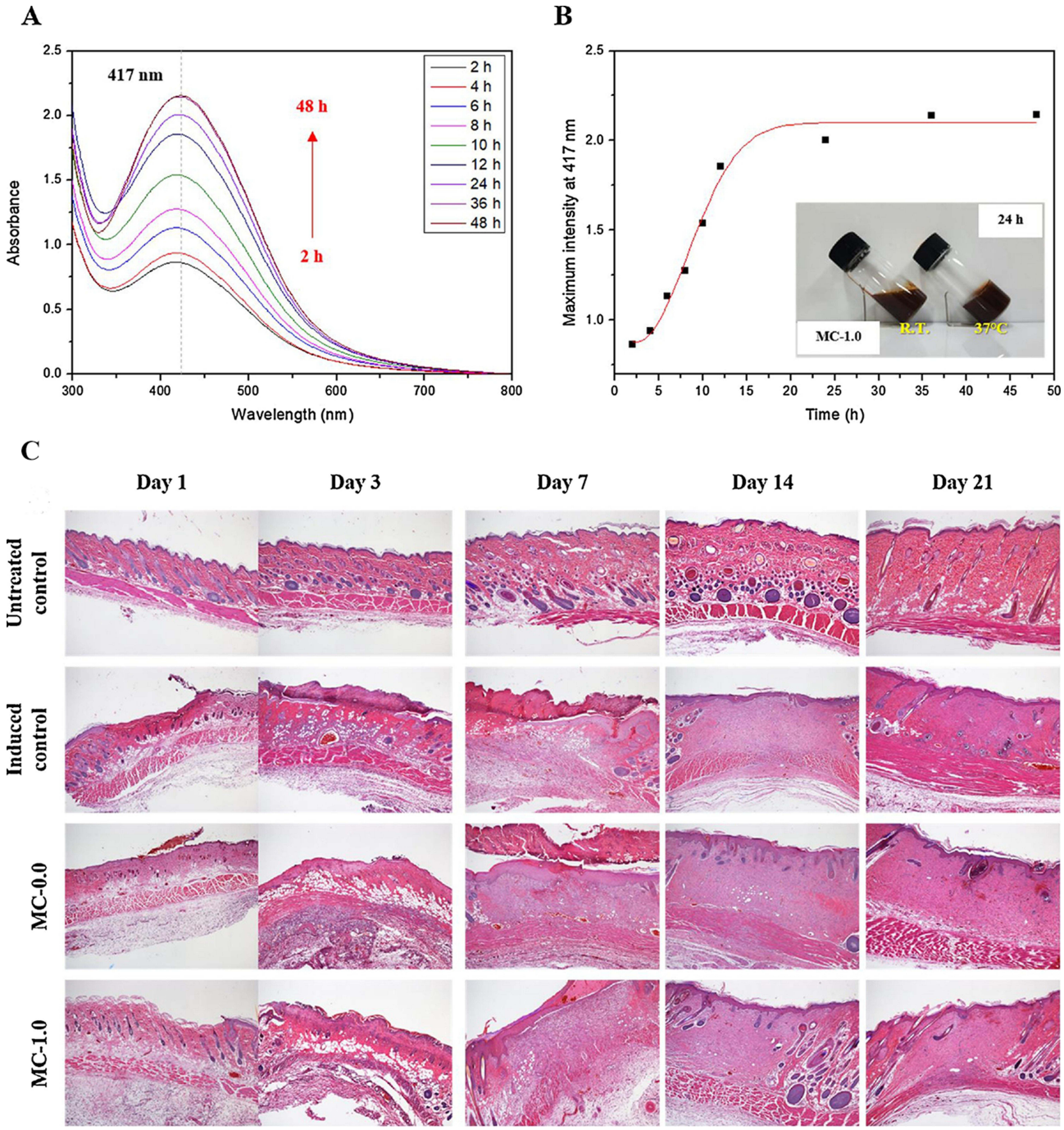

Figure 2 An example of AgNPs in burn wound. (**A** and **B**) UV–vis absorption spectra of silver oxide NPs synthesized from an MC solution with 1.0 wt% silver acetate over 48 hours. (**C**) Evaluation of the healing effects of ointments on burn-induced skin damage through histopathological analysis using Hematoxylin and Eosin (H&E) staining (x40). Reprinted from *Carbohydr Polym*, volume 181, Kim MH, H Park HC. Injectable methylcellulose hydrogel containing silver oxide nanoparticles for burn wound healing. 579–586, copyright 2018, with permission from Elsevier.[43]

release of silver ions (Ag+), which not only helps to combat infection but also stimulates cellular activities like migration and angiogenesis, crucial for tissue repair. In vivo studies demonstrate its superior performance compared to standard treatments, highlighting its potential as a cutting-edge therapeutic option[44] Additionally, a biodegradable gelatin/silver nanoparticle composite cryogel has shown remarkable properties. This cryogel exhibits excellent antibacterial and antibiofilm activities, effectively addressing the challenges of high exudate production in burn wounds. Its high water absorption capacity allows for optimal moisture balance, while its hemostatic capabilities are vital for managing blood loss, particularly in severe injuries. Experimental models have confirmed its effectiveness in promoting wound contraction, collagen deposition, and angiogenesis.[45] Another promising approach is a sandwich-structured composite wound dressing with AgNPs firmly anchored to prevent systemic toxicity while ensuring sustained antimicrobial activity. This dressing has demonstrated long-term efficacy in reducing infection rates and enhancing healing in porcine models of severe burns.[46]

Radiosterilized porcine skin functionalized with AgNPs represents another new approach. This method effectively prevents infections in deep burns and shows substantial antibiofilm effects against multidrug-resistant *Pseudomonas aeruginosa* while maintaining a favorable cytotoxicity profile.[47] The use of radiosterilized pig skin impregnated with AgNPs also serves as a scaffold for autologous skin cells, promoting extracellular matrix deposition and improving overall wound healing in both pre-clinical and clinical settings.[48] Collectively, these studies underscore the significant potential of AgNPs in developing advanced wound dressings. These dressings not only exhibit strong antibacterial properties but also effectively promote wound healing, making them highly valuable for managing burn injuries. The incorporation of AgNPs into various delivery systems and materials enhances their efficacy and expands their applications in burn wound care.

Gold Nanoparticles

Gold nanoparticles (AuNPs) have emerged as potent agents for enhancing burn wound treatment due to their unique properties and potential to improve therapeutic outcomes.[49] These nanoparticles are renowned for their biocompatibility, ease of surface modification, and ability to serve as carriers for various therapeutic agents, making them highly effective in addressing the complex requirements of burn wound healing.[50] A key function is their ability to improve the delivery of vascular endothelial growth factor (VEGF), a vital protein for angiogenesis and tissue regeneration. AuNPs can be engineered with negatively charged surfaces, which facilitates the efficient transdermal delivery of VEGF across the skin barrier, significantly boosting wound repair by enhancing vascularization. This targeted delivery helps overcome the limitations associated with traditional VEGF administration methods, which often struggle to reach lesion sites effectively.[51] The surface modification of AuNPs for targeted delivery emphasizes their adaptability and effectiveness in enhancing specific healing processes in burn wounds (Figure 3).

The therapeutic potential of phytochemical-capped AuNPs has also been explored with promising results for skin regeneration in both surgical and burn wounds. These Phyto-AuNPs demonstrated significant improvements in skin regeneration, characterized by a thicker epidermis, reduced levels of metalloproteinase-1 (MMP-1), and increased activity of superoxide dismutase (SOD). These findings indicate that Phyto-AuNPs can modulate the wound healing environment, reducing matrix degradation while enhancing antioxidant defenses, which are crucial for tissue repair.[52] The use of phytochemicals in capping AuNPs highlights the potential for combining nanotechnology with natural compounds to achieve synergistic healing effects.

Additionally, the environmentally friendly "green" synthesis of AuNPs using plant extracts, such as Tragopogon dubius, not only makes the production process sustainable but also imbues these nanoparticles with notable antibacterial properties. The synthesized AuNPs have been shown to effectively reduce bacterial loads, particularly against pathogens like Staphylococcus aureus, which is commonly involved in wound infections. By lowering the bacterial presence in burn wounds, AuNPs promote a more conducive environment for healing, further facilitating tissue regeneration and repair.[53] This method not only provides a sustainable approach to nanoparticle synthesis but also enhances the biological activity of AuNPs, broadening their applicability in burn wound treatment.

These studies collectively illustrate the versatility and promising outcomes of AuNPs in burn wound healing. The ability of AuNPs to enhance various aspects of the healing process, from promoting angiogenesis and tissue regeneration to providing antibacterial protection, underscores their potential as multifaceted therapeutic agents. However, while

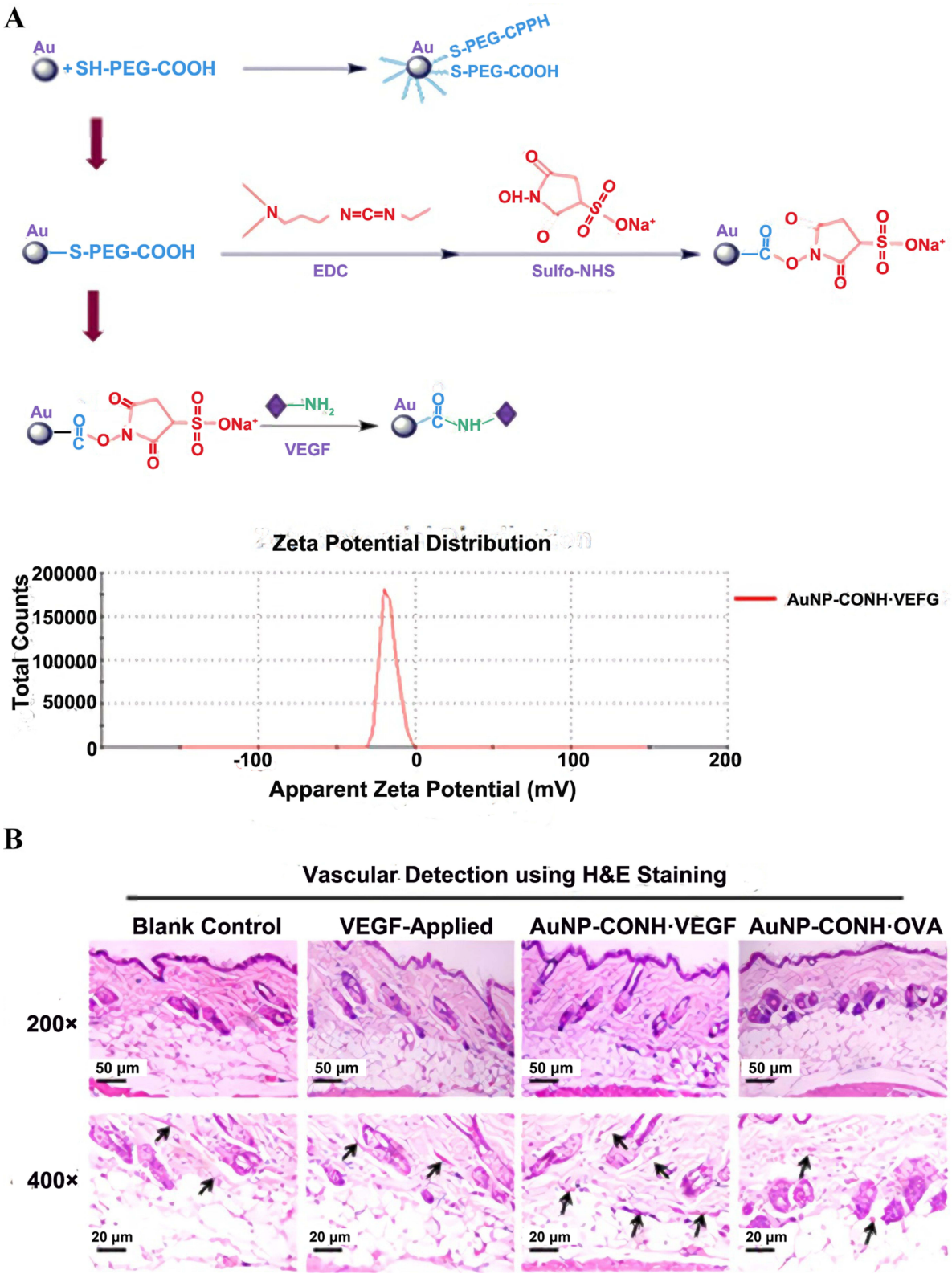

Figure 3 Representative example of AuNPs in the treatment of burn wound. (**A**) The synthesis process for AuNPs-COOH with VEGF, and the Zeta potential measurement after conjugation of AuNP-PEG-COOH with VEGF (AuNP-CONH-VEGF). (**B**) H&E staining was conducted on skin cross sections 7 days after transdermal treatment with blank control, VEGF-Applied, AuNP-CONH-VEGF, and AuNP-CONH-OVA. Scale bars were set at 50 μm (top panels) and 20 μm (bottom panels). Reproduced with permission from Chen Y, Gao J, Zhang Z, et al. Transdermal Vascular Endothelial Growth Factor Delivery with Surface Engineered Gold Nanoparticles. *ACS Appl Mater Interfaces*. 2017;9:5173–5180. Copyright © 2017 American Chemical Society.[51]

initial findings are encouraging, further research is necessary to fully understand the mechanisms by which AuNPs exert their effects and to optimize their use in clinical settings.

Zinc Oxide Nanoparticles

Advances in nanotechnology have highlighted the potential of zinc oxide nanoparticles (ZnO NPs) in enhancing burn wound treatment due to their antimicrobial, antioxidant, and wound-healing properties. Research has shown that a cream formulated with ZnO NPs and calendula extract significantly promotes tissue regeneration and fibroblast proliferation in burn-injured Wistar rats. This indicates that ZnO NPs not only possess inherent antimicrobial and antioxidant properties but also work synergistically with calendula to enhance wound healing processes.[54] In another approach, incorporating ZnO NPs into wheat gluten films enriched with vitamins A and E has demonstrated substantial benefits in wound healing, including improved wound contraction, re-epithelialization, and collagen deposition in mouse models. The vitamins may enhance the antioxidant effects and cellular signaling pathways involved in healing, thereby creating a robust platform for advanced wound care materials.[55] The combination of ZnO NPs with essential vitamins suggests a comprehensive strategy to enhance various aspects of wound healing.

Further research has explored incorporating ZnO NPs with biopolymers to develop gels with enhanced rheological properties and improved burn wound healing. These formulations demonstrated superior mechanical stability and facilitated more effective wound management.[56,57] Integrating biopolymers with ZnO NPs provides a versatile platform for developing advanced wound care materials. The immobilization of ZnO NPs alongside bromelain on silk fibroin nanofibers has resulted in a highly effective antibacterial and anti-inflammatory dressing for second-degree burns. This dressing not only provides a physical barrier against infection but also releases ZnO NPs and bromelain gradually, which can modulate inflammatory responses and promote fibroblast activity—essential for effective healing.[58] The combination of ZnO NPs with proteolytic enzymes like bromelain represents a novel approach to modulating the wound environment for improved healing outcomes. Flexible films composed of chitosan, alginate, and bentonite, integrated with ZnO NPs, have also been developed. These films demonstrated excellent antibacterial activity and promoted dermal burn healing, emphasizing the importance of film composition in wound treatment efficacy.[59] The use of natural polymers in combination with ZnO NPs provides a biocompatible and effective means of treating burn wounds (Figure 4). Additionally, a new bioactive hydrogel enriched with ZnO NPs and vitamin C derived from decellularized extracellular matrix has shown remarkable results in burn wound management in rabbits. The hydrogel's formulation promotes significant wound contraction and reduces inflammation while enhancing collagen synthesis, highlighting the importance of ZnO NPs in facilitating tissue repair and regeneration.[60] Overall, the integration of ZnO NPs into various formulations underscores their potential as versatile agents in burn wound healing, operating through mechanisms that enhance cell proliferation, reduce infection, and accelerate tissue regeneration, making them a promising option for advanced therapeutic strategies in wound care.

Titanium Dioxide Nanoparticles

Recent developments in nanotechnology have significantly advanced the treatment of burn wounds, particularly through the application of titanium dioxide nanoparticles (TiO_2 NPs). These nanoparticles are increasingly recognized for their multifunctional properties, which offer new avenues for improving wound care. One noteworthy strategy involves creating membranes from chitosan and cellulose that are integrated with sulfur-doped TiO_2 NPs. Utilizing a freeze gelation technique, these membranes exhibit significant swelling capacity, biodegradability, and proangiogenic properties. The inclusion of TiO_2 NPs in these membranes has been shown to promote angiogenesis, the formation of new blood vessels, which is vital for supplying nutrients and oxygen to the healing tissue. Additionally, TiO_2 NPs can enhance cellular metabolic activities, fostering an environment conducive to effective wound healing.[61] In another development, multifunctional polycaprolactone yolk-shell particles (YSPs) have been engineered to incorporate TiO_2-Ag nanoparticles and Ganoderma lucidum polysaccharides. These components are included for their antibacterial and antioxidant properties, while iron oxide nanoparticles are added for their photothermal therapeutic effects. The YSPs exhibit exceptional biocompatibility along with potent antioxidant and antibacterial properties.[62] Their efficacy in improving burn wound healing has been notably enhanced when combined with laser-assisted therapy, underscoring the potential of TiO_2 NPs in conjunction with other therapeutic modalities (Figure 5). Furthermore, a hybrid sponge dressing has been developed by combining dopamine-modified hyaluronic acid, gelatin, polyhexamethylene

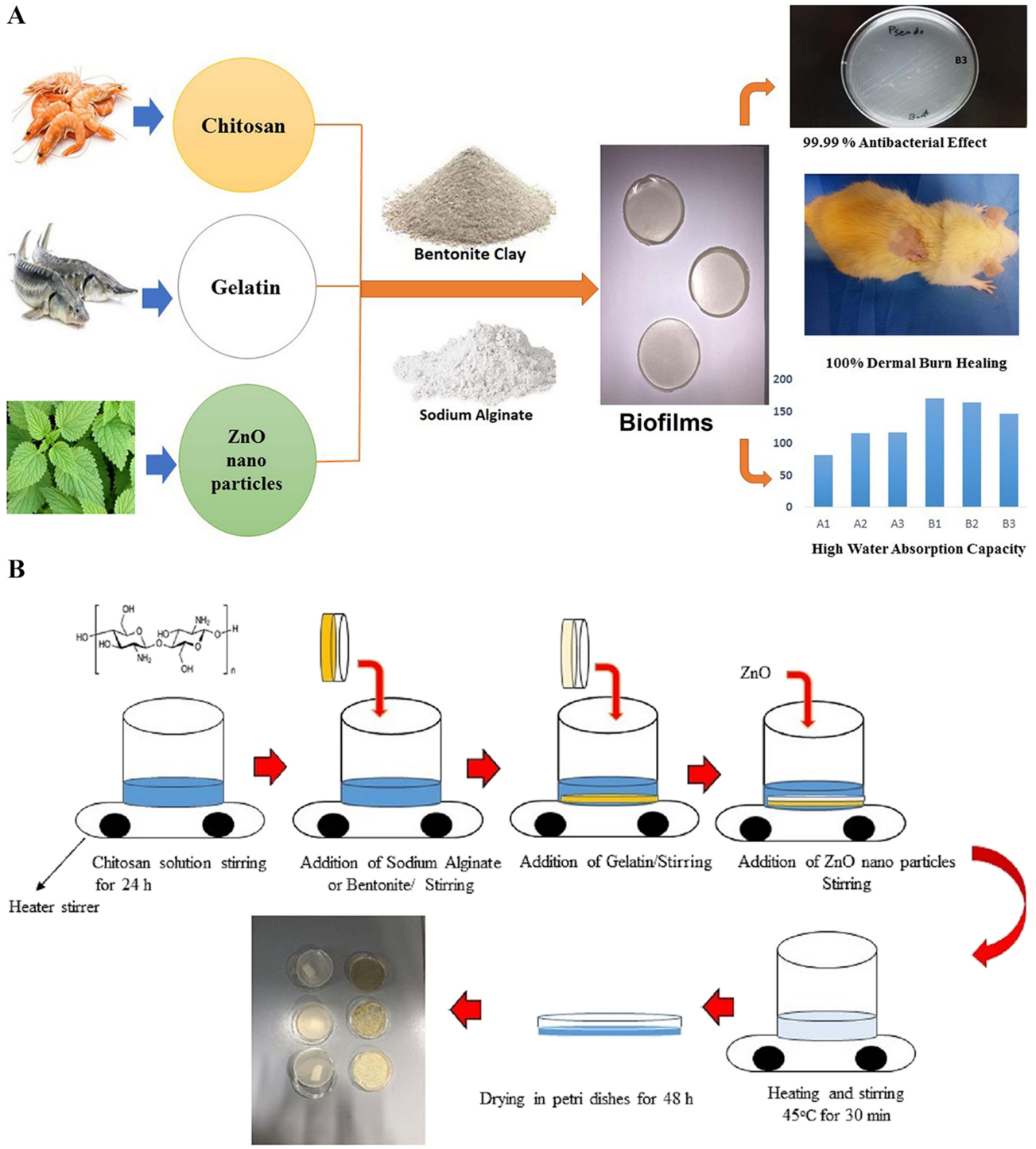

Figure 4 An example of ZnO NPs in treating burn wounds. (**A**) Highly flexible and transparent chitosan/bentonite films, integrated with gelatin and ZnO nanoparticles obtained through green synthesis, were developed as an effective skin dressing for treating burn injuries. (**B**) A schematic illustration of the composite film preparation process. Reprinted from *Int J Biol Macromol*, volume 184, Nozari M, Gholizadeh F. Studies on novel chitosan/alginate and chitosan/bentonite flexible films incorporated with ZnO nano particles for accelerating dermal burn healing: in vivo and in vitro evaluation. 235–249, Copyright 2021, with permission from Elsevier.[59]

biguanide, and TiO_2 NPs. This innovative dressing features remarkable mechanical strength, effective wet adhesion, and strong antibacterial properties. The ability of the dressing to scavenge reactive oxygen species (ROS) is particularly beneficial, as excess ROS can impede healing and promote inflammation. In vivo studies have demonstrated that this multifunctional sponge dressing significantly accelerates the healing of infected full-thickness burn wounds by promoting key processes such as

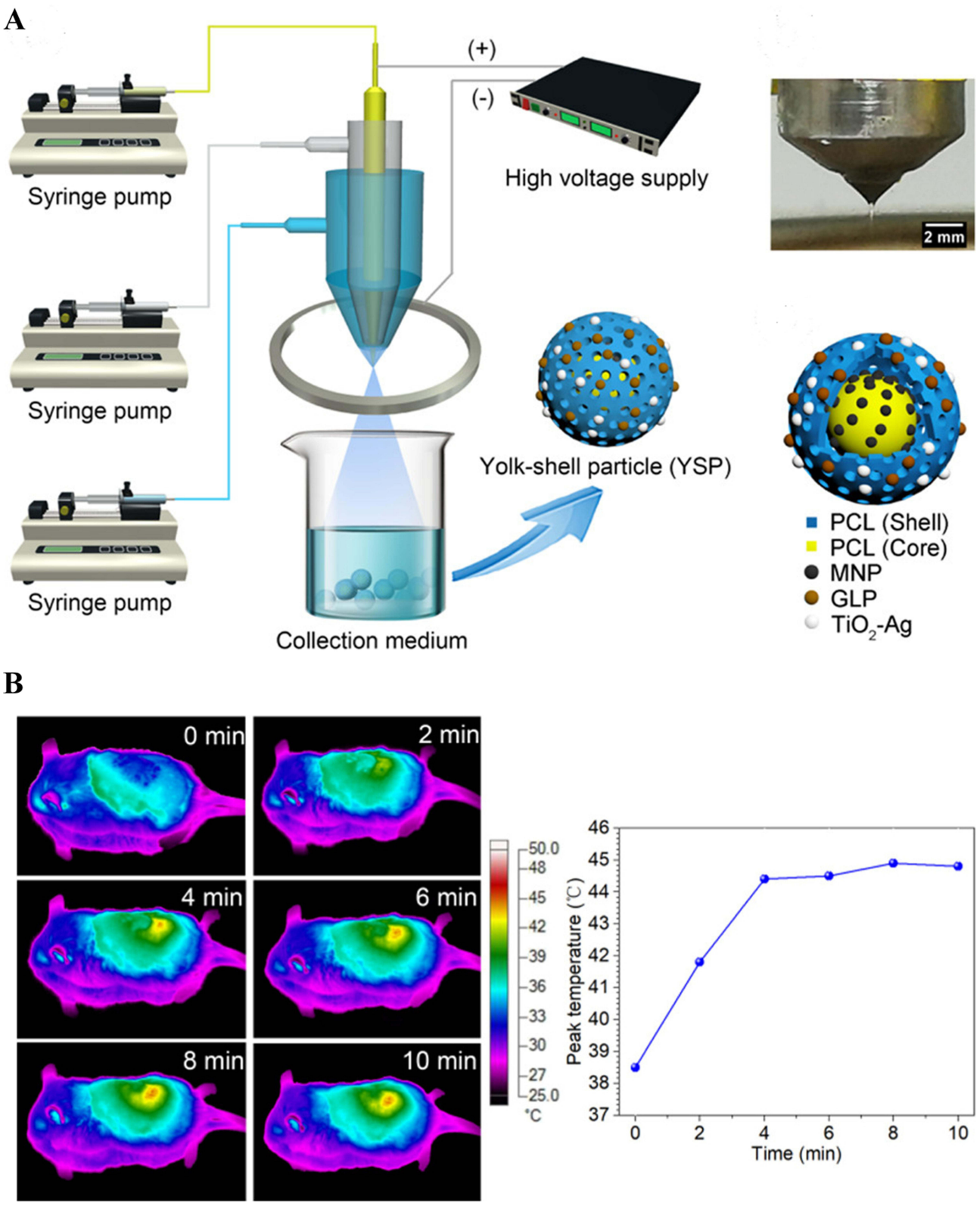

Figure 5 The application of TiO_2 NPs in burn wounds. (**A**) Schematic diagrams of the trineedle coaxial electrospraying system and collection apparatus utilized in this study. (**B**) Representative thermal graphs and the temperature rise curve of the Laser plus YSP group. Reproduced with permission from Zhang C, Li Y, Hu Y, et al. Porous Yolk-Shell Particle Engineering via Nonsolvent-Assisted Trineedle Coaxial Electrospraying for Burn-Related Wound Healing. ACS Appl Mater Interfaces. 2019;11:7823–7835, Copyright 2019, American Chemical Society.[62]

reepithelialization, collagen deposition, and angiogenesis. Moreover, it modulates inflammatory responses, reducing excessive inflammation that can complicate healing.[63] Overall, TiO_2 NPs contribute to a comprehensive approach to burn wound management by improving angiogenesis, supporting cellular metabolism, and controlling inflammation.

Polymer-Based Nanoparticles

Polymer-based nanoparticles (PNPs) represent a cutting-edge advance in burn wound treatment, showing exceptional versatility and efficacy. These nanoparticles are designed to deliver therapeutic agents in a controlled manner while minimizing cytotoxic effects.[62] Their unique properties make them highly suitable for addressing the complexities associated with burn wounds, including infection control, inflammation reduction, and tissue regeneration.

Biodegradable Polymer-Based Nanoparticles

Biodegradable PNPs have emerged as a significant kind of materials in burn wound treatment, offering notable benefits such as sustained drug release and reduced cytotoxicity. Quercetin-loaded PLGA nanoparticles exemplify the effectiveness of this approach. A prominent example is quercetin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles, which have demonstrated remarkable effectiveness in enhancing wound healing. In studies involving Wistar albino rats, these nanoparticles not only accelerated wound closure but also mitigated inflammation. Quercetin, a naturally occurring flavonoid known for its strong antioxidant and anti-inflammatory properties, is encapsulated within PLGA nanoparticles, which improves its solubility and cellular uptake, thereby maximizing its therapeutic benefits in burn treatment.[64] Another noteworthy application is the formulation of a bio-nanocomposite that combines carmustine with gold nanoparticles. This innovative approach not only provides anti-tumor effects but also promotes tissue healing in burn wounds. The presence of gold nanoparticles enhances the delivery and efficacy of carmustine, showing a multifaceted strategy that addresses both cancer treatment and wound care simultaneously.[65] Additionally, marine collagen sponges infused with phyto-silver nanoparticles represent an advancement in burn therapy. Marine collagen is well-regarded for its biocompatibility and regenerative potential, making it an excellent scaffold for wound healing. When combined with phyto-silver nanoparticles, which offer antimicrobial properties, these sponges facilitate sustained drug release and promote tissue regeneration. The synergy between the collagen matrix and the nanoparticles creates an effective therapeutic environment conducive to healing.[66] This emphasizes the potential of integrating natural materials with nanotechnology for innovative burn wound therapies. The application of biodegradable polymer-based nanoparticles in burn wound healing exemplifies the potential of nanomedicine to address complex medical challenges. By ensuring sustained drug release and minimizing cytotoxicity, these nanoparticles offer a promising solution for enhancing the healing process.

Synthetic Polymer-Based Nanoparticles

Synthetic polymers such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA) have shown significant efficacy in nanoparticle-based therapies for burn wound treatment. These polymers serve as functional carriers for therapeutic agents, enhancing drug stability and enabling controlled release. A prime example is the use of curcumin-loaded PEG integrated into chitosan-gelatin nanoparticles (C-PEG-CGNPs). In experimental studies on rats, these nanoparticles facilitated significant improvements in burn wound healing, marked by enhanced fibroblast distribution, accelerated reepithelialization, and reduced inflammation. The combination of curcumin—known for its potent anti-inflammatory and antioxidant properties—with PEG and chitosan-gelatin matrices results in a synergistic effect that optimizes the wound repair process, potentially by modulating inflammatory pathways and promoting cellular proliferation through the regulation of key proteins like Bcl-2 and caspase-3.[67] Another approach involves hyaluronate nanoparticles incorporated into polymer films containing vitamin E and Aloe vera extract. This formulation provides a dual mechanism: the polymer films support controlled release of vitamin E, an antioxidant that helps protect skin cells, while Aloe vera contributes its renowned healing and soothing effects. This strategy exemplifies the potential of combining synthetic polymers with natural extracts, enhancing overall skin regeneration and wound healing through a multifaceted approach.[68] Chitosan-silver curcumin nanocomposites (Chi-Ag Cur NC) represent yet another promising application in burn wound care. These nanocomposites leverage the antibacterial properties of silver alongside the anti-inflammatory benefits of curcumin. The green synthesis approach used in creating these nanocomposites not only maintains biocompatibility with human dermal fibroblasts but also ensures the efficacy of the antibacterial components against common pathogens

associated with burn wounds. By targeting bacterial infections while simultaneously promoting healing, Chi-Ag Cur NC can address two critical aspects of burn wound management.[69] Overall, synthetic polymers like PEG and PVA significantly enhance the controlled release and bioavailability of therapeutic agents, making them excellent candidates for advanced wound healing therapies. Their integration into nanomedicine represents a cutting-edge approach to overcoming the complexities of burn wound treatment.

Natural Polymer-Based Nanoparticles

Natural polymers offer unique advantages in developing nanoparticle-based therapies aimed at enhancing the healing process while ensuring compatibility with biological tissues. A notable example involves the use of cinnamon nanoparticles encapsulated within chitosan-gelatin nanoparticles (CNP-CGNPs). Research conducted on rats with diabetic foot ulcers revealed that these nanoparticles significantly accelerated wound healing. The treatment not only expedited wound closure but also demonstrated improved histomorphometric outcomes, which can be attributed to the combination of chitosan and gelatin that leveraged cinnamon's intrinsic antimicrobial and anti-inflammatory properties, thereby optimizing the healing process.[70] Another promising application is a biodegradable composite hydrogel made from gelatin and silver nanoparticles. This hydrogel exhibited robust antibacterial and antibiofilm properties, making it particularly effective for treating infected burn wounds. In studies, it was shown to promote wound contraction, stimulate collagen deposition, and enhance angiogenesis while simultaneously reducing inflammation. The integration of silver nanoparticles into the gelatin matrix significantly boosted the antimicrobial efficacy of the hydrogel, providing an effective solution for burn wounds prone to infection.[45] Furthermore, microwave-modified chitosan-curcumin nanoparticles have demonstrated superior physicochemical properties and sustained drug release profiles. These nanoparticles not only exhibited strong antimicrobial activity against common pathogens but also encouraged cell migration in human dermal fibroblasts, which is crucial for effective wound healing. The microwave treatment enhanced the stability and bioavailability of curcumin—known for its anti-inflammatory and antioxidant effects—thereby amplifying its therapeutic potential.[71] Overall, the application of natural polymer-based nanoparticles in burn wound healing illustrates their ability to synergistically enhance the healing process through various molecular mechanisms, such as promoting cell proliferation, modulating inflammation, and facilitating tissue regeneration. The development of these advanced materials continues to hold promise for improving clinical outcomes in burn wound management.

Extracellular Vesicles in Burn Wound Healing

Exosomes

Recent research has underscored the significant therapeutic potential of exosomes in burn wound treatment through various mechanisms. Exosomes, small membrane-bound vesicles secreted by cells, are rich in proteins, lipids, and nucleic acids, which they transfer to recipient cells, influencing numerous cellular processes.[72,73] One critical insight from next-generation sequencing studies is the identification of specific microRNA (miRNA) profiles within plasma exosomes from burn patients. These miRNAs are implicated in modulating gene expression associated with the wound healing response. Notably, certain upregulated miRNAs were found to interact with key genes involved in cellular proliferation and inflammation, illustrating how exosomes can regulate the post-burn cellular environment and promote recovery.[74] Furthermore, exosomes derived from human induced pluripotent stem cell (iPSC) keratinocytes have shown remarkable efficacy in accelerating burn wound healing. Specifically, miR-762 within these exosomes has been shown to enhance the migration of keratinocytes and endothelial cells, crucial for angiogenesis and re-epithelialization. This mechanism underscores the capacity of iPSC-derived exosomes to facilitate vital processes in wound healing, such as cellular migration and blood vessel formation.[75] Adipose-derived mesenchymal stem cell (ADMSC) exosomes, particularly when integrated into a controlled-release hyaluronan hydrogel, have also demonstrated significant therapeutic effects. This hydrogel system not only ensures sustained release of the exosomes but also fosters a favorable microenvironment for cell proliferation, migration, and collagen remodeling—essential processes for effective wound repair.[73] Additionally, innovative applications combining exosome-laden hydrogels with antimicrobial peptides have emerged. This approach not only promotes wound healing but also mitigates scar formation by regulating fibroblast activity and inhibiting excessive collagen deposition. The synergistic effects of these therapies illustrate a novel strategy for enhancing healing while minimizing scarring, which is often a major concern

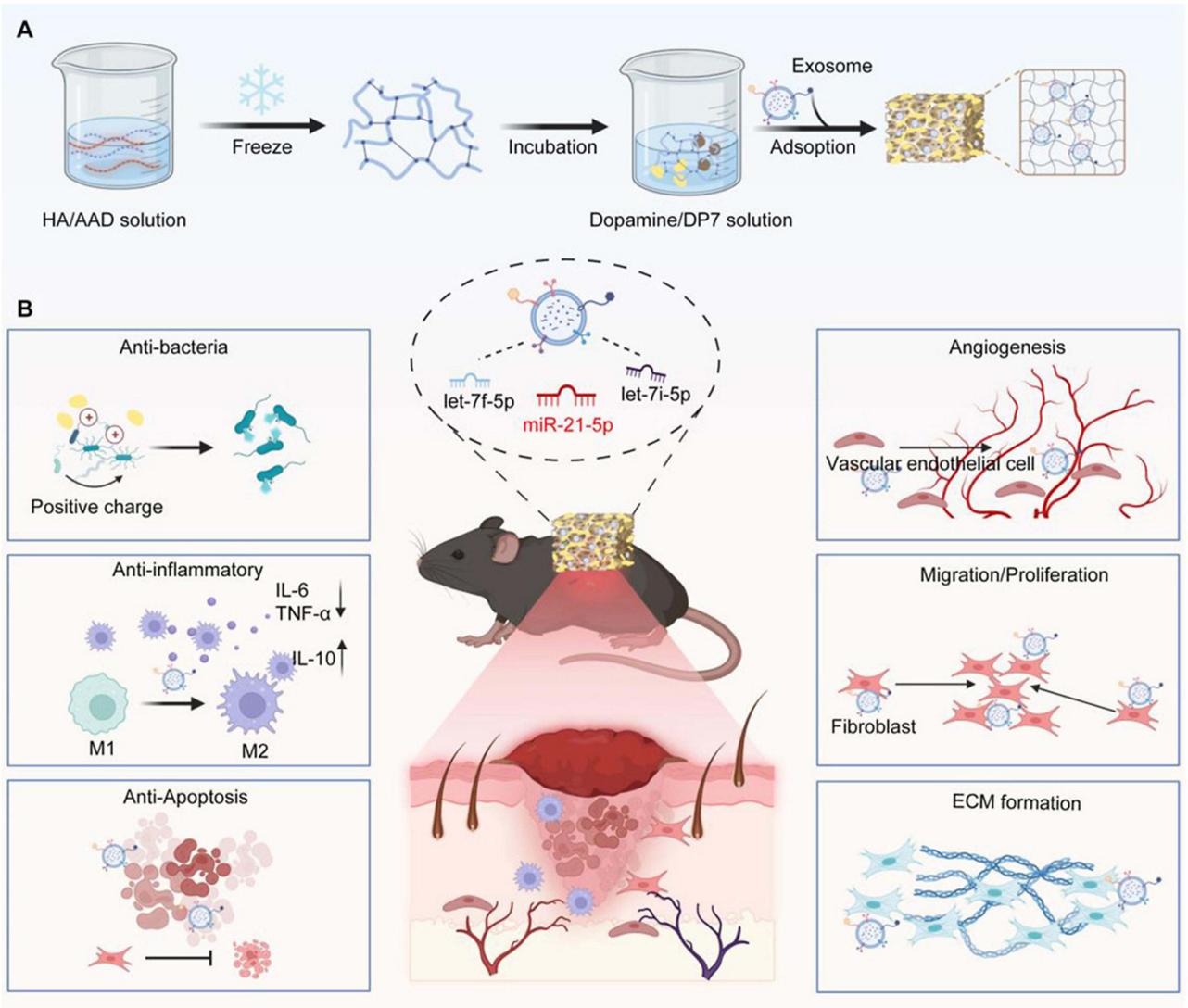

Figure 6 Exosomes in improving burn wounds healing. (**A**) Preparation of HD-DP7 hydrogels and HucMSC-Exos-loaded HD-DP7/Exo. (**B**) HD-DP7/Exo facilitates scar-free healing of infected deep second-degree burn wounds by exhibiting antibacterial action, anti-apoptotic effects, anti-inflammatory properties, promoting angiogenesis, enhancing reepithelialization, and regulating extracellular matrix synthesis. Reprinted from *Biomaterials*, volume 308, Yang Y, Zhang J, Wu S, et al. Exosome/antimicrobial peptide laden hydrogel wound dressings promote scarless wound healing through miR-21-5p-mediated multiple functions. 122558, Copyright 2024, with permission from Elsevier.[76]

in burn recovery (Figure 6).[76] Overall, exosomes represent a promising avenue for burn wound therapy, operating through complex molecular interactions that enhance healing processes, improve tissue regeneration, and potentially reduce complications associated with burn injuries.

Other EVs

In addition to exosomes, other types of EVs have also shown significant potential in enhancing burn wound treatment through various mechanisms. Plasma EVs released after severe burn injuries have been found to modulate macrophage phenotypes and functions, mimicking immune responses observed in burn victims and implicating EVs in post-burn immune dysfunction.[77] This highlights the role of EVs in regulating immune responses following burn injuries. Small extracellular vesicles (sEVs) from human menstrual blood-derived mesenchymal stem cells have emerged as promising agents in managing third-degree burns. These sEVs facilitate wound closure and promote neoangiogenesis, enhancing the formation of new blood vessels essential for effective healing. The regenerative properties of these sEVs illustrate their capability to address severe burn injuries.[78] Additionally, factors and EVs isolated from human lipoaspirate fluid have demonstrated a significant ability to accelerate wound healing in rat models. These EVs not only enhance the quality of healed skin by promoting the regeneration of cutaneous

appendages but also minimize scar formation, showcasing their therapeutic potential.[79] Similarly, microvesicles derived from induced pluripotent stem cells (iPSCs) have been shown to expedite the healing of deep second-degree burns. The healing effect is primarily mediated by miR-16-5p, a microRNA that promotes keratinocyte migration, highlighting the essential role of microRNAs carried by EVs in tissue repair.[80] Various EVs exert their beneficial effects by modulating immune responses, enhancing cell migration, and improving overall wound healing quality through intricate biological pathways. This positions EVs as a transformative approach in burn care, offering targeted and effective treatments that meet the multifaceted needs of wound healing.

Engineered EVs

With the development of engineered EVs, the therapeutic potential of EVs in burn wound treatment is further enhanced. Engineered EVs can be designed to carry specific cargo, such as growth factors, cytokines, or miRNAs, to target and modulate specific pathways involved in wound healing. For instance, engineered EVs could be loaded with growth factors to stimulate angiogenesis or with anti-inflammatory cytokines to reduce inflammation.[81]

Although engineered EVs offer a targeted and effective approach to promoting wound healing and tissue regeneration, their application in burn wounds is limited by challenges related to production scalability, storage stability, and safety concerns. The large-scale production of engineered EVs that maintain consistent quality and functionality remains a significant hurdle. Additionally, ensuring the stability of EVs during storage and transport is crucial for their effective clinical application. Safety concerns, including the potential for immune reactions or unintended effects, also need to be thoroughly addressed.[82]

Further research is needed to address these challenges and optimize the use of engineered EVs for burn wound treatment. This includes developing robust manufacturing processes, establishing standardized protocols for EV storage and transport, and conducting comprehensive safety assessments. By overcoming these obstacles, the full therapeutic potential of engineered EVs can be realized, paving the way for their effective application in clinical settings.

Mechanisms of Action

Antimicrobial Properties

NPs exhibit remarkable antimicrobial activity, particularly useful in burn wound management, where infections often complicate healing. Their antimicrobial effects are multifaceted, involving physical and chemical interactions with microbial cells that lead to their destruction. One prominent mechanism is the generation of reactive oxygen species (ROS) by silver (Ag) and zinc oxide (ZnO) nanoparticles. These ROS disrupt bacterial cell membranes, proteins, and nucleic acids, ultimately leading to cell death. For instance, Ag NPs bind to bacterial cell walls, causing structural damage and the release of silver ions, which interfere with microbial respiration. This action is particularly effective against antibiotic-resistant strains like *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, both of which are common in burn wounds. Research demonstrates that green-synthesized Ag and ZnO NPs, characterized by techniques such as UV-visible spectroscopy and scanning electron microscopy, display high antibacterial activity against these pathogens when incorporated into cotton bandages.[83] Nanoparticles also target bacterial biofilms, which are resilient microbial communities that protect bacteria from antibiotics. An approach using curcumin-nisin-based poly(L-lactic acid) nanoparticles (CurNisNp) in antimicrobial photo-sonodynamic therapy (aPSDT) has shown efficacy in breaking down biofilms. This method, by generating ROS in response to light and ultrasound irradiation, not only inhibits biofilm growth but also accelerates skin re-epithelialization in infected burn wounds.[16] Silver nanoparticles incorporated into hydrogels, synthesized via gamma radiation, have proven to be highly effective antimicrobial agents. These hydrogels release silver ions over time, killing pathogens like Staphylococcus aureus and Candida albicans. Their ability to maintain microbial inhibition while promoting fluid absorption makes them ideal for treating burns.[84] Additionally, polycaprolactone-gelatin-silver membrane (PCLGelAg) has exceptional antibacterial efficacy, effectively eliminating both Gram-positive and Gram-negative bacteria with the lowest minimum bactericidal concentration (MBC). All three dressings—PCLGelAg, Aquacel, and UrgoTul—demonstrated antibacterial activity within the first 24 hours, promoting wound healing and preventing infection and inflammation (Figure 7).[85] When combined zinc oxide (ZnO) nanoparticles with hydrogels, they offer dual benefits—antimicrobial action and anti-inflammatory effects. By inhibiting bacterial growth and reducing inflammation at the wound site, these composite materials promote faster healing of burn wounds.[86] In summary, nanoparticles provide a potent, multi-targeted approach to combating

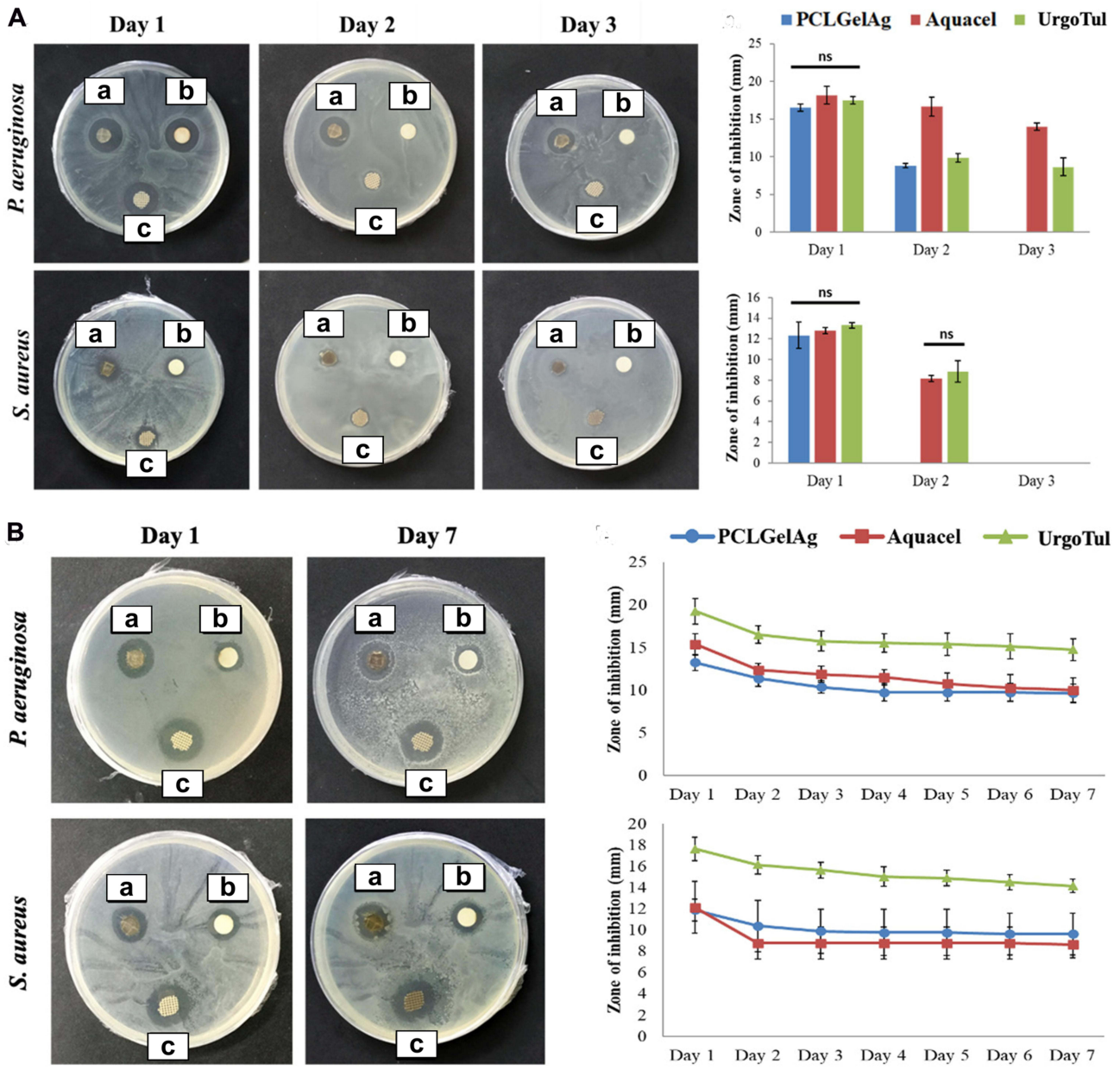

Figure 7 Polycaprolactone-gelatin-silver membrane (PCLGelAg) showed excellent antibacterial efficacy. (**A**) Inhibition zones and average diameters for P. aeruginosa and S. aureus treated with (a) Aquacel, (b) PCLGelAg, and (c) UrgoTul. Disks were transferred to fresh agar plates every 24 hours for 3 days. (**B**) Inhibition zones and average diameters of the wound dressings: (a) Aquacel, (b) PCLGelAg, and (c) UrgoTul against P. aeruginosa and S. aureus, observed every 24 hours for 7 days. Adapted from Do TB, Nguyen TN, Ho MH, et al. The Efficacy of Silver-Based Electrospun Antimicrobial Dressing in Accelerating the Regeneration of Partial Thickness Burn Wounds Using a Porcine Model. *Polymers*. 2021;13. Creative Commons.[85]

microbial infections in burn wounds. Through ROS generation, membrane disruption, biofilm degradation, and sustained antimicrobial release, nanoparticles enhance both the elimination of pathogens and the wound healing process.

Anti-Inflammatory Effects

Nanoparticles exhibit significant anti-inflammatory properties, which are crucial for effective burn wound healing. Several nanoparticle-based approaches have been effective in mitigating excessive inflammation, preventing infection, and promoting tissue regeneration. A prominent example is a bio-functional hydrogel incorporating methacrylate gelatin (GelMA) with silver nanoparticles embedded in γ-cyclodextrin metal-organic frameworks (Ag@MOF) and hyaluronic acid-epigallocatechin gallate (HA-E). This hydrogel modulates immune responses by promoting the polarization of

macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, which is crucial for resolving inflammation and promoting tissue repair. This polarization shift is mediated by the activation of the noncanonical Wnt signaling pathway, which plays a role in immune regulation and angiogenesis, contributing to improved burn wound healing through enhanced collagen deposition and accelerated re-epithelialization.[87]

Aloe vera peel-derived nanovesicles (AVpNVs) also demonstrate significant anti-inflammatory properties by downregulating the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, in lipopolysaccharide (LPS)-stimulated macrophages and keratinocytes. This reduction in cytokine levels prevents chronic inflammation and fibrosis by inhibiting myofibroblast differentiation. The molecular mechanism involves the suppression of transforming growth factor-beta (TGF-β)-mediated pathways, which are associated with fibrosis and scar formation.[88] In another study, biosynthesized silver nanoparticles (AgNPs) incorporated into an ointment with Rhodiola rosea demonstrated potent anti-inflammatory effects. The AgNPs exert their influence by regulating both pro-inflammatory (IL-1β, IL-6) and anti-inflammatory (IL-10) gene expression. This dual regulation helps modulate the balance between inflammatory and reparative phases of wound healing. The ointment also reduced epidermal thickness and mast cell infiltration, further illustrating its ability to mitigate the inflammatory response and promote wound closure.[89] Similarly, a multifunctional nanocomposite combining hexachlorocyclotriphosphazene, Phloretin, and AgNPs (HPA) demonstrated a synergistic effect in controlling excessive inflammation. The sustained release of Phloretin from the nanoplatform scavenges reactive oxygen species (ROS) and inhibits the overproduction of pro-inflammatory cytokines, such as IL-6 and TNF-α, within the wound microenvironment. This regulation of oxidative stress and inflammation promotes collagen deposition and tissue regeneration (Figure 8).[90] In the context of corneal burns, synthetic high-density lipoprotein nanoparticles (HDL NPs) complexed with microRNAs (miR-HDL NPs) showed an ability to reduce inflammation by targeting inflammatory signaling pathways at a molecular level, specifically by inhibiting the NF-κB pathway. This downregulation of NF-κB decreases the expression of pro-inflammatory cytokines and enhances epithelialization in alkali-burn-induced wounds.[91] Collectively, these studies highlight the critical role of nanoparticles in modulating the inflammatory response during burn wound healing. By targeting molecular pathways, such as the noncanonical Wnt, NF-κB, and TGF-β pathways, nanoparticles help to fine-tune the immune response, reduce excessive inflammation, and promote a more efficient healing process.

Promotion of Angiogenesis and Tissue Regeneration

Nanoparticles have shown considerable potential in promoting angiogenesis and tissue regeneration, crucial for effective burn wound healing. Various nanoparticle-based strategies have demonstrated efficacy in enhancing wound repair, primarily through molecular pathways that influence cellular behavior, growth factors, and the extracellular matrix (ECM). One notable example involves an injectable hydrogel based on hyaluronic acid incorporating copper sulfide nanoparticles (CuS/HA). This hydrogel exhibited a photothermal effect that significantly promoted angiogenesis by upregulating vascular endothelial growth factor (VEGF), a critical growth factor for new blood vessel formation. VEGF binds to its receptors (VEGFR-1 and VEGFR-2) on endothelial cells, triggering intracellular signaling pathways like PI3K/AKT and MAPK, which promote endothelial cell proliferation, migration, and tube formation. The hydrogel also increased collagen deposition, supporting ECM remodeling and enhancing wound healing.[92] Similarly, chitosan/collagen hydrogels loaded with cerium oxide and cerium peroxide nanoparticles demonstrated significant pro-angiogenic properties, particularly with cerium peroxide. Cerium peroxide induces neovascularization by modulating oxidative stress through the regulation of reactive oxygen species (ROS). Controlled ROS levels act as signaling molecules, stimulating angiogenesis by activating hypoxia-inducible factor-1α (HIF-1α), which in turn upregulates VEGF expression. This oxidative modulation, alongside the structural support provided by the hydrogel, accelerates wound healing by enhancing blood vessel formation at the wound site.[93] TiO2 nanoparticles also promote burn wound healing through specific interactions with blood serum proteins. TiO2 nanoparticles adsorb proteins like fibrinogen and fibronectin, facilitating coagulation and forming a protective layer over the wound. This not only prevents infection and inflammation but also provides a scaffold for cell adhesion and migration, leading to faster tissue regeneration. Additionally, TiO2-induced coagulation stabilizes the wound environment, allowing for more efficient cellular proliferation and ECM deposition, which are essential for reducing healing time and minimizing scar formation.[94] Moreover, a multifunctional hydrogel based on carboxymethyl cellulose, polyacrylamide, and polydopamine (CMC/PAAm/PDA) loaded with vitamin C and curcumin further illustrates the role of nanoparticles in tissue regeneration. Curcumin-loaded nanoparticles enhance the anti-inflammatory response by inhibiting the nuclear factor-kappa B (NF-κB) pathway, which reduces the expression of pro-inflammatory cytokines like TNF-α and IL-6. By

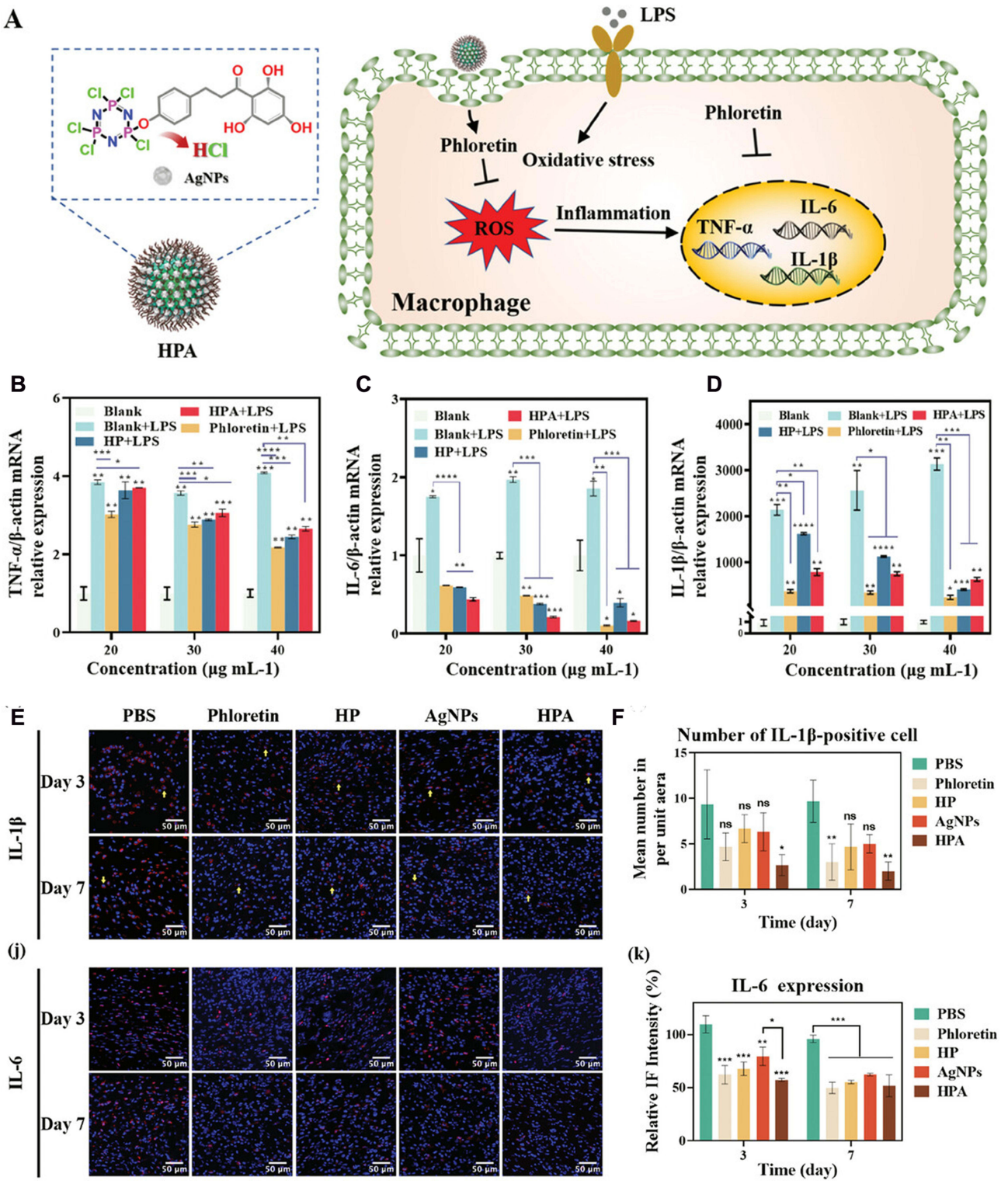

Figure 8 HPA exhibited anti- inflammatory effect. (**A**) Mechanism of HPA's antioxidative and anti-inflammatory effects in Raw 264.7 cells. (**B–D**) qRT-PCR results for TNF-α, IL-6, and IL-1β mRNA in cells pretreated with Phloretin, HP, and HPA (20, 30, or 40 μg mL−1) for 6 hours and stimulated with LPS (1 μg mL−1) for 24 hours. (**E**) IL-1β and IL-6 immunofluorescence in wound tissue on days 3 and 7. (**F**) IL-1β and IL-6 expression intensity on days 3 and 7. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Reprinted from Su Y H, Chen X, Jing X, et al. Antimicrobial, Antioxidant, and Anti-Inflammatory Nanoplatform for Effective Management of Infected Wounds. *Adv Healthc Mater.* 2024; (13):e2302868. © 2023 Wiley-VCH GmbH.[90]

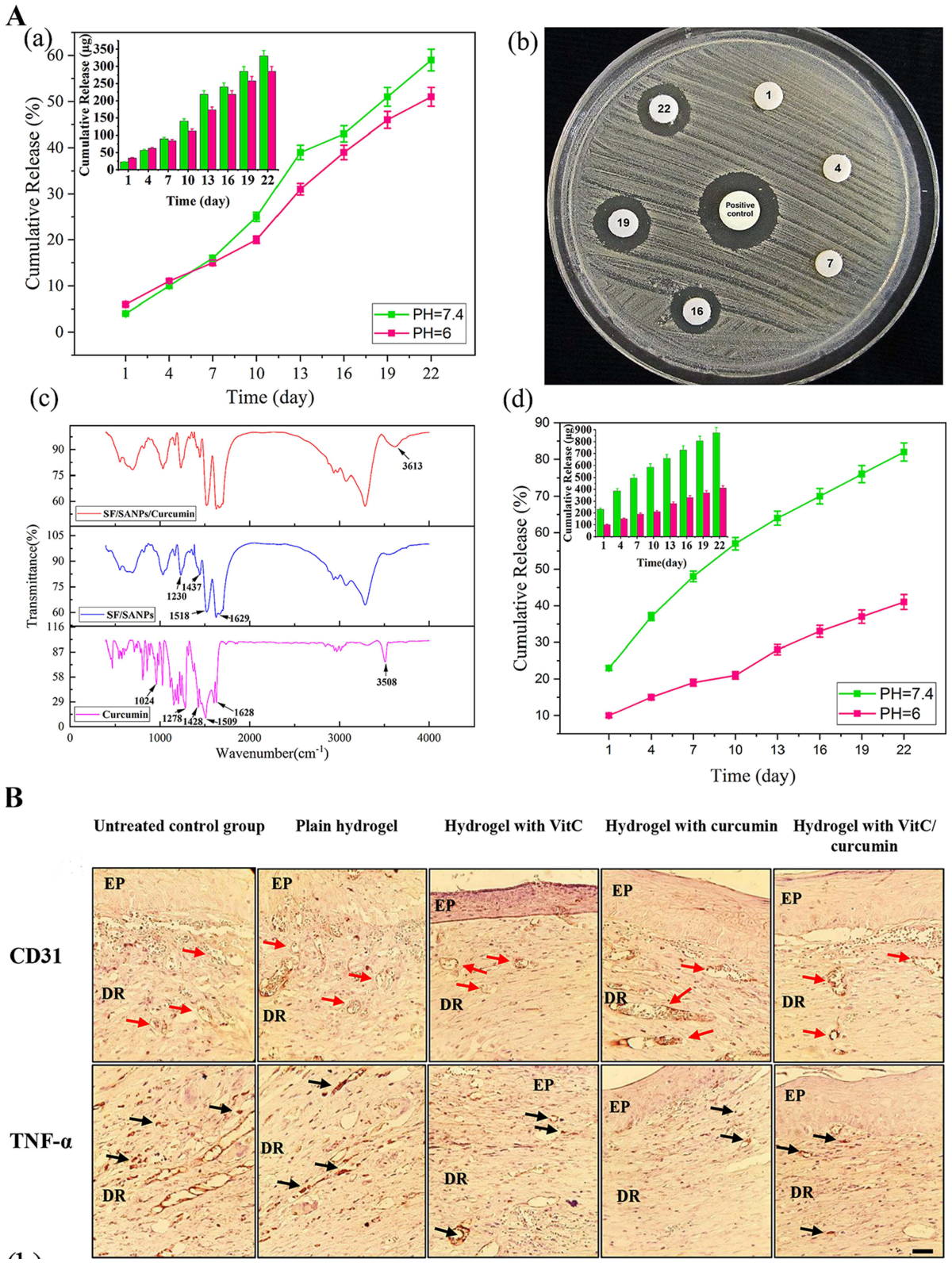

Figure 9 The example of NPs promote burn wound healing through enhancing angiogenesis and tissue regeneration. (**A**) Drug delivery evaluation: (a) Release kinetics of curcumin from SF/SANPs at pH 6 and 7.4, (b) MRSA inhibition zone assay using curcumin release from various time points, (c) FTIR analysis of curcumin, SF/SANPs, and SF/SANPs containing curcumin, confirming successful drug loading, (d) Release kinetics of VitC from CMC/PAAm/PDA at pH 6 and 7.4. (**B**) General images of the burn wounds after treatment with untreated control group, plain hydrogel, hydrogel with VitC, hydrogel with curcumin, and hydrogel with VitC/curcumin. Reprinted from *Int J Biol Macromol*, volume 236, Babaluei M, Mottaghitalab F, Seifalian A, Farokhi M. Injectable multifunctional hydrogel based on carboxymethyl cellulose/polyacrylamide/polydopamine containing vitamin C and curcumin promoted full-thickness burn regeneration. 124005, Copyright 2023, with permission from Elsevier.[95]

dampening inflammation, curcumin supports the transition from the inflammatory phase to the proliferative phase of healing. Additionally, curcumin promotes angiogenesis by increasing VEGF and CD31 expression, which drives neovascularization and collagen deposition, thereby facilitating faster wound closure and re-epithelialization (Figure 9).[95] In conclusion, the multifaceted roles of nanoparticles in modulating key molecular pathways, such as VEGF signaling, oxidative stress regulation, and ECM remodeling, are critical for promoting angiogenesis and tissue regeneration in burn wounds.

Future Directions and Emerging Trends

The field of burn wound treatment is undergoing a significant transformation, driven by the integration of personalized medicine and nanoparticle-based therapies. NPs can be engineered to deliver therapeutic agents—such as drugs, growth factors, or genetic materials—directly to the wound site, enhancing the precision and efficacy of treatment. This ability to fine-tune the composition, size, and surface properties of NPs allows for treatments that are better tailored to individual patient needs, improving outcomes and reducing adverse effects.[96] Moreover, the combination of NPs with advanced drug delivery technologies like hydrogels, microneedles, and transdermal patches offers a controlled and sustained release of therapeutics, optimizing drug concentrations at the wound site over extended periods, thus improving patient compliance.[6] Despite these advances, there remain significant challenges in translating NP-based therapies from laboratory research to clinical practice. Key barriers include the scalability of NP production, the need for stringent regulatory approval, and concerns about the long-term safety and potential toxicity of NPs. Additionally, manufacturing large quantities of nanoparticles while maintaining consistency in their size, purity, and bioactivity is a significant obstacle. Regulatory frameworks will also need to evolve to address the complexities of nanoparticle-based products, which often involve novel materials and delivery methods. Preclinical and clinical trials are crucial to addressing these challenges, particularly in establishing the safety, efficacy, and cost-effectiveness of these therapies. Looking ahead, future research should focus on addressing knowledge gaps in NP behavior, including their long-term effects in the human body, immune system interactions, and the optimization of delivery systems for different types of burn wounds. Innovations such as scalable NP production methods, better safety profiles, and standardized treatment protocols will be essential to facilitate regulatory approval and clinical adoption. These advancements, coupled with personalized medicine approaches, hold the potential to bring NP-based burn wound therapies from the bench to bedside, significantly improving patient outcomes and establishing a new standard of care in burn wound management.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Goh MD, Du M, Peng WR, Saw PE, Chen Z. Advancing burn wound treatment: exploring hydrogel as a transdermal drug delivery system. *Drug Deliv*. 2024;31(1):2300945. doi:10.1080/10717544.2023.2300945
2. Oryan A, Alemzadeh E, Moshiri A. Burn wound healing: present concepts, treatment strategies and future directions. *J Wound Care*. 2017;26(1):5–19. doi:10.12968/jowc.2017.26.1.5
3. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. *Nat Rev Dis Primers*. 2020;6:11. doi:10.1038/s41572-020-0145-5
4. Kowalske KJ. Burn wound care. *Phys Med Rehabil Clin N Am*. 2011;22:213–227. doi:10.1016/j.pmr.2011.03.004
5. Abazari M, Ghaffari A, Rashidzadeh H, Momeni Badeleh S, Maleki Y. Current status and future outlook of nano-based systems for burn wound management. *J Biomed Mater Res B Appl Biomater*. 2020;108:1934–1952. doi:10.1002/jbm.b.34535
6. Wang W, Lu KJ, Yu CH, Huang QL, Du YZ. Nano-drug delivery systems in wound treatment and skin regeneration. *J Nanobiotechnology*. 2019;17. doi:10.1186/s12951-019-0514-y
7. Ziauddin T, Hussain A, Nazir U. Abid, Nanoengineered Therapeutic Scaffolds for Burn Wound Management. *Curr Pharm Biotechnol*. 2022;23:1417–1435. doi:10.2174/1389201023666220329162910
8. Khan NU, Chengfeng X, Jiang MQ, et al. alpha-Lactalbumin based scaffolds for infected wound healing and tissue regeneration. *Int J Pharm*. 2024;663:124578. doi:10.1016/j.ijpharm.2024.124578
9. Song J, Razzaq A, Khan NU, Iqbal H, Ni J. Chitosan/poly (3-hydroxy butyric acid-co-3-hydroxy valeric acid) electrospun nanofibers with cephradine for superficial incisional skin wound infection management. *Int J Biol Macromol*. 2023;250:126229. doi:10.1016/j.ijbiomac.2023.126229

10. Eldebany N, Abd Elkodous M, Tohamy H, et al. Elkhenany, Gelatin Loaded Titanium Dioxide and Silver Oxide Nanoparticles: implication for Skin Tissue Regeneration. *Biol Trace Elem Res*. 2021;199:3688–3699. doi:10.1007/s12011-020-02489-x
11. Fong F J. Wood, Nanocrystalline silver dressings in wound management: a review. *Int J Nanomed*. 2006;1:441–449. doi:10.2147/nano.2006.1.4.441
12. Yuan Y, Ding L, Chen Y, et al. Nano-silver functionalized polysaccharides as a platform for wound dressings: a review. *Int J Biol Macromol*. 2022;194:644–653. doi:10.1016/j.ijbiomac.2021.11.108
13. Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. *Crit Care*. 2015;19:243. doi:10.1186/s13054-015-0961-2
14. Prudovsky I, Kacer D, Lindner V, Rappold J, Carter DW. Tranexamic acid reduces inflammation, edema and burn wound conversion in a rodent model. *Burns*. 2024;50:947–956. doi:10.1016/j.burns.2024.01.024
15. Son B, Lee S, Kim H, et al. Low dose radiation attenuates inflammation and promotes wound healing in a mouse burn model. *J Dermatol Sci*. 2019;96:81–89. doi:10.1016/j.jdermsci.2019.10.004
16. Pourhajibagher M, Pourakbari B, Bahador A. Contribution of antimicrobial photo-sonodynamic therapy in wound healing: an in vivo effect of curcumin-nisin-based poly (L-lactic acid) nanoparticle on Acinetobacter baumannii biofilms. *BMC Microbiol*. 2022;22:28. doi:10.1186/s12866-022-02438-9
17. Tavakoli M, Mirhaj M, Varshosaz J, et al. Keratin- and VEGF-Incorporated Honey-Based Sponge-Nanofiber Dressing: an Ideal Construct for Wound Healing. *ACS Appl Mater Interfaces*. 2023;15:55276–55286. doi:10.1021/acsami.3c11093
18. Wu W, Jia S, Xu H, et al. Supramolecular Hydrogel Microspheres of Platelet-Derived Growth Factor Mimetic Peptide Promote Recovery from Spinal Cord Injury. *ACS Nano*. 2023;17:3818–3837. doi:10.1021/acsnano.2c12017
19. Ding JY, Chen MJ, Wu LF, et al. Mesenchymal stem cell-derived extracellular vesicles in skin wound healing: roles, opportunities and challenges. *Mil Med Res*. 2023;10(36). doi:10.1186/s40779-023-00472-w
20. Hade MD, Suire CN, Mossell J. Suo, Extracellular vesicles: emerging frontiers in wound healing. *Med Res Rev*. 2022;42:2102–2125. doi:10.1002/med.21918
21. Xiong Y, Lin Z, Bu P, et al. A Whole-Course-Repair System Based on Neurogenesis-Angiogenesis Crosstalk and Macrophage Reprogramming Promotes Diabetic Wound Healing. *Adv Mater*. 2023;35:e2212300. doi:10.1002/adma.202212300
22. Broussard KC, Powers JG. Wound dressings: selecting the most appropriate type. *Am J Clin Dermatol*. 2013;14:449–459. doi:10.1007/s40257-013-0046-4
23. Hall C, Hardin C, Corkins CJ, et al. Chan, Pathophysiologic Mechanisms and Current Treatments for Cutaneous Sequelae of Burn Wounds. *Compr Physiol*. 2017;8:371–405. doi:10.1002/cphy.c170016
24. Huang R, Hu J, Qian W, Chen L, Zhang D. Recent advances in nanotherapeutics for the treatment of burn wounds. *Burns Trauma*. 2021;9:tkab026. doi:10.1093/burnst/tkab026
25. Evers LH, Bhavsar D, Mailander P. The biology of burn injury. *Exp Dermatol*. 2010;19:777–783. doi:10.1111/j.1600-0625.2010.01105.x
26. Wang Z, Qi F, Luo H, Xu G, Wang D. Inflammatory Microenvironment of Skin Wounds. *Front Immunol*. 2022;13:789274. doi:10.3389/fimmu.2022.789274
27. Zhang Y, Wang S, Yang Y, et al. Scarless wound healing programmed by core-shell microneedles. *Nat Commun*. 2023;14:3431. doi:10.1038/s41467-023-39129-6
28. Pereshein AV, Kuznetsova SV, Shevantaeva ON. On the Nonspecific Resistance in Burn Injury: pathophysiological Aspects (Review. *Sovrem Tekhnologii Med*. 2021;12:84–93. doi:10.17691/stm2020.12.3.11
29. Schwacha MG. Macrophages and post-burn immune dysfunction. *Burns*. 2003;29:1–14. doi:10.1016/s0305-4179(02)00187-0
30. Ren H, Zhao F, Zhang Q, Huang X, Wang Z. Autophagy and skin wound healing. *Burns Trauma*. 2022;10:tkac003. doi:10.1093/burnst/tkac003
31. Korkmaz HI, Ulrich MMW, Celik G, et al. NOX2 Expression Is Increased in Keratinocytes After Burn Injury. *J Burn Care Res*. 2020;41:427–432. doi:10.1093/jbcr/irz162
32. Taskaeva YS, Bgatova NP, Savchenko SV, Grebenshchikova AS, Oshchepkova NG, Kuznetsov EV. Ultrastructure of Endothelial Cells of Myocardial Capillaries in Burn Septicotoxemia. *Bull Exp Biol Med*. 2021;171:393–398. doi:10.1007/s10517-021-05235-y
33. Shpichka A, Butnaru D, Bezrukov EA, et al. Timashev, Skin tissue regeneration for burn injury. *Stem Cell Res Ther*. 2019;10:94. doi:10.1186/s13287-019-1203-3
34. Sampaio LP, Hilgert GSL, Shiju TM, Santhiago MR, Wilson SE. Topical Losartan and Corticosteroid Additively Inhibit Corneal Stromal Myofibroblast Generation and Scarring Fibrosis After Alkali Burn Injury. *Transl Vis Sci Technol*. 2022;11:9. doi:10.1167/tvst.11.7.9
35. Palackic A, Jay JW, Duggan RP, et al. Therapeutic Strategies to Reduce Burn Wound Conversion. *Medicina*. 2022;58. doi:10.3390/medicina58070922
36. Kiley JL, Greenhalgh DG. Infections in Burn Patients. *Surg Clin North Am*. 2023;427–437. doi:10.1016/j.suc.2023.02.005
37. Ladhani HA, Yowler CJ, Claridge JA. Burn Wound Colonization, Infection, and Sepsis, Surg Infect. *Larchmt*. 2021;22:44–48. doi:10.1089/sur.2020.346
38. Saeg F, Orazi R, Bowers GM, Janis JE. Evidence-Based Nutritional Interventions in Wound Care. *Plast Reconstr Surg*. 2021;226–238. doi:10.1097/PRS.0000000000008061
39. Farinas AF, Bamba R, Pollins AC, Cardwell NL, Nanney LB, Thayer WP. Burn wounds in the young versus the aged patient display differential immunological responses. *Burns*. 2018;44:1475–1481. doi:10.1016/j.burns.2018.05.012
40. White-Dzuro CG, Pollins AC, Kalmar CL, et al. Rescuing the negative effects of aging in burn wounds using tacrolimus applied via microcapillary hydrogel dressing. *Burns*. 2022;48:1885–1892. doi:10.1016/j.burns.2022.02.003
41. Jiang H, Li L, Li Z, Chu X. Metal-based nanoparticles in antibacterial application in biomedical field: current development and potential mechanisms. *Biomed Microdevices*. 2024;26:12. doi:10.1007/s10544-023-00686-8
42. Kalantari K, Mostafavi E, Afifi AM, et al. Wound dressings functionalized with silver nanoparticles: promises and pitfalls. *Nanoscale*. 2020;12:2268–2291. doi:10.1039/c9nr08234d
43. Kim MH, H Park HC. Injectable methylcellulose hydrogel containing silver oxide nanoparticles for burn wound healing. *Carbohydr Polym*. 2018;181:579–586. doi:10.1016/j.carbpol.2017.11.109

44. Feng L, Liu Y, Xiang Q, et al. Injectable Antibacterial Hydrogel with Asiaticoside-Loaded Liposomes and Ultrafine Silver Nanosilver Particles Promotes Healing of Burn-Infected Wounds. *Adv Healthc Mater*. 2023;12:e2203201. doi:10.1002/adhm.202203201
45. Huang Y, Bai L, Yang Y, Yin Z, Guo B. Biodegradable gelatin/silver nanoparticle composite cryogel with excellent antibacterial and antibiofilm activity and hemostasis for Pseudomonas aeruginosa-infected burn wound healing. *J Colloid Interface Sci*. 2022;608:2278–2289. doi:10.1016/j.jcis.2021.10.131
46. Yang J, Huang Y, Dai J, Shi X, Zheng Y. A sandwich structure composite wound dressing with firmly anchored silver nanoparticles for severe burn wound healing in a porcine model. *Regen Biomater*. 2021;8:rbab037. doi:10.1093/rb/rbab037
47. Perez-Diaz MA, Alvarado-Gomez E, Martinez-Pardo ME, et al. Development of Radiosterilized Porcine Skin Electrosprayed with Silver Nanoparticles Prevents Infections in Deep Burns. *Int J Mol Sci*. 2022;23. doi:10.3390/ijms232213910
48. Ortega-Sanchez C, Perez-Diaz M, Melgarejo-Ramirez Y, et al. Radiosterilized Pig Skin, Silver Nanoparticles and Skin Cells as an Integral Dressing Treatment for Burns: development. *Pre-Clin Clinical Pilot Pharm*. 2023. doi:10.3390/pharmaceutics15082105
49. Qiu L, Wang C, Lan M. Antibacterial Photodynamic Gold Nanoparticles for Skin Infection. *ACS Appl Bio Mater*. 2021;4:3124–3132. doi:10.1021/acsabm.0c01505
50. Rad MR, Kazemian H, Yazdani F, et al. Antibacterial Activity of Gold Nanoparticles Conjugated by Aminoglycosides Against A. *Baumannii Isolates from Burn Pat Recent Pat Antiinfect Drug Discov*. 2018;13:256–264. doi:10.2174/1574891X13666180828115543
51. Chen Y, Gao J, Zhang Z, et al. Transdermal Vascular Endothelial Growth Factor Delivery with Surface Engineered Gold Nanoparticles. *ACS Appl Mater Interfaces*. 2017;9:5173–5180. doi:10.1021/acsami.6b15914
52. Lee J, Kim J, Go J. Lee, Transdermal treatment of the surgical and burned wound skin via phytochemical-capped gold nanoparticles. *Colloids Surf B Biointer*. 2015;135:166–174. doi:10.1016/j.colsurfb.2015.07.058
53. Layeghi-Ghalehsoukhteh S, Jalaei J, Fazeli M, Memarian P, Shekarforoush SS. Evaluation of 'green' synthesis and biological activity of gold nanoparticles using Tragopogon dubius leaf extract as an antibacterial agent. *IET Nanobiotechnol*. 2018;12:1118–1124. doi:10.1049/iet-nbt.2018.5073
54. Hashemi SS, Pakdin A, Mohammadi A, et al. Study the Effect of Calendula officinalis Extract Loaded on Zinc Oxide Nanoparticle Cream in Burn Wound Healing. *ACS Appl Mater Interfaces*. 2023;15:59269–59279. doi:10.1021/acsami.3c17350
55. Sajjad A, Ali H, Zia M. Fabrication and evaluation of vitamin doped Zno/AgNPs nanocomposite based wheat gluten films: a promising findings for burn wound treatment. *Sci Rep*. 2023;13:16072. doi:10.1038/s41598-023-43413-2
56. Blinov AV, Kachanov MD, Gvozdenko AA. Synthesis and Characterization of Zinc Oxide Nanoparticles Stabilized with Biopolymers for Application in Wound-Healing Mixed Gels. *Gels*. 2023;9. doi:10.3390/gels9010057
57. Melnikova N, Balakireva A, Orekhov D. Zinc Oxide Nanoparticles Protected with Terpenoids as a Substance in Redox Imbalance Normalization in Burns. *Pharmaceuticals*. 2021;14. doi:10.3390/ph14060492
58. Hasannasab M, Nourmohammadi J, Dehghan MM, Ghaee A. Immobilization of bromelain and ZnO nanoparticles on silk fibroin nanofibers as an antibacterial and anti-inflammatory burn dressing. *Int J Pharm*. 2021;610:121227. doi:10.1016/j.ijpharm.2021.121227
59. Nozari M, Gholizadeh F. Studies on novel chitosan/alginate and chitosan/bentonite flexible films incorporated with ZnO nano particles for accelerating dermal burn healing: in vivo and in vitro evaluation. *Int J Biol Macromol*. 2021;184:235–249. doi:10.1016/j.ijbiomac.2021.06.066
60. Singh H, Hassan S, Nabi U, et al. Bashir, Multicomponent decellularized extracellular matrix of caprine small intestine submucosa based bioactive hydrogel promoting full-thickness burn wound healing in rabbits. *Int J Biol Macromol*. 2024;255:127810. doi:10.1016/j.ijbiomac.2023.127810
61. Aleem AR, Shahzadi L, Nasir M, et al. Developing sulfur-doped titanium oxide nanoparticles loaded chitosan/cellulose-based proangiogenic dressings for chronic ulcer and burn wounds healing. *J Biomed Mater Res B Appl Biomater*. 2022;110:1069–1081. doi:10.1002/jbm.b.34981
62. Zhang C, Li Y, Hu Y, et al. Porous Yolk-Shell Particle Engineering via Nonsolvent-Assisted Trineedle Coaxial Electrospraying for Burn-Related Wound Healing. *ACS Appl Mater Interfaces*. 2019;11:7823–7835. doi:10.1021/acsami.8b22112
63. Li J, Sun X, Dai JY, et al. Biomimetic multifunctional hybrid sponge via enzymatic cross-linking to accelerate infected burn wound healing. *Int J Biol Macromol*. 2023;225:90–102. doi:10.1016/j.ijbiomac.2022.12.024
64. Cetin N, Menevse E, Celik ZE, et al. Sahin, Evaluation of burn wound healing activity of thermosensitive gel and PLGA nanoparticle formulation of quercetin in Wistar albino rats. *J Drug Delivery Sci Technol*. 2022;75. doi:10.1016/j.jddst.2022.103620
65. Yi S, Yang F, Jie C, Zhang G. A novel strategy to the formulation of carmustine and bioactive nanoparticles co-loaded PLGA biocomposite spheres for targeting drug delivery to glioma treatment and nursing care. *Artif Cells Nanomed Biotechnol*. 2019;47:3438–3447. doi:10.1080/21691401.2019.1652628
66. Sundar G, Joseph J, Chellamma P. Abraham, Marine collagen polymeric sponge impregnated with phyto-silver nanoparticles for burn therapy. *Polymer Bull*. 2022;6117–6136. doi:10.1007/s00289-022-04347-3
67. Ravanfar K, Amniattalab A, Mohammadi R. Curcumin-Polyethylene Glycol Loaded on Chitosan-Gelatin Nanoparticles Enhances Burn Wound Healing in Rat. *J Burn Care Res*. 2022;43:1399–1409. doi:10.1093/jbcr/irac048
68. Pereira GG, Detoni CB, Balducci AG, Rondelli V, Colombo P, Guterres SS. Sonvico, Hyaluronate nanoparticles included in polymer films for the prolonged release of vitamin E for the management of skin wounds. *Eur J Pharm Sci*. 2016;83:203–211. doi:10.1016/j.ejps.2016.01.002
69. Rajabloo Z, Mobarak Qamsari E, Kasra Kermanshahi R, Farzaneh F. Green synthesis of chitosan-silver nanocomposite reinforced with curcumin nanoparticles: characterization and antibacterial effect. *Polymer Bull*. 2022;5333–5352. doi:10.1007/s00289-022-04270-7
70. Hajati Ziabari A, Asadi Heris M, Mohammad Doodmani S, Jahandideh A, Koorehpaz K, Mohammadi R. Cinnamon Nanoparticles Loaded on Chitosan- Gelatin Nanoparticles Enhanced Burn Wound Healing in Diabetic Foot Ulcers in Rats. *Int J Low Extrem Wounds*. 2022;15347346221101245. doi:10.1177/15347346221101245
71. Basit HM, Mohd Amin MCI, Ng SF, Katas H, Shah SU, Khan NR. Formulation and Evaluation of Microwave-Modified Chitosan-Curcumin Nanoparticles-A Promising Nanomaterials Platform for Skin Tissue Regeneration Applications Following Burn Wounds. *Polymers*. 2020;12. doi:10.3390/polym12112608
72. Wang Y, Zhang T, Li K, et al. Hu, Adipose Mesenchymal Stem Cell Derived Exosomes Promote Keratinocytes and Fibroblasts Embedded in Collagen/Platelet-Rich Plasma Scaffold and Accelerate Wound Healing. *Adv Mater*. 2023;35:e2303642. doi:10.1002/adma.202303642
73. Zhu D, Hu Y, Kong X, et al. Enhanced burn wound healing by controlled-release 3D ADMSC-derived exosome-loaded hyaluronan hydrogel. *Regen Biomater*. 2024;11:rbae035. doi:10.1093/rb/rbae035

74. Li SJ, Cai ZW, Yang HF, et al. A Next-Generation Sequencing of Plasma Exosome-Derived microRNAs and Target Gene Analysis with a Microarray Database of Thermally Injured Skins: identification of Blood-to-Tissue Interactions at Early Burn Stage. *J Inflamm Res*. 2021;14:6783–6798. doi:10.2147/JIR.S343956
75. Bo Y, Yang L, Liu B, et al. Exosomes from human induced pluripotent stem cells-derived keratinocytes accelerate burn wound healing through miR-762 mediated promotion of keratinocytes and endothelial cells migration. *J Nanobiotechnology*. 2022;20:291. doi:10.1186/s12951-022-01504-8
76. Yang Y, Zhang J, Wu S, et al. Exosome/antimicrobial peptide laden hydrogel wound dressings promote scarless wound healing through miR-21-5p-mediated multiple functions. *Biomaterials*. 2024;308:122558. doi:10.1016/j.biomaterials.2024.122558
77. Willis ML, Mahung C, Wallet SM, Barnett A, Cairns BA, G. L. Plasma extracellular vesicles released after severe burn injury modulate macrophage phenotype and function. *J Leukoc Biol*. 2022;111:33–49. doi:10.1002/JLB.3MIA0321-150RR
78. Rohani Ivari J, Mahdipour E. Adipose tissue versus stem cell-derived small extracellular vesicles to enhance the healing of acute burns. *Regener Med*. 2021;16:629–641. doi:10.2217/rme-2020-0199
79. Wu Y, Hong PL, Zhang Q, et al. Lipoaspirate fluid derived factors and extracellular vesicles accelerate wound healing in a rat burn model. *Front Bioeng Biotechnol*. 2023;11:1185251. doi:10.3389/fbioe.2023.1185251
80. Yan Y, Wu R, Bo Y, et al. Induced pluripotent stem cells-derived microvesicles accelerate deep second-degree burn wound healing in mice through miR-16-5p-mediated promotion of keratinocytes migration. *Theranostics*. 2020;10:9970–9983. doi:10.7150/thno.46639
81. Xiong Y, Chen L, Liu P, et al. Liu, All-in-One: multifunctional Hydrogel Accelerates Oxidative Diabetic Wound Healing through Timed-Release of Exosome and Fibroblast Growth Factor. *Small*. 2022;18:e2104229. doi:10.1002/smll.202104229
82. Zhang Y, Li M, Wang Y. Exosome/metformin-loaded self-healing conductive hydrogel rescues microvascular dysfunction and promotes chronic diabetic wound healing by inhibiting mitochondrial fission. *Bioact Mater*. 2023;26:323–336. doi:10.1016/j.bioactmat.2023.01.020
83. Khatami M, Varma RS, Zafarnia N, Yaghoobi H, Sarani M, Kumar VG. Applications of green synthesized Ag, ZnO and Ag/ZnO nanoparticles for making clinical antimicrobial wound-healing bandages. *Sustainable Chem Pharm*. 2018;10:9–15. doi:10.1016/j.scp.2018.08.001
84. Rita S, Antaryami S. Radiation Synthesis of Hydrogels with Silver Nanoparticles for Use as an Antimicrobial Burn Wound Dressing. *Polym Sci Ser B*. 2022;64:188–197. doi:10.1134/s1560090422020117
85. Do TB, Nguyen TN, Ho MH, et al. The Efficacy of Silver-Based Electrospun Antimicrobial Dressing in Accelerating the Regeneration of Partial Thickness Burn Wounds Using a Porcine Model. *Polymers*. 2021;13. doi:10.3390/polym13183116
86. Rata DM, Cadinoiu AN, Daraba OM, Gradinaru LM, Atanase LI, Ichim DL. Influence of ZnO Nanoparticles on the Properties of Ibuprofen-Loaded Alginate-Based Biocomposite Hydrogels with Potential Antimicrobial and Anti-Inflammatory Effects. *Pharmaceutics*. 2023;15. doi:10.3390/pharmaceutics15092240
87. Xiong Y, Xu Y, Zhou F, et al. Bio-functional hydrogel with antibacterial and anti-inflammatory dual properties to combat with burn wound infection. *Bioeng Transl Med*. 2023:e10373. doi:10.1002/btm2.10373
88. Ramirez O, Pomareda F, Olivares B, et al. Aloe vera peel-derived nanovesicles display anti-inflammatory properties and prevent myofibroblast differentiation. *Phytomedicine*. 2024;122:155108. doi:10.1016/j.phymed.2023.155108
89. Bold BE, Urnukhsaikhan E. Mishig-Ochir, Biosynthesis of silver nanoparticles with antibacterial, antioxidant, anti-inflammatory properties and their burn wound healing efficacy. *Front Chem*. 2022;10:972534. doi:10.3389/fchem.2022.972534
90. Su Y H, Chen X, Jing X, et al. Antimicrobial, Antioxidant, and Anti-Inflammatory Nanoplatform for Effective Management of Infected Wounds. *Adv Healthc Mater*. 2024;(13):e2302868. doi:10.1002/adhm.202302868
91. Wang J, Calvert AE, Kaplan N, et al. HDL nanoparticles have wound healing and anti-inflammatory properties and can topically deliver miRNAs. *Adv Ther*. 2020;3. doi:10.1002/adtp.202000138
92. Zhou W, Zi L, Cen Y, You C. Tian, Copper Sulfide Nanoparticles-Incorporated Hyaluronic Acid Injectable Hydrogel With Enhanced Angiogenesis to Promote Wound Healing. *Front Bioeng Biotechnol*. 2020;8:417. doi:10.3389/fbioe.2020.00417
93. Zubairi W, Tehseen S, Nasir M, Anwar Chaudhry A, Ur Rehman I, Yar M. A study of the comparative effect of cerium oxide and cerium peroxide on stimulation of angiogenesis: design and synthesis of pro-angiogenic chitosan/collagen hydrogels. *J Biomed Mater Res B Appl Biomater*. 2022;110:2751–2762. doi:10.1002/jbm.b.35126
94. Seisenbaeva GA, Fromell K, Vinogradov VV, et al. Dispersion of TiO(2) nanoparticles improves burn wound healing and tissue regeneration through specific interaction with blood serum proteins. *Sci Rep*. 7(2017):15448. doi:10.1038/s41598-017-15792-w
95. Babaluei M, Mottaghitalab F, Seifalian A, Farokhi M. Injectable multifunctional hydrogel based on carboxymethyl cellulose/polyacrylamide/polydopamine containing vitamin C and curcumin promoted full-thickness burn regeneration. *Int J Biol Macromol*. 2023;236:124005. doi:10.1016/j.ijbiomac.2023.124005
96. Kim HS, Sun X, Lee JH, Kim HW, Fu X, Leong KW. Advanced drug delivery systems and artificial skin grafts for skin wound healing. *Adv Drug Deliv Rev*. 2019;(146):209–239. doi:10.1016/j.addr.2018.12.014