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REVIEW

Optimization of Metal-Based Nanoparticle Composite Formulations and Their Application in Wound Dressings

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Abstract: Metal-based nanoparticles (MNPs) have great potential for applications in wound healing and tissue engineering, and due to their unique structures, high bioactivities, and excellent designability characteristics, an increasing number of studies have been devoted to modifying these species to generate novel composites with desirable optical, electrical, and magnetic properties. However, few systematic and detailed reviews have been performed relating to the modification approaches available for MNPs and their resulting composites. In this review, a comprehensive summary is performed regarding the optimized modification formulations of MNPs for application in wound dressings, and the techniques used to prepare composite wound dressings are discussed. In addition, the safety profiles of the novel nanocomposite formulations and the limitations of the reported systems are evaluated. More importantly, a number of solution strategies are proposed to address these limitations. Overall, this review provides new ideas for the design of MNPs to facilitate their application in the field of skin tissue repair, and also looks into the future direction of MNPs in the biomedical field.

Keywords: metal-based nanoparticles, nanocomposite, wound dressing, multi-functional, review

Introduction

Wound healing is a complex biological process, especially in the case of chronic wounds, such as diabetic foot ulcers and pressure sores. The complex pathogenesis, slow healing, and high recurrence tendencies of these wounds not only severely affect the patient's quality of life, but they also place a significant burden on family finances and social healthcare resources. Currently, traditional medical dressings such as gauze and cotton pads are the main choice for wound care due to their low cost nature and wide applicability. However, these dressings suffer from poor adhesion properties, a lack of bioactivity, and disposability, thereby demonstrating evident limitations in the management of complex or chronic wounds. New multifunctional dressings to fulfill the ideal conditions for wound healing must therefore be developed.

Since they were first proposed by Faraday experiments in the mid-19th century, metal nanoparticles (MNPs) have been rapidly developed for use in biomedical applications, such as drug delivery, biosensing, and tissue engineering, due to their unique surface structures, excellent biological activities, good biocompatibilities, and diverse surface modification possibilities. As promising therapeutic candidates, MNPs have been demonstrated to possess antimicrobial and anti-inflammatory activities, in addition to promoting cell proliferation, thereby indicating their potential to significantly accelerate the wound healing process. In addition, MNPs can achieve the targeted delivery and intelligent release of drugs or biomolecules through surface functionalization/modification, thereby inspiring the development of a new generation of multifunctional wound dressings.[1]

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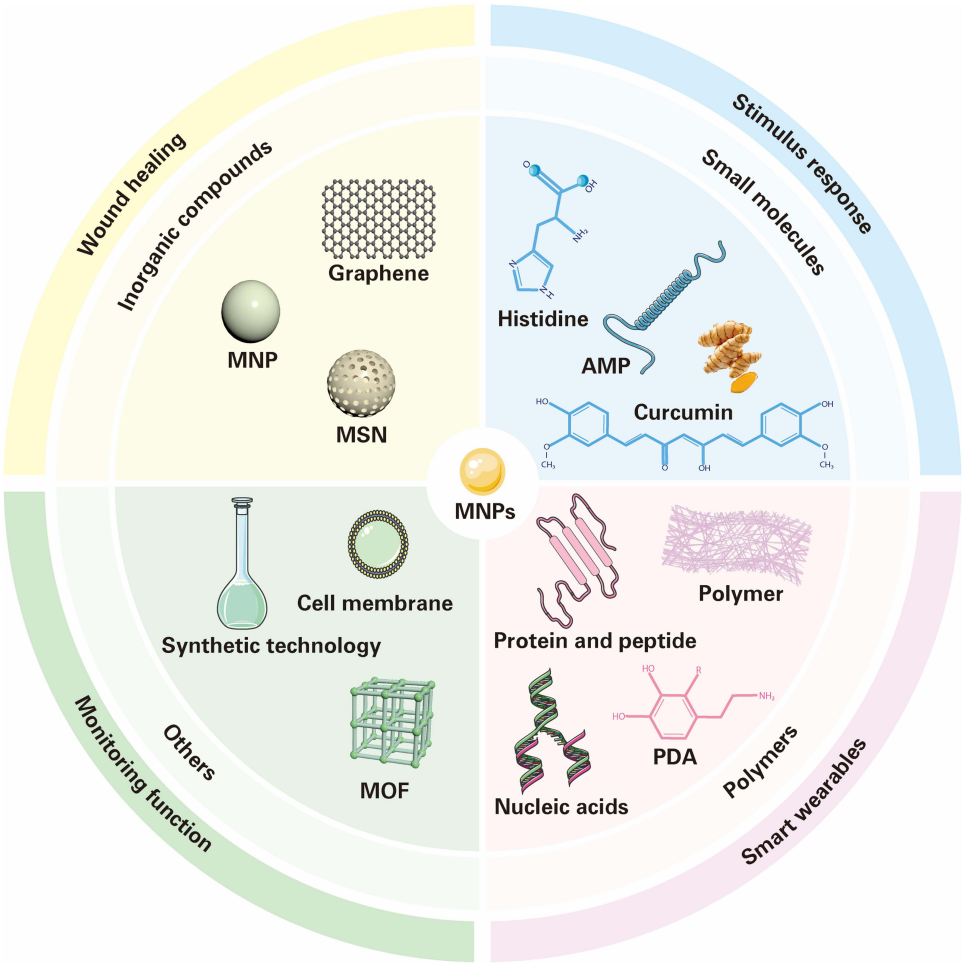
Graphical Abstract



Compared with traditional commercially available dressings, modern MNP-based dressings show significant performance advantages. For example, antimicrobial hydrogel dressings containing silver nanoparticles (AgNPs) not only provide a moist environment, but they also significantly reduce the risk of infection and accelerate tissue repair. In addition, dressings incorporating copper oxide nanoparticles (CuONPs) are able to accelerate wound repair by promoting the proliferation of local vascular endothelial cells, facilitating neovascularization, and supporting collagen synthesis and cell migration.[2] As a result of such advances, an increasing number studies have focused on the preparation of multifunctional composite dressings through the modification of MNPs.[3] In addition to inheriting various desirable properties attributed to the MNPs themselves (eg, antimicrobial, antioxidant, and cell proliferation promotion effects), these composite dressings can also exhibit intelligent response functions (eg, responses to environmental changes in the pH, temperature, and light) through their incorporation of bioactive molecules, polymers, or other nano-materials, thereby further enhancing their effectiveness in complex wound treatment.[4] Through such innovations, composite dressings can achieve more precise drug delivery, promote multiple biological processes (eg, vascular regeneration and nerve repair), and reduce inflammatory responses, greatly enhancing the efficiency of wound healing. However, a systematic review of the design and optimization of MNP-based composite multifunctional dressings is lacking in the current literature.

Thus, in this review, we systematically present the research progress of MNP-based composites in the field of wound healing, and comprehensively summarize the optimization strategies of MNP-based composite dressing formulations, focusing on their performance enhancements in the areas of wound healing, sensing, and smart response materials. In addition, this review describes the preparation methods available for MNP-based composite dressings and discusses optimization of the production process to enhance the production efficiency and reduce the associated costs. Notably, such approaches are aimed at promoting the widespread application of MNP-based composite dressings in clinical practice. Furthermore, this review innovatively classifies MNP-based composites into three types, namely implantable, filled, and topical dressings, according to the means of application. It also describes in detail the unique advantages of each type of dressing in different application scenarios. Moreover, optimization strategies are proposed to address challenges related to the material degradability, safety, and preparation technologies to further promote the development of such composites. Additionally, the potential of combining MNP composites with advanced therapeutic treatments, such as gas therapy and cell therapy, is considered, and the integration of emerging technologies, such as ultrasound conduction, three-dimensional imaging, and artificial intelligence is explored. The combination of these technologies is expected to enhance the precision and personalization of trauma treatment, while also promoting the development in the field of trauma treatment, opening up a new research direction, and providing broad application prospects for future research and clinical practice.

Metal-Based Nanoparticles to Promote Wound Healing

MNPs are clusters composed of metal atoms or compounds, with examples including AgNPs, AuNPs, ZnONPs, and TiO_2NPs, among others. Their structural advantages, such as a small size, high surface area, and good bioactivity, impart them with superior physical and chemical properties compared to traditional materials; therefore, they have been widely used in biomedical applications.[5,6] In recent years, MNPs have been reported to promote wound healing through various mechanisms (Figure 1), such as adhering to and penetrating bacterial cell membranes, inducing oxidative stress to exert

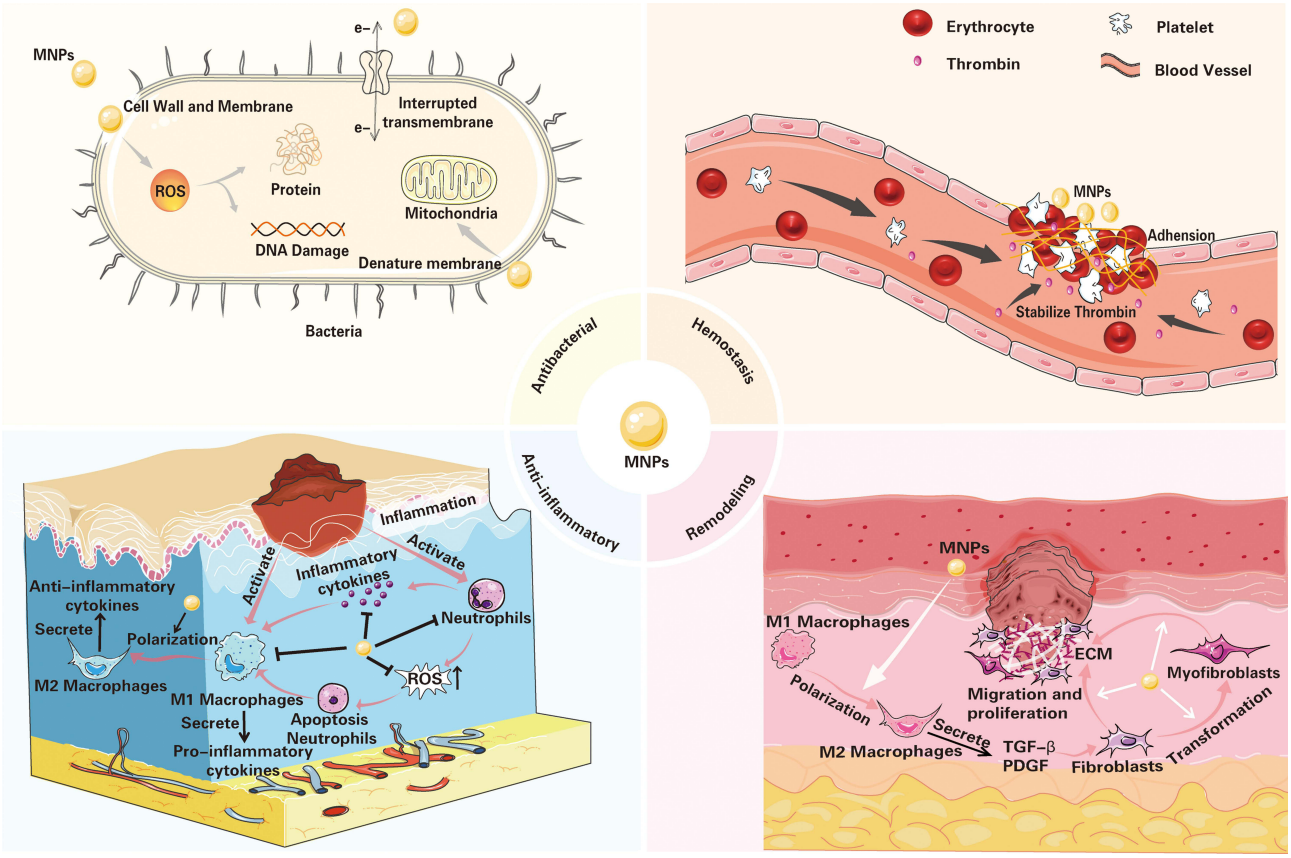


Figure 1 Wound-healing mechanism in the presence of MNPs.

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antimicrobial effects,[7] regulating cytokines to exert anti-inflammatory effects,[8] activating platelets, stabilizing thrombin to exert hemostatic effects,[9] and regulating fibroblasts (Fbs) to promote tissue remodeling.[10] Importantly, their excellent performances have been confirmed through both in vitro and in vivo experiments. However, single MNPs possess high surface energies and are prone to aggregation, which ultimately affect their performances. Therefore, to improve the stabilities of these species, attempts have been made to modify MNPs using a variety of materials that promote wound healing, to ultimately obtain composites with richer properties.

In this review, the use of MNP-based composites in promoting wound healing is summarized. Initially, the available optimization strategies and synthetic routes for the formulation of MNP-based composites are highlighted, and the applications of different dressing types in various wounds are described. Finally, safety issues associated with the design and syntheses of MNP-based composites are discussed.

Optimization Strategies for the Formulation of MNP-Based Composites

The introduction of surface modifiers can enhance the stabilities and surface activities of MNPs, while also reducing their cytotoxic properties, and promoting wound healing.

Inorganic Compounds

Mesoporous Silica

Mesoporous silica nanoparticles (MSNs) are porous nanomaterials that are known for their high specific surface areas, large pore volumes, tunable pore sizes, good thermal stabilities, and high biocompatibilities.[11,12] They are commonly used as carriers for MNPs and play an important role in controlling the particle sizes, uniform distributions, and release characteristics of MNPs.[13,14] Various composite materials of MSNs and MNPs have been used to optimize the antibacterial, hemostatic, sustained-release, and antioxidant properties of MNPs, thereby promoting wound healing.

To prepare such composite materials, MSNs can be combined with MNPs through various techniques (eg, core–shell formation, grafting, and embedding) to achieve enhanced, synergistic, and cooperative effects in the promotion of wound healing.[15–17] It has been found that such combinations exhibit an improved stabilities and dispersions compared to the original MNPs, and their contact areas are also enhanced (Figure 2). In addition, through regulation of the MNP particle size and release properties, MSNs can prolong their time of action and reduce their levels of cytotoxicity.[18] Combinations of MSNs and MNPs can also promote wound healing through synergistic effects. More specifically, the modification of CeONPs with MSNs addresses the weak hydrophilicity of the CeONPs, promotes their reactive oxygen species (ROS)-scavenging function,[19] and enhances their tissue adhesion properties to accelerate wound healing.[20] In addition, MNPs and MSN can jointly promote wound healing. In one study, Fe_3O_4@SiO_2@Ag bifunctional nanocomposites were synthesized via a surface-protected etching method. Initially, an ultrathin silica layer (<5 nm) was coated on the surface of Fe_3O_4NPs to form a protective layer, which exhibited enhanced antioxidant properties and protected Fe_3O_4 from external influences. Subsequently, AgNPs were incorporated into the core-shell structure to form Fe_3O_4@SiO_2@Ag. In addition, the outer layer of silica was transformed into a mesoporous structure with uniform pores using the cationic surfactant templating approach, thereby regulating the release rate of silver and enhancing the antimicrobial performance.[21,22] The abundant silanol groups present in the MSNs can also be grafted with various functional groups to obtain composite materials with desirable properties. For example, photosensitizers can be grafted to the structure to introduce photodynamic effects, and growth factors can be grafted to promote angiogenesis.[23] Overall, the performances of MSN-modified MNPs are significantly enhanced compared to those of single MNPs. Figure 2 presents a schematic representation of the surface modification of MNPs along with the potential application forms of the resulting MNP-based nanocomposites.

Notably, the carrier shape plays a significant role in the design of composite materials. This property not only affects the antimicrobial properties of the material, but it also influences the loading capacity.[24] For example, a flower-shaped carrier can enhance the MNP loading efficiency because of its porous structure and large specific surface area.[25] The design of flower-shaped MSNs should therefore be considered in the future, and the loading capacities of these species should be compared with those of spherical, conical, and virus-like MSNs to provide new insights for the development of efficient carriers. Additionally, although the introduction of acetylene groups can enhance the photothermal performance

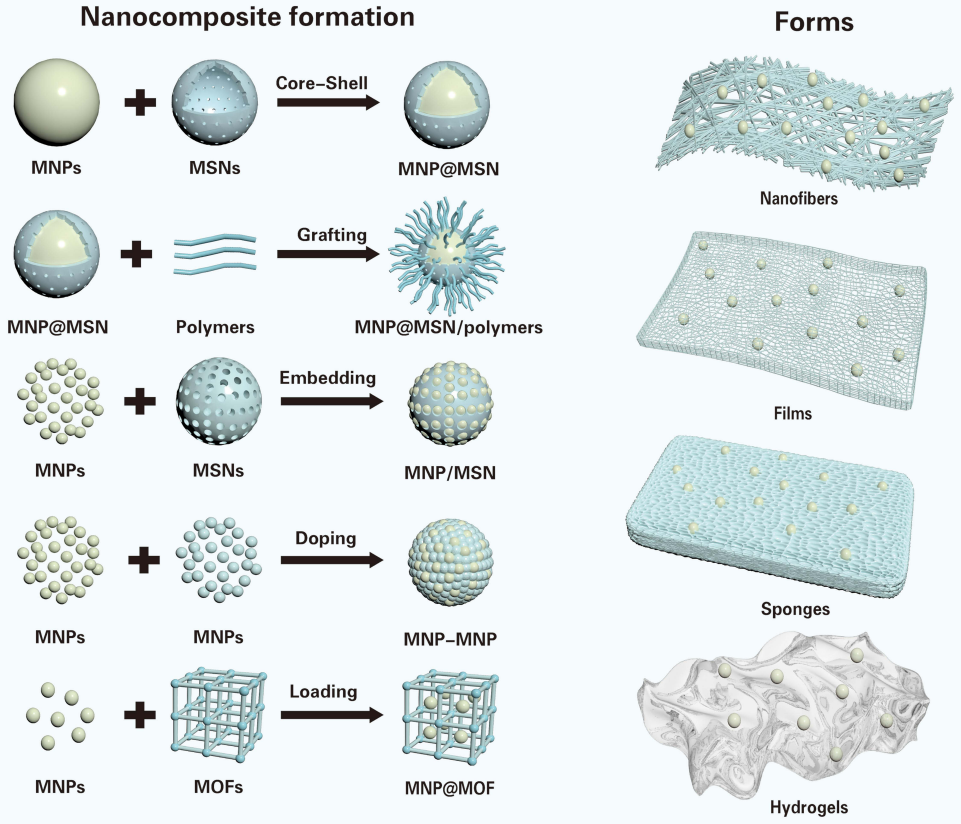

Figure 2 Surface modification of MNPs and application forms of MNP-based nanocomposites.

of a material,[26] there is currently no relevant research regarding the introduction of this group into MNP@MSN composites. In the future, it would be desirable to introduce active groups through grafting, plasma, and other technologies for the potential development of new composite wound dressings.

Metal-Based Nanomaterials

Single MNPs are generally unable to meet the complex demands of the entire wound-healing process. To address this issue, various bimetallic and multi-metallic nanocomposites have been designed by combining different MNPs to accelerate wound healing. More specifically, numerous synthetic approaches have been described for the preparation of bimetallic or multi-metallic nanocomposite materials, including common techniques such as doping, embedding, and core–shell formation.[27–29] In recent years, new techniques such as plasma immersion ion implantation, atomic layer deposition, and microfluidic control technology have also been reported. These approaches were found to enhance the original material properties to give performances similar to those of MNP composites while reducing the amount of required MNPs. As a result, the degrees of toxicity and drug resistance were lowered accordingly (Figure 3).[30] In addition, synergistic effects can be produced using different MNPs. For example, a one-step wet chemical approach has been used to incorporate noble metal nanoparticles (NMNPs) exhibiting plasmonic properties (eg, AuNPs, AgNPs, and PtNPs) as the core material and metal-based nanomaterials exhibiting excellent photocatalytic activities (eg, CuSNPs, ZnONPs, TiO_2NPs, and liquid metal nanoparticles (LMNPs)) as the outer shell material.[31] A strong coupling between the two layers can enhance the plasmonic absorption of the core and increase the contact surface area. Moreover, the outer shell protects the core from oxidation or corrosion, and the strong coupling between the two layers enhances the plasma absorption of the core and increases the contact surface area (Figure 3). In the case of the LM@Au composite, for example, the photothermal conversion can reach 65.9% under near-infrared (NIR) light irradiation, which is a significantly higher value than that achieved using AuNPs (ie, 13.2%), representing an approximately five-fold

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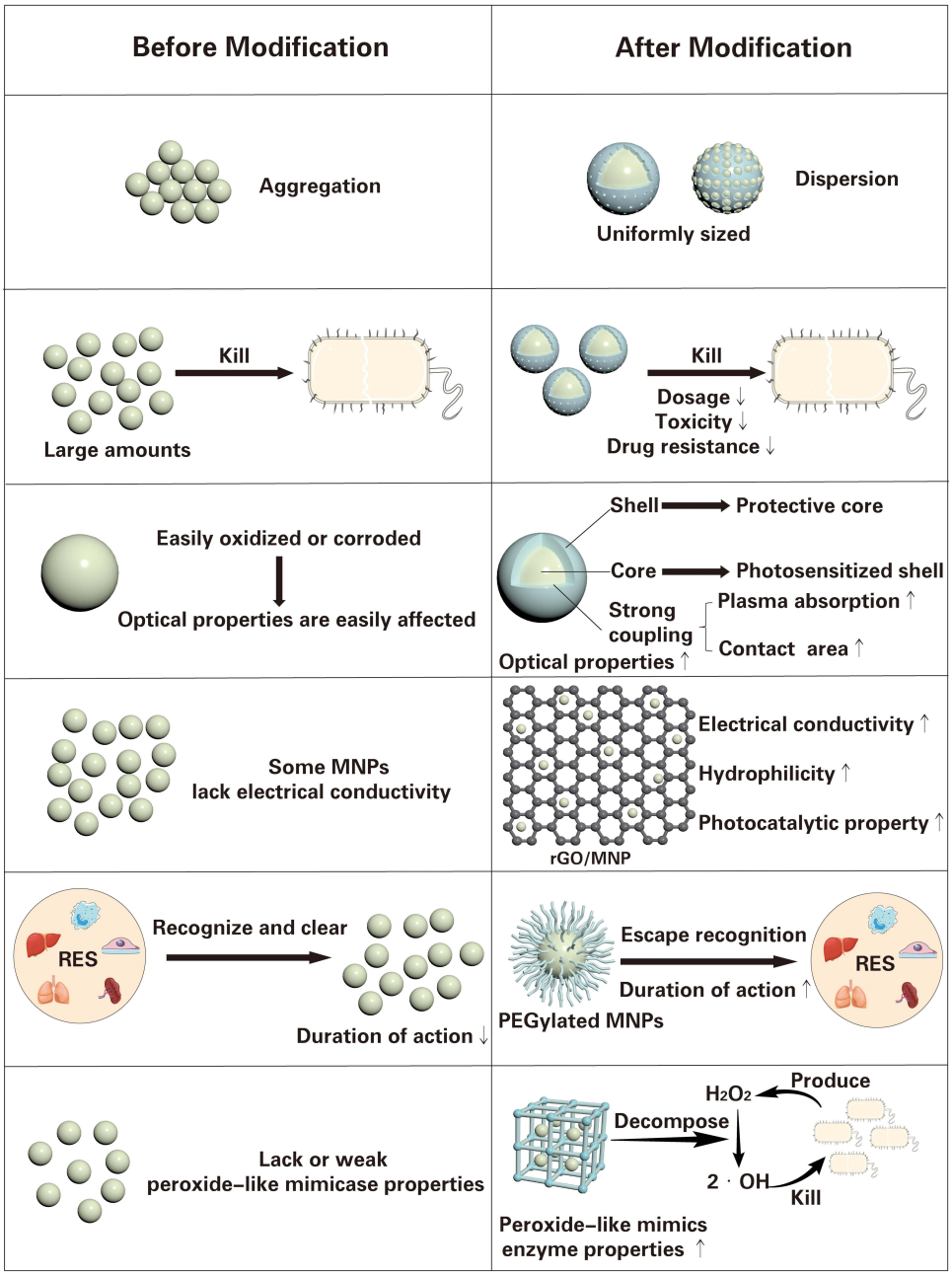

Figure 3 Drawbacks associated with single MNPs, and their functional optimization after modification with different materials.

improvement.[32,33] This increase promotes sufficient heat and ROS generation, which significantly enhances the antimicrobial activity of the composite.

Notably, for some narrow and deep wounds, such as tetanus wounds, wound opening is commonly carried out to improve hypoxia. However, this treatment not only increases the wound area, but it also renders the resulting scars more prominent. Considering recent reports that CeO_2NPs can increase the rate of O_2 generation in hypoxic environments,[34] it would be desirable to combine CeO_2NPs with materials such as CuONPs and AgNPs, which exhibit antibacterial, anti-inflammatory, hemostatic, and epithelialization-promoting properties, to develop novel wound dressings that can combine these effects with the spontaneous production of O_2 under light irradiation. This technique would be expected to achieve the noninvasive repair of deep and narrow wounds. Additionally, since the wound healing process consumes O_2, it is essential to monitor the O_2 content in the wound microenvironment. Recently, an Au:CuO nanocomposite film has been

developed for the high-sensitivity O_2 detection.[35] Inspired by this development, the two aforementioned designs could be combined for monitoring and regulating the O_2 contents of wound areas to promote more efficient wound healing (Figure 4).

Carbon-Based Nanomaterials

Carbon-based nanomaterials (CNMs), such as fullerenes, graphene oxide (GO), diamond, and carbon nanotubes, have shown great potential in the field of skin tissue repair because of their antimicrobial, anti-inflammatory, nerve cell repair, and epidermal regeneration properties.[36,37] In recent years, an increasing number of composite materials have been designed based on CNMs and MNPs to optimize the biological performances of MNPs while promoting wound healing through the unique structures, excellent electrical, optical, and thermal properties, and abundant functional groups of the CNMs.[38,39]

Composites of MNPs and CNMs have been demonstrated to inhibit the compounding of photogenerated electron–hole pairs through the formation of heterojunction interfaces, which expands the light absorption ranges of the MNPs and enhances their light absorption intensities. Additionally, CNMs can act as photostabilizers and photosensitizers, enhancing the photocatalytic performances of the MNPs and leading to increased ROS production under near-infrared light (NIR) irradiation; ultimately, this can lead to enhanced antimicrobial properties.[40,41] Furthermore, the surfaces of CNMs contain abundant oxygen-containing functional groups (eg, hydroxyl and carboxyl groups), to which MNPs (M = Au, Ag, or Cu) can be grafted.[42,43] This has been found to enhance the MNP hydrophilicity,[44] allowing for absorption of the wound exudate, an improved wound cleanliness, and more rapid wound healing. Moreover, both MNPs and CNMs are known to exhibit excellent electrical conductivities. In composite materials based on reduced graphene oxide (rGO), the MNPs can be reduced to metal ions through an electron transfer effect, thereby leading to superior antibacterial and anti-

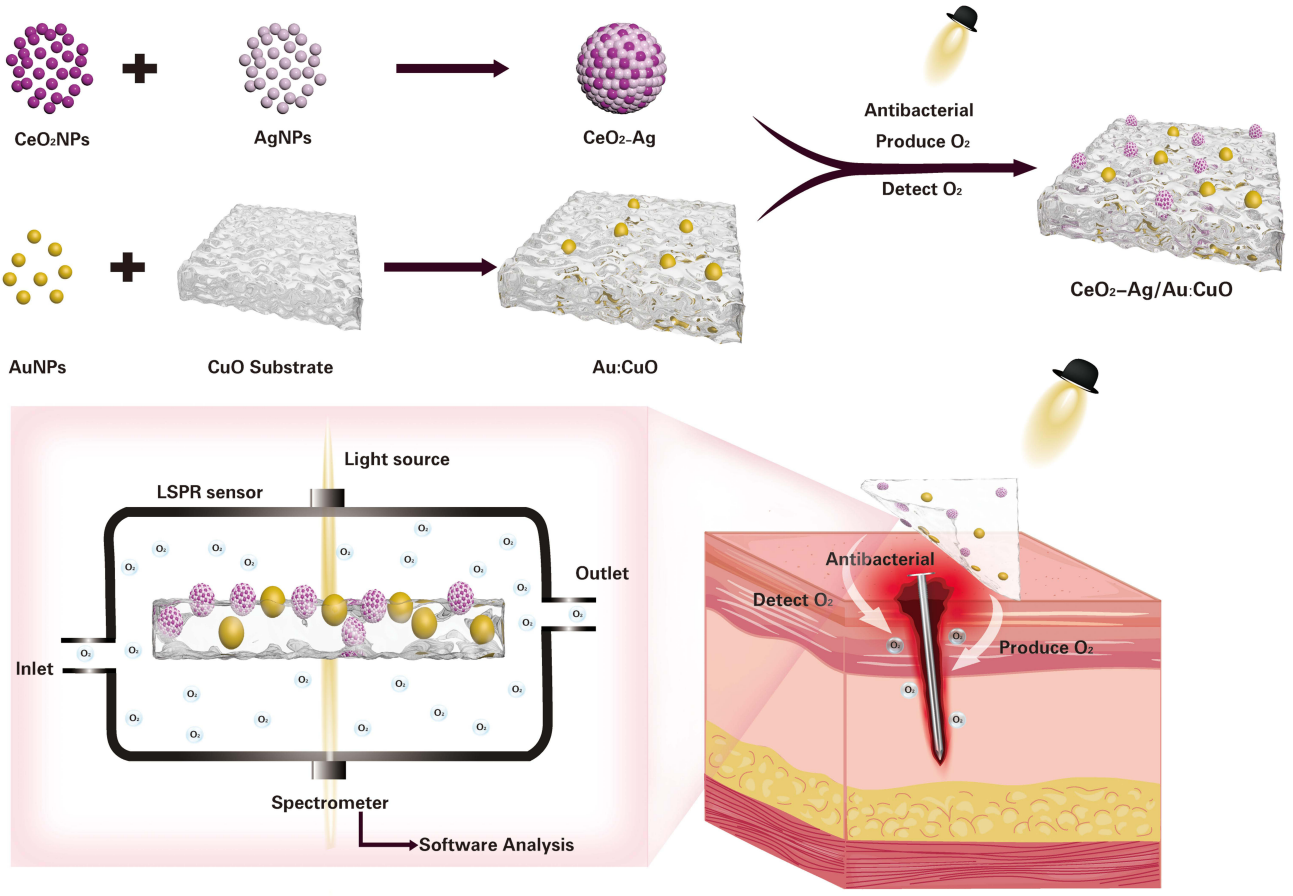

Figure 4 Schematic illustration of the CeO_2-Ag/Au:CuO nanocomposite film and its antimicrobial, oxygen-generating, and oxygen-detecting mechanisms of action.

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inflammatory effects, while also promoting angiogenesis to accelerate wound healing. In this process, the rGO can significantly reduce the MNP resistance and improve the particle conductivity (Figure 3).[45] Therefore, wound dressings based on rGO/AgNPs and rGO/CuONPs can be designed to promote cell migration and angiogenesis under an external electric field. Currently, the commonly used methods for preparing CNM and MNP composites include one-pot pyrolysis, in situ synthesis, self-assembly and electrochemical deposition.[46,47] Among them, in situ synthesis has become the most popular approach in recent years, simplifying the preparation process and yielding highly compatible composites with stable physical properties, high interfacial bond strengths, and clean interfaces. However, it is difficult to ensure the uniform dispersion of MNP on the CNM surface.[48] Therefore, to address this issue, CeO_2NPs have been used to inhibit MNP aggregation.[49] By assembling CeO_2NPs on the surface of rGO and using an in situ generation method to form composite MNPs, a uniform dispersion of MNPs can be obtained, leading to an enhanced bioactivity and accelerated wound healing.

Notably, graphene can also enhance the thermal conductivity and heat dissipation properties of MNPs.[50] Consequently, composite heat sinks/films composed of these two materials have been applied in the communications industry, electronic products, and medical equipment; however, there have been no relevant reports regarding the application of such composite materials in wound dressings. Inspired by this, the preparation of graphene- and MNP-based composite materials that demonstrate excellent thermal conductivities and heat dissipation properties would be expected to provide a safe and effective treatment method for acute wounds, such as burns that require a combination of local cooling and heat dissipation.

MNPs Modified by Small Molecules

Amino Acids and Small Molecular Peptides

Owing to their simpler structures, varying functional groups, and smaller degrees of steric hindrance, it has been reported that a number of amino acids and small molecular peptides are superior to traditional surface modifiers.[51] These species can easily and controllably complex with MNPs, in addition to tuning their stabilities and antimicrobial activities. Consequently, they have attracted growing attention in the field of wound healing.

Amino acids and small molecular peptides can form complexes with MNPs through their active amino, carboxyl, and side-chain groups. The resulting electrostatic and covalent interactions between these species can prevent MNP aggregation, thereby increasing their colloidal stabilities and enhancing their antibacterial, vascular regeneration, and re-epithelialization properties to promote wound healing.[52] In addition, histidine-modified MNPs, such as those based on AgNPs, can bind to bacterial surface receptors, thereby enhancing their targeted accumulation at the infection site, exerting more specific and effective antimicrobial properties, and accelerating wound healing. Furthermore, serine, tyrosine, and glutathione can provide MNPs with good size and shape tunabilities to promote cell uptake.[53] Once inside the cells, the amino acids and small molecular peptides can promote redistribution of the MNP surface charges to accelerate metal ion release and enhance the antimicrobial, anti-inflammatory, and epidermal regeneration properties of the MNPs.[54] Moreover, MNPs modified with arginine and lysine have been demonstrated to exhibit high surface-to-volume ratios, which has led to increased bacterial capture rates in the local environment. For example, the OO4@AA (AA = amino acid) composite can capture >90% of Escherichia coli cells in the fifth regeneration cycle, indicating that amino acids can also enhance the MNP reusability.[55] This not only reduces the requirements for raw materials, but it also provides a new design concept for the development of environmentally friendly antimicrobial wound dressings.

Plant Extracts

Plant extracts contain secondary metabolites that have specific functions in the plant itself. Such secondary metabolites include phenols, flavonoids, terpenoids, and alkaloids, which can act as reducing, stabilizing, or capping agents during the synthesis of MNPs in the green synthesis method.[56] In addition, these species can effectively modify and stabilize the MNPs, endowing them with a good biocompatibility, dispersibility, and multiple functions, which can significantly enhance their anti-infective and anti-inflammatory properties to accelerate wound healing.[57]

Plant extracts are known to optimize the anti-infective properties of MNPs via various mechanisms. For example, curcumin can form a chelate with AgNPs through binding of its carbonyl and phenolic groups. This promotes binding to

bacterial cells and triggers the release of large amounts of Ag^+ on the surface and in the vicinity of the bacteria, thereby inducing bacterial death and enhancing the anti-infective properties of the wound dressings.[58] Additionally, curcumin and citrus essential oils are known to inhibit the bacterial quorum sensing systems, leading to enhanced antimicrobial and antibiofilm capabilities for the modified MNPs (eg, ZnONPs), and reducing the healing times of infected wounds.[59] Furthermore, due to its ability to act as a photosensitizer, curcumin can be laser irradiated to produce single-linear oxygen, which leads to a synergistic antimicrobial effect with the AgNPs. Compared with the antimicrobial activity of the AgNP-loaded fibrous membrane alone (66.96%), the antimicrobial activity of the curcumin@AgNP core–shell-structured fibrous membrane against *Staphylococcus aureus* reached 93.04%, thereby greatly enhancing the anti-infective properties of the wound dressing.[60]

In addition to controlling infections, plant extracts promote wound healing by enhancing the anti-inflammatory properties of MNPs. Research has confirmed that extracts from Eucommia ulmoides leaves, black elderberry fruits, and artemisinin, among others, can significantly enhance the inhibition of inflammatory signaling pathways (eg, NF-κB and COX-2) upon combination with AgNPs, ZnONPs, and AuNPs. Such systems have also been demonstrated to assist in downregulating the expression of the TNF-α, IL-1β, TNF-α, and IL-6 pathways, thereby minimizing inflammation of the wound.[61,62] Furthermore, owing to the strong antioxidant properties of honey and curcumin, these species can neutralize the ROS generated by AgNPs and ZnONPs during the wound repair process, thereby protecting the skin tissue from oxidative stress-induced inflammation, and accelerating wound healing.[63,64] Overall, MNPs modified with plant extracts have demonstrated excellent anti-infective and anti-inflammatory capabilities, indicating their potential for use in wound-dressing formulations, especially for the treatment of diabetic ulcers, burns, and other wounds.

Currently, the majority of research carried out into plant extract-based MNPs is limited to the antibacterial and anti-inflammatory fields, with many potential properties remaining largely unexplored, such as the ability to reduce scar formation and improve aesthetics.[65] In one unique example, Cu_2ONPs have recently been demonstrated to induce fibroblast apoptosis and reduce proliferative scar formation. It may therefore be desirable to combine honey or curcumin (which can reduce scar formation) with Cu_2ONPs to prepare superior wound dressings.[66,67]

MNPs Modified by Polymers

Proteins and Peptides

Proteins and peptides (eg, collagen, insulin, and antimicrobial peptides) are natural substances that are produced by all organisms. They are known to exhibit excellent wound-healing abilities, in addition to good biocompatibilities, biodegradability characteristics, and ease of modification, thereby leading to their increased application as surface modifiers for MNPs.[68] Because of the structural diversity of proteins and peptides compared to that of the amino acids, they are able to significantly improve the dispersibility, stability, and biocompatibility attributes of MNPs, while also enriching their biomedical and optical properties for extended applications in wound healing.[69] For example, the combination of antimicrobial peptides with antibacterial MNPs (eg, AgNPs or ZnONPs) leads to enhanced antibacterial properties, promotes the healing of infected wounds, and allows reduced MNP dosages to be used, thereby lowering the treatment cytotoxicity.[70,71] In addition, AgNPs modified with functional groups (eg, amino and carboxyl groups) were found to produce stable IAgNPs, which helped maintain the balance between pro-inflammatory factors (IL-6, TNF-α) and anti-inflammatory factors (IL-10), thereby modulating wound inflammation. It was demonstrated that after 11 d of treating diabetic mouse wounds with AgNPs alone, the expression levels of IL-6 and TNF-α were reduced by only 10%, while the IL-10 level was elevated by 45%. In contrast, the expression levels of IL-6 and TNF-α were reduced by ~45% in the IAgNP treatment group, while that of IL-10 was elevated by ~50%, indicating more pronounced inflammatory factor modulation. In addition, treatment with the IAgNPs stimulated the re-epithelialization of keratinocytes (KCs), promoted fibroblast proliferation, migration, and extracellular matrix production, and accelerated skin remodeling to advance wound healing.[72]

Furthermore, various proteins (eg, casein, cell-penetrating peptides, and antimicrobial peptides) have been demonstrated to endow MNPs with new interfacial functions, significantly improving the MNP internalization efficiency, biological distribution, and the effectiveness in promoting wound healing.[73] For example, when LL37 is attached to the surfaces of AuNPs via Au–S bonds using chemical reduction combined with post-modification, cellular uptake of the

AuNPs is significantly increased, and the resulting enhanced antimicrobial properties prevent wound infection.[74] In addition, lactoferrin, transferrin, and antimicrobial peptides can interact with receptors on the target cells, allowing the MNPs to be released at specific sites. This, in turn, promotes MNP accumulation in the target tissues and promotes the wound healing process.[75]

Moreover, the localized surface plasmon resonance (LSPR) effects of NMNPs, such as AuNPs and PtNPs, has led to the application of these species in the field biosensors.[76,77] For example, collagen was found to promote plasmon coupling between AuNPs, leading to a shift in the LSPR peak and producing a colorimetric reaction. Therefore, using this colorimetric reaction and the specific recognition of collagen by biomarkers, it should be possible to monitor wound indicators.[78] Recently, composite materials of AuNPs and collagen have been reported as biosensors for monitoring blood glucose, and the wound-healing advantages of AuNPs in diabetic wounds have been confirmed.[79] However, the ability of a collagen–AuNP composite material to achieve both monitoring and treatment simultaneously has yet to be demonstrated, and should be a future research direction for the treatment of diabetic wounds.

Polysaccharides

Polysaccharides (eg, chitosan, bacterial cellulose, and hyaluronic acid) are natural biopolymers. Owing to their desirable biomimetic properties, biocompatibilities, biodegradabilities, and water absorption/retention performances, they have become ideal materials for use in the preparation of wound dressings.[80] When combined with MNPs, the polysaccharides not only significantly enhance the dispersion, penetration, and controlled release of the MNPs, they also impart their antibacterial, anti-inflammatory, and other activities onto the final composite, thereby accelerating wound healing.[81]

Currently, the most commonly used in situ method for the preparation of polysaccharide–MNP composite materials involves utilizing the abundant active sites on the polysaccharide surfaces to reduce metal ions into MNPs, which are consequently fixed into the porous polysaccharide network structure. This promotes a uniform dispersion of the MNPs and has been found to lead to controlled release, thereby enhancing the biomedical activity and promoting wound healing.[82,83] For example, the loading of AgNPs into bacterial cellulose can achieve the slow release of Ag^+ ions, with only 16.5% of Ag^+ being released within 72 h.[84] Importantly, this avoids a sudden burst release of Ag^+, which could damage the wound and normal skin tissue. In addition, this approach reduces the levels of inflammatory factors and cells in the wound, thereby promoting the proliferation, proliferation, and migration of Fbs, and accelerating the wound healing process.[85,86] Moreover, chitosan, the only naturally occurring alkaline polysaccharide with a positive charge, can bind to the negative charges on the surfaces of microorganisms to alter the membrane permeability and mediate the infiltration of MNPs into the microorganisms. As a result, membrane rupture and cytoplasmic leakage occur, ultimately causing microbial death and enhancing the anti-infective properties of the dressing.[87]

It has also been demonstrated that polysaccharides can synergistically promote wound healing in combination with MNPs. For example, polysaccharides such as hyaluronic acid and alginate have been used to mimic the extra cellular matrix (ECM), providing support for cell adhesion, proliferation, and tissue regeneration.[88] Furthermore, due to their the high flexibilities, rich hydrophilic groups, and porous network structures, polysaccharides can be used to absorb exudates and blood from irregularly shaped wounds.[89] Moreover, MNPs such as AuNPs, CuONPs, and ZnONPs have been demonstrated to exhibit excellent antibacterial, anti-inflammatory, and proangiogenic properties, and their combination with polysaccharides can provide effective treatments for infected or burn wounds. In this context, a composite of chitosan, hyaluronic acid and AgNPs (CS-HA-AgNPs) synthesized by a green synthesis method was found to combine the biomimetic properties of CS and HA as well as the antimicrobial properties of AgNPs. As a result, the healing of diabetic foot ulcers was significantly accelerated, thereby laying the groundwork for the treatment of non-healing wounds.[90]

However, it should be noted that polysaccharides have limitations in terms of their wound-dressing applications, such as weak mechanical properties and inadequate adhesion to moist wounds.[91] Although these issues have been partly addressed by adding chemical cross-linking agents or synthetic polymers, such modifications tend to reduce the material biocompatibility and degradability, while also complicating the preparation process and increasing costs.[92] Therefore, future research should focus on optimizing the performances of polysaccharides to enhance their wound-healing capabilities in MNP-based composite dressings.

Biochromes

Melanin and its biomimetic material, polydopamine (PDA), are high-molecular-weight materials with strong NIR light absorption properties. Because of their excellent photothermal conversion efficiencies, light absorption ranges, and biodegradabilities, these materials have received widespread attention in the field of photothermal therapy.[93] It has been reported that the catechol groups enriched on the surfaces of such materials can chelate metal ions and can also be complexed with MNPs via redox reaction methods. This leads to a greater stability, hydrophilicity, and biocompatibility, in addition to enhanced cell adhesion and photothermal effects, ultimately resulting in improved anti-infective and antioxidant properties to accelerate wound healing.[94,95]

More specifically, melanin and PDA can reduce the bandgaps of MNPs to promote their absorption of visible and infrared light, and to achieve a controlled release of metal ions upon light induction.[96] Such properties are desirable since they can prolong the treatment duration through the gradual release of the active substance. In addition, melanin and PDA have been found to enhance the photothermal conversion capabilities of MNPs (eg, AuNPs) in the NIR region, reaching a photothermal conversion efficiency of up to 42.3%, and killing bacteria through local heating.[97] Furthermore, the introduction of a strongly adhesive and antibacterial PDA coating can promote the effective capture of bacteria, interfere with their metabolic state, accelerate apoptosis, and enhance the anti-infective capability of the composite material.[98] In recent years, mesenchymal stem cells (MSCs) labeled with Fe_3O_4NPs have shown great potential for the targeted therapy of damaged tissues under the guidance of an external electromagnetic field (EMF).[99,100] However, an EMF can potentially interfere with the MSC behavior.[101] Notably, it has been reported that the excellent anti-inflammatory and cell adhesion properties of PDA coatings can promote the migration of MSCs to the site of inflammation, in addition to enhancing the adsorption of MSCs onto the Fe_3O_4NPs. Even without an external EMF, this approach can significantly promote the homing and anti-inflammatory abilities of MSCs, thereby accelerating the healing of burn wounds.[102,103] Furthermore, the abundant free phenolic groups present in melanin and PDA can eliminate the excessive ROS produced by MNPs, thereby reducing inflammation in the wound.[104] Overall, the combination of composite materials with photothermal and cell therapies has great potential to promote wound healing.

Interestingly, melanin and PDA have been found to significantly enhance the photoacoustic effects of MNPs.[105] Currently, photoacoustic technology is used to achieve precise wound measurement, detect biomarkers, and image wound structures, all of which help assess the severity and progression of wound healing.[106,107] However, the photoacoustic properties of composite materials of melanin or PDA combined with MNPs have yet to be studied in the context of wound monitoring. Such formulations would be expected to enable the real-time imaging of the wound microenvironment without invasion, thereby aiding clinical diagnosis and treatment, and potentially replacing skin biopsies to reduce patient suffering. Therefore, the development of new dressings based on these formulations can be considered a promising direction for future research.

Nucleic Acids

Owing to the structural controllability, sequence tunability, and ease of modification of nucleic acids (eg, DNA, mRNA, miRNA, siRNA, and oligonucleotides), these compounds have been used as synthetic templates. As previously reported, they can be complexed with MNPs through electrostatic interactions, ligand binding, chemical bonding, and self-assembly to obtain MNPs with the desired shape, size, and particle spacing. Notably, such systems have demonstrated show great potential in wound healing and biosensor applications.[108,109] More specifically, nucleic acid-modified MNPs regulate the expression of proteins involved in inflammation, angiogenesis, tissue remodeling, and other related signaling pathways, thereby leading to superior wound-healing capabilities. For example, CNP-miR146a can eliminate excessive ROS in wounds, while also reducing the expression of pro-inflammatory cytokines by downregulating the NFκB pathway, alleviating wound inflammation and oxidative stress, and accelerating diabetic wound healing.[110] Similarly, Dicer-substrate small interfering RNA (DsiRNA) can increase the expression levels of the vascular growth-related mediators PGE2 and VEGF by silencing the target gene prostaglandin transporter (PGT).[111] Furthermore, the complexation of AgNPs with LTF (lactoferrin) to form AgLTF led to an excellent antimicrobial activity against *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa*, in addition to promoting skin cell migration. Consequently, AgLTF achieved 100% wound closure within 48 h, whereas AgNPs alone only achieved 69.29% closure within

72 h. Consequently, the combination of DsiRNA with AgLTF is expected to promote wound healing in burns or implants that are susceptible to infection or exhibit weak angiogenesis.[112] Additionally, some nucleic acids have been demonstrated to optimize the tissue-remodeling ability of MNPs. For example, AuNPs modified with Anti-miRNA-378a can promote the reconstruction of damaged tissues by upregulating vimentin expression, guiding the differentiation of keratinocytes at the wound edge into highly migratory and proliferative mesenchymal cells, and potentially becoming a new option for the treatment of challenging wounds.[113] Furthermore, tetrahedral framework nucleic acids (tFNAs) are novel carrier materials bearing abundant modification sites, and they are known to exhibit an excellent transdermal permeability along with high cellular uptake rates.[114] tFNAs also possess anti-inflammatory, antioxidant, anti-scarring, and pro-angiogenic effects,[115,116] and so it is proposed that following their encapsulation of MNPs, the resulting composite materials may be suitable for use in the treatment of burns, chronic ulcers, and other wounds.

Furthermore, nucleic acids can assist MNPs in achieving specific molecular sensing and detection capabilities. For example, DNA-AuNP fluorescent nanoprobes were applied to wounds and were used to detect vimentin mRNA levels in cells, in addition to monitoring the wound EMT process.[117,118] Inspired by this, DNA-AuNPs, nanoceria-FAM-ssDNA, and other fluorescent nanoprobes have been described for detecting other target mRNAs in wounds (Figure 5),[119,120] such as the key regulatory factors for KCs, the epidermal barrier function (eg, APC mRNA),[121] and wound healing progression markers (eg, MMP-9 mRNA).[122] Notably, monitoring the extent of wound damage and repair is clinically important for promoting wound healing and preventing complications.

However, nucleic acid-modified MNPs face many challenges in their application, such as high costs, off-target effects, limited stabilities, and limited durations of action.[124] Additionally, research in the area of nucleic acid-MNP composite materials for tissue regeneration is in its relatively early stages, and the safety issues (eg, immunotoxicity and cytotoxicity) associated with such formulations require further evaluation.

Synthetic Polymers

Compared to natural polymers, synthetic polymers such as polyethylene glycol (PEG), polylactic acid (PLA), and polyethylene oxide (PEO) are known to exhibit superior amphiphilic properties, oxygen permeabilities, extensibility characteristics, controllable degradabilities, mechanical properties, tensile strengths, and elasticities, in addition to controllable degradabilities, thereby rendering them indispensable in the design of wound dressings.[125,126] In addition, their composites with MNPs have been demonstrated to achieve superior wound-healing performances compared to single MNPs. In such composite materials, the synthetic polymers primarily act as carriers to significantly improve the MNP stability and dispersibility, while also optimizing their release and physicochemical properties.[127] For example, the loading of AuNPs into PEG407 extended the NP release and contact time with the wound, thereby maximizing the

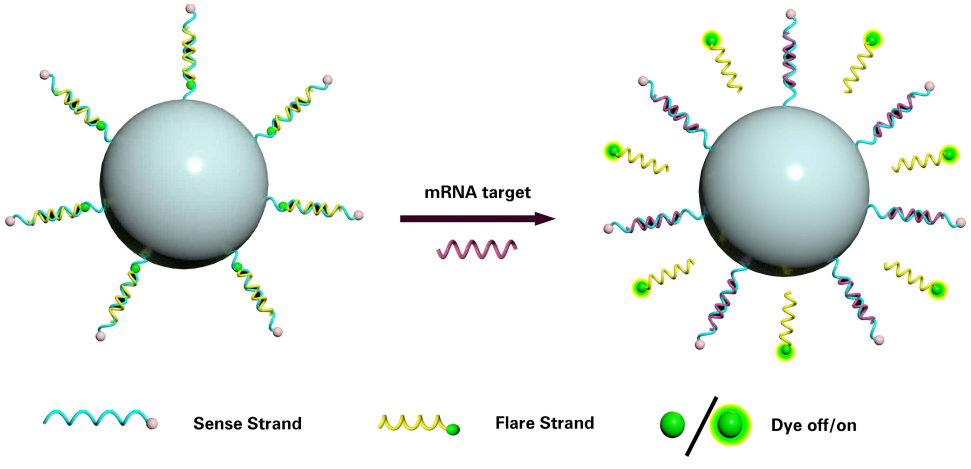

Figure 5 Schematic illustration of the imaging principle of a nanofluorescent probe. The fluorescence is quenched when the fluorophore is close to the AuNP surface, and when the target vimentin mRNA is present, the fluorescence chain is competitively replaced, and is subsequently released from the AuNP to restore the fluorescence signal and realize intracellular imaging.[123]

therapeutic effect of the material.[128] Research has indicated that percutaneously permeating MNPs are cleared by the reticuloendothelial system (RES), which affects their efficacy. Therefore, PEG-modified MNPs have been used to impart unique stealth properties by shielding their surface charges, reducing RES uptake, and prolonging their duration of action in wounds (Figure 3).[129,130] In another study, PHMB@Au NPs synthesized via a green synthetic method using poly (hexamethylene bis(guanidine) (PHMB) as a reducing agent for modification of the AuNPs showed enhanced NIR absorption and photo-thermal conversion efficiencies, and rapidly removed bacteria from wounds under light irradiation, thereby inhibiting biofilm formation and accelerating wound healing.[131] Synthetic polymers have also been shown to affect the oxidation states of the MNP surfaces. More specifically, polyacrylic acid (PAA) can regulate the Ce^{3+}/Ce^{4+} ratio in CeNPs, neutralize excess ROS in cells, exert antioxidant effects, and protect normal skin tissue from oxidative stress.[132]

The use of ultrasound technology to detect the depths of wounds has recently become a research hotspot. Although flexible electronic patches are a new trend in this field;[133] however, their sensing capabilities are inadequate. The use of flexible polymers, such as PMMA and PI would therefore be desirable as the base and coupling agents, while AuNPs could be employed as the filler and sensor to develop a new type of dressing that can simultaneously promote wound healing and allow the non-contact detection of wound depths under ultrasound assistance (Figure 6). Such systems would be of great significance for monitoring the wound-healing process and evaluating the effectiveness of wound treatment.

Others

MOF-Modified MNPs

Metal–organic frameworks (MOFs) are porous crystalline materials that are mainly composed of metal ions or metal clusters connected by coordination networks with organic ligands. Because of their tunable pore structures, high porosities, large specific surface areas, abundant active sites, and flexible designs, MOFs have become an ideal choice for modifying MNPs. More specifically, MOFs are commonly combined with MNPs through ligand interactions, physical adsorption, synergistic synthesis, and surface modification, and the resulting materials have been widely used in the field of wound healing.[134,135] MOFs can also serve as carriers for MNPs. More specifically, it has been reported that MNPs encapsulated by MOFs can achieve higher loading capacities, delivery efficiencies, and sustained-release performances, significantly improving the utilization and therapeutic effects of MNPs in wound dressings.[136] To achieve the controlled release of MNPs at specific sites, stimuli-responsive MOFs have been designed, which exhibit rapid responses to changes

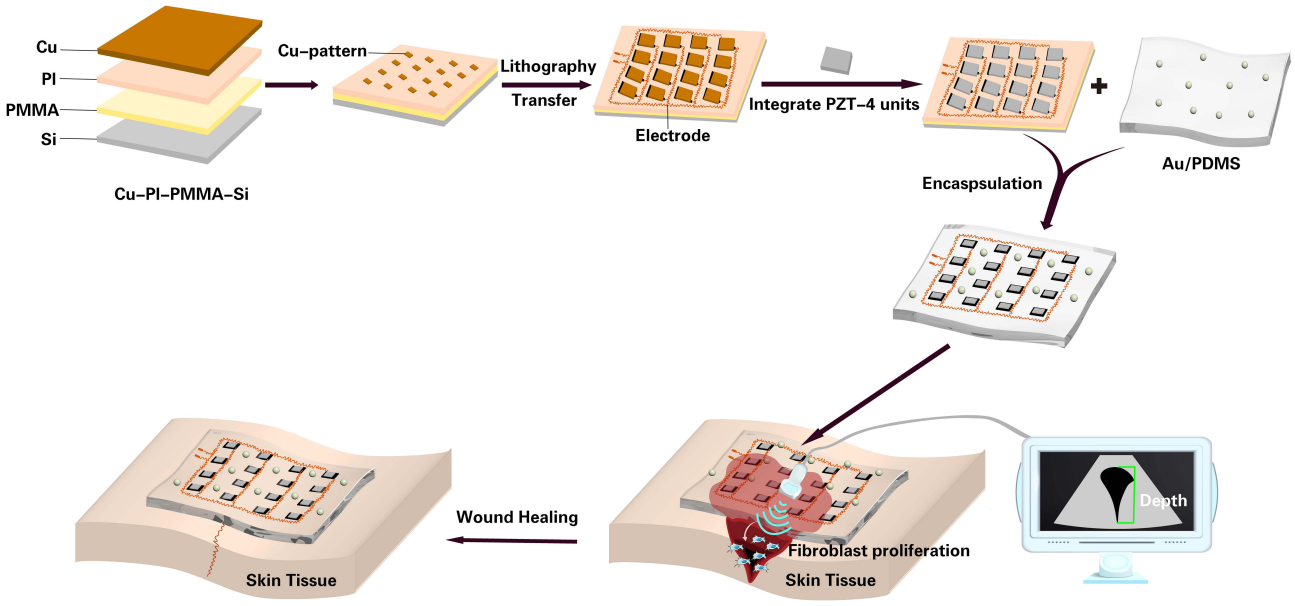

Figure 6 Schematic design of a flexible electronic patch based on AuNPs and its mechanism for achieving wound depth detection and promoting wound healing under ultrasound conditions.

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in the wound microenvironment (eg, pH, humidity, or temperature) or in the presence of external stimuli (eg, light or magnetic fields).[137,138] For example, the encapsulation of MNPs in pH-responsive MOFs, such as zeolitic imidazolate frameworks (ZIF-8 and ZIF-67), allows the composite material to degrade into metal ions and organic ligands in the acidic environments of infectious or inflammatory wounds.[139,140] These materials have been demonstrated to exhibit good antibacterial, anti-inflammatory, pro-angiogenic, and collagen-depositing effects, synergizing with the slow release of MNPs from the framework to demonstrate superior wound healing effects compared to the MNPs alone.[141] For example, MOF/Ag releases large amounts of Zn^{2+} and Ag^{+} under NIR irradiation, and achieves an almost 100% bactericidal efficacy against high concentrations of *Staphylococcus aureus* and *Escherichia coli* (10^7 CFU/mL) even at extremely low doses (0.16 mg/mL).[142]

Furthermore, MOFs can improve the stability and dispersibility characteristics properties of the MNPs, thereby enhancing their enzyme-like, photoelectric, and catalytic activities.[143] It has been demonstrated that MOF-modified MNPs (eg, AgNPs and UsAuNPs) exhibit superior peroxidase-like characteristics, and are capable of decomposing H_2O_2 into hydroxyl radicals to kill the bacteria and reduce wound infection levels (Figure 3).[144,145] In another study, photosensitive MOFs (eg, ZIF-8) were combined with NMNPs (eg, AuNPs, AgNPs, and PtNPs) to generate Schottky junctions, effectively promote the separation and transfer of photoinduced charges, and produce enhanced photocatalytic performances.[146] Consequently, these composite materials exhibited significantly enhanced photocatalytic ROS generation levels and photothermal effects under visible light irradiation, effectively killing bacteria or tumor cells and presenting great potential for application in infectious and cancerous wounds.[147]

Recently, gas therapy has become a popular topic in wound repair research. It has been reported that MOF-modified MNPs (eg, based on a combination of MIL-101 with PtNPs, CuNPs, or CoNPs) can convert water into H_2,[148,149] which exerts anti-inflammatory, ischemia-improving, skin-repairing, and cell proliferation-promoting effects.[150] Although this formulation has not yet been applied in the biomedical field, it is conceivable that it may convert the wound exudates into H_2 gas, thereby promoting the healing of chronic wounds, and representing a new direction of research.

Cell Membrane-Modified MNPs

The cell membrane is an emerging modifier of MNPs, with common modification approaches including charge modulation, lipid coating, functionalized modification, and self-assembly. These modifications not only impart protective and stabilizing effects on the intracellular substances, but they also participate in information exchange and directed transport. Cell membrane-coated MNPs (CMC@MNPs) not only retain the physicochemical properties of MNPs, but they also inherit various natural attributes from the cell membrane, such as immune evasion, targeted lesion delivery, and detoxification. These characteristics therefore effectively enhance the therapeutic efficacies of MNPs in wound healing.[151,152]

It has been reported that the membrane CD47 proteins of cells such as red blood cells, white blood cells, and platelets can be recognized by macrophages as "self".[153] As a result, Fe_3O_4NPs, AuNPs, and other MNPs that are coated with these cell membranes exhibit immune evasion effects, leading to a longer circulation times within the body, and significantly enhancing their utilization.[154] In addition, it has been demonstrated that cell membrane coatings can enhance the targeted therapeutic abilities of MNPs. For example, cancer cell membranes (CCMs) possess homologous targeting properties because of the presence of adhesion molecules on their surfaces (eg, epithelial cell adhesion molecules, N-cadherin, and galactose-3),[155] which can be recognized by receptors on homologous cancer cells. Furthermore, it has been reported that non-homologous targeting properties are exhibited by the membranes of white blood cells, macrophages, red blood cells, and mesenchymal stem cells, wherein the surface chemokines (eg, CCL2, VECAM-1, and ICAM-1) exhibit natural chemotactic effects on the inflammatory signals.[156] Based on this principle, cancer cell membrane-coated MNPs (eg, Fe_3O_4NPs) can be homologously targeted to cancerous lesions,[157] whereas macrophage membrane-coated MNPs (eg, MnO_2NPs) can target inflammatory lesions in a non-homologous manner,[158] thereby indicating their great potential for use in wound repair. Recent research has also indicated that fluorescent nanoprobes (AuNP-pep) can reflect the process of cell apoptosis by detecting the activity of caspase-3, a key executive enzyme in apoptosis. Indeed, the sensitivity of caspase-3 detection and the fluorescence imaging intensity were significantly enhanced by targeting the cell membrane with AuNP-pep.[159] Figure 7 shows a schematic diagram of the

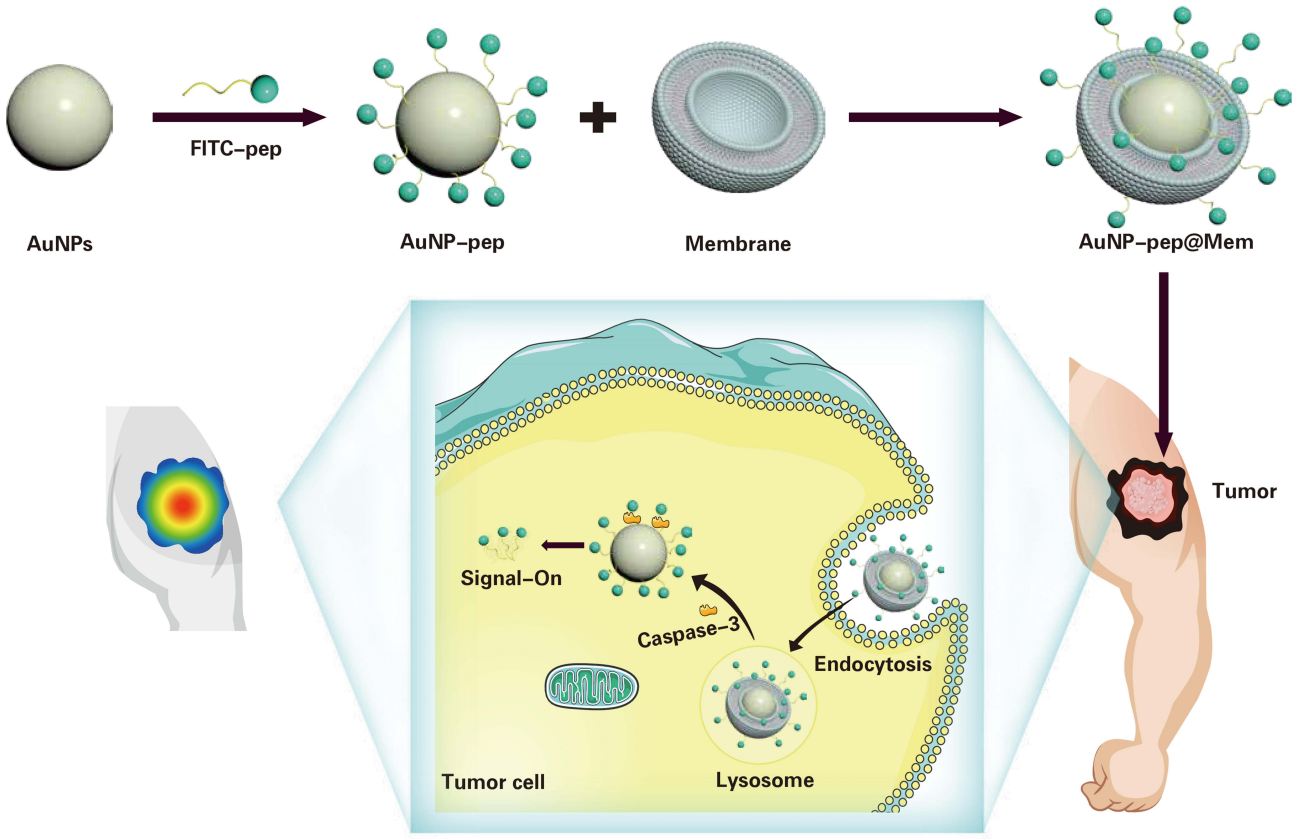

Figure 7 Schematic design of AuNP-pep@Mem, its targeting to cancer tissues, and its ability to enhance fluorescence imaging.

AuNP-pep@Mem system and its targeting and fluorescence imaging capabilities in the context of cancerous tissues. In future work, targeted cell membrane-coated AuNPs should be investigated as potential probes to detect early cancerous lesions, closed wounds, and other imperceptible necrotic areas. Overall, this would accelerate the removal of necrotic tissue and reduce the risk of secondary necrosis and infection.

In another study, it was reported that CMC@MNPs inherited specific molecular receptors on the surface of the source cell membrane, allowing them to "disguise" themselves as source cells and bind to harmful molecules, thereby weakening their invasion of normal cells. For example, Escherichia coli membrane-coated AuNPs were demonstrated to inhibit bacterial adhesion by competing for the binding sites of host cells.[160] Moreover, macrophage membrane-coated MNPs, neutrophil membrane-coated MNPs, and red blood cell membrane-coated MNPs were demonstrated to absorb and clear bacterial toxins and proinflammatory cytokines,[161] indicating that CMC@MNPs demonstrate good detoxification effects that can alleviate infection or inflammation to a certain extent during wound healing.

Impact of Various Synthetic Approaches on the Properties of Metal Nanoparticles

MNPs are widely used in wound healing due to their unique physicochemical properties, which are largely influenced by their particle size, morphology, and dispersibility, which in turn depend directly or indirectly on the method employed for their synthesis. An in-depth study into the effects of different synthetic approaches on the MNPs properties could therefore lead to enhanced properties, while also reducing the dependence on subsequent surface modification, lowering costs, and advancing clinical applications.

Physical synthetic methods (eg, ball milling, laser ablation, and evaporative condensation) rely on mechanical energy or high-energy beams for the preparation of MNPs, and are known to offer significant advantages, including high purities and the absence of chemical residues. The resulting NPs are particularly suitable for applications requiring high biocompatibilities, such as in the areas of wound dressings, biosensors, and three-dimensional (3D)-printed scaffolds.[162] In terms of the particle size and morphology, physical methods are effective in ensuring a high uniformity

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and consistency.[163] Although the particle size of the generated particles may be large and the morphology is usually spherical, this simple geometry is also a significant advantage in many applications, especially in biomedical applications such as tissue engineering, drug delivery, and magnetic resonance imaging contrast agents, where large, spherical particles are required.[164]

In contrast, chemical synthetic methods (eg, chemical reduction, solvothermal, and electrochemical approaches) have become mainstream techniques for the preparation of MNPs due to the ability to produce highly controllable particle sizes, morphologies, and dispersions.[165] By adjusting the concentration of the reducing agent (eg, sodium borohydride or citric acid), the reaction temperature, the time, and the pH, the particle size can be precisely regulated to achieve a uniform distribution of particle sizes in the range of 2–20 nm. This highly controllable property renders chemical methods particularly suitable for applications requiring high specific surface areas, such as antimicrobial therapies and drug delivery.[166] In addition, chemical methods show great flexibility in terms of modulating the product morphology. For example, by adjusting the solvent polarity and crystal surface selectors, solvothermal methods can generate particles with specific morphologies, such as rods, cubes, and polyhedra.[167] Among them, rod-shaped particles demonstrate a unique advantage in wound healing due to their high aspect ratios that enhance cellular uptake and vascularization.[168] In addition, cubic particles exhibit excellent performances in catalytic and antimicrobial applications due to the high exposure of specific crystalline surfaces.[169] Furthermore, electrochemical methods can also efficiently generate particles in a variety of morphologies by controlling the electrolyte concentration and current density, thereby providing the appropriate design freedom to meet different biomedical needs. Moreover, by introducing surfactants or stabilizers (eg, PVP, PEG, or citric acid), chemical methods can also significantly enhance the dispersions and long-term stabilities of the produced particles, ensuring a good reliability and efficacy in complex biological environments.[170]

In recent years, the green synthetic approach (ie, biosynthesis) has received growing attention in the preparation of MNPs due to its environmental friendliness and biophilic nature. The green synthetic method utilizes plant extracts, microorganisms, or enzymes as reducing and stabilizing agents, and is capable of generating nanoparticles with small and uniformly distributed particle sizes (typically 5–30 nm) under mild conditions.[171] The natural substances present on the surfaces of particles generated via this approach spontaneously form a stabilizing protective layer, which prevents aggregation of the particles and significantly improves their biocompatibility.[172] This imparts the green synthetic method with unique advantages in biomedical fields such as antimicrobial therapies and wound healing. MNPs synthesized by this method not only demonstrate high levels of biosafety and environmental friendliness, but they also meet strict biocompatibility requirements due to the avoidance of toxic chemical reagents.[173]

Overall, physical, chemical, and green synthetic methods each have significant advantages and show great flexibility and potential in controlling the particle sizes, morphologies, dispersions, and stabilities of MNPs. Physical methods are characterized by their high purities, chemical residue-free, and large-scale production advantages. In addition, chemical methods are extremely flexible in terms of their ability to precisely regulate the particle size, provide morphological diversity, and ensure a good dispersion and stability. Consequently, chemical methods have become the mainstream choice for multifunctional particle preparation. Furthermore, green methods stand out for their environmental friendliness and biocompatibility, and are especially suitable in the context of sustainable biomedical applications.[174] With the continuous advancement of technology, combining the advantages of these three methods and introducing real-time monitoring and dynamic regulation techniques will be expected to further promote innovation of the MNP preparation processes and lay a solid foundation for employing these materials in a wide range of nanomedical applications.

Application of MNP-Based Composites in Wound Dressings

MNP-based composites have been used to prepare new smart wound dressings to meet the repair requirements of different wound types. As discussed above, such composites are desirable due to their excellent wound repair, smart response, and biosensing properties. Based on the different application forms of these dressings, they have been categorized in Table 1 and Figure 8 as implantable, filler, or topical dressings.

Table 1 Categories of Different MNP-Based Wound Dressings

Type of Dressing	MNP-based Composite	Technique	Application	Wound Type	Reference
Implantable dressing	OCOS-AgNPs-pADM	In-situ synthesis	Pieces of OCOS-AgNPs-pADM implanted into Sprague-Dawley rats can provide superior wound coverage and excellent anti-infective properties, in addition to promoting dermal reconstruction, reducing scar hyperplasia, and repairing full-thickness wounds.	Full-thickness wounds	[175]
	PCL/Y_2O_3 scaffolds	PCL scaffolds loaded with Y_2O_3 nanoparticles	PCL/Y_2O_3 scaffolds implanted subcutaneously in rats can prevent oxidation, remove free radicals, stimulate cell proliferation, and stimulate the production of angiogenic factors such as VEGF and EGFR.	Hypoxic and ischemic wounds	[176]
	PCL/Gelatin/MgO	Electrospinning	Upon subcutaneous implantation, PCL/Gelatin/MgO membranes significantly accelerate diabetic wound healing by suppressing inflammatory responses, promoting angiogenesis, and boosting granulation formation.	Diabetic wounds	[177]
	C_3N_4-PDA-Ag @CS	Solution casting	A C_3N_4-PDA-Ag@CS film implantation in mice accelerates wound healing in the infected mice by promoting collagen deposition and accelerating epidermal regeneration.	Infected wounds	[178]
	METMET@MSNs-MNFs	Electrospinning	Magnetothermal responsive polymer electrospun nanofibers implanted in the skin can control the release of drugs, rapidly inhibit the growth of melanoma cells, and prevent the recurrence of skin cancer.	Melanneocytoma	[179]
Filler dressing	Ebs@dZnONPs/HGT	Cross-linking	The hydrogel is injected into the infected wound and gelatinized by ultraviolet radiation, resulting in a perfect fit, thereby killing bacteria, absorbing the effusion, and promoting healing of the infected wound.	Infected wounds	[180]
	BT-CTS	Cross-linking	Wounds are filled with the thermogels, which were subsequently heated to produce ROS under NIR irradiation, killing skin tumor cells and inhibiting tumor growth. Simultaneously, the adhesion, proliferation, and migration of normal skin cells are promoted, and chronic wound closure is accelerated.	Cancerous wounds	[181]
	MSN-CeO_2 @PNIPAM	Cross-linking	As temperatures close to body temperature, the hydrogel can dynamically gelate from the liquid state, reduce the level of oxidative stress at the wound site, and accelerate the healing speed of diabetic wounds.	Diabetic wounds	[182]
	HMC-HA/AgNPs	Silver nanoparticles (AgNPs) were introduced into a hydroxypropyl methylcellulose hydroxyapatite scaffold hydrogel	The hydrogel fills full-layer skin defects in mice, resulting in excellent antibacterial, re-epithelialization, and scar inhibition effects.	Burn wounds	[183]
	M@M-Ag-Sil-MA	The Sil-MA hydrogel system was co-coated with metformin-supported mesoporous silica microspheres (MET@MSNs) and AgNPs	After in situ photocuring in diabetic wounds, the hydrogel inhibits bacterial proliferation and NET formation, while promoting macrophage M2 polarization, and accelerating tissue repair and reconstruction.	Diabetic wounds	[184]
	MoS_2@Au@BSA NSs	Defect-rich molybdenum disulfide nanosheets loaded with bovine serum albumin-modified gold nanoparticle (MoS_2@Au@BSA NSs) heterostructures were designed and anchored onto injectable hydrogels	Glucose oxidation-like Au catalyzes the oxidation of glucose to produce gluconic acid and H_2O_2, and it converts these species into hydroxyl radicals (•OH), which destroy the bacteria. When the pH of the wound reaches the alkaline state, MoS_2 @Au@BSA simulates superoxide dismutase to convert the superoxide anion into O_2 and H_2O_2, and to decompose H_2O_2 into O_2, thereby alleviating oxidative stress, alleviating hypoxia, and promoting glucose oxidation.	Diabetic wounds	[185]

(*Continued*)

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Table 1 (Continued).

Type of Dressing	MNP-based Composite	Technique	Application	Wound Type	Reference
External dressing	SAmCHO/Gel-ADH (SG) hydrogels	Cross-linking	When sprayed on mass or irregular wounds, the hydrogel can rapidly form a film and generate an effective barrier against *Staphylococcus aureus* and *Candida albicans* for 12 h.	Irregular and mass wounds	[186]
	CS/CA/Ag	Shape memory frozen gels were prepared by mixing chitosan (CS) and citric acid (CA) at low temperatures. Silver nanoparticles (AgNPs) were introduced into the frozen gels by reducing silver using tannic acid (TA) as a reducing agent	The CS/CA/Ag frozen gel can absorb a large amount of blood and promote blood cell adhesion. In addition, it exhibits a good antibacterial ability against *S. aureus* and *E. coli* and can significantly promote wound healing in full-layer wound models infected with *S. aureus*.	Full-layer wound models infected with Staphylococcus aureus	[187]
	GT/Ag cryogels	GT cryogels were coated with Ag NPs	Externally applied to burn wounds, the cryogel can effectively absorb wound exudates and allow gas exchange. The sterilization effects against MRSA and PA on burn wounds are excellent, and the cryogel can effectively remove mature biofilms, in addition to promoting hemostasis, wound contraction, collagen deposition, and angiogenesis, while relieving inflammation.	Burn wounds	[188]
	Ag@MOF-loaded CSNPs-PACS bilayer	Ag-metal–organic framework loaded chitosan nanoparticles (0.1%Ag@MOF/1.5%CSNPs) and polyvinyl alcohol/sodium alginate/chitosan (PACS) were used as the upper and lower layers to prepare a bilayer composite dressing	The upper layer (Ag@MOF/CSNPs) inhibits bacterial proliferation and avoids direct contact with the wound surface, leading to hemolysis and cell death. The underlying dressing (PACS0.25) exhibits good swelling and water retention properties, in addition to water vapor permeability, and biocompatibility. The double layer can adhere to a large number of red blood cells and platelets and promote blood coagulation and cell proliferation.	Infected wounds	[189]

Implantable Dressings

Implantable dressings are implanted into the skin tissue during invasive surgical procedures. They are characterized by their ability to form strong bonds with the surrounding tissues, rendering them less prone to displacement and avoiding the inconvenience and pain associated with frequent dressing changes. Owing to their long-lasting sustained-release effects, these dressings have long service lives and are particularly suitable for the treatment of chronic wounds, such as diabetic foot ulcers and burns.[190]

Currently, research is being conducted to prepare MNP-based implantable dressings using techniques such as electrospinning, solvent casting, extrusion, and compression molding.[177,178] Electrospinning, which can precisely control the morphology and quality of a material, has become an important process in the preparation of implantable dressings.[191,192] Studies have found that implanting MNP-based composites, such as polylactic acid (PLA)/gelatin/MgO electrospun membranes with PCL/Y_2O_3 composite scaffolds,[176,193] into the subcutaneous tissue of rats can accelerate wound healing by inhibiting bacterial infection and promoting blood vessel formation, thereby indicating the promising application prospects of such systems. However, electrospinning materials are typically required to be sufficiently soluble and conductive, which limits the variety of dressings that can be prepared using this approach. In contrast, 3D printing allows for the use of a wider range of materials and has been employed in the construction of artificial skin for skin grafts. Indeed, the anatomical structure of the skin was successfully simulated using this approach, and the resulting material was able to sense both temperature and pressure.[194,195] However, 3D-printed MNP-based composites are currently mainly used for bone repair and dentistry,[196,197] leaving significant research space in the field of wound repair. In the future, this technology will hopefully be utilized for the development of MNP-based implantable dressings that provide patients with more intelligent, precise, and personalized wound healing treatment approaches.

Ensuring the safety and degradability of materials is crucial in the design of implantable dressings. It has been reported that some MNPs, such as ZnONPs and AgNPs, may cause immune reactions in the body.[198] Therefore, in the preparation of dressings, it is necessary to strictly control the particle size, shape, concentration, and other related influencing factors of the MNPs to minimize their potential side effects. Additionally, to avoid the prolonged retention of

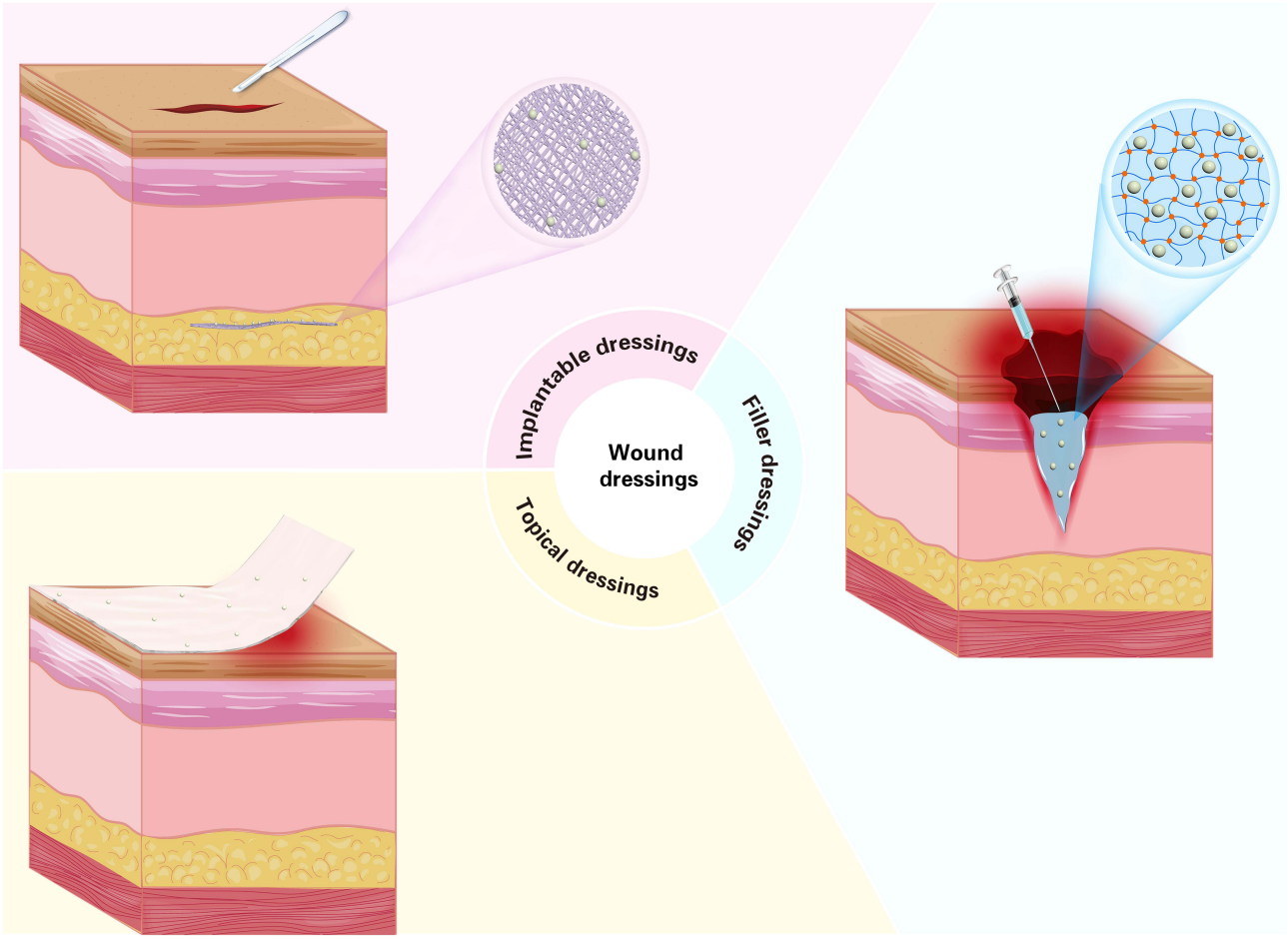

Figure 8 Application forms of wound dressings.

MNPs in the body, biodegradable MNPs, such as MgONPs and CuONPs, should be selected whenever possible.[199,200] MNPs with poor degradability properties (eg, AuNPs, AgNPs, and CuONPs) can be encapsulated inside amphiphilic polymers, such as aldehyde-modified dextran and PEG-PCL polymer micelles,[201,202] to reduce the non-specific adsorption of MNPs to biological tissues. Furthermore, coupling with easily degradable materials, such as CuSNPs and iron oxide NPs,[203,204] should also improve the in vivo degradation properties of MNPs.

Filler Dressings

Filler dressings are filled into wounds by means of minimally invasive injections. They are characterized by their ability to fit into various shapes of wounds, and to fill the cavities and defects within these wounds.[205] Consequently, they are of particular interest for the treatment of irregularly shaped wounds, such as diabetic foot ulcers and burns, among others. Currently, filler dressings are mainly based on injectable hydrogels, which are polymeric materials that provide a moist environment conducive to cell adhesion and proliferation, while also serving as a carrier for the delivery and controlled release of MNPs.[206] As a result, these types of filler dressings are one of the most advanced wound dressings available at present.

In recent years, cross-linking has become the primary means to preparate injectable hydrogels, wherein physical cross-linking can endow the hydrogels with dynamic, reversible, and biocompatible properties.[207,208] It has been reported that the physically cross-linked hydrogel MSN-CeO_2@PNIPAM can undergo a sol–gel transition at physiological temperature to fill irregularly shaped diabetic wounds and greatly reduce the level of oxidative stress.[182] In addition, physically cross-linked hydrogels, such as magnesium-containing black titanium dioxide nanoparticle-chitosan (BT-CTS)

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, have been used for wound treatment after skin tumor excision. Owing to its facile injectability, rapid gelation, and photothermal therapy (PTT)/photodynamic therapy (PDT) effects, BT-CTS can rapidly fill tissue defects at the excision site, generate ROS, release Mg^{2+} under NIR irradiation, inhibit the growth of tumor cells, and promote the adhesion, proliferation, and migration of skin cells.[181] Due to the many advantages of physically cross-linked hydrogels, such dressings can also be used for the treatment of exudative cavities, perianal fistulas, and other wounds. However, the poor mechanical stabilities of physically cross-linked hydrogels limit their potential applications.[209] This problem can be solved using physicochemical double cross-linking and enzymatic cross-linking strategies.[210,211] For example, oxidized alginate (ADA) and catechol-modified gelatin (Gel-Cat) have been employed as polymer backbones, and physicochemical double-cross-linked hydrogels have been constructed by introducing cross-linking agents containing Schiff bases. This led to a system that exhibited an enhanced stability, elasticity, and abrasion resistance, wherein the resulting hydrogels demonstrated the potential to be applied in load-bearing soft tissues or dynamic wounds, such as wounds on the soles of the feet, heels, and joints.[212] When considering the preparation of these hydrogels, the enzymatic cross-linking reactions can be carried out under mild conditions without imparting any side effects on the tissues, thereby rendering such reactions a novel approach for the preparation of injectable hydrogels. For example, horseradish peroxidase can catalyze the binding of cross-linking agents to silk glycoprotein polymers to form cross-linked structures. Importantly, the enzyme exhibits substrate specificity that enhances interactions between the cross-linking agent and the polymer, thereby improving the mechanical stability of the silk gelatin-based hydrogel. In addition, the enzymatic reaction occurs rapidly, and the hydrogel can quickly gel and fill tissue defects present in exudative wounds. However, future research in this area should focus on maintaining the enzyme activity and achieving considerable cost reductions.

Topical Dressings

Topical dressings were the earliest reported dressings and are also among the most widely used. These dressings directly cover the wound surface to protect it from infection and external irritation while maintaining cleanliness. They are particularly suitable for the treatment of superficial and moderately deep wounds such as abrasions, minor burns, and surgical incisions. In this context, topical dressings based on various MNP-based composites have been developed, including films, patches, hydrogels, hydrocolloids, sponges, and sprays.

Currently, work is underway to prepare topical dressings with different specifications using techniques such as electrospinning, solution casting, freeze drying, electrochemical deposition, and in-situ synthesis.[213–215] These dressings can be tailored and adjusted to meet the required sizes and shapes, and can be easily applied and fixed to a wound using a strong adhesion or tape. Additionally, because of the different preparation processes employed, these dressings exhibit a selection of characteristics that promote wound healing via different mechanisms. For example, MgONP composite nanofiber membranes prepared by electrospinning possess a high surface area and a porous structure, providing an excellent flexibility, breathability, and elasticity; such dressings are beneficial for wound ventilation and drainage.[216] Furthermore, the freeze-drying technology has been used to produce sponges based on CS/PVA-PD-FeO NPs and CS - PVA - Cur @ Ag,[217,218] whose porous structures can effectively absorb wound exudates and blood, providing protection and isolation for the wound. By controlling the freezing rate, drying temperature, and other preparation conditions, the porosity and pore size of the sponge can be adjusted to enhance its absorption performance and MNP loading capability with the aim of promoting wound healing.[219]

In recent years, spray dressings have been continuously developed owing to the increasing clinical demand for treating large wounds with irregular shapes.[220] For example, spraying a polyvinyl alcohol/chitosan/nanosilver (PVA/CH/Ag) liquid hydrogel onto infected wounds can form a uniform and stable film on the surface, protecting the wound from infection and facilitating exudate penetration.[221] Additionally, the dosage and application range of this dressing can be adjusted according to the number of sprays, and it can be easily removed during debridement, thereby reducing patient pain and discomfort, and rendering it particularly suitable for the treatment of large wounds.[222] Considering the many advantages of spray dressings, autologous or allogeneic cells (such as KCs, Fbs, and melanocytes) have been combined with fibronectin to prepare sprays for wound treatment. Such formulations have been demonstrated to exhibit excellent healing effects in burns, lower limb ulcers, and lacerations, and may become an alternative to skin grafting in the near future.[223] It is therefore possible to combine the above cells with CuONPs, ZnONPs, and other MNPs that exhibit anti-

infective anti-inflammatory, and angiogenesis abilities. Moreover, these composites can be combined with film-forming materials, such as PVA, PVP, chitosan, and Bletilla striata, as a matrix to prepare spray dressings, and to explore whether such formulations can achieve the desired therapeutic effects. In addition, the ability of the MNPs themselves to interact with KCs or Fbs should also be investigated to determine the efficacy of the dressing.

Safety of MNP-Based Composites

Safety of the Surface Modifiers

MNP-based composites have received considerable attention owing to their excellent wound-healing abilities, and so the exposure of humans to these materials is expected to increase significantly in the future. Although many studies have shown that surface modifiers can significantly improve the wound healing abilities of MNPs, the potential risks arising from the surface modifiers themselves and their interactions with MNPs must be evaluated during dressing design.

More specifically, safety assessments of MNP-based composites should consider the mechanical properties of surface modifiers. For example, although natural polymers (eg, collagen, hyaluronic acid, and chitosan) are favored for their good biocompatibilities, their mechanical strengths are relatively weak, which can lead to their deformation or fracture under external forces when used alone.[224] Such structural failures may result in a disturbed MNP release behavior, which in turn affects the wound repair outcome. To address this issue, the tensile strength, compressive strength, flexural strength, hardness, impact toughness, and fatigue properties of the materials should be evaluated to ensure that they are resistant to wear and tear and are not susceptible to fracture, excessive deformation, or rupture during long-term usage.[225] Simultaneously, the mechanical properties could be enhanced by introducing cross-linking agents or blending with synthetic polymers to enable the composites to meet the requirements of implantable or filled dressings.[226] In addition, the biocompatibility, metabolic behavior, and degradation properties of the materials should be fully evaluated. Considering that certain modifiers, such as graphene, carbon nanotubes, and MSNs, are not easily degraded in living organisms, such systems should be assessed for the long-term potential biotoxicity and safety risks.[227,228] More specifically, their dissolution rates and release behaviors can be analyzed to ensure that their degradation behaviors meet the biocompatibility standards. Furthermore, liver and kidney function assessments and histological analyses can be combined with animal experiments to detect the distribution of these materials and their metabolites in vivo to avoid long-term accumulation effects.[229] It has also been reported that the degradation rates and biocompatibility characteristics of graphene and carbon nanotubes can be significantly improved through surface functionalization (eg, by the introduction of hydrophilic groups or biocompatible polymers), enzymatic degradation (eg, peroxidase-catalyzed degradation), or nanostructure tuning (eg, reduction of size or doping of heteroatoms).[230,231] Similarly, the degradation and dissolution behaviors of MSNs in physiological environments can be accelerated by modulating their pore densities, decreasing the degree of Si–O cross-linking, or loading degradation catalysts (eg, phosphatase).[232]

In addition to the above considerations, safety assessments should also fully consider the modifier cytotoxicity, genotoxicity, inflammatory response, and oxidative stress. For example, certain MOF components (eg, Cd^{2+}, Ni^{2+}, Pb^{2+}, benzene dicarboxylic acid, and imidazole) may trigger skin inflammation upon material degradation. When the concentration of metal ions released from decomposition of the MOF is too high, oxidative stress may occur, ultimately leading to cytotoxicity.[233] Therefore, when selecting a MOF as a modifier, the type, concentration, and possible toxicity of its components should be fully considered, and its potential risks should be minimized through rational design, concentration control, and safety assessments. For example, the cytotoxicities of these materials can be assessed by detecting cell survival and apoptosis using the MTT assay (cell viability $\geq$ 90%), the LDH release assay, and Annexin V/PI (PI = propidium iodide) staining. In addition, the Ames, Comet, and Micronucleus assays can be employed to detect gene mutations or a risk of DNA damage. Simultaneously, the degree of inflammatory response can be assessed by detecting ROS production, the antioxidant enzyme activity (eg, SOD, CAT), and by determining inflammatory factors such as TNF-α, IL-6, or immune cell infiltration.[234–236]

Based on the above considerations, the necessity to focus on the ethical and quality control issues of modifiers is also apparent. For example, research into the design of MNP dressings based on cell membrane encapsulation remains limited, potentially due to the insufficient availability of cell membrane sources, high extraction difficulties, short shelf

lives, and stringent screening requirements.[237] To overcome these obstacles, additional sources of cell membranes (eg, bacterial cell membranes or stem cell membranes obtained through in vitro induced differentiation) can be explored. Furthermore, membrane extraction techniques should be improved and efficient screening methods should be developed to ensure the safety and efficacy of cell membrane-enveloped dressings for practical applications.

In addition to evaluating the safety of the modifier itself, it is necessary to consider whether the interaction between the modifier and the MNP could have a potential negative impact on human health. For example, when negatively charged MNPs were modified using polymers with different surface charges, it was found that the composites modified with positively charged polymers exhibited higher toxicities, while those modified with neutral polymers were less toxic. This phenomenon may be related to the interactions between charged species leading to enhanced cellular uptake and a greater degree of intracellular toxicity.[238] It is worth noting that the potential cytotoxicity of MNP-based composites is not only affected by the surface charge, but may also be related to the shape, size, surface properties, concentration, exposure time, dissolution rate, and release behavior of the nanocomposites.[239,240] Therefore, a systematic experimental design and cytotoxicity evaluation system must be established to comprehensively assess the effects of these key factors in future studies.

Overall, to ensure the safe application of MNP-based composites in wound healing, the surface modifiers and their interactions with the MNPs should be evaluated in depth, in addition to performing careful material design. In the future, safety assessments related to MNP-based composites should ensure that they are harmless to normal cellular activity, whilst also taking into account key factors such as the biodegradability, immunogenicity, biocompatibility, long-term stability, and mechanical properties. Moreover, these materials should demonstrate an excellent environmental adaptability to avoid triggering immune rejection or allergic reactions. Most importantly, the interaction of MNP-based composites with living organisms must be comprehensively evaluated to ensure that they will not interfere with normal physiological functions during long-term usage, thereby laying a solid safety foundation for their clinical applications.

Safety of the Preparation Technologies

The methods and techniques employed during the preparation of MNP-based composites may lead to MNP aggregation, morphological changes, impurity doping, impaired modifier performances, increased levels of energy consumption, and environmental pollution. It is therefore important to study and optimize the preparation techniques and process conditions to enhance the performances and safety profiles of these composites.

The rapid and efficient nature of physical methods (eg, thermal deposition, electrochemical deposition, one-pot synthesis, and high-energy ball milling), in addition to their circumvention of toxic chemical reagents, has rendered them extremely popular due to their ability to avoid the potential environmental and health hazards associated with chemical methods. However, physical methods tend to be energy intensive, with processes such as thermal deposition and high-energy ball milling continuously consuming large amounts of energy, which increases preparation costs and is not conducive to sustainability goals. In addition, due to the thermodynamically driven equilibrium, the mutual attraction between MNPs will increase, which can lead to aggregation, reduced dispersions, and a poor homogeneity, ultimately affecting the safety and wound-healing-promoting properties of the composites.[241] Furthermore, the high temperature and pressure conditions required may alter the material morphology, rendering it unsuitable for its intended function. Therefore, when selecting a suitable preparation technique, low-energy methods with appropriate process conditions should be considered whenever possible. More importantly, the damage to modifiers by physical methods should not be ignored. For example, the high electric field and high shear force generated during electrostatic spinning can damage the cell membrane integrity. This can also occur due to the strong penetration effects of high-energy radiation sources, leading to the leakage of membrane-encapsulated MNPs, potential DNA/RNA strand breaks, base damage, and base-pair mutations. These problems ultimately reduce the stability and safety profiles of the composites.[242,243] In response to these issues, several optimization strategies have emerged in recent years. For example, ultrasound-assisted methods can utilize cavitation effects to prevent MNP aggregation and enhance their dispersion and homogeneity at low temperatures.[244] Other techniques, such as 3D printing, self-assembly, and low-temperature plasma, can achieve precise regulation of the morphologies and structures of composites under low energy conditions, and are particularly suitable for the preparation of composites containing biologically active components (eg, cell membranes and nucleic acids).[245] These considerations

highlight the importance of optimizing the particle dispersion and protecting the bioactive components during composite preparation. In addition, these alternative protocols are in line with the need for sustainable development and are expected to open new pathways for the preparation of efficient and safe MNP-based composites.

Chemical methods such as solution methods, co-precipitation, thermal decomposition and vapor phase deposition are also important techniques for the preparation of MNP-based composites. Compared with physical methods, these chemical methods are more flexible and allow control of the particle morphology, size, and distribution by precisely adjusting the reaction conditions. For example, thermal decomposition and vapor phase deposition are particularly suitable for the preparation of high-purity, high-quality MNPs, and they are able to precisely regulate the crystal structures and distributions of particles to meet the requirements of different applications.[246] In contrast, solution and co-precipitation methods are usually employed to prepare homogeneous MNPs under milder conditions, wherein the size and morphology of the particles can be precisely controlled by adjusting parameters such as the solvent type and concentration and the reaction temperature.[247] In addition, these methods are able to introduce functional molecules through surface modification, thereby functionalizing the material and enhancing its biocompatibility, providing more possibilities for innovation in biomedicine, drug delivery, and other applications. However, the application of chemical methods also faces many challenges. For example, the complexity of the chemical reaction process, the variation of reaction rates and the difficulty in precisely controlling the reaction conditions (eg, temperature, reaction time, and reactant ratios) may lead to an inhomogeneous material morphology and distribution, which may affect the composite properties.[248] To address these issues, the spatial confinement effect of the template method can be utilized to uniformly disperse and arrange the nanomaterials in a template while precisely controlling the morphology and structure of the MNP-based composite to enhance its dispersion and stability.[249,250] Moreover, chemical methods require the use of large amounts of organic solvents, reactants, and catalysts, and the wastes generated during these reactions can be toxic and potentially harmful to human health and the environment. These methods also require complex equipment and processes, as well as appropriate waste disposal procedures, which significantly increase the production costs associated with the dressings, and are not conducive to the use of such treatments.[251] Therefore, in addition to the use of green solvents or water-soluble reagents to minimize the use of organic solvents and reduce the negative impact on the environment, more economical, efficient, non-toxic, and environmentally friendly preparation techniques must be developed in the future to meet the requirements of sustainable development.

In recent years, green synthetic methods have become a hot research topic in the field of nanomedicine, wherein environmentally friendly and sustainably renewable biomolecules, as well as non-toxic, low-energy and mild reaction conditions, have been employed for the preparation of MNP-based composites.[252] Due to the highly selective, specific, and self-assembly characteristics of biomolecules, green synthesis can be used to control the morphologies, sizes, and functional properties of MNPs by modulating the structure, function, and selective attachment of metal ions. For example, the polyphenolic compounds present in plant extracts not only act as reducing agents, but also confer additional antioxidant and bioactive functions to the materials.[253] Another important advantage of the green synthetic method is its environmental friendliness. Compared with traditional physical and chemical methods, this approach significantly reduces the generation of toxic by-products during the preparation process and is more in line with the current requirements of sustainable development.[254] The MNP-based composites prepared by this method excel in performance and can be used for high-purity, high-activity, wound dressing applications.

Outlook

The development of metal nanoparticle (MNP)-based composites is expected to become an important tool for future wound repair because of their ability to promote wound healing and to exhibit smart responses and biosensing capabilities. Although these characteristics provide a more effective and reliable treatment approach for wounds, to further advance the development of MNP-based composites for wound repair and promote their clinical application, several aspects must be investigated further.

Currently, MNP-based composites based on AgNPs, ZnONPs, and CuONPs have been extensively studied in the field of nanomedicine, especially in biomedical applications such as drug delivery, antimicrobial therapy, diagnostic imaging, and wound healing. However, research into the application of MNPs in the field of wound healing remains in its infancy.

In recent years, transition metal nanoparticles such as palladium NPs (PdNPs), ruthenium NPs (RuNPs), and other novel MNPs have been widely used in a variety of fields such as energy storage, sensing, and medical diagnosis/therapies due to their excellent angiogenesis, cellular bioprocess modulation, controlled release, and magnetism characteristics, in addition to their desirable catalytic activities;[255,256] however, their applications in wound dressing design are still limited at present. In addition, certain metal oxide-based NPs such as zinc silicate NPs ($ZnSiO_3$ NPs) have also become a research hotspot in the field of regenerative medicine due to their good biocompatibilities and potential to promote nerve repair.[255] Studies have shown that promoting nerve repair facilitates the release of neurotransmitters from nerve endings, which not only promotes blood circulation and stimulates blood vessel regeneration, but also stimulates cell proliferation and differentiation in the surrounding tissues and promotes wound tissue remodeling. Therefore, in the future, these novel MNPs can be applied to the design of wound dressings, giving full play to their advantages in nerve repair, vascular regeneration, and sensing. Combined with a smart response platform and the integration of these nanomaterials into flexible electronic sensors, multimodal smart dressings can be developed to achieve real-time monitoring and the personalized treatment of wounds. These innovative designs are not only expected to accelerate wound healing, but also to significantly improve patients' quality of life and open up broader application prospects in the field of nanomedicine.

In recent years, the development of new MNP properties has become a research hotspot in the field of nanomedicine, especially in terms of their mechanical activity attributes (eg, physical deformation, contraction, or expansion) under external mechanical stimuli such as stress, magnetic fields, electric fields, and light irradiation. It has been found that the mechanical activities of MNPs can mimic the contraction of muscles under mechanical stimuli, in addition to regulating the mechanical properties of the local tissue, and promoting cell proliferation, migration, and differentiation.[257] However, research into the application of MNPs in wound dressings is still limited, as mentioned above. In the future, nanomaterials with excellent loading functions, such as mesoporous silica nanoparticles and metal–organic frameworks, should be combined with MNPs that exhibit excellent magnetic and photothermal properties (eg, $CoFe_2O_4$NPs and Fe_3O_4NPs) to achieve the targeted delivery of cargo (ie, MNPs). In one current example, under the influence of the magnetic effect photothermal effects, mechanical contraction of the wound is triggered, resulting in rapid wound closure without causing secondary damage to the skin tissue (Figure 9).[258] The development of this novel dressing is expected to improve the efficiency of wound repair and provide superior treatment options for patients.

With the rapid development of nanotechnology and biomedical engineering, the clinical application of electronic wearable devices in wound repair is becoming increasingly popular. These devices can not only be deeply integrated with artificial intelligence and big data technologies as an important tool for condition monitoring, follow-up and treatment guidance, but they can also detect key physiological parameters such as temperature, humidity, and pH in real time through integrated sensors, which in turn indirectly reflect the wound healing process, and provide personalized treatment plans through data analysis.[259] In addition, the electronic wearable device can be combined with a drug release system to release the active ingredients in the MNP-based composite by modulating external stimuli to further promote targeted wound healing. This intelligent treatment method has the potential to improve the accuracy of treatment while also adjusting the treatment plan based on real-time feedback, thereby meeting the personalized requirements of different patients.[260]

Currently, MNP-based modified composites, such as PEG-AuNPs, PCL/AgNPs/BP, and Ag/PDA/g-C_3N_4, have demonstrated great potential for application in the repair of chronic refractory wounds due to their excellent anti-infective, vascular regeneration, and neurological repair properties, which are especially suitable for wounds with complex healing mechanisms.[261,262] However, the healing processes of these wounds are often slow, and real-time monitoring and dynamic regulation would help accelerate wound recovery. However, to date, the design of MNP-based composites as wearable devices for wound treatment has yet to be reported. In the future, these materials could be designed as smart sensors with biomarker detection functions (eg, for lactate and glucose) and be applied externally to the skin surface to realize intelligent wound monitoring and repair. It is worth noting that the integration of electronic wearable devices with wound dressings still faces many challenges, such as low sensitivity and specificity, a limited pathogen detection range, a poor flexibility, short battery lives, and high costs. Therefore, further technological

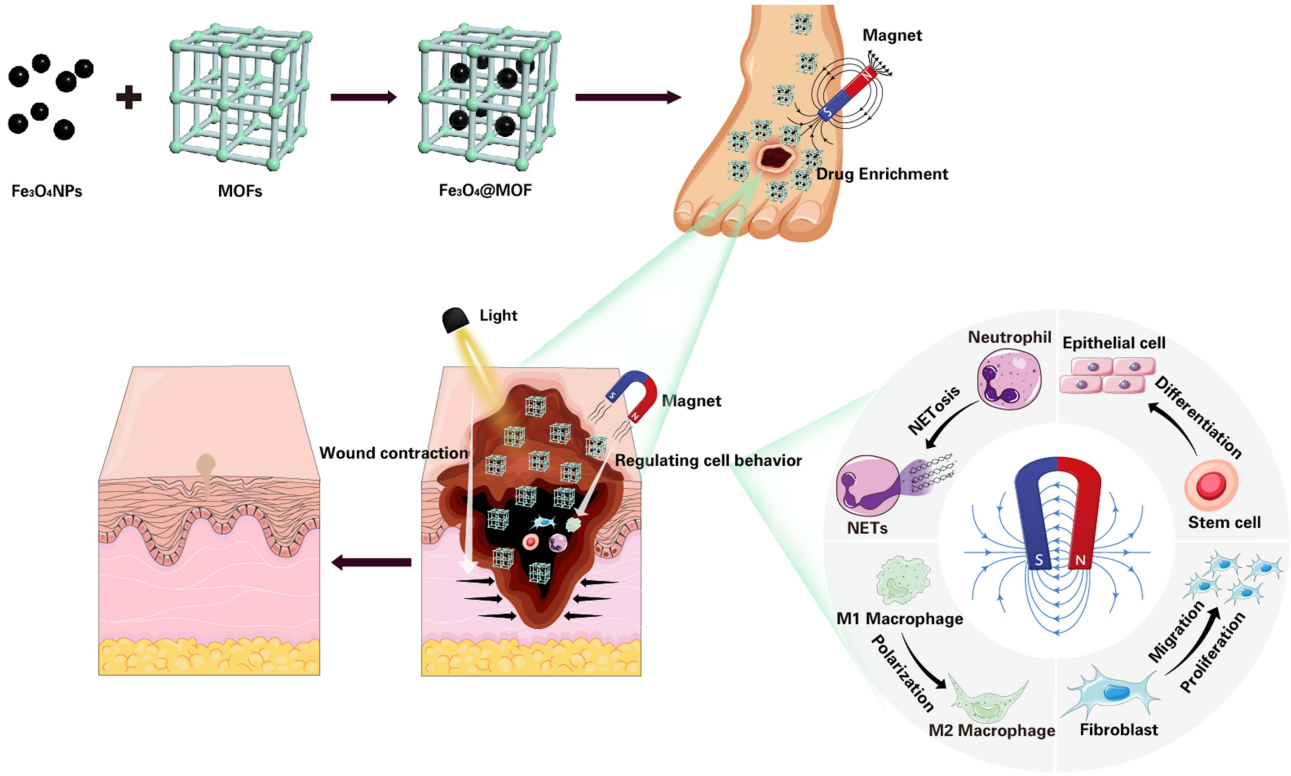

Figure 9 Schematic design of the Fe_3O_4NPs@MOF and its mechanism of promoting wound healing under a magnetic field and photothermal conditions.

innovations and research are required to overcome these issues, promote the widespread application of electronic wearable devices in wound repair, and enhance their clinical value.

In conclusion, this review summarizes the design strategies of MNP-based composites modified with different materials to improve their performances in wound therapy, sensing, and smart response applications. In addition, the challenges associated with current modification schemes are presented, and potential improvements are discussed, aiming to provide inspiration for the design of multifunctional wound dressings. Furthermore, the advantages of implantable, refillable, and topical dressings in different wounds are considered according to different application scenarios to provide new options for the treatment of different kinds of wounds. Moreover, the safety issues surrounding of MNP-based composites and their preparation techniques are discussed, and potential solutions are proposed. Some innovative concepts and research ideas are also suggested in the context of current research hotspots, especially in terms of developing new materials, new properties, and smart wearable devices. Ultimately, it is anticipated that this review will further promote the development of MNP-based composite dressings toward personalization and intelligence, while expanding their clinical applications.

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Disclosure

The authors report no conflicts of interest in this work.

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