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Review

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Engineered Nanomaterials for Infection Control and Healing Acute and Chronic Wounds

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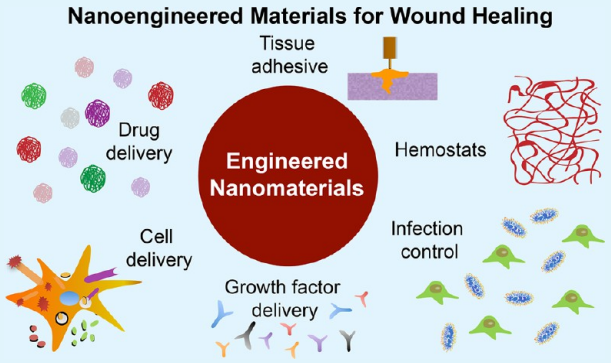
ABSTRACT: Nanoengineered biomaterials have dramatically expanded the range of tools used for infection control and to accelerate wound healing. This review thoroughly describes the developments that are shaping this emerging field and evaluates the potential wound healing applications of recently developed engineered nanomaterials for both acute and chronic wounds. Specifically, we will assess the unique characteristics of engineered nanomaterials that render them applicable for wound healing and infection control. A range of engineered nanomaterials, including polymeric-, metallic- and ceramic-based nanomaterials, that could be used as therapeutic delivery agents to accelerate regeneration of damaged dermal and epidermal tissues are also detailed. Finally, we will detail the current state of engineered nanomaterials for wound regeneration and will identify promising new research directions in infection control.



KEYWORDS: *engineered nanomaterials, nanoparticles, nanocomposites, wound healing, infection control, antimicrobial*

1. INTRODUCTION

Wounds affect over 6 million people in the US at an annual cost of $25 billion.[1−3] This high health and cost burden underlines the importance of research in this field. Wounds are classified as either acute or chronic. Acute wounds heal within a predictable time period (1−12 weeks depending on the nature of the wound); however, accelerated wound healing is desirable for recovery, overall health, and cost.[4] Chronic wounds do not heal in a predicted time period, are more susceptible to infection, and are considerably more difficult to manage.[5]

Chronic wounds include pressure ulcers, diabetic ulcers, and vascular ulcers (including venous and arterial ulcers). Age, peripheral neuropathy, peripheral arterial diseases, immunocompromised status, and venous insufficiency are some of the risk factors of chronic wounds. In addition, diabetes is also one of the major risk indicators for chronic wounds, and the lifetime risk of developing a foot ulcer in a diabetes patient is estimated to be 25%.[6] The most dreaded consequence of an unhealed diabetic foot ulcer is limb amputation due to infection, which occurs in 2.1−13.7 per 1000 diabetic patients;[6] this incidence increases to as high as 80% mortality at five years postamputation according to long-term studies.[7] Therefore, there are multifaceted research efforts to develop improved clinically relevant therapeutic approaches aimed at both infection control and achieving faster healing of acute and chronic wounds.

The ability of a range of biomaterials to accelerate wound healing and to control infection has been proposed and tested.[8,9] Both synthetic and natural polymers could act as therapeutic agents to accelerate regeneration of damaged dermal and epidermal tissues. Most of these polymeric biomaterials are able to mimic some of the physical and biological characteristics of native tissues due to high water content, biocompatibility, and biodegradable nature. Natural polymers investigated for wound healing applications include polysaccharides (chitosan, chitin, dextran, alginates, chondroitin, and heparin), proteoglycans, and proteins (collagen, gelatin, fibrin, silk fibroin, and keratin).[10−14] A range of synthetic polymers are also investigated for their ability to facilitate re-epithelialization. Some of the synthetic polymers investigated for wound healing include poly(glycolic acid) (PGA), poly-D,L-lactide-*co*-glycolide (PLGA), poly(vinyl alcohol) (PVA), poly(lactic acid) (PLA), poly(acrylic acid) (PAA), poly(ε-caprolactone) (PCL), poly(ethylene glycol) (PEG), and poly(vinylpyrrolidone) (PVP). However, most of these polymers lack bioactivity and the ability to accelerate the wound healing process; thus, several nanomaterials are incorporated within the polymeric network. Engineered nanomaterials are used to obtain sustained and controlled release of therapeutics to accelerate the healing process and provide bioactive characteristics.

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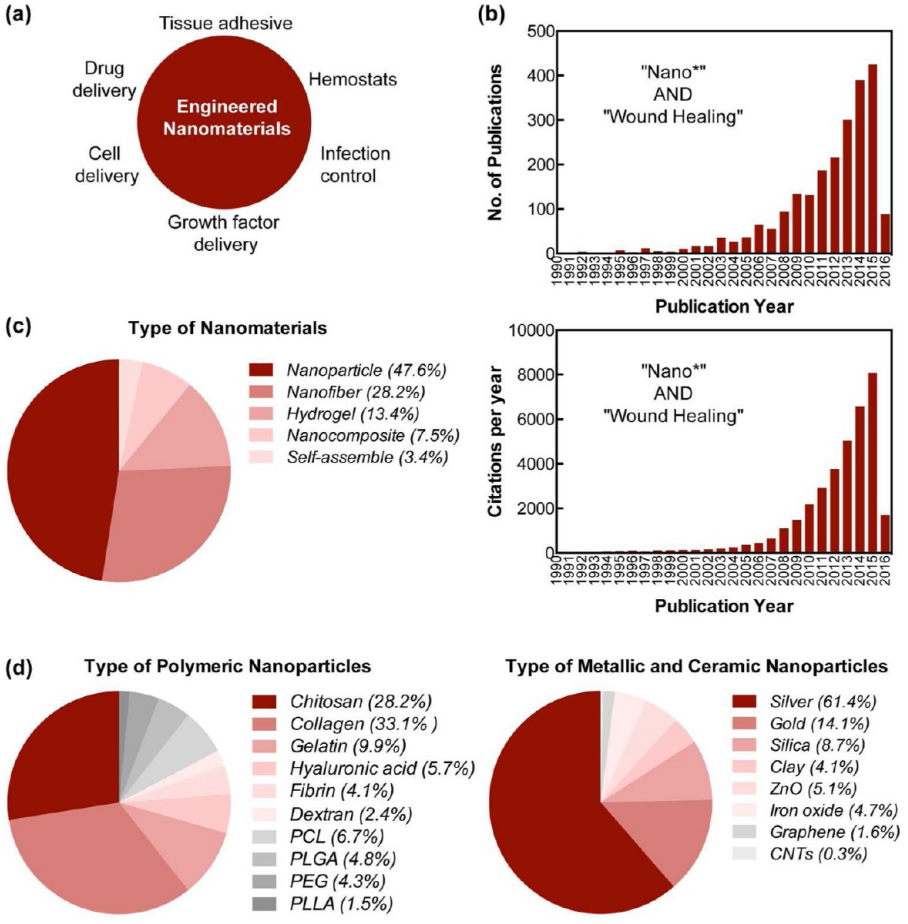

Figure 1. Number of publications in "wound healing" and "nano*" according to Web of Science. (a) Application of nanoengineered materials in wound healing. (b) A steady increase in the number of publications and citations indicates growing interest in the application of nanomaterials for wound healing. (c,d) Types of nanomaterials investigated for wound healing applications. (Data obtained from ISI Web of Science, March 2016).

A range of engineered nanomaterials are investigated for biomedical applications including tissue engineering, stem cell therapeutics, biosensing, immunomodulation, and drug/gene delivery due to their unique physical, chemical, and biological characteristics.[15−21] By combining engineered nanomaterials with synthetic or natural polymers, nanocomposite biomaterials with desired characteristics can be designed.[22−26] Recently, engineered nanomaterials have found more acceptance in wound healing applications as evident by the increase in publications (Figure 1). A range of polymeric, metallic, and ceramic nanomaterials are investigated for wound healing applications.[27−29] Some of the most commonly investigated nanostructures include nanoparticles, nanofibers, nanocomposites, nanoengineered hydrogels, and self-assembled nanostructures.[30] These newly developed nanomaterials are used as tissue adhesives, hemostats, antimicrobial agents, and drug/therapeutics/cell delivery agents.

Most nanomaterials are topical administration to minimize the perceived risks associated with internal use. For example, topically applied antimicrobials are more effective than systemically administrated antimicrobials in reducing infections in granulating wounds.[31] Moreover, exposure of nanoparticles in external wounds is more localized and controlled compared to systemic administrative.[32] Undesirable effects of nanomaterials, if any, can be easily detected and controlled due to the accessibility of the target area. The external nature of the whole system permits applied treatments to focus on both faster wound closure and aesthetic remodeling.

Recently, the development of effective antimicrobial wound dressings that utilize silver nanoparticles triggered expanded research on the use of nanoparticles and their composites for enhanced wound healing.[32−35] Although the impact of silver nanoparticles will enable faster healing of acute accidental and surgical wounds,[36,37] the true benefits of nanomaterials are seen in the dramatically improved healing times in cases of recalcitrant chronic wounds. The healing potential of nanoparticles combined with robust and flexible polymer systems will lead to ideal nanocomposite systems for wound dressing and tissue regeneration.[38−40]

In this review, we will focus on a range of engineered nanomaterials (size <500 nm) that are currently used for infection control and wound healing applications. First, we will provide a brief overview of the biological aspect of the wound healing process. Then, we will critically evaluate various engineered nanomaterials, including polymeric-, metallic-, and ceramic-based nanomaterials, that are currently being investigated for wound healing and infection control. Specifically, we will highlight new developments that are shaping this emerging field and evaluate potential applications of these engineered nanomaterials. We will review the unique characteristics of engineered nanoparticles that render them applicable for wound healing and infection control. Finally, we will detail the current state of engineered nanomaterials for wound

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regeneration and will identify promising new research directions in infection control.

2. ACUTE AND CHRONIC WOUND HEALING PROCESSES

Wound healing is a complex and well-orchestrated process that is initiated immediately after injury. This process follows a cascade of events involving different cell types, growth factors, and cytokines, which act through distinct, but overlapping, sequential phases of (a) hemostasis and tissue inflammation, (b) cellular proliferation and new tissue formation, and (c) tissue remodeling (Figure 2).[4] Pathogenic infection of the

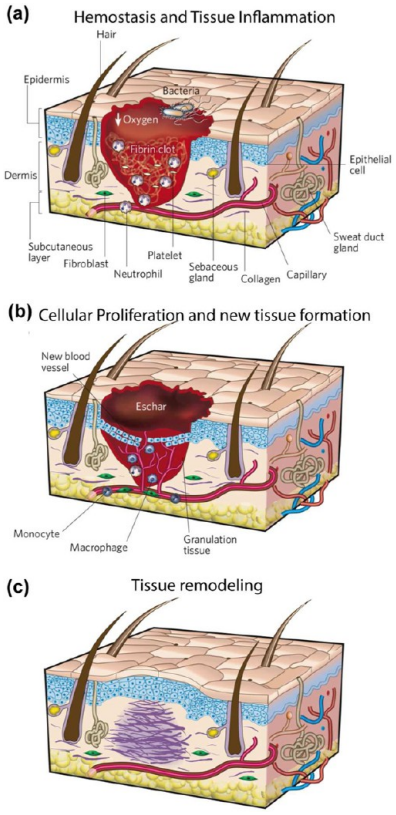

Figure 2. Stages of wound healing include (a) hemostasis and tissue inflammation, (b) cellular proliferation and new tissue formation, and (c) tissue remodeling. Adapted and reprinted with permission.[4] Copyright 2008, Macmillan Publishers Ltd.: Nature.

wounds can extend the healing process and may result in life threatening conditions. Recent reports indicate that stem cells and progenitor cells are involved in the wound healing process, indicating that it is a systemic response rather than a local response to injury.[41]

Breakage of blood vessels during injury results in bleeding; therefore, the first protective step is to achieve hemostasis though vascular constriction, platelet aggregation, and coagulation. The fibrin clots that form during this process have three major tasks: (1) plug the broken blood capillaries to stop bleeding, (2) limit pathogen entry into the bloodstream, and (3) act as a provisional extracellular matrix (ECM) for migration and proliferation of the cells involved in wound healing. Simultaneously, the activated platelets off-load growth factors, such as vascular endothelium growth factors (VEGFs), platelet-derived growth factors (PDGFs), transforming growth factors (TGFs), fibroblast growth factors (FGFs), and epidermal growth factors (EGFs). The growth factors attract pro-inflammatory neutrophils, monocytes, and lymphocytes and initiate inflammation.[42] Neutrophils are the first to clean up the wound bed from invading microbes and dead cells of the host.[43] Monocytes divide and differentiate into macrophages, which in turn secrete cytokines that mount strong secondary inflammatory responses by recruiting additional pro-inflammatory cells. Ultimately, the macrophages induce apoptosis of inflammatory cells and clean up any dead cells; this action reduces inflammation and initiates cell proliferation.

During the proliferation phase, fibroblasts secrete type III collagen to replace the damaged ECM. Endothelial cells proliferate on the ECM and form new blood vessels (angiogenesis), which supply oxygen, nutrients, and growth factors to facilitate tissue growth. The wound is filled with granulation tissue made of new connective tissue and blood vessels. This phase ends with wound closure, which is accomplished via traction forces generated by the fibroblasts.[44]

Remodeling is the longest phase in wound healing and begins when TGF-β and cytokines released from the platelets and activated macrophages induce the fibroblasts to differentiate into contracting myofibroblasts. Minor superficial injuries do not need extensive remodeling; they heal without scarring by keratinocyte regeneration and minimal ECM production. Major injuries undergo extensive remodeling over a long period, in some cases as long as two years. The wound contracts approximately 10−20 μm per day, and a large amount of ECM is produced during this time.[45] The cells in the granulation tissue undergo apoptosis, and the cell-rich granulation tissue results in the formation of scar tissue.[46] The density of the blood vessels in the granulation tissue is reduced, and the wound becomes pale in color due to reduced blood flow.[47] This results in the formation of striated scar tissue consisting of collagen fibers and myofibroblasts.[48] The strength of the skin over the scar gradually increases, but it never surpasses 80% of the strength of native tissue.[49]

Because of infection or impaired wound healing, the above-mentioned cascade of events is absent or derailed in chronic wounds. Excessive neutrophil infiltration and/or an abundance of pro-inflammatory cytokines, reactive oxygen species, and wound proteases can stall the healing process at the inflammation phase. The wound proteases cause deficiencies in growth factors and ECM proteins, which are central to the process of wound healing.[50,51] Recruitment, survival, and proliferation of progenitor cells are also often defective in chronic wounds.[52] The net result is that the wound does not close for want of granulation tissue, which may be aggravated further by repeated infections. Externally supplied growth factors can reverse some of the deficits in impaired wound healing. Recombinant PDGF-BB was approved by the FDA as early as in 1998 as a topical application to improve healing of chronic wounds in diabetic patients.[53,54] However, despite the best wound management, only 59% of diabetic foot ulcers were healed without amputation,[55] which highlights the need for a more practical, safe, and effective therapy for nonhealing chronic wounds.

3. POLYMERIC NANOMATERIALS

Macromolecular bulk polymers are used as nanoparticle carriers for controlled and sustained release of encapsulated or entrapped therapeutics. The molecular weight of the polymeric nanoparticles is tunable, and a range of characteristics, such as

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size, shape, and hydrophilicity, can be modulated. Nanomaterials derived from natural and synthetic polymers are investigated for infection control and wound healing applications due to their unique physiochemical and biological characteristics (Table I). Polymeric nanoparticles are normally bigger than metallic or ceramics nanoparticles; those that are 500 nm or less in size are described in this review.

3.1. Natural Polymers. *3.1.1. Chitosan-Based Nanoengineered Materials.* Chitosan is derived from partial deacetylation of chitin and consists of D-glucosamine and *N*-acetyl-D-glucosamine.[56] The amino groups present on the chitin backbone offer many opportunities for functional modifications to modulate mechanical stiffness, physiological stability, and biochemical characteristics. Chitin is deacetylated and cleaved to obtain chitosan; the level of deacetylation and final molecular weight may vary. Increasing the degree of deacetylation and molecular weight of chitosan promotes the protein loading capacity but decreases the release rate of entrapped therapeutics from the nanoparticles.[57] Chitosan has been investigated extensively for a range of biomedical applications including tissue engineering, infection control, wound healing, therapeutic delivery, and hemostatic applications.[56,58−60]

Chitosan is bioactive and has inherent characteristics to facilitate wound healing. For example, in vitro testing of chitosan nanoparticles showed significant induction of lymphocyte proliferation and nitric oxide (NO) production.[61] NO is involved in wound healing through angiogenesis, migration of epithelial cells, and proliferation of keratinocytes. In vivo testing of excision wounds in Sprague−Dawley rats with chitosan nanoparticles showed enhanced production of NO; this supports a role for chitosan nanoparticles in wound healing.[61]

By combining chitosan (CS) with free fatty acids, such as oleate and linoleate, polymeric micelles CS:OA and CS:LA, respectively, can be obtained via ionic interactions.[62,63] Both CS:OA and CS:LA were mucoadhesive and had positive effects on cell viability. Because of the amphiphilic nature of micelles, topical delivery of poorly soluble drugs for infection control and wound healing applications were investigated. Sustained delivery of clarithromycin and silver sulfadiazine from chitosan nanoparticles was reported.

The hemostatic and wound healing properties of chitosan nanoparticles (CS-NPs) loaded with adenosine diphosphate (ADP) or fibrinogen (FN) were investigated.[64] ADP binds to the receptors on platelets and facilitates the wound healing process. Fibrin derived from fibrinogen provides the physical framework for physical stability and aids in hemostasis. Scanning electron microscopy (SEM) showed that the positively charged CS-NPs adhered to the negatively charged membranes of red blood cells (RBC). CS-NPs strongly interact with blood and accelerate clotting. The incorporation of ADP and FN to CS-NPs further facilitates the clotting process with ADP being the most effective molecule.[64] ADP/FN in CS-NPs interacts with blood-derived thrombin and results in the formation of profuse fibrin networks. The combinatorial effect of ADP and FN has not been investigated to date, but synergistic effects on blood clotting are expected.

In another study, chitosan/sodium tripolyphosphate (CS-TPP) nanoparticles were synthesized for therapeutic delivery.[65] Administration of CS-TPP nanoparticles encapsulated with standardized extract from the leaves of *Arrabidaea chica* showed ∼60% reduction in indomethacin-induced acute lesions on gastric mucosa in rats. A comparative study between free extract

Table I. Polymeric Nanomaterials for Wound Healing and Infection Control

polymeric nanomaterials	remarks (type of nanomaterial, specific role in wound healing and infection control)
chitosan	Chitosan nanoparticles have antimicrobial properties and have been shown to facilitate wound healing due to inherent bioactivity. They are also used for the controlled release of therapeutics (drugs, complex extracts, growth factors, and genes) to aid in the wound healing process.
fibrin	Fibrin, being a part of the provisional ECM that attracts and aids in proliferation of the cells involved in wound healing, is the preferred polymeric nanomaterial for wound healing. Fibrin-based nanomaterials are used to deliver growth factors and antibiotics. Bandages made of fibrin nanoparticles impregnated in a chitosan hydrogel have also shown accelerated wound healing.
hyaluronic acid (HA)	HA has the ability to promote cellular proliferation and secrete collagen, which help in wound healing. An HA-based nanocomposite sponge shows accelerated blood clotting and enhanced angiogenesis.
poly-D,L-lactide-*co*-glycolide (PLGA)	Lactate released from PLGA facilitates wound repair by reducing muscular atrophy and improving reperfusion. PLGA is usually used in combination with drugs or growth factors for wound healing applications. The wound healing property of curcumin is enhanced when PLGA is used as a delivery vehicle. Sustained and controlled release of NO from PLGA nanoparticles are found to be useful in infection control, wound healing, and epithelialization.
poly(L-lactide) (PLLA)	PLLA nanoparticles are used for sustained drug delivery for wound healing. Nanofibrous electrospun PLLA scaffolds have been shown to enhance sustained and controlled delivery of therapeutics for wound healing.
poly(ε-caprolactone) (PCL)	PCL is an FDA-approved biocompatible and biodegradable polymer extensively used in blends and composites for biomedical applications. PCL nanoparticles are used as drug carriers in wound healing. PCL-PEG has been used to overcome the clinical limitations of lipophilic hypericin in photodynamic therapy (PDT), and enhanced infection control and wound healing is observed in comparison with hypericin in DMSO applications.
poly(ethylene glycol) (PEG)	PEG-based nanoparticles are used to increase the bioavailability of plant-derived compounds with proven wound healing properties. Therapeutic drugs loaded in PEG nanoparticles are shown to retain bioactivity and show an inhibitory effect on inflammation and ulceration. Extensive keratinization and epidermis reformation are also observed due to sustained and controlled release of therapeutics.

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and encapsulated extract demonstrated a 4-fold reduction in the amount of encapsulated extract needed to achieve the equivalent healing response of free extract for ulcerative gastrointestinal lesions in rats.[65] In addition, the free extract was cytotoxic at higher concentrations (250 and 500 mg/L), but the encapsulated CS-TPP nanoparticles promoted cell proliferation. It is important to note that long-term efficacy of CS-TPP still needs to be investigated for in vivo delivery of therapeutics.

In a similar study, chitosan-fibrin (CS-FN) nanoparticles were synthesized and investigated for antibacterial and wound healing applications.[66] The CS-FN nanoparticles completely inhibited the growth of *Escherichia coli* and *Staphylococcus* and were not toxic to fibroblast cells even at a higher concentration (100 μg/mL). For in vivo wound healing studies, open excision wounds were made in male albino rats and treated with saline or CS-FN nanoparticles every other day for 10 days. CS-FN nanoparticle-treated wounds were completely healed on day 14, whereas it took significantly more time (22 days) for the saline-treated wounds to heal completely.[66]

CS-NPs were also investigated for gene therapy applications. Genes for two growth factors, PDGF-BB and FGF-2, were cloned in an expression vector and loaded onto chitosan nanoparticles.[67] Gene-loaded CS-NPs were delivered into mice through subcutaneous and intramuscular routes. Though recombinant PDGF-BB and FGF-2 proteins were expressed in the mice sera, antibodies against them were also produced due to an immune response. The effect of gene delivery on wound healing was not investigated, and it took ~60 days after delivery for the recombinant proteins to be expressed. The two months of lag time severely limits applications of this material for accelerated wound healing.

The process of wound healing culminates in the regeneration of the lost tissue, which includes cell proliferation followed by tissue remodeling. The ECM, in addition to several other molecules, provides a scaffold made of geometrically arranged collagen nanofibers that guide the cells in tissue remodeling. ECM also provides a highly defined microenvironment that is essential for the regeneration of damaged tissue. Although it is difficult to mimic the chemical and biological characteristics of ECM, physical and structural characteristics can be mimicked using electrospinning or self-assembled techniques.[68] Chitosan alone cannot form electrospun scaffolds, but it is often blended or modified with different synthetic and/or natural polymers. For example, by combining chitosan with collagen, mechanically stable electrospun scaffolds could be obtained.[56] The addition of collagen also facilitates proliferation and migration of fibroblasts, which aids in the wound healing process. In another approach, a hydrophilic and porous three-dimensional nanofibrous network was fabricated using deacetylated chitosan (CS-DD) with and without arginine-modified chitosan (CS-A).[69] Male Wistar rats were wounded and monitored for 14 days after injury; treatment with both CS-DD and CS-A showed faster wound closure than that of the control group. After 21 days, rats treated with CS-A showed significantly higher wound closure than rats treated with CS-DD or the control group. Both of these approaches indicate the utility of nanofibrous chitosan-based scaffolds for accelerated wound healing.

In another study, a chitosan and poly(ethylene oxide) (PEO) blend loaded with VEGF were electrospun into CS/PEO nanofibrous scaffolds.[36] Additionally, poly lactic-*co*-glycolic acid (PLGA) nanoparticles loaded with platelet-derived growth factor BB (PDGF-BB) were dispersed in the nanofibers. In vitro release of the growth factors was biphasic with burst release of VEGF on day 1 and sustained release of PDGF-BB over a period of 7 days. Enhanced proliferation of human dermal fibroblasts on CS/PEO scaffolds was observed when compared to tissue culture polystyrene (TCPS) controls.[36] Plates containing CS/PEO scaffolds with PDGF-BB-loaded nanoparticles exhibited significantly higher cell growth compared to TCPS and CS/PEO scaffolds without growth factors. The effect of CS/PEO nanofiber scaffolds with and without VEGF and PDGF-BB growth factor on wound healing was investigated on full-thickness skin wounds of Sprague–Dawley rats. Untreated wounds and the wounds treated with commercial Hyrofera Blue were maintained as controls. Wound closure was significantly higher in the wounds treated with CS/PEO nanofiber scaffolds containing the growth factors than in other treatments. Though all wounds were closed after 4 weeks of treatment, wounds treated with CS/PEO nanofiber scaffolds with growth factors showed the smallest scar formation and more hair coverage due to the faster healing process.[36] This study demonstrates a promising approach for enhanced wound healing by dual growth factor delivery.

3.1.2. Fibrin-Based Nanomaterials and Nanocomposites. Fibrin is a biopolymer of fibrinogen, which is formed by the action of thrombin.[70] Fibrin, together with blood platelets, forms the hemostatic plug that stops bleeding at a wound site prior to the initiation of the healing process. Fibrin is preferred for the delivery of protein growth factors, which can be denatured by the heat and organic solvents that are used for the preparation of certain other polymeric scaffolds. Degraded fibrin fragment E also increased cell adhesion, differentiation, and angiogenesis to promote wound healing.[71] Enzymatically degradable fibrin nanoparticles and nanotubes were synthesized and tested for their ability to deliver VEGF, which is a potent activator of vasculogenesis and angiogenesis. Treatment of human umbilical vein endothelial cells with fibrin nanoparticles and nanotubes loaded with VEGF increased cell proliferation, migration, and patterned alignment; this increase is most likely due to the combined action of VEGF and the fibrin degradation products released within the system.[72]

Recombinant human EGF (rhEGF), which stimulates cell proliferation and facilitates wound healing, was encapsulated in chitosan nanoparticles. Nanoparticles loaded with rhEGF were added to a fibrin gel made from thrombin and fibrinogen. Encapsulated rhEGF was found to be more stable than the free form in simulated wound environments.[70] Incorporation of chitosan nanoparticles in a fibrin gel matrix was helpful in controlling the burst release of rhEGF. In vitro release kinetics showed a sustained release of 65% of rhEGF over a period of 4 days. The results also indicated that a sustained release over a period of 2 weeks could be achieved by increasing the concentration of fibrinogen and thrombin. The rhEGF released from the hybrid matrix was able to retain bioactivity and facilitate proliferation of fibroblast cells in vitro.[70]

In another study, fibrin nanoparticles loaded with ciprofloxacin (broad spectrum antibiotic) and fluconazole (FDA-approved broad spectrum antifungal compound) were tested for their antimicrobial properties as a drug delivery system for healing infected wounds.[73] Results showed a pH-dependent release profile of the encapsulated drug and dose-dependent antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. These results highlighted the ability of the nanomaterial system to respond to pH change.[73]

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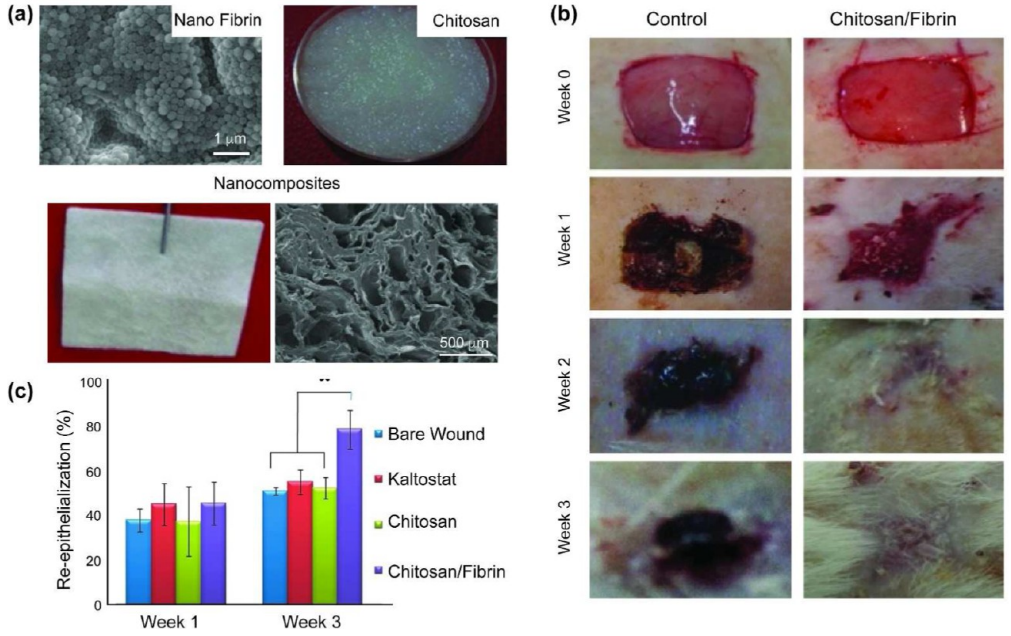

Figure 3. Chitosan-nanofibrin composite for accelerated wound healing. (a) SEM image showing nanofibrin combined with chitosan results in the formation of a porous mat. (b) Application of a chitosan-fibrin nanocomposite significantly enhances wound healing ability and (c) re-epithelialization of wounded tissue. Adapted and reprinted with permission.[74] Copyright 2012, Mary Ann Liebert, Inc.

Chitosan and fibrin bandages (CFB), consisting of fibrin nanoparticles impregnated in a chitosan hydrogel, were fabricated, characterized, and tested for several parameters that promote wound healing (Figure 3).[74] The CFBs were found to be microporous, flexible, and biodegradable. CFBs showed high cell viability, cell adhesion, and enhanced blood clotting when compared to chitosan-only bandages and to Kaltostat (a commercial calcium sodium alginate dressing). In male Sprague–Dawley rats, partial thickness skin wounds treated with CFBs showed 98% wound closure. However, the wounds treated with either chitosan-only or Kaltostat bandages and the controls (bare wounds) showed only 70% wound closure. These results were supported by enhanced collagen deposition and the formation of granulation tissue in the epidermis in the rats treated with CFBs. The presence of fibrin nanoparticles, in conjunction with the biodegradation of chitosan matrix, might produce an additive effect on wound healing.[74]

3.1.3. Hyaluronic Acid. Growth factors suffer from rapid degradation; thus, they are used in high dosages and for shorter periods but with the risk of developing malignant tumors.[75−77] Therefore, sustained delivery of a physiological dosage is preferred in regenerative therapies, especially when dealing with chronic wounds, which can take several months to heal. In a recent approach, fibrin nanoparticles loaded with VEGF were prepared and loaded into a chitosan and hyaluronic acid blend to prepare a nanocomposite sponge for wound dressing.[78] Hyaluronic acid was included because of its ability to promote cellular proliferation and secrete collagen. In vitro release of VEGF showed an initial burst release followed by a sustained release profile for a week, making it a suitable biomaterial for wound dressing. The nanocomposite sponge showed a higher blood clotting ability compared to those of either Kaltostat or the chitosan/hyaluronic acid sponge. Additionally, the nanocomposite sponge showed enhanced angiogenesis as indicated by capillary-like tube formation when tested in vitro using human dermal fibroblasts and human umbilical vein endothelial cells.[78]

3.2. Synthetic Polymeric Nanomaterials. *3.2.1. Poly-D,L-lactide-co-glycolide (PLGA) Nanoparticles.* Under in vivo conditions, PLGA releases lactate, which facilitates wound repair by reducing muscular atrophy and improving reperfusion in ischemic hind limb wounds.[79] However, PLGA nanoparticles are usually used in combination with drugs or growth factors for wound healing applications. rhEGF is effective against nonhealing diabetic foot ulcers, but its short half-life limits its bioavailability. For this problem to be circumvented, rhEGF was loaded on PLGA nanoparticles and tested on the full-thickness diabetic wounds of rats.[80] PLGA nanoparticles facilitated a slow and sustainable release of rhEGF over a period of 24 h, thereby maintaining its effective concentration to promote wound healing. The wounds treated with the rhEGF-loaded PLGA nanoparticles showed an accelerated healing rate compared with wounds treated with nanoparticles without growth factors or controls.[80]

In another study, poly(ether)urethane-polydimethylsiloxane/fibrin-based scaffolds loaded with PLGA nanoparticles were fabricated.[81] The PLGA nanoparticles were loaded with VEGF and basic fibroblast growth factor (bFGF) that were to undergo a controlled release. The resulting data revealed that the full-thickness skin wounds in healing impaired diabetic mice (db/db) showed significant wound closure when treated with growth factor-loaded scaffolds compared to control scaffolds without growth factors. However, the rate of wound closure was not significantly different from wounds treated with scaffolds containing free VEGF and bFGF. Scaffolds in the presence of growth factors (free or encapsulated with PLGA) resulted in complete re-epithelialization, enhanced granulation tissue formation/maturity, and collagen deposition.[81]

Recently, curcumin, a plant-derived compound, has been shown to promote healing of acute and chronic wounds.[82,83] However, therapeutic application of this compound is reduced due to its limited hydrophilicity, stability, and photosensitivity.

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For these challenges to be overcome, curcumin was encapsulated in PLGA (PLGA-CC) nanoparticles.[82] The release kinetics showed an initial burst release of 40% curcumin in the first 24 h, followed by a sustained release from 40% to 75% over a period of 8 days. PLGA-CC nanoparticles at a concentration of 100 μg/mL did not show significant cytotoxicity to keratinocytes as indicated by LDH and MTT assays. Under in vivo conditions, the wounds treated with PLGA-CC nanoparticles showed complete closure, whereas the wound treated with free curcumin and PLGA nanoparticles alone showed only 75% recovery. In histological observations, the wounds treated with PLGA-CC nanoparticles showed complete re-epithelialization and significantly increased the deposition of connective tissue.[82] This approach of sustained delivery of therapeutics can significantly enhance the efficacy of difficult-to-solubilize drugs.

The importance of NO in wound healing is underscored by its reported role in inflammation, cellular proliferation, ECM matrix deposition, angiogenesis, and matrix remodeling.[84] However, NO delivery using a conventional delivery platform is challenging due to its gaseous nature. Attempts to deliver NO using metallic nanoparticles, liposomes, and dendrimers resulted in a maximum delivery period of 24 h,[85,86] which is not sufficient for wound healing. In a recent study, sustained and controlled release of NO for extended periods was achieved using PLGA-polyethylenimine (PEI) nanoparticles.[87] PEI/diazenium-diolate (PEI/NONOate) reacting NO was first synthesized with the secondary amine groups of PEI and then incorporated into PLGA nanoparticles. A sustained release of NO from PEI/NONOate was observed for 6 days without any burst release. The NO-releasing nanoparticles showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, which are the two major infectious agents of open wounds. Accelerated wound healing and epithelialization was observed when MRSA-infected full-thickness wounds in mice were treated with NO-releasing nanoparticles.[87]

Besides growth factors, certain secreted lipids and proteins also play roles in wound healing. Recently, annexin A1 (ANXA1), a protein secreted from neutrophils as a component of extracellular vesicles, was shown to stimulate intestinal mucosal wound repair in a murine model of colitis.[88] PLGA-PEG-maleimide nanoparticles were decorated with the KLW-VLPK peptide of type IV collagen for mucosa targeting and encapsulated with an ANXA1 mimetic peptide for wound repair.[89] In vivo studies in annexin A1 knockout mice showed that a single administration of the nanoparticles by intraperitoneal injection and intramucosal injection was sufficient to accelerate the repair of acute epithelial injury and closure of intestinal mucosal biopsy-induced wounds, respectively.

Nanofiber scaffolds loaded with drugs and growth factors are useful as wound dressing materials due to compatible biophysical and structural characteristics. Collagen-PLGA nanofiber scaffolds conjugated with CD29 antibodies were investigated for wound healing.[90] Full-thickness skin wounds were made in rats, and skin grafts made of nanofiber scaffolds decorated with bone marrow-derived mesenchymal stem cells (BM-MSCs) were sutured over the wounds. Compared with untreated controls, all of the wounds treated with nanofiber scaffolds, with or without BM-MSCs, promoted wound healing. The wounds that were treated with nanofiber scaffolds containing BM-MSCs achieved complete wound closure in 10 days. Histological observations showed the formation of a thin epidermal layer with several skin appendages, including hair follicles and sebaceous glands. Increased expression of collagen, and epidermal differentiation markers keratin 10 (early), filaggrin (middle), and involucrin (terminal) were also observed. The wounds treated with empty nanofiber scaffolds were closed in 15 days, whereas it took 18 days for the untreated wounds to close.[90] This study clearly indicates that use of nanofibrous scaffolds accelerates the wound healing process.

3.2.2. Poly(L-lactide) (PLLA). Dual-layer nanofiber wound dressing mats loaded with nitrofurazone (antibiotic drug used for treating infected wounds) in both layers were fabricated with poly(L-lactide) (PLLA) and sericin nanofiber blend as the first layer and pure PLLA nanofibers as the second layer.[91] Sericin, a protein that envelops silk fibers created by silkworms, was included to enhance the hydrophilic property that facilitates cellular proliferation. This in vitro study showed an initial burst release of nitrofurazone from the PLLA-sericin blend fiber layer followed by a sustained release profile from the PLLA layer. The release of the entrapped drug was further fine-tuned by varying the drug concentration in the different layers. When used as a dressing material for full-thickness wounds in rats, wound size reduction was 97% for the wounds dressed with the nitrofurazone-loaded dual-layer nanofiber mats but 84% for the commercially available woven dressing.[91]

The PLLA film functionalized with type 1 collagen was used as a biomimetic controlled drug delivery system for wound healing.[92] Indomethacin, an anti-inflammatory drug used for wound healing, was encapsulated within PCL and polyesterurethane (PU) nanoparticles. Although PU nanoparticles showed a 20% burst release at 2 h followed by a sustained release over a period of 48 h (91%), PCL nanoparticles released 60 and 92% of the drug in 2 and 24 h, respectively. The same trend was observed even after the encapsulated nanoparticles were loaded on the PLLA film. As a result, PU nanoparticles were shown to be better carriers for drug delivery. Interestingly, for unknown reasons, the PLLA film loaded with indomethacin-encapsulated PU nanoparticles showed significantly lower cell viability compared to the empty film (functionalized with collagen) and the film loaded with indomethacin-encapsulated PCL nanoparticles.[92]

In another study, growth factors were encapsulated in dextran glassy nanoparticles (DGN) before electrospinning in PLLA to avoid loss of the bioactivity of the protein due to denaturation. Wound dressing membranes were fabricated by electrospinning of PLLA, PLLA fibers loaded with bFGF (bFGF-PLLA), and bEGF-encapsulated in DGN (bFGF/DGN-PLLA). The bFGF/DGN-PLLA membranes released double the quantity of active bEGF from bFGF-PLLA, indicating enhanced protection due to encapsulation in DGN; the release was sustained for 30 days. The cells seeded on the bFGF/DGN-PLLA membrane surface showed enhanced proliferation compared to those of the bFGF-PLLA membrane. The in vivo study showed significant wound healing, capillary vessel density, and collagen type I expression for the group treated with the bFGF/DGN-PLLA membrane when compared with control (PLLA or bFGF-PLLA) membranes.[93]

3.2.3. Poly(ε-caprolactone) (PCL). PCL is a biocompatible, biodegradable, and FDA-approved polymer that is extensively used in the blends and composites for biomedical applications. Radially aligned PCL nanofibers were prepared using the conventional electrospinning setup except for the collector,

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which included a ring electrode and a point electrode.[94] Ex vivo grafting of these fibers into a piece of dura with a circular hole at the center showed the movement of fibroblasts from the surrounding tissue to the center of the scaffold along the radially aligned nanofibers. On day 4, the migrated cells covered the entire surface of the radially aligned scaffold, whereas a cell-free region was observed in the randomly aligned scaffold. Coating the scaffold with fibronectin improved this process. Highly organized type I collagen was observed on the radially aligned scaffolds, and haphazard arrangements were observed on randomly aligned scaffolds. These results provide data for methods that might help to heal the wound more aesthetically with reduced scar tissue formation.[94]

Nanofiber mats, with or without antibacterial gatifloxacin hydrochloride (Gati), were electrospun by blending PCL with thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAM) and a collagen substitute, egg albumin (EA), to increase the wound healing efficiency through efficient tissue regeneration.[95] Release kinetics of Gati in PBS showed an initial burst release for 10 h, followed by slow and controlled release for 29 days, which is a suitable system for drug release over the long period that is typically required for wound healing. Circular discs of nanofiber mats inhibited the growth of *Staphylococcus aureus* as indicated by zones of inhibition that measured up to 35 mm in 24 h. Full-thickness wounds were made in rats and infected with *S. aureus*. The infected wounds were subjected to a one-time dressing using gauze or nanofiber mats loaded with 10 and 15% Gati. On day 21 postdressing, wound healing was 85−95% in the wounds dressed with nanofibers, whereas it was only 45% in the wound dressed with gauze.[95]

Photodynamic therapy (PDT) can be used as an alternative to antibiotics in infection control for wounds. In PDT, a photosensitizer is administered first and then activated by light only on the required location to achieve precise targeting. The activated photosensitizer produces singlet oxygen molecules that kill the microbes. Hypericin is a new generation photosensitizer from *Hypericum perforatum* (St. John's Wort) with potential antimicrobial activity,[96] but its lipophilic property limits its clinical applications. For circumventing this problem, hypericin was encapsulated in amphiphilic PCL-PEG. The hypericin encapsulated in PCL-PEG showed an initial burst release followed by a slow release over a period of 48 h. Photoactivated nanoparticles produced 100-fold higher amounts of reactive oxygen species than the hypericin in DMSO, and they efficiently inhibited in vitro biofilm formation by MRSA. Wound healing was studied in Wistar rats by making two circular full-thickness skin wounds on the dorsum of the animals. The wounds were infected with *S. aureus* on day 1 and treated with hypericin-loaded PCL-PEG nanoparticles, PBS, and hypericin in DMSO. On day 10, the wounds treated with hypericin-loaded PCL-PEG nanoparticles showed the maximum closure with a few completely healed wounds, whereas some wounds treated with hypericin in DMSO developed abscess and edema. Although the animals treated with hypericin-loaded PCL-PEG nanoparticles showed 100% survival during the study period, only 50 and 75% of the animals treated with PBS and hypericin in DMSO, respectively, survived.[97]

3.2.4. Other Types of Polymeric Nanomaterials. A biocompatible wound dressing material was synthesized based on a thermoresponsive and thermoreversible triblock copolymer hydrogel with water-soluble poly(2-(methacryloyloxy)ethyl phosphorylcholine) (PMPC) flanked by water insoluble poly(2-hydroxypropyl methacrylate) (PHPMA).[98] Self-assembled copolymers formed gel networks of micelles with bridging chains between the micelles. In hydrating conditions at 20 and 60 °C, the hydrodynamic radii of copolymer micelles were observed to be around 30 and 80 nm when the PMPC degree of polymerization was 250−300 and 400, respectively. In gels containing up to 20% copolymers, the cell viability was 80% of the control (without copolymer) for 72 h. Exposure of 3D tissue-engineered skin to 20% gel for 4 days did not cause any structural change to the skin, and MTT assays did not indicate any significant reduction in cell proliferation. Therefore, these thermoresponsive and biodegradable copolymers may be useful in developing better wound dressing materials loaded with drugs and growth factors.[98]

In other studies, PEG nanoparticles were used to increase the bioavailability of quercetin and curcumin for improved wound healing.[83] Dermal drug delivery capacity was studied in vitro in the skin of newborn pigs using Franz vertical cells under nonocclusive conditions. As determined by high-performance liquid chromatography, transdermal delivery of quercetin and curcumin was found to be the highest in the stratum corneum followed by epidermis, dermis, and receptor fluid. For in vivo studies, cutaneous inflammation and ulceration were induced by applying phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA) on the shaved skin on the backs of the mice. The inhibitory effect of PEG-curcumin and PEG-quercetin on inflammation and ulceration was determined by edema formation and myeloperoxidase (MPO) activity, respectively. Curcumin was more bioactive in encapsulated form than in freely dispersed form. PEG-curcumin provided more inhibition of edema (91 versus 74%) and MPO activity (68 versus 40%) than PEG-quercetin. Examination of the skin biopsies was obtained 72 h after treatment; both PEG-curcumin- and PEG-quercetin-treated skin showed extensive keratinized areas and a thin layer of migrating epithelium over the dermis, indicating reformation of the epidermis. Leukocyte infiltration was less severe, especially in the dermis, and congestion of blood vessels was less evident. Skin treated with PEG-curcumin showed extensive re-epithelialization with multiple layers of thick epidermis.[83]

4. METALLIC NANOMATERIALS

Silver and gold are the two major noble-metal nanoparticles that are used in wound healing applications (Table II). Metal nanoparticles exhibit a range of properties, such as enhancing mechanical strength, controlled release, and antibacterial activity against both bacteria and fungi, which make them excellent candidates for topical use in wound healing. Here, we review the promising wound healing applications, and the mechanism of action of metallic nanoparticles and their composites.

4.1. Silver Nanoparticles (AgNPs). Silver has a long history as an antimicrobial agent for preventing infections during wound healing. Silver treatments were initially with a 1% silver nitrate solution in the beginning of the 19th century, followed by silver sulfadiazine cream formulations in the 1960s, and now, silver is being used in the form of metallic silver nanoparticles (AgNPs). AgNPs have been reported to be effective against bacteria, yeast, and fungi;[99−101] although AgNPs were shown to inhibit the growth of both Gram-negative and -positive bacteria, they were more effective against the former.[32,99,102] When used in combination with antibiotics, AgNPs showed synergistic (ceftazidime), additive (ampiclox,

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Table II. Metallic and Ceramic Nanomaterials for Wound Healing and Infection Control

metallic and ceramic nanomaterials	remarks (type of nanomaterial, specific role in wound healing and infection control)
silver nanoparticles (AgNPs)	AgNPs are effective in controlling bacterial, fungal, and yeast infections and improving wound healing. Wound dressing materials containing AgNPs are in clinical use. Nanocomposites loaded with AgNPs are investigated for wound dressing and controlled release of therapeutics.
gold nanoparticles (AuNPs)	Biologically inert AuNPs are functionalized with antibiotics, antioxidants, and ROS scavengers for improved wound healing. Direct use in tissue welding for healing of cut wounds was also demonstrated. AuNPs are also investigated for gene delivery.
silica nanoparticles	Mesoporous silica nanoparticles are considered ideal for delivering growth factors to facilitate wound healing due to a high surface-to-volume ratio. NO-releasing silica nanoparticles showed increased fibroblast proliferation, collagen deposition, and angiogenesis in the wound area. Tissue adhesive for joining cut wounds was also developed using a silica nanoparticle solution.
synthetic silicate clay	Nanosilicate clays are desired in wound healing application due to their sustained delivery characteristics. Layered silicate clays are able to induce blood clotting due to their charged interactions with clotting factors and developed as hemostatic agents. Nanosilicate-based hydrogels are explored for traumatic injuries requiring accelerated hemostasis.
bioactive glass	Bioactive glass particles bind to soft tissue through apatite layers that are formed on their surface upon contact with cells and have been shown to increase angiogenesis due to release of ionic dissolution products.
zinc oxide nanoparticles (ZnONPs)	ZnONPs are mainly used for infection control in wound healing. ZnOP nanoflowers are shown to play a direct role in promoting angiogenesis, cell proliferation, and chemotaxis, which can be exploited for wound healing applications.

kanamycin, streptomycin, polymyxin B), and antagonistic (chloramphenicol) effects against pathogens.[32] Antibacterial activity of AgNPs increased with decreasing size of the nanoparticles.[102] Size-dependent antimicrobial activity of AgNPs was also observed with *Pseudomonas* sp., *Penicillium* sp., and *Aspergillus niger*.[101] The size-dependent microbial activity of AgNPs was in fact due to the size-dependent release of silver ions.[103]

AgNPs unleash multiple strategies to be effective as a broad-spectrum antimicrobial agent. They are oxidized in aqueous solutions in the presence of oxygen, resulting in the release of silver ions under acidic conditions. It must be noted that it is not the AgNPs that are responsible for the antimicrobial action, it is the silver ions that they carry and release.[103] Electrostatic interactions between silver ions (positive) and the cell membrane (negative) of microorganisms result in a fatal interaction. For example, a majority of AgNPs are localized on bacteria cell membranes and induce a massive loss of intracellular potassium, a decrease in cellular ATP levels, and a rapid breakdown of proton motive force, resulting in cell lysis.[104] In addition, silver ions inactivate enzymes of the respiratory chain and TCA cycle by binding to amino acids with a thiol group and induce hydroxyl radical formation, resulting in bacterial cell death.[105] AgNP-mediated dephosphorylation of the tyrosine residues of bacterial proteins involved in the signal transduction pathway and in essential enzymes may also inhibit the growth of the organisms.[106] The formation of free radicals and radical-induced membrane damage causes microbial cell death.[99] It was thought that such a multifaceted mode of action would guard against the development of microbial resistance against AgNPs; however, there are reports suggesting that aggressive clinical use of AgNPs must be done with caution. Survival fitness of *E. coli* was increased at sublethal concentrations of AgNPs,[103] and microbial resistance to AgNPs was developed by de novo mutations in existing genes.[107] These results clearly show that more research is warranted in this direction. In addition to preventing infections, AgNPs also aid in faster and aesthetic wound healing.[108−110]

Antimicrobial wound dressing material was developed by self-assembling AgNPs on the surface of bacterial cellulose and demonstrated to be effective in controlling the growth of *E. coli*, *S. aureus*, and *P. aeruginosa*.[111] Mussel-inspired poly(dopamine methacrylamide-*co*-methyl methacrylate, MADO) nanofibers were surface functionalized with AgNPs in a one-step electrospinning process (Figure 4).[108] In this method, AgNPs were coated uniformly without any aggregation on the polymer surface, and the catechol redox chemistry used for the synthesis rendered the AgNPs insensitive to oxygen, endowing them with long-term antimicrobial activity. Studies of the release kinetics of Ag^+ from MADO-AgNPs showed 13% burst release on day 1, followed by a sustained release for 5 days in physiological conditions. MADO-AgNPs nanofibers effectively prevented the growth of Gram-negative *E. coli* as well as Gram-positive *P. aeruginosa* and *S. aureus*. Fibroblast cells treated with MADO-AgNPs for 72 h showed 85% viability compared to the untreated control. For in vivo studies, partial thickness skin wounds were made on the dorsal side of Wistar rats and covered with MADO-AgNP nanofibers. Wounds covered with MADO nanofibers or cotton gauze were used as controls. After 15 days, the wounds treated with MADO-AgNPs and MADO showed 92 and 65% healing, respectively, which was significantly higher than the healing rate observed with the wounds treated with cotton gauze (51%). These results show

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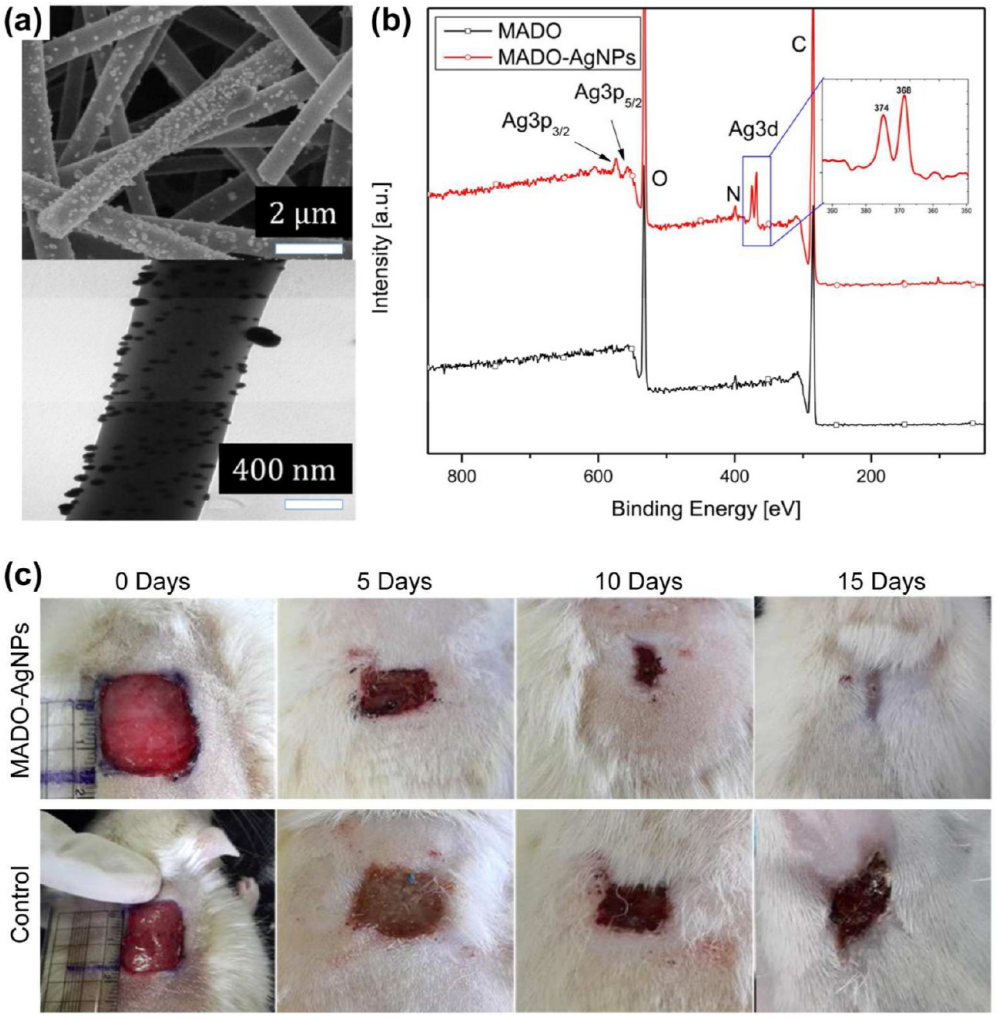

Figure 4. Mussel-inspired electrospun nanofibers loaded with silver nanoparticles (AgNPs) for wound dressing application. (a) SEM and TEM images of electrospun scaffold made from poly(methyl methacrylate-*co*-dopamine methacrylamide) (MADO) and AgNPs. (b) XPS showing the presence of AgNPs as evident by the Ag-related peaks. (c) Wound appearance at 0, 5, 10, and 15 days after grafting with MADO-AgNP and control nanofibers. Adapted and reproduced with permission.[108] Copyright 2015, American Chemical Society.

that the ECM-like property of MADO and the infection control properties of AgNPs contribute to faster wound healing.

In Sprague−Dawley rats, AgNPs showed a 17% improved healing rate compared to that of silver sulfadiazine at day 13; AgNP treatment accomplished complete wound healing 4 days before that of silver sulfadiazine.[112] While treating second-degree, deep-dermal burn wounds in humans, AgNPs showed complete wound healing 10−14 days earlier than with silver sulfadiazine.[113] Apart from faster wound healing, thermal wounds in mice treated with AgNPs showed minimum hypertrophic scarring and normal hair growth.[110] In acute burn and excision wound models, mice treated with nanohybrid AgNPs/nanoscale silicate platelets (AgNP/NSP) showed superior wound healing compared to mice treated with polymer-dispersed AgNPs, Aquacel (commercial wound dressing material with ionic silver), and silver sulfadiazine.[40] This is a significant observation given the fact that wound healing without scar formation is the most desirable outcome for patients. Currently, wound-dressing materials containing AgNPs are regularly used in clinical practice. Use of wound care products with AgNPs posing local or systemic toxicity due to silver ions is considered to be low or negligible;[114] however, significant efforts have been made to reduce the toxicity by improving the efficiency of nanoparticles so that the lowest concentration can be used with controlled release. Typical wound healing systems often consist of AgNPs and a polymer. A significant reduction in silver cytotoxicity was observed when AgNPs were combined with chitosan, which ensured control over its exposure to cells.[112] Combinations of silver nanoparticles with PVA and chitosan provided improved wound healing and infection control.[88] Uniform distribution and pH-dependent release was observed when AgNPs were incorporated in the electrospun fibers made of partially carboxymethylated cellulose.[35]

4.2. Gold Nanoparticles (AuNPs). Gold nanoparticles (AuNPs) are desirable due to their stability, custom size, and ease of surface functionalization. The light-absorbing ability of the AuNPs was used for tissue welding to facilitate healing of cut wounds.[115] Gold nanoshells with peak extinction (matching the near-infrared wavelength) were used as exogenous chromophores to absorb the near-infrared energy while welding surgically cut wounds.[115] The tensile strength of the welded site was equal to that of the uncut tissue, and histological examination showed good wound-healing response. Biologically inert AuNPs are normally functionalized before being used for wound healing. Antibiotics showed enhanced activity when

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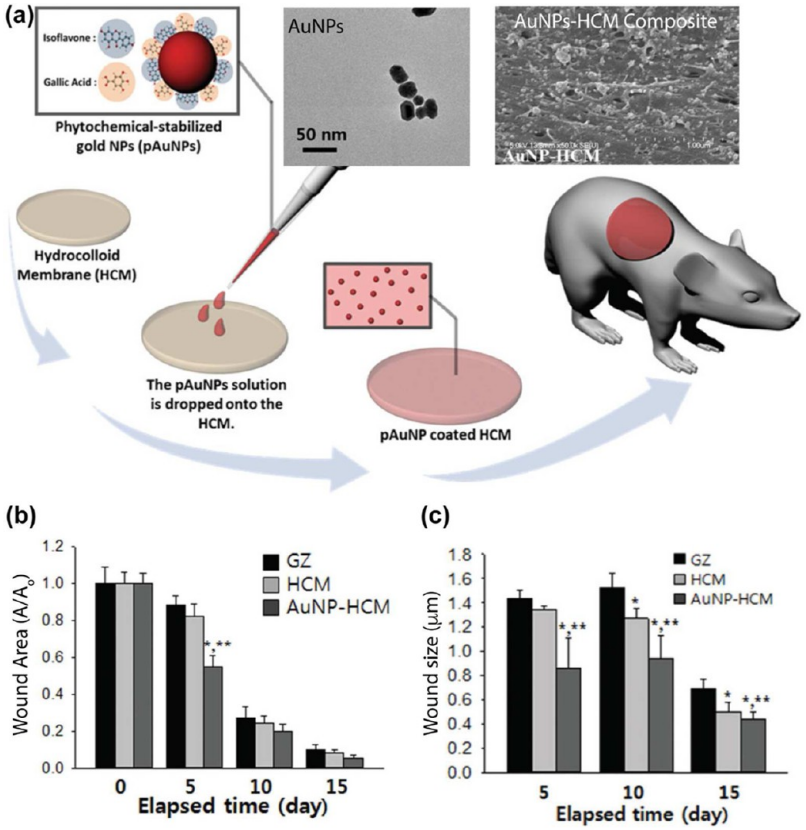

Figure 5. Gold nanoparticles (AuNPs) coated on a hydrocolloid membrane (HCM) for curing cutaneous wounds. (a) Schematic showing the fabrication of a nanocomposite wound healing patch from AuNPs and HCM. (b) Wound area and (c) wound size significantly decreases when treated with AuNP-HCM. Adapted and reproduced with permission.[128] Copyright 2015, Royal Society of Chemistry.

conjugated to AuNPs. Vancomycin conjugated to AuNPs could effectively inhibit the growth of vancomycin-resistant enterococci.[116] AuNPs capped with *p*-mercaptobenzoic acid and conjugated with a particular thiol group showed 99.9% inhibition of methicillin-susceptible *S. aureus* (MSSA) and MRSA.[117] Similarly, inactive amino-substituted pyrimidine (4,6-diamino-2-pyrimidinethiol) conjugated to AuNPs showed antibacterial activities against *E. coli* and *P. aeruginosa* by severely affecting membrane potential, ATP level, and binding of ribosomes to tRNAs.[118,119] The role of surface chemistry in AuNP-mediated microbicidal activity was investigated in detail by synthesizing AuNPs carrying different cationic functionalities varying in chain length and nonaromatic and aromatic characteristics. It was found that AuNPs with cationic and hydrophobic functional groups (e.g., *n*-decane end group) were the most effective against Gram-negative and -positive bacteria.[120] These studies highlight specifically how AuNPs can be useful in the treatment of infected wounds.

An AuNP-loaded polymeric network can further accelerate wound healing and assist with infection control. Compared with pure chitosan, the AuNP-chitosan nanocomposite showed enhanced proliferation of human fibroblasts in vitro. In male Sprague−Dawley rats, it showed improved healing of surgical wounds when compared to Tegaderm (commercial wound dressing material containing chlorhexidine gluconate) and bare chitosan. Also, hemostasis (as observed after 90 s) and wound epithelialization were more pronounced in the treatment with the AuNP-chitosan nanocomposite than with pure chitosan.[121]

In another study, negatively charged AuNPs and positively charged gold nanorods (AuNRs) were incorporated into a decellularized porcine diaphragm to produce a biocompatible scaffold suitable for wound healing. The diaphragm scaffolds incorporated with AuNPs and AuNRs showed enhanced cell proliferation and free radical generation, which appeared to be dependent on shape and concentration of the nanomaterial uses.[122] The possibility of a novel application for AuNPs in wound healing was indicated by controlled behavior of fibroblast cell detachment, patterning, and regrowth on artificially engineered AuNP-based surfaces that were triggered by nonthermal laser irradiation. AuNP-mediated cell detachment was evident because irradiation of fibroblasts on the control glass surface under the same conditions did not result in their detachment.[123] The age of the cell, intensity and duration of laser power, and AuNP patterning could be used for controlling the spatial organization of the cells for efficient wound healing.

Inappropriate inflammation due to oxidative stress is a primary reason for reduced wound healing in diabetes patients. Delivery of epigallocatechin gallate (antioxidant) and α-lipoic acid (ROS scavenger) in combination with AuNPs was shown to facilitate wound healing in a diabetic mouse model due to increased angiogenesis and reduced oxidation and inflammation.[124,125] Further enhancement in wound healing was observed when the same material was topically applied using a propulsion device. The enhanced result was possibly due to the deep cutaneous delivery, which might protect the compounds from the enzyme that are abundant in the wound surface.[126] Liposome encapsulation of the *Calendula officinalis* extract showed significantly enhanced wound healing in vitro when it was combined with AuNPs.[127]

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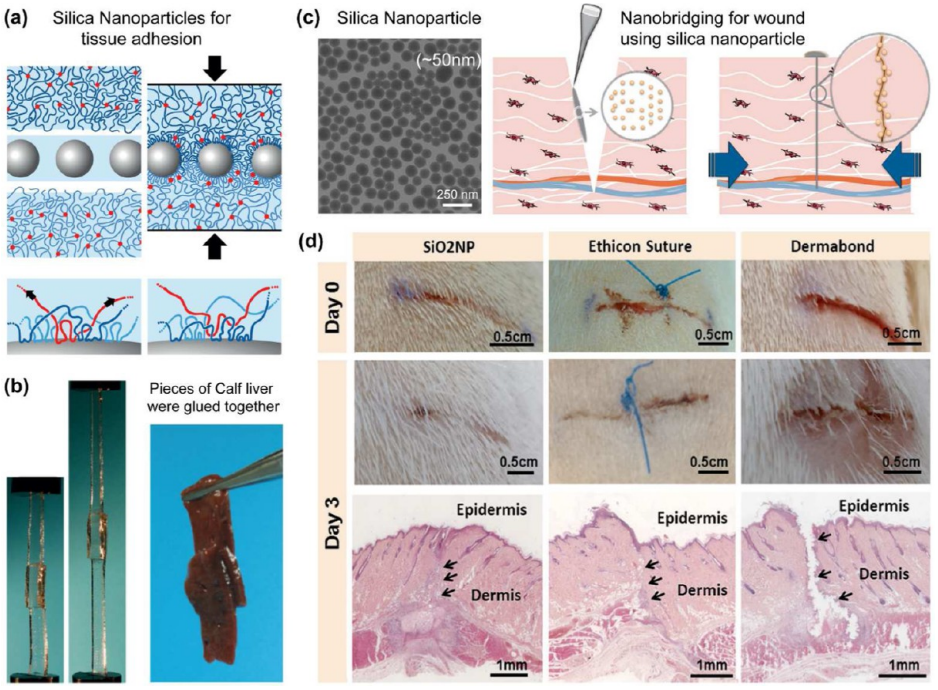

Figure 6. Silica nanoparticles for tissue adhesive. (a) Silica nanoparticles act as connectors between gel surfaces. Adsorbed polymer chains act as bridges between nanoparticles. (b) Hydrogel and calf liver glued together by spreading silica nanoparticle solution. (c) TEM image of silica nanoparticles (~50 nm). The concept of nanobridging for wound closure. A droplet of nanoparticle solution spread over the wound surface forms numerous connectors to link the wound edges together. (d) Wound healing ability of silica nanoparticles (SiO2NP), nonresorbable suture (Ethicon), and 2-octyl cyano-acrylate (Dermabond). (a,b) Adapted and reproduced with permission.[138] Copyright 2014, Macmillan Publishers Limited. (c,d) Adapted and reproduced with permission.[139] Copyright 2014, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Dressing the wounds with plain or pharmaceutically functionalized hydrocolloid membranes (polyurethane membrane coated with hydrophilic polymeric colloids) provide accelerated healing with reduced pain due to the membrane's mechanical characteristics, biocompatibility, and physiological stability.[128] The surface of a hydrocolloid membrane coated with AuNPs showed significantly enhanced wound healing abilities in eight-week-old Sprague–Dawley rats (Figure 5).[128] For example, the wound closure rate was significantly enhanced in the treated group (membrane coated with AuNPs) versus the control group (gauze or uncoated membrane). Significant increases in collagen, vascular endothelial growth factor, angiopoietins, and superoxide dismutase enzymes with concomitant decreases in matrix metalloproteinase 1 and TGF-β1 were observed in the group treated with the AuNP-coated membrane, indicating synergistic regulation of angiogenesis and connective tissue formation along with antioxidant effects.

In a recent study, AuNPs were immobilized and protected by polyvinylpyrrolidone on large 500 nm nanosilica to form a gold–silica core–shell structure.[39] The AuNPs were allowed to grow as nanoshells on the surface of SiO_2 until they were connected to each other. The wound healing capacity of this nanocomposite was studied by topical application on full-thickness skin excision wounds in adult male Sprague–Dawley rats with recombinant human bFGF as a positive control. The nanocomposite and bFGF-treated group had similar wound closure rates on days 7 and 14 postwounding. On day 18 after injury, nanocomposite treatment produced complete healing, whereas the wounds of the rh-bFGF treatment had not completely healed.[39]

Gene therapy for wound healing was investigated by delivering anti-microRNA (miRNA) oligonucleotides using AuNPs. Integrin β3 is an integral cell surface protein implicated in promoting cell migration and angiogenesis,[129,130] and vimentin is a major intermediate filament of the cytoskeletal system shown to be essential for wound healing.[131] Genes of these two proteins are negatively regulated by miRNA 378a (miR-378a). NIH/3T3 cells transfected with anti-miR-378a showed accelerated fibroblast migration, differentiation, and tube formation, and transgenic mice expressing anti-miR-378a showed enhanced wound healing.[132] Encouraged by these results, nanoparticle-based delivery of anti-miR-378a was attempted for enhanced wound healing in a mouse model. Thiol-modified anti-miR-378a fragments were conjugated to methoxy PEG thiol and coated on the surface of AuNPs. Punch wounds were made in wild type CD-1 mice on the backside of the neck, and a single dose of nanoparticles was administered in the area adjacent to the wound by intradermal injection. On day 4, wounds treated with AuNPs carrying anti-miR-378a showed better wound closure compared to that of the wounds treated with AuNPs carrying blank vector.[132]

5. CERAMIC-BASED NANOMATERIALS

A range of ceramic nanoparticles are investigated for wound healing and infection control (Table II). Ceramic nanoparticles are used for controlled delivery of thereputics due to a high surface-to-volume ratio and charged surface. Some ceramic nanomaterials include silica, silicate clays, bioglass, and zinc oxide nanoparticles. Because of the semicrystalline nature of these nanomaterials, ionic dissolution products of nanomaterials have also shown a positive influence on angiogenesis and wound healing.

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5.1. Silica Nanoparticles. The mesoporous nature of silica nanoparticles was considered an ideal property for delivering growth factors to facilitate the wound healing process. For example, in situ encapsulation of bFGF in mesoporous silica nanoparticles (MSNs) was performed by the water-in-oil microemulsion method.[133] The loading efficiency of bFGF in MSNs was 72%, and the release kinetics showed 50% release on day 8 and approximately 75% on day 15. The bFGF-loaded MSNs were able to enter the human umbilical vein endothelial cells and remained in the cytoplasm. Treating the cells with bFGF-loaded MSNs promoted cell proliferation, indicating that this is a promising system for wound healing.[133]

In another study, silica nanoparticles were used to release NO to facilitate the wound healing process. Silica nanoparticles with a secondary amine functional group were synthesized from tetraethoxysilane or tetramethoxysilane by the sol−gel method.[134] The secondary amino groups were subsequently converted to NO-releasing *N*-diazeniumdiolate groups by exposing the nanoparticles to elevated pressures of NO gas for 3 days. These particles were capable of releasing NO when exposed to water. The structure and concentration of silane precursors and the reaction conditions could be varied to obtain nanoparticles that differ in the quantity and duration of NO release.[134] Further control over the NO release could be achieved by incorporating the NO-releasing silicate nanoparticles into electrospun polyurethane fibers.[135] In another study, PEG and chitosan were incorporated during the sol−gel process to obtain NO-releasing nanocomposites.[136] Heating the nanocomposites facilitated the thermal reduction of nitrite due to the presence of glucose, resulting in the formation of NO-releasing silica nanoparticles. The trapped NO was released when exposed to water. NO-releasing silica nanoparticles increased the fibroblast proliferation and migration in vitro by promoting collagen deposition and angiogenesis in the wound area. Wounds treated with NO-releasing silica nanoparticles showed complete closure within 12 days after surgery. In contrast, complete wound closure was significantly delayed in the wounds treated with empty nanoparticles or untreated wounds. The wound closure percentage at day 7 relative to the initial wound size was significant in comparing the NO-treated group with the untreated group.[137]

Tissue adhesives are commonly used for efficient healing of cuts and surgical incisions. Currently available tissue adhesives that rely on in situ polymerization are problematic to use in clinical practice and are limited by toxicity, lack of strength, and swelling complications. Development of more efficacious tissue adhesives is further challenged by the fact that tissue joining should happen quickly and in the wet conditions of profuse bleeding. The tissue should also stay intact after adhesion while withstanding a constant flow of body fluid and, in some cases, constant tissue movements, as in heart muscles. Recently, a simple aqueous silica nanoparticle solution was developed that can be conveniently and efficiently used as a tissue adhesive for joining natural calf tissue ex vivo (Figure 6).[138] The same group has further refined it as a very interesting nanobrindging technology for rapid and strong closure and healing of deep wounds made in the skin and liver of rats.[139] In this method, a droplet of nanoparticle solution is spread over the wound surface of a tissue and brought into contact by gentle manual pressure. The nanoparticles are absorbed by the tissue to form numerous connectors and join the tissue together within an extraordinarily short period (approximately 1 min or less). Silica nanoparticles were synthesized by the Stöber method, and the tissue adhesion of nanoparticles was evaluated. The nanoparticle solution was spread on one edge of the wound, and the two edges were brought together and pressed into contact manually for less than 1 min to seal the wound. At day 7 after sealing, there was no evidence of wound reopening, pathological inflammation, or necrosis, indicating efficient healing. The scars formed after nanobridging were more aesthetic (less scar and more hair in the wounded area) in comparison with suturing or the use of cyanoacrylate glue. In addition, the nanoparticle solution was also applied on the bleeding injured area. There was no postsurgery bleeding syndrome, and histopathology done at day 3 postsurgery showed that hemostasis, biliostasis, and wound closure were achieved without affecting the liver function.[139]

Extremely fast release kinetics of the loaded drugs are a major limitation to the use of collagen in the fabrication of wound dressing material. For addressing this problem, drug was loaded in silica nanoparticles before incorporating them in a collagen-based nanocomposite hydrogel system.[140] Although direct loading of the drug in collagen hydrogels showed complete release in 24 h, the nanocomposite hydrogel system with the drug encapsulated in silica nanoparticles showed sustained release over a period of 7 days. Incorporation of silica nanoparticles also slowed the enzymatic degradation of collagen, which increases the durability of the dressing material by protecting the collagen from the metalloproteases that are abundant in the wound site.[140]

Wound healing is greatly influenced by the chemotactic movement of different cell types toward the wound site. Microtubules are part of the intracellular cytoskeleton, and their depolymerization enhances cell motility. It was recently discovered that the Fidgetin-like 2 gene in humans encodes a microtubule depolymerizing enzyme that affects cellular movement by severing the microtubules. Further, it was hypothesized that a small interfering RNA (siRNA) can mediate downregulation of Fidgetin-like 2, and this action should improve cell movement and, thereby, wound healing.[141] Hydrogel/glass composites were made using tetramethylorthosilicate, chitosan, and PEG, which contained silicate nanoparticles of 10 nm in size.[136,142] These silicate nanoparticles were encapsulated with the siRNAs targeted to the Fidgetin-like 2 gene (NPsiRNA-FL2). Full-thickness wounds and thermal burn wounds in mice were topically treated with single doses of NPsiRNA-FL2 suspension immediately after injury at day 0 or days 0 and 2. A significant decrease in the expression of the Fidgetin-like 2 gene in the wounds treated with NPsiRNA-FL2 indicated successful functional delivery of siRNA from the nanoparticles to the cells in the wounded tissue. Treatment of the wounds with NPsiRNA-FL2 accelerated wound closure in vivo, and the second treatment at day 2 after injury further accelerated the resolution of the excisional wound. Histopathology showed that the wounds were completely re-epithelialized by day 7, and hair follicles were clearly visible by day 10 in the NPsiRNA-FL2-treated wounds but absent in untreated wounds and wounds that were treated with nontargeted NPsiRNA.

5.2. Synthetic Silicate Clay. Nanosilicate clays are ultrathin nanoparticles consisting of silicates, magnesium, lithium, and sodium.[22−24] They have been used in biomedical applications including regenerative medicine, therapeutic delivery, wound healing, and bone tissue engineering. Considering the blood clotting ability of aluminosilicate clay, such as montmorillonite (MMT), MMT nanoparticles

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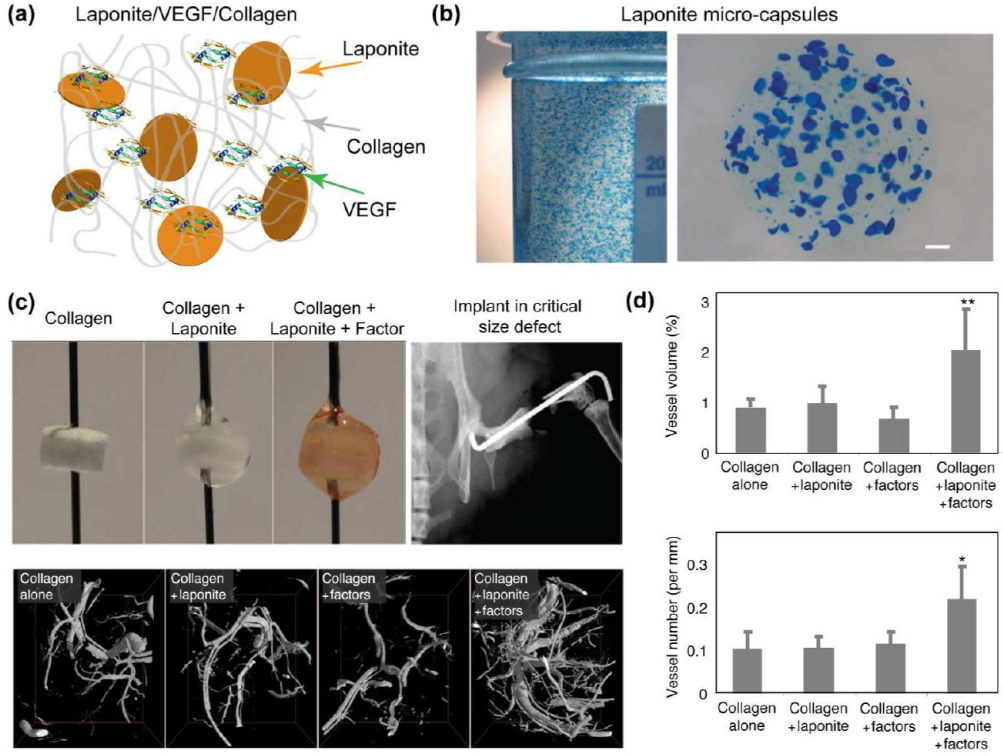

Figure 7. Nanosilicate for growth factor delivery to promote angiogenesis. (a) Schematic showing loading of VEGF on silicate nanoparticles (Laponite) in collagen gel. (b) Laponite/collagen gels support network organization of endothelial cells in vitro (scale bars = 100 μm). (c) VEGF-loaded Laponite-collagen gels induce angiogenesis in a murine femoral defect. (d) The sustained release of VEGF from Laponite significantly increases in vessel volume and vessel number. Adapted and reproduced with permission.[144] Copyright 2011, Wiley-VCH Verlag GmbH & Co.

functionalized with EGF (MMT-EGF) were evaluated for epithelial wound healing in vitro.[38] The role of EGF is implicated in cell proliferation and migration during the wound healing process. Incorporation of 0.3% for EGF was estimated to displace only a few cationic sites on the MMT surface, thus leaving enough Na^+ ions to carry out cationic activation required for blood clotting. They showed that treating the human spontaneously transformed keratinocyte cell line (HaCaT) with MMT-EGF nanocomposite resulted in activation of EGFR along the cell membrane, which promoted cell growth and migration. Western blot analysis indicated the activation phosphoinositide 3-kinase (PI3K)/AKT pathway and mitogen-activated protein kinase (MAPK) pathways in MMT-EGF-treated HaCaT cells. The gene expression of VEGF and thrombospondin indicated that MMT-EGF activates normal proliferation and migration signals in HaCaT cells. In vitro wound scratch assays showed that MMT-EGF treatment induced cell migration, resulting in complete wound closure.[38]

Nanosilicates, such as Laponite, are also explored for growth factor delivery to enhance angiogenesis.[143,144] Because of the presence of both positive and negative charges on the nanosilicate surface, they strongly interact with proteins such as VEGF (Figure 7).[144] In addition, nanosilicate addition to collagen stabilizes the nanocomposite network due to strong physical interactions. The nanocomposite hydrogels were also shown to promote the tubule formation of cultured endothelial cells. The presence of strong ionic interactions between Laponite and protein means no chemical conjugation is needed. Incorporation of VEGF within Laponite-collagen gel enhances angiogenesis in vivo. The ability of the nanocomposite gel to enhance angiogenesis can be used to promote wound healing.[144] In another study, nanosilicates have been used to release growth factor-rich stem cell secretome.[145] They fabricated nanocomposite hydrogels using photocrosslinking nanosilicates and gelatin methacrylate (GelMA). They showed that nanoclay can modulate the release of secretome and induce angiogenesis. Although the current study showed application of nanosilicate-based hydrogels for cardiac tissue engineering, it can be readily applied for wound healing applications.

Nanosilicate-based hydrogels are also explored for traumatic injuries requiring accelerated hemostasis.[146] Penetrating injuries result in loss of blood and, depending on the body parts involved, damage can happen to internal organs, which presents the risk of shock and infection. Injectable nanocomposite hydrogels may be introduced into a wound site to form a physiologically stable artificial matrix and promote the natural clotting cascade. They showed that injectable nanosilicate-gelatin hydrogels could be demonstrated to decrease in vitro blood clotting times by 77% and shown to form stable clot-gel systems under in vivo conditions.[146] The enhanced hemostatic ability of the nanoengineered hydrogel was attributed to the ability of nanosilicates to attract plasma components, providing a mechanism for clotting enhancement. It is expected that, after achieving hemostasis, this hydrogel may promote wound healing while delivering therapeutic agents.

Antimicrobial ciprofloxacin was intercalated in layered silicate MMT nanoparticles and gelled in biodegradable gelatin to prepare a composite hydrogel material with controlled release property for wound dressings.[147] Physical analysis showed that the interlayer space of MMT was 0.74 nm and slightly larger ciprofloxacin molecules could be intercalated by electrostatic interaction. The presence of MMT nanoparticles reduced the rate of biodegradation of the gelatin that will enable the hydrogel to remain intact for a longer duration for drug release.

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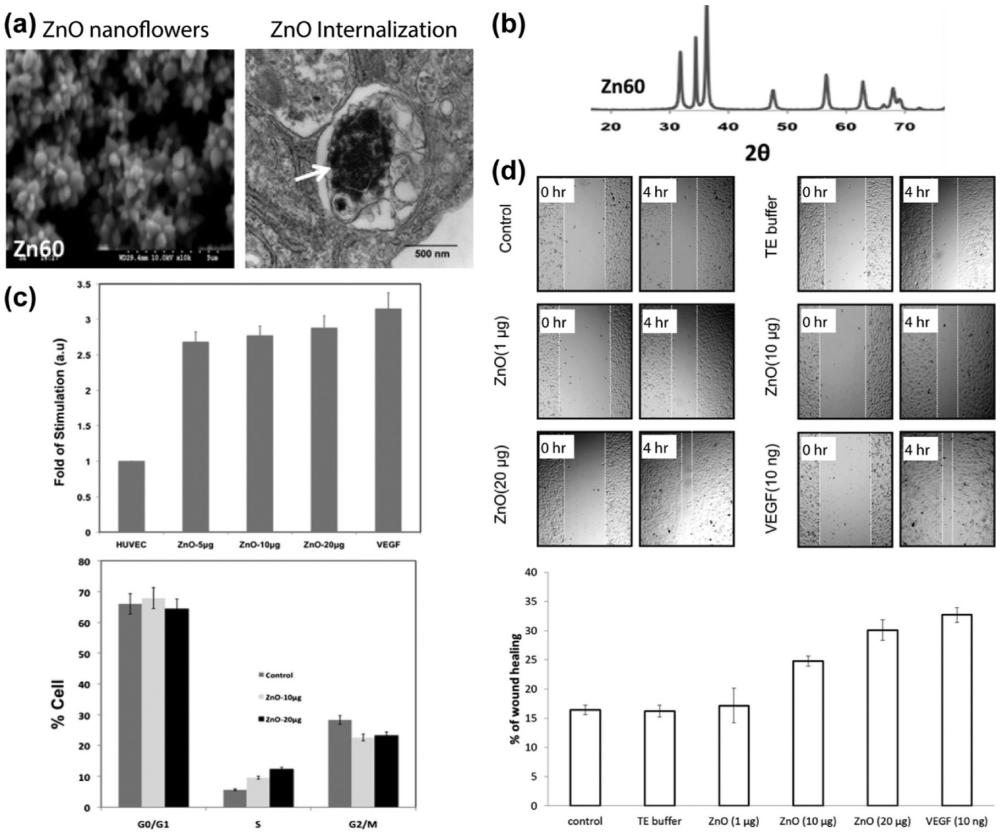

Figure 8. ZnO nanoflowers for wound healing applications. (a) SEM image of ZnO nanoflowers and cellular internalization of ZnO. (b) XRD data showing the diffraction pattern of ZnO. (c) Effect of ZnO concentration on stimulating cell proliferation and cell cycle. (d) Effect of ZnO nanoflowers on in vitro wound healing characteristics compared to those of VEGF. Adapted and reproduced with permission.[162] Copyright 2012, Royal Society of Chemistry.

The composite hydrogel will be useful for infection control in wound healing as it showed controlled release of 43% ciprofloxacin over a period of 150 h. In in vitro wound healing scratch assays, application of the composite hydrogels to human alveolar basal epithelial cells showed increased proliferation and cell migration toward the wound area in 24 h.[147]

In another study, mafenide (Maf) was intercalated between the nanosize layers of laponite (Lap) to be used as an antibiotic elution gel for the healing of burn wounds. This system was further modified by including Lap/Maf/Alg film. The film showed 211% water absorption capacity in comparison to 186% for alginate alone. However, both the gel and the film would need further modifications to overcome the problem of burst release and cytotoxicity.[148] The same research group has functionalized laponite by intercalation of arginine (Lap/Arg), glutamic acid (Lap/Glu), leucine (Lap/Leu), and lysine (Lap/Lys) amino acids.[149] Over a period of 24 h, release of amino acids and Mg^{2+} in simulated wound exudate fluid was found to be the maximum in Lap/Lys and Lap/Glu gels, respectively. Extracts from all four gels, except Lap/Glu, were found to be biocompatible. This data suggests that cyclization of glutamic acid to pyroglutamic acid in the presence of minerals might result in cytotoxic behavior. In vitro scratch assays in the presence of these extracts did not show any improvement in wound closure over the controls.[149] This is in contrast with an earlier report in which laponite was shown to be nontoxic at concentrations below 1 mg/mL and increased osteoblast growth in culture.[150]

Bacterial cellulose and MMT were combined to develop nanocomposites that can be used to fabricate wound dressing materials with superior infection control properties. Strong mechanical properties and a high water absorption capacity of the composite make it a desirable material for wound dressing. The cation exchange property of MMT was exploited to functionalize it with sodium, calcium, and copper ions. Bacterial cellulose sheets were completely impregnated with the functionalized MMTs in such a way that almost all of the pores were completely filled. Bacterial cellulose impregnated with Cu-MMT was found to be the most efficient nanocomposite, showing an 80−85% reduction in colony forming units (CFUs) against Gram-negative *E. coli* and Gram-positive *S. aureus*.[151]

5.3. Bioglass Nanoparticles. Bioactive glass nanoparticles are extensively investigated for biomedical applications, including bone tissue engineering, angiogenesis, and wound healing applications.[152−155] It is shown that ionic dissolution products of bioglass play a major role in stimulating cell proliferation, angiogenesis, and wound healing. However, the exact mechanism of interaction between the dissolved ionic and human cells are not fully understood. Recent studies have shown that bioactive glass nanoparticles can bind to soft tissue through apatite layers that are formed on their surface upon contact with cells.[156,157] It is shown that bioglass stimulates the secretion of angiogenic growth factors from human stromal cells and facilitates angiogenesis.[156] The 45S5 Bioglass (45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5) particles were shown to have the potential to increase angiogenesis in vitro

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and in vivo through their dissolution products.[156,157] Sol−gel-derived bioactive glass particles showed better bioactivity and biocompatibility than those of the melt-derived bioglass particles.[158] Recent studies have investigated bioglass nanoparticles for their ability to stimulate angiogenic growth in cultured human umbilical vein endothelial cells (HUVECs).[159] HUVECs treated with bioglass nanoparticles showed increased expression of pro-angiogenic genes. In vitro studies showed that bioglass nanoparticles also induce cell proliferation, angiogenic tube formation, and wound closure.[159] Recent study have shown stimulatory effects of bioactive microparticles on gap junction communication in HUVECs. They also showed that application of the dry powder of bioglass to the full thickness wounds in rats showed significantly higher wound closure ($P < 0.05$) than that of the control without bioglass application.[160]

5.4. Zinc Oxide Nanoparticles. Similar to AgNPs, zinc oxide nanoparticles (ZnONPs) also have antimicrobial activities. The efficacy of ZnONP activity strongly depends on the nanoparticle size and the release of free Zn^{2+} ions from ZnO colloidal solution.[161] On the basis of in vitro and in vivo wound healing and angiogenesis assays, it was shown that zinc oxide nanoflowers play a direct role in wound healing by promoting angiogenesis and chemotaxis of cells (Figure 8).[162] Wound dressing bandages fabricated from ZnONPs and chitosan/chitin showed enhanced blood clotting ability (in comparison with Kaltostat and blood alone) and antibacterial characteristics (in comparison with chitosan/or chitin). In vivo studies showed that nanocomposite bandages result in enhanced wound healing compared to bare wound and Kaltostat and facilitated collagen deposition and re-epithelialization.[163,164] Other studies showed that ZnONPs enhance fibroblast cell proliferation and can be used for wound healing applications.[165] As per the FDA, ZnO is a generally regarded-as-safe (GRAS) substance, and it is used to treat open wounds and rashes. However, research on the safety profile of ZnO when used with nanoparticles remains inconclusive with contradicting results.[166]

6. EMERGING TRENDS AND FUTURE PROSPECTS

A diverse range of new engineered nanomaterials have been developed and tested in the past few years, revealing unique property combinations for biomedical applications. Carbon-based nanoparticles, such as graphene, have been extensively investigated for tissue engineering applications. Despite interesting characteristics and strong potential, only limited studies have investigated graphene for wound healing and infection control applications. Graphene has strong potential for wound healing as it has a large water absorption capacity, antibacterial activity, and the capacity to add mechanical strength to the composites.[167,168] Graphene oxide nanoparticles (GONPs) showed higher antibacterial activity against *E. coli* when compared with reduced graphene oxide, graphite, and graphite oxide.[169] Extremely sharp edges of the graphene oxide nanowalls deposited on a stainless steel substrate could cause damage to the cell membrane by direct contact and bring down bacterial survival as much as 95% within an hour in comparison that of a bare stainless steel substrate used as control.[170] It was reported that graphene nanosheets might limit bacterial growth through enhanced lipid peroxidation under the influence of ROS.[171] Although the zero-dimensional fullerenes and one-dimensional carbon nanotubes enter the cells by penetration or endocytosis, the two-dimensional graphene oxides cut through the cell membranes of *E. coli*, causing lethal damage to cellular integrity.[172] Additional damage is caused by the extraction of membrane lipids, which is facilitated by the unique two-dimensional structure of graphene oxide with sp2 carbons. Such antimicrobial activity through physical damage could help to avoid the development of microbial resistance to nanoparticles.

In addition, GONPs can be photothermally activated using a near-infrared (NIR) laser. Activated GONPs showed more pronounced inhibition of bacterial (*S. aureus* and P. *aeruginosa*), yeast (*Saccharomyces cerevisiae* strain 20207), and fungal (*Candida utiliz* strain 20260) growth than GONPs.[173] For studying the effect of activated GONPs on infected injuries in vivo, wounds were made on thoracic and lumbar regions of albino mice and infected with *S. aureus*. Treatments were started after the infection spread on the wound surface and continued every day. First, a suspension of GONPs was applied, followed by Nd:YAG laser (NIR laser, 1064 nm) irradiation for 180 s. On day 12, it was clear that the infected wounds treated with GONPs and laser showed improved healing compared to the untreated wounds and the wounds treated with laser alone.[173]

Furthermore, multicomponent biomaterials can combine multiple characteristics that are required to facilitate wound healing and infection control. For example, multicomponent biomaterials consisting of chitosan, gelatin, and fibrin nanoparticles; each of these individual components has been shown to facilitate wound healing, infection control, homeostasis, and therapeutic delivery. It is expected that future studies will focus on multifunctional and multicomponent biomaterials.

Additive tissue manufacture is another emerging area that can be used for wound healing applications. One of the challenges in wound healing is vascularization, but appropriate patterning of the vascularized structure and accelerated wound healing can be achieved. Three-dimensional bioprinting technology can be used to print different types of cells in complex architecture. Spatiotemporal patterning of cells can significantly aid in cellular reorganization, vascularization, and re-epithelialization that are prerequisite for complete wound healing.

Finally, a very important aspect of wound healing is developing nanomaterial strategies that could minimize the chances of sepsis, a potentially life-threatening complication of an infection. For example, severe burn injury imposes a high risk for the development of sepsis, delayed wound healing, and increased mortality.[174] Sepsis initiates a complex interplay of host pro-inflammatory and anti-inflammatory processes, and there are competing theories that define host immune response to sepsis.[175] While designing new materials, care must be taken to determine whether the material has immunomodulatory properties and whether patients have entered an immunosuppressive phase of sepsis. Finally, it would be critical to make such assessment of engineered nanomaterial response at the human level because of the lack of similarity in the human and mouse genomic response to injury.

7. CONCLUSIONS

A range of engineered nanomaterials has been developed to improve clinically relevant therapeutic approaches for infection control and faster healing. Engineering nanomaterials, such as nanofibrous and nanocomposite scaffolds loaded with drugs, growth factors, and/or cells, are attractive materials because they can accelerate wound healing and aid in infection control to achieve faster healing. As new bioactive nanomaterials including ceramics and metallics emerge, it is possible to mimic

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some of the physical and chemical properties of native tissues. These bioactive nanomaterials not only aid in wound healing but also play important roles in infection control. In addition, advanced manufacture and development of multicomponent systems are expected to aid in designing the next generation of wound-healing nanomaterials.

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Notes

The authors declare no competing financial interest.

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