



# Nanomaterials for application in wound Healing: current state-of-the-art and future perspectives

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## Abstract

Nanoparticles are the gateway to the new era in drug delivery of biocompatible agents. Several products have emerged from nanomaterials in quest of developing practical wound healing dressings that are nonantigenic, antishar stress, and gas-exchange permeable. Numerous studies have isolated and characterised various wound healing nanomaterials and nano-products. The electrospinning of natural and synthetic materials produces fine products that can be mixed with other wound healing medications and herbs. Various produced nanomaterials are highly influential in wound healing experimental models and can be used commercially as well. This article reviewed the current state-of-the-art and briefly specified the future concerns regarding the different systems of nanomaterials in wound healing (i.e., inorganic nanomaterials, organic and hybrid nanomaterials, and nanofibers). This review may be a comprehensive guidance to help health care professionals identify the proper wound healing materials to avoid the usual wound complications.

**Keywords** Electrospinning · Nanomaterials · Wound healing

## Introduction

Nanomaterial-based wound healing is a significant tool that treats and prevents wound infections with diverse advantages versus standard-of-care (SOC) [1]. Wounds are the “silent

epidemic” that impairs the patients’ quality-of-life (QoL) [2]. In 2018, an economic analysis of acute and chronic wounds showed that around eight million beneficiaries suffered from  $\geq 1$  type of wound or related infection [3]. Ideal wound dressings are exudate-absorbents with high swelling capacity and porosity, good water vapour transmission rate (WVTR), antibacterial, and antiinflammatory properties. They show excellent elasticity and flexibility, drug loading capacity, tensile strength, spreadability, and provide a moist wound environment that accelerates healing, but most of the available dressings do not have some of these characteristics [4–7]. Table 1 lists the currently used dressings with their advantages and disadvantages in wound healing [8, 9]. Conventional wound care (e.g., herbal medicines, honey, bandages, and dressings) leaves scars regardless of the aesthetical as well as the plausible functional modifications [10–12].

Honey exhibits interesting immunostimulatory, antimicrobial, antioxidant, and antiinflammatory actions in wound healing (Table 1) [13]. However, honey displays some disadvantages or adverse effects upon its topical use in wounds. For example, honey-impregnated dressings may be hard to prepare; high temperatures make it more fluid; transient stinging sensation may occur; it may increase the blood glucose concentration in diabetic patients at large wounded areas; excessive application may dehydrate tissues; and

## Key points

- Tailored wound nanobandages as well as inorganic/natural polymer/antibiotic-based nanocomposites in combination with biomolecules and growth factors, may be a successful strategy in wound healing.
- International health guidelines should consider the high cost, structural defects, physical stability, mechanical durability, and toxicity of the synthesised nanoparticles for wound healing.

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**Table 1** The currently available wound dressings, their advantages, and disadvantages/limitations in wound healing

Wound Dressing	Advantages	Disadvantage(s)/Limitation(s)	Reference(s)
<i>Woven gauze</i>	<ul style="list-style-type: none"> <li>– Absorbs wound exudate</li> <li>– Allows the wound to form an eschar</li> </ul>	<ul style="list-style-type: none"> <li>– Difficult to remove</li> <li>– Cause mechanical debridement and/or wound trauma</li> <li>– Formation of granuloma due to woven gauze residuals</li> <li>– Releases lint</li> </ul>	[25, 26]
<i>Nonwoven gauze</i>	<ul style="list-style-type: none"> <li>– Utilised as a primary/secondary wound dressing on infected and noninfected injuries, large/irregularly shaped wounds, or in packing strips to prevent premature wound closure</li> <li>– Prevents wound exudate</li> <li>– Possesses greater absorbency</li> <li>– Nonocclusive</li> <li>– ↑ permeability</li> </ul>		[25]
<i>Semipermeable film</i>	<ul style="list-style-type: none"> <li>– Transparent</li> <li>– Provides a compatible, superficial, and visual wound inspection</li> <li>– ↑ epithelialisation</li> </ul>	<ul style="list-style-type: none"> <li>– Not suitable for wounds with major exudate</li> </ul>	[27]
<i>Hydrocolloids</i>	<ul style="list-style-type: none"> <li>– Comprise sodium carboxymethylcellulose (NaCMC) and gelatine (i.e., gel-forming substances)</li> <li>– The hydrocolloid fiber at contact with an exudate produces a gel, allowing painless evacuation; suited to shallow wounds and cavity wounds</li> <li>– May be left on wounds for 7 days</li> </ul>	<ul style="list-style-type: none"> <li>– Excessive amounts of exudate may lead to maceration</li> <li>– Possible overgranulation</li> <li>– Not recommended in case of suspected anaerobic infection</li> <li>– Adhesive hydrocolloids may cause fragile friable skin trauma upon removal</li> </ul>	[28]
<i>Foam dressings</i>	<ul style="list-style-type: none"> <li>– Used as a secondary dressing for wound packaging</li> <li>– Could be kept on wound site up to one week, depending on the level of exudate</li> </ul>	<ul style="list-style-type: none"> <li>– Undesirable odour after removal</li> <li>– A hydrofiber dressing needs a supportive secondary dressing</li> <li>– Not suitable for dry wounds</li> </ul>	[29]
<i>Alginates</i>	<ul style="list-style-type: none"> <li>– Produced from several types of algae</li> <li>– Available as ribbon, flat sheets, or rope</li> <li>– Appropriate for shallow/cavity wounds</li> </ul>	<ul style="list-style-type: none"> <li>– Not suitable for the debridement of dry eschar</li> <li>– Inapplicable to low-level exudate wounds due to the risk of dry wound bed</li> <li>– Painful to remove</li> </ul>	[29]
<i>Hydrogels</i>	<ul style="list-style-type: none"> <li>– Available as an amorphous gel in a tube (used in cavity wound), flexible sheets, and hydrogel-impregnated gauze</li> <li>– ↑ autolytic debridement <i>via</i> the rehydration of eschar and slough</li> <li>– Nonadherent</li> <li>– Relieve pain</li> <li>– Create and maintain a moist environment</li> </ul>	<ul style="list-style-type: none"> <li>– Unfavourable for infected wounds</li> <li>– Require a secondary supportive dressing</li> <li>– Maceration occurs in case of high-exudate wounds</li> <li>– Amorphous gels require secondary dressing</li> <li>– Need frequent application</li> </ul>	[29]
<i>Hyaluronic acid</i>	<ul style="list-style-type: none"> <li>– Antimicrobial</li> <li>– ↑ porosity</li> <li>– Indicated for oedema and water absorption ulcers with diabetic foot ulcers</li> </ul>	<ul style="list-style-type: none"> <li>– Limited cell adhesion/proliferation</li> <li>– Low mechanical stability</li> <li>– Expensive</li> </ul>	[30]
<i>Charcoal dressing</i>	<ul style="list-style-type: none"> <li>– Comprises of activated charcoal</li> <li>– Management of complex injuries with discharges, purulent, contaminated bacterial infection, and unpleasant scent</li> </ul>	<ul style="list-style-type: none"> <li>– Some types do not maintain a moist wound environment</li> <li>– Needs a secondary dressing tape for attachment</li> </ul>	[29]

Table 1 (continued)

Wound Dressing	Advantages	Disadvantage(s)/Limitation(s)	Reference(s)
<i>Silver dressing (e.g., foams, alginates, films, mesh, hydrocolloids and gels)</i>	<ul style="list-style-type: none"> <li>– Broad-spectrum antibacterial</li> </ul>	<ul style="list-style-type: none"> <li>– May require a secondary dressing</li> <li>– Transient skin staining</li> <li>– Burning sensation</li> <li>– Contraindicated in patients who are sensitive to silver</li> <li>– Painful</li> <li>– Wounds do not heal rapidly with adherent dressings</li> </ul>	[29]
<i>Paraffin or petroleum gauze (e.g., white or soft paraffin and for medicinal antiseptic mesh, cotton, ray, viscose or gauze)</i>	<ul style="list-style-type: none"> <li>– Paraffin Gauze dressings help moisturise oily skin</li> </ul>		[31]
<i>Medical-grade honey dressings</i>	<ul style="list-style-type: none"> <li>– Available as gels, ointments, and sheets</li> <li>– Indicated for infected/highly contaminated and malodorous wounds</li> </ul>	<ul style="list-style-type: none"> <li>– Contraindicated in patients who are sensitive to bee venom</li> <li>– Diabetic patients require monitoring because open wounds absorb glucose and fructose</li> <li>– Require frequent changing (i.e., honey is diluted and increasing exudate levels)</li> <li>– Burning sensation</li> <li>– May require a secondary dressing</li> <li>– Require 6–12 months of constant wear for better outcomes</li> </ul>	[29]
<i>Silicone dressings</i>	<ul style="list-style-type: none"> <li>– Soft and noninvasive</li> <li>– Suitable for hypertrophic scars and keloids</li> <li>– Self-applied at home</li> </ul>		[32]
<i>Skin substitutes (e.g., autografts, acellular xenografts, and autografts)</i>	<ul style="list-style-type: none"> <li>– Replace the damaged skin</li> <li>– Require less vascularised wound bed</li> <li>– ↓ scar formation</li> <li>– ↑ dermal components of the healed wound</li> </ul>	<ul style="list-style-type: none"> <li>– Liable to rejection</li> <li>– Possible transmission of infection</li> <li>– Limited lifespan</li> </ul>	[8]
<i>Traditional/passive dressings (e.g., gauze, bandages, wool dressings, and plaster)</i>	<ul style="list-style-type: none"> <li>– Protect the wound from foreign impurities and other contaminants</li> <li>– Control bleeding</li> <li>– Absorb exudate</li> <li>– Provide cushion</li> </ul>	<ul style="list-style-type: none"> <li>– Require frequent changing</li> <li>– Do not offer a moist wound environment</li> <li>– Damage the skin and cause pain as well as bacterial invasion</li> </ul>	[9, 33, 34]
<i>Interactive dressings (e.g., films, membranes, sprays, and sponges)</i>	<ul style="list-style-type: none"> <li>– Provide a moist environment at the wound area</li> <li>– ↑ reepithelialisation</li> <li>– Function as a barrier against pathogens</li> <li>– Good mechanical properties</li> <li>– ↑ water vapour transmission rate (WVTR)</li> <li>– Synthesised from natural polymers, such as pectin, collagen, alginate, cellulose, and collagen</li> <li>– Biocompatible and biodegradable</li> <li>– ↑ patient adherence</li> <li>– Deliver nutrients, growth factors, stem cells, and plant extracts</li> </ul>	<ul style="list-style-type: none"> <li>– Limited antibacterial activities</li> </ul>	[35]
<i>Bioactive dressings (e.g., wafers, nanofibers, sponges, hydrogels, foams, and transdermal patches)</i>		<ul style="list-style-type: none"> <li>– No obvious limitations</li> </ul>	[36, 37]

pollen/bee proteins in the honey may lead to hypersensitivity [14–16]. Limitations to these traditional materials besides restitutio ad integrum (i.e., the delay of tissue integrity restoration) aggravate wounds, especially chronic wounds [17]. Therefore, potential wound healing materials would boost the clinical outcomes [18].

Innovative polymeric nanofibers, polymeric nanoscaffolds, and nanoceria have emerged in the management of wound healing [19, 20]. Nanomaterials of natural origin and drug delivery vehicles are fit for cellular responses, penetrability, and active drug delivery in wound healing because of the high surface area-to-volume ratios and their nano size [21, 22]. Biocellulose functionalised with silver nanoparticles (AgNPs) act as an effective coating against Gram-negative bacteria and accelerate open wound healing [23]. Silver nanoparticle-coated polyester-nylon dressings were highly biocompatible, showed antibacterial efficacy, facilitated the normal development of human cells in-vitro, and exhibited a normal biodistribution with low toxicity in-vivo [24]. The currently available reviews may have focused only on one or two nanotechnology systems in wound healing (e.g., diabetic ulcers). Herein, we outline the different systems of nanomaterials in wound healing (i.e., inorganic nanomaterials, organic and hybrid nanomaterials, and nanofibers) (Fig. 1). We also shed light on the main concerns regarding the future use of nanomaterials in wound healing.

### Inorganic/organic nanocomposites in wound healing

Inorganic/organic nanocomposite scaffolds have lured attention because of displaying unique antibacterial and mechanical properties upon blending an inorganic nanoparticle with a supporting polymer matrix (Table 2) [38,

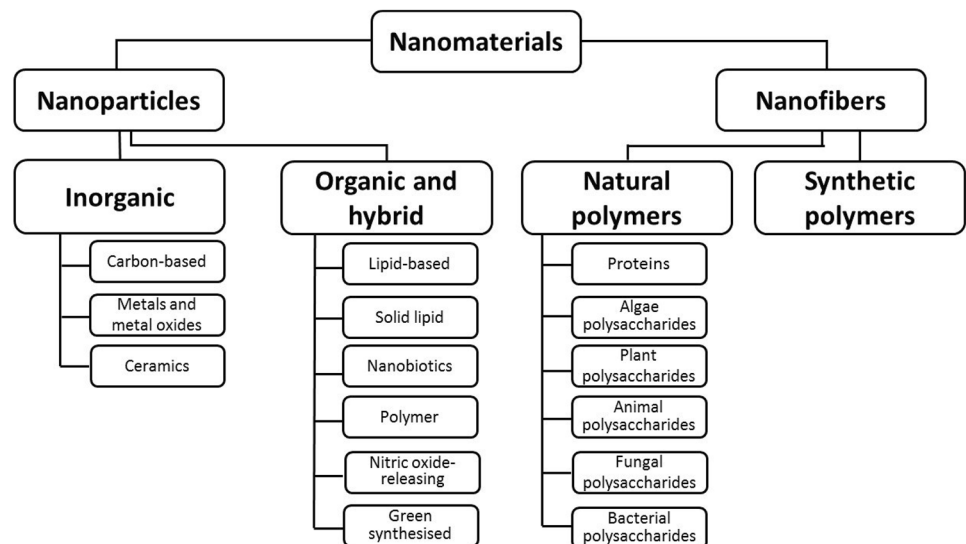
39]. Inorganic/organic nanocomposites have met the increasing demands of wound healing due to their nature, their inorganic/organic material ratio, and the size and distribution of the inorganic nanoparticles in the polymer matrices [40]. For example, the intermediate-modified gold nanoparticles (AuNPs) combined with polycaprolactone (PCL)/gelatin nanofibers are active against multidrug resistant (MDR) bacteria in-vivo [41]. Electrospun scaffolds of copper sulfide (Cu<sub>2</sub>S) nanoparticles with polylactic acid (PLA)/PCL polymers heal diabetic full-thickness skin wounds and significantly stimulated angiogenesis in-vivo [40].

Natural (e.g., dextran, chitosan, and alginates) and synthetic polymers (e.g., poly[ε-caprolactone] and poly[acrylic acid] [PAA]) are utilised to fabricate skin tissue engineering scaffolds [53–55]. While natural polymers are biocompatible and enzymatically biodegradable, their strength is inadequate, and they exhibit uncontrolled degradability. The structural, mechanical as well as the chemical properties of synthetic polymers are controllable. However, low biocompatibility, limited ability to promote wound healing, loss of mechanical properties, and the production of toxic products during degradation, limit their application in wound management [40, 53, 56, 57].

### Inorganic nanoparticles and nanocomposites in wound healing

Attractive bionanocomposites incorporate a range of inorganic nanomaterials (e.g., carbon-based nanoparticles, metal and metal oxide nanomaterials, and ceramic nanoparticles) that have promising bioactive, mechanical, and bactericidal characteristics to accelerate wound healing (Table 3) [58]. Such criteria are based on surface charge and functionalisation, polydispersity index (PDI), dimension, and architecture.

**Fig. 1** A schematic representation of the discussed nanoparticles and nanofibers in the current review article



**Table 2** Examples of inorganic/organic nanocomposites in wound healing

Inorganic/Organic Nanocomposite	Reference
Polymer-based silver nanoparticles (AgNPs)	[42]
Polypropylene-G-poly(ethylene glycol) comb-type graft copolymers containing gold nanoparticles (AuNPs)	[43]
Poly-propylene polyethylene glycol (PPEG) membranes impregnated with Au and Au cobalt oxide nanoparticles (AuCoONPs)	[44]
Poly (3-hydroxy octanoate-co-3-hydroxy-10-undecenoate) (PHOU)-encapsulated Au clusters	[45]
Silver nanoparticles mixed with polypropylene-g-PEG (PP-g-PEG)	[46]
Iodinated poly-3-hydroxy butyrate (PHB)	[47]
AuNPs incorporated into the autooxidised soybean oil polymer	[48]
PLinaS-g-PEG-coating of magnetic iron oxide nanoparticles	[49]
AuNPs and CoONPs embedded into PP-g-PEG	[50]
AuNPs mixed with acrylic resins	[51]
AuNPs-embedded poly(propylene-co-imidazole)	[52]

Therefore, combining different inorganic nanoparticles would lead to desirable therapeutic effects [59].

### Carbon-based nanomaterials

Carbon-based nanomaterials (two-dimensional graphene, one-dimensional carbon nanotubes, zero-dimensional-structure fullerene, nanodiamonds, and diamond-like carbon) are involved in the four wound healing phases and are able to deliver antibiotics, antioxidants, growth factors or stem cells [60–64]. Carbon-based nanomaterials are used in tissue engineering, targeted drug delivery, and skin care due to their physicochemical properties and large surface area [63, 65]. The production of reactive oxygen species (ROS) in addition to the hydrophobic nature of carbon nanomaterials are responsible for their inherent antimicrobial activity [66–72].

#### (a) Graphene

Graphene oxide, graphite oxide, graphite, and reduced graphene oxide nanofilms have excellent antibacterial activities [73–76]. Graphene and graphene oxide strongly induce ROS-independent oxidative stress when interacting with bacteria [76–78]. In graphene, the arrangement of carbon atoms generates electrons that move to the cells of the microorganisms due to the potential of the cell membrane [79]. The graphene oxide nanofilm enriched with epoxy coating had higher biocompatibility, accelerated infected wound healing in mice, and killed *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) [80]. Graphene oxide with laser enhanced the healing of fungal and bacterial wound infections (Table 3) [63, 65, 81].

Chitosan-coated electrospun nanofibers are rising as materials for drug release, tissue engineering, and wound healing [82–87]. Chitosan-polyvinyl alcohol (PVA) nanofibers containing graphene impeded the proliferation of *E. coli* and *Agrobacterium* cells but

not yeast, by disrupting the DNA structure or other genetic material in mice and Van Beveren rabbits [79]. Graphene oxide/copper (Cu)-incorporated chitosan/hyaluronic acid composite significantly accelerated the healing of intractable bacterial wound infections with acceptable biocompatibility in-vitro and in-vivo [88]. Graphene dressing scaffolds-mesenchymal stem cell combination enhanced cutaneous wound healing and infection control *via* chemical and mechanical stimuli [89]. Notwithstanding these advantages, structural defects that occur during the production of graphene (e.g., hexagons that transform into pentagons and single/multiple vacancies) influence its intrinsic properties and therapeutic effects [90, 91].

#### (b) Carbon nanotubes

Single-walled and multiwalled carbon nanotubes significantly affect the bacterial membrane integrity, metabolic activity, and morphology *via* ROS and heavy metal residues [92–97]. Particularly, single-walled nanotubes show a higher antibacterial activity than multiwalled nanotubes because of their smaller size that provides a larger surface area and disturbs the bacterial membrane. A recent in-vitro study revealed that carbon nanotube-mercury composite has treated burn-related infections with significant antibacterial action against different *Acinetobacter baumannii* (*A. baumannii*) species. The carbon nanotube-mercury composite also increased the mRNA expression levels of platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and vascular endothelial growth factor A (VEGF) that are considered as wound healing factors [98]. Combinations of carbon nanotubes with AgNPs and titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) had higher antibacterial effect [99, 100]. Hydroxyl functionalised single-walled nanotubes posed an elevated antibacterial activity on *Paracoccus denitrificans* (*P. denitrificans*) [101]. Chitosan

**Table 3** The properties/actions and applications of carbon-based nanomaterials, metal and metal oxide nanomaterials, and ceramic nanoparticles in wound healing

Inorganic Nanomaterials	Distinctive Properties/Actions	Application(s)	Reference(s)
<p>1. Carbon-Based Nanomaterials</p> <p><i>Graphene-based materials (e.g., graphite, graphene oxide, graphene oxide, and reduced graphene oxide nanofilms)</i></p>	<ul style="list-style-type: none"> <li>- Excellent antibacterial activities</li> <li>- ↑ reactive oxygen species (ROS)</li> <li>- <b>Graphene oxide with laser:</b> ↑ healing of fungal and bacterial wound infections</li> <li>- <b>The graphene oxide nanofilm enriched with epoxy coating:</b> <ul style="list-style-type: none"> <li>✓ biocompatible</li> <li>✓ ↑ infected wound healing in mice</li> <li>✓ killed <i>Escherichia coli</i> (<i>E. coli</i>) and <i>Staphylococcus aureus</i> (<i>S. aureus</i>)</li> </ul> </li> <li>- <b>Chitosan-polyvinyl alcohol (PVA) nanofibers containing graphene:</b> impede the proliferation of <i>E. coli</i> and <i>Agrobacterium</i></li> <li>- <b>Graphene oxide/Cu)-incorporated chitosan/hyaluronic acid composite:</b> <ul style="list-style-type: none"> <li>✓ ↑ biocompatibility</li> <li>✓ ↑ healing of intractable bacterial wound infections</li> </ul> </li> <li>- <b>Graphene dressing scaffolds-mesenchymal stem cell combination:</b> <ul style="list-style-type: none"> <li>✓ ↑ cutaneous wound healing</li> <li>✓ ↑ infection control <i>via</i> chemical and mechanical stimuli</li> </ul> </li> </ul> <p><i>Disadvantages</i></p> <p>The production of graphene causes structural defects that influence its innate properties and therapeutic effects. These defects include:</p> <ul style="list-style-type: none"> <li>✓ hexagons transform into pentagons</li> <li>✓ single/multiple vacancies</li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing dressings</li> </ul>	[63, 65]; [73–81]; [88–91]

Table 3 (continued)

Inorganic Nanomaterials	Distinctive Properties/Actions	Application(s)	Reference(s)
<i>Carbon nanotubes (e.g., single-walled and multiwalled carbon nanotubes)</i>	<ul style="list-style-type: none"> <li>- Significantly affect the bacterial:               <ul style="list-style-type: none"> <li>✓ membrane integrity</li> <li>✓ metabolic activity</li> <li>✓ morphology</li> </ul> </li> <li>- <b>Carbon nanotube-mercury composites:</b> antibacterial effect against different <i>Acinetobacter baumannii</i> (<i>A. baumannii</i>) species</li> <li>✓ ↑ mRNA levels of epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor A (VEGFA)</li> <li>- <b>Combinations of carbon nanotubes with silver nanoparticles (AgNPs) and titanium dioxide nanoparticles (TiO<sub>2</sub>NPs):</b> higher antibacterial effect</li> <li>- <b>Hydroxyl functionalised single-walled nanotubes:</b> elevate antibacterial activity on <i>Paracoccus denitrificans</i> (<i>P. denitrificans</i>)</li> <li>- <b>Chitosan complexed with single-walled and multiwalled carbon nanotubes:</b> <ul style="list-style-type: none"> <li>✓ ↑ fibroblast proliferation</li> <li>✓ ↑ collagen deposition</li> <li>✓ ↑ tensile strength</li> <li>✓ ↑ reepithelialisation of wounds</li> </ul> </li> <li>- <b>The electrospun carbon nanotube/PVA/EGF composite dressing:</b> <ul style="list-style-type: none"> <li>✓ ↑ wound healing</li> <li>✓ controlled EGF release</li> <li>✓ ↑ fibroblasts</li> </ul> </li> <li><i>Disadvantages</i> <ul style="list-style-type: none"> <li>- Exposure to carbon nanotubes:               <ul style="list-style-type: none"> <li>✓ ↑ inflammation</li> <li>✓ ↑ genotoxicity</li> <li>✓ alters cell spreading</li> <li>✓ alters cell adhesion</li> <li>✓ alters cell viability and migration</li> <li>✓ alters the wound healing of dermal fibroblasts</li> </ul> </li> <li>- <b>Multiwalled carbon nanotubes:</b> <ul style="list-style-type: none"> <li>✓ ↓ DNA synthesis in human dermal fibroblasts</li> <li>✓ ↓ adhesion-related genes</li> <li>✓ damage the cytoskeleton while disturbing actin stress fibers</li> </ul> </li> <li>- <b>Low doses of topical multiwalled carbon nanotubes:</b> <ul style="list-style-type: none"> <li>- ↑ keratinocyte cytotoxicity</li> <li>- ↑ skin allergies</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> </ul>	<ul style="list-style-type: none"> <li>[92–95]</li> <li>[96–105]</li> </ul>

Table 3 (continued)

Inorganic Nanomaterials	Distinctive Properties/Actions	Application(s)	Reference(s)
<i>Fullerenes</i> (e.g., <i>Buckminsterfullerene</i> [ $C_{60}$ ], $C_{70}$ [ <i>ethylenediamine</i> ] <sub>8</sub> )	<ul style="list-style-type: none"> <li>- ↓ ROS and inflammation</li> <li>- ↑ wound closure</li> <li>- Support cell migration</li> <li>- Alter the release of harmful mediators from mast cells</li> <li>- Combat bacteria</li> <li>- <b>Fullerene water suspensions:</b> antibacterial activity against <i>Bacillus subtilis</i> (<i>B. subtilis</i>) in-vitro</li> <li>- <math>C_{70}</math>-<b>(ethylenediamine)</b><sub>8</sub> <ul style="list-style-type: none"> <li>✓ strong antibacterial activity against <i>E. coli</i></li> <li>✓ ↑ wound healing</li> <li>✓ regulates the immune response and the secretion of growth factors</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Hard-to-heal wounds</li> </ul>	[61, 107, 110]
<i>Nanodiamonds</i>	<ul style="list-style-type: none"> <li>- Biocompatible</li> <li>- Nontoxic</li> <li>- Excellent physical and adsorption properties</li> <li>- ↑ drug durability and the dispersion of water-insoluble drugs</li> <li>- ↑ wound healing</li> <li>- ↑ mechanical characteristics of the injectable hydrogels without affecting their thermosensitive gelation properties</li> <li>- Avoid damaging normal tissues</li> <li>- Able to formulate a biocompatible, thermosensitive, and multipurpose hydrogel</li> <li>- Able to formulate a delivery platform for the controlled release of biomolecules and growth factors</li> <li>- <b>The thermosensitive hydrogel using gelatin, chitosan, and nanodiamonds:</b> sustains the release of exogenous human VEGF</li> <li>- <b>Doxorubicin-loaded carboxylated nanodiamond-cellulose nanocomposite membrane:</b> greater doxorubicin concentrations with lower cytotoxicity</li> <li>- <b>Chitosan/bacterial cellulose composite films including nanodiamonds:</b> biocompatible and flexible as a wound dressing</li> <li>- <b>Electrospun chitosan-based biopolymers containing medical grade nanodiamonds and bacterial cellulose:</b> potentially suitable for wound healing</li> </ul>	<ul style="list-style-type: none"> <li>- Drug nanoformulations</li> <li>- Wound healing</li> </ul>	[111–120]



Table 3 (continued)

Inorganic Nanomaterials	Distinctive Properties/Actions	Application(s)	Reference(s)
<i>Diamond-like carbon coatings</i>	<ul style="list-style-type: none"> <li>- Chemically stable</li> <li>- Superior biocompatibility and mechanical properties</li> <li>- Antibacterial</li> <li>- Control inflammation</li> <li>- ↑ cell adhesion after the incorporation of different nanoparticles</li> <li>- ↑ bioactivity properties</li> <li>- <b>Diamond-like carbon film coatings enriched with Cu or Ag:</b> ↑ antibacterial activity against bacterial colonisation</li> <li>- <b>The bandage of diamond-like carbon-AgNPs-coated synthetic silk tissue:</b> eradicated almost all bacterial strains, including Methicillin-resistant <i>S. aureus</i> (MRSA)</li> <li>- <b>Diamond-like carbon impregnated with AgNPs:</b> <ul style="list-style-type: none"> <li>✓ ↑ angiogenesis</li> <li>✓ prevent bacterial colonisation of both <i>Staphylococcus epidermidis</i> (<i>S. epidermidis</i>) and <i>S. aureus</i></li> <li>✓ ↑ Ag ions</li> <li>✓ long-term tissue regeneration</li> </ul> </li> <li>- <b>Diamond-like carbon-TiO2 composite:</b> <ul style="list-style-type: none"> <li>✓ biocompatible</li> <li>✓ ↑ wound healing</li> <li>✓ astringent</li> <li>✓ antibacterial</li> <li>✓ ↑ cell adhesion</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> </ul>	[121–129, 131]
<b>2. Metal and Metal Oxide Nanomaterials</b> <i>Silver nanoparticles (AgNPs)</i>	<ul style="list-style-type: none"> <li>- Antiinflammatory activities</li> <li>- Broad spectrum bacterial</li> <li>- ↑ reepithelialisation</li> <li>- ↑ wound closure</li> <li>- ↑ ROS</li> <li>- ↑ bacterial clearance from infected wounds</li> <li>- ↓ cytokine release</li> <li>- ↓ lymphocytic infiltration</li> <li>- ↓ mast cell infiltration</li> <li>- No adverse effects</li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> <li>- Foam dressings</li> <li>- Textiles</li> <li>- Clothing</li> <li>- Food packaging</li> </ul>	[138, 144–148, 158–161]

Table 3 (continued)

Inorganic Nanomaterials	Distinctive Properties/Actions	Application(s)	Reference(s)
<b>Gold nanoparticles (AuNPs)</b>	<ul style="list-style-type: none"> <li>- High chemical stability</li> <li>- Simple synthesis</li> <li>- Absorb near infrared (NIR) light</li> <li>- ↓ activity of multidrug resistant (MDR) bacteria</li> <li>- ↓ bacterial adenosine triphosphate (ATP)</li> <li>- Antioxidant</li> <li>- ↑ transcutaneous codelivery of other drugs</li> <li>- ↑ collagen deposition</li> <li>- ↑ reepithelialisation</li> <li>- ↑ granulation tissue formation</li> <li>- ↑ wound closure</li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> <li>- Tissue repair</li> <li>- Smart drug delivery</li> </ul>	[22, 59, 162–168]
<b>Zinc oxide nanoparticles (ZnONPs)</b>	<ul style="list-style-type: none"> <li>- Bactericidal and bacteriostatic</li> <li>- ↑ ROS and apoptosis</li> <li>- ↑ aggregate stability</li> <li>- ↓ toxicity</li> <li>- ↑ permeability <i>via</i> the skin and lipid membranes</li> <li>- ↑ collagen synthesis</li> </ul>	<ul style="list-style-type: none"> <li>- Delayed wound healing and burns</li> </ul>	[59, 139, 173–177]
<b>Copper nanoparticles (CuNPs)</b>	<ul style="list-style-type: none"> <li>- ↑ wound closure</li> <li>- Regulate cells, cytokines, and growth factors involved in wound healing</li> <li>- ↑ proliferation of keratinocytes and fibroblasts</li> <li>- ↑ epithelialisation</li> <li>- ↑ collagen synthesis</li> <li>- ↑ angiogenesis</li> <li>- ↑ transforming growth factor beta (TGF-β), VEGF, matrix metalloproteinase-2 (MMP-2), hypoxia-inducible factor 1-α (HIF-1α), interleukin-10 (IL-10), and tumour necrosis factor alpha (TNF-α)</li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> </ul>	[181–183]
<b>Silica nanoparticles (SiNPs)</b>	<ul style="list-style-type: none"> <li>- Extracellular matrix remodelling</li> <li>- ↑ silicic acid</li> <li>- ↑ migration of skin fibroblasts</li> <li>- Maintain drug release</li> <li>- ↓ fibroblast toxicity</li> <li>- ↑ mechanical strength and stability of the hydrogel nanocomposites</li> </ul>	<ul style="list-style-type: none"> <li>- Wound dressings</li> <li>- Scaffold preparations</li> </ul>	[184–186]
<b>Titanium dioxide nanoparticles (TiO<sub>2</sub>NPs)</b>	<ul style="list-style-type: none"> <li>- Antiinflammatory and antibacterial activities</li> <li>- ↑ swelling and WVTR</li> <li>- ↑ hydrophilicity</li> <li>- High biocompatibility</li> <li>- Activation of factor XII (FXII)</li> <li>- ↑ PDGF, IL-8, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1-α), MIP-1-β, and VEGF</li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> </ul>	[188]

Table 3 (continued)

Inorganic Nanomaterials	Distinctive Properties/Actions	Application(s)	Reference(s)
<i>Super paramagnetic iron oxide nanoparticles (SPIONs)</i>	<ul style="list-style-type: none"> <li>- Broad spectrum antibacterial</li> <li>- Ease-of-amalgamation</li> <li>- Surface modification</li> <li>- ↓ toxicity</li> <li>- High biodegradability</li> <li>- ↑ wound healing ability of thrombin</li> <li>- ↑ half-life of thrombin</li> <li>- ↑ skin tensile strength</li> </ul>	<ul style="list-style-type: none"> <li>- Wound healing</li> <li>- Imaging contrast materials</li> <li>- Drug delivery vehicles</li> </ul>	[192, 194–197, 209]
3. Ceramic Nanoparticles			
<i>Bioactive glass ceramic-based nanoparticles</i>	<ul style="list-style-type: none"> <li>- Slowly release silicon and calcium ions at wound sites</li> <li>- ↑ expression of connexin 43 between endothelial cells and fibroblasts</li> <li>- ↑ cell proliferation and angiogenesis</li> <li>- ↑ HIF-1 and VEGF</li> <li>- Protect endothelial cells from hypoxia</li> <li>- <b>Encapsulated dense bioactive glass ceramic nanoparticles into gelatin-chitosan polymer:</b> <ul style="list-style-type: none"> <li>✓ ↑ alkaline phosphate activities</li> <li>✓ ↑ bone formation</li> </ul> </li> <li>- <b>The multifunctional poly-citrate-siloxane elastomer-based bioactive glass ceramic nanoparticles:</b> <ul style="list-style-type: none"> <li>✓ effective materials in bone tissue regeneration</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Bone tissue regeneration</li> <li>- Wound healing</li> </ul>	[204–207]

complexed with single-walled and multiwalled carbon nanotubes improved the tensile strength, deposition of collagen, proliferation of fibroblast, and the reepithelialisation of wounds, but with an increase in fibrosis in-vitro and in-vivo [97]. The electrospun carbon nanotube/PVA/EGF composite dressing accelerated wound healing in-vitro and in-vivo and displayed a controlled release of EGF with favourable activity to accelerate the growth of fibroblasts (Table 3) [102].

Exposure to carbon nanotubes induces inflammation and genotoxicity and affects the wound healing of dermal fibroblasts by altering cell spreading, adhesion, migration, and viability [103]. Multiwalled carbon nanotubes inhibited DNA synthesis and the levels of adhesion-related genes while damaging the cytoskeleton and disturbing actin stress fibers simultaneously in both NIH 3T3 murine fibroblasts and human dermal fibroblasts [104]. Low doses of topical multiwalled carbon nanotubes also induced keratinocyte cytotoxicity and aggravate skin allergies [105].

#### (c) *Fullerenes*

Fullerenes and their derivatives may target hard-to-heal wounds by reducing inflammation, combating bacteria, altering the release of harmful mediators from mast cells, supporting cell migration, and accelerating wound closure (Table 3) [61]. Fullerene water suspensions are adsorbed on the bacterial membranes of *Bacillus subtilis* (*B. subtilis*) and initiate ROS-independent oxidative stress in-vitro [106–109]. Buckminsterfullerene (known as  $C_{60}$ )—the most studied fullerene—is strongly hydrophobic and marginally water-soluble [106]. The fullerene derivative  $C_{70}$ -(ethylenediamine)<sub>8</sub> significantly inhibited *E. coli* and controlled the immune defense as well as the production of growth factors, accelerating wound healing in-vivo [110]. The amino groups on the ethylenediamine moiety form electrostatic interactions on the outer bacterial membrane, whereas the inner membrane strongly interacts with the  $C_{70}$  hydrophobic surface via hydrophobic interactions, triggering cytoplasm leakage [110].

#### (d) *Nanodiamonds*

Nanodiamonds are attractive for drug nanoformulations because they are small in size, biocompatible and nontoxic, possess excellent physical and adsorption properties, improve the durability of drugs, and facilitate the dispersion of water-insoluble drugs (Table 3) [111–115]. Nanodiamonds also accelerate wound healing while protecting normal cells/tissues [116]. They have the potential to formulate a thermosensitive, biocompatible, multipurpose hydrogel platform, and other

systems for the delivery of controlled release growth factors and biomolecules. Nanodiamonds improve the mechanical characteristics of the injectable hydrogels without affecting its thermosensitive gelation properties. For instance, the thermosensitive hydrogel using gelatin, chitosan, and nanodiamonds sustains the release of exogenous human VEGF [117]. Doxorubicin-loaded carboxylated nanodiamond-cellulose nanocomposite membrane exhibited greater doxorubicin concentrations with lower cytotoxicity in-vitro [118]. The chitosan/bacterial cellulose composite films including nanodiamonds were biocompatible and flexible as a wound dressing [119]. The electrospun chitosan-based biopolymers containing medical grade nanodiamonds and bacterial cellulose also were suitable for wound healing [120].

#### (e) *Diamond-like carbon coating*

Diamond-like carbon film carbon coatings are chemically stable and exhibit superior biocompatibility, mechanical properties, and antibacterial efficacy due to their hydrophobic nature that alters the cell membrane, causing bacterial death [121–125]. Diamond-like carbon controls inflammation, enhances bioactivity properties and cell adhesion, and reduces the attachment and growth of bacteria [126–128]. Diamond-like carbon film coatings enriched with toxic elements (e.g., Ag or Cu) possess higher antibacterial activity against bacterial colonies (e.g., *Staphylococcus epidermidis* [*S. epidermidis*] and *S. aureus*) that increase the risk of life-threatening bacteraemia [129–131]. The bandage of diamond-like carbon-AgNPs-coated synthetic silk tissue killed almost 100% of all bacterial strains, including methicillin-resistant *S. aureus* (MRSA) [132]. The diamond-like carbon impregnated with AgNPs activated angiogenesis and prevented bacterial colonisation of both *S. epidermidis* and *S. aureus* due to the rapid Ag ion release, allowing long-term tissue regeneration in-vitro [133]. The diamond-like carbon-TiO<sub>2</sub> composite was biocompatible, increased cell attachment, and improved wound healing in-vivo due to its astringent and antibacterial actions (Table 3) [134].

### **Metals and metal oxide nanomaterials**

Compared with the traditional wound healing agents (i.e., plant extracts, honey, and larvae), metal and metal oxide nanomaterials are more favourable because they possess better intrinsic qualities, such as catalytic, optical, and melting properties [135]. The nano size and shape, surface properties, porosity, and the ability of metals to resist

decomposition in aqueous solutions, contribute to their efficacy in biological applications [59, 136, 137]. Zinc oxide (ZnO), Au, Ag, and CuO have interesting physicochemical (e.g., lower melting points) and antibacterial properties due to their small size [138, 139]. Gold and Ag are famous by their unique ‘Surface Plasmon Resonance (SPR)’ property—a resonant oscillation of conductive electrons on the metal film when excited by a polarised light—that is controlled by the composition, shape, and size of nanoparticles. Surface-enhanced Raman spectroscopy (SERS), biomedicine, and photocatalysis as well as photothermal therapy gave much attention to the SPR phenomenon [140–143].

#### (a) *Silver nanoparticles (AgNPs)*

Metal-based nanoparticles such as AgNPs have wide medical and commercial applications. Other commercially available and daily products comprise AgNPs include: Aquacel Ag and CuraFoam AG Silver Foam dressings, textiles, clothing, and food packaging [138, 144, 145]. Silver nanoparticles have gained deep interests for wound healing applications due to their distinctive physicochemical, antibacterial, and antiinflammatory properties [146]. Silver nanoparticles enhance wound healing by reducing the release of cytokines, mast cell infiltration, and lymphocytes [147, 148]. Silver nanoparticle dressings are bactericidal because of the synergistic interaction between Ag ions and the bacterial cell wall, plasma membrane, DNA and proteins, and the enzymes of the electron transport system (Table 3) [145, 149–151].

Silver nanoparticle-incorporated cotton fabric and dressings increased bacterial clearance from infected wounds and significantly decreased the time of wound healing by approximately 72 h without observed side effects [152–157]. Conjugates of AgNPs-biopolymer (ABP) are synergistic, noncytotoxic, and Generally Recognized As Safe (GRAS) biomaterials in acute and chronic wounds (Fig. 2) [145]. Experimental models documented the synergism of AgNPs with natural rubber latex (NRL), keratin, collagen, silk, gelatin, chitosan, starch, cellulose, and hyaluronic acid [145].

The poly(methyl methacrylate-co-dopamine methacrylamide (MADO)-AgNPs wound dressings inhibited the growth of *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa* (*P. aeruginosa*). Using the MADO-AgNPs wound dressing resulted in complete skin wound healing in rats and increased epithelialisation within 2 weeks [158, 159]. Coupling of reduced graphene oxide with Ag-silver chloride (AgCl) nanoparticles generated more oxygen free radicals and improved wound healing with a broad-spectrum antibacterial activity. Reduced graphene oxide/Ag–AgCl nanomaterials accelerated the wound closure and ameliorated reepithelialisation in

mice after burn injury owing to the antiinflammatory and antioxidant properties of AgNPs [160, 161].

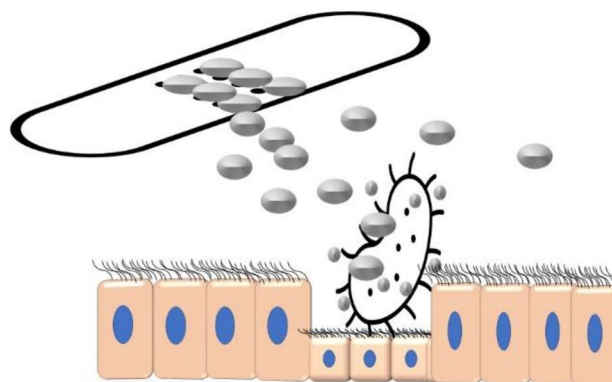
#### (b) *Gold nanoparticles (AuNPs)*

Gold nanoparticles (AuNPs) are used in tissue repair, wound healing, and smart drug delivery because of their simple synthesis and chemical stability, SPR, and their ability to absorb near infrared (NIR) light [22, 162–165]. Gold nanoparticles are antioxidants that help wounds heal by preventing the release of ROS (Table 3) [166]. Gold nanoparticles crossed the skin subcutaneous layer and spread over the epidermis layer, facilitating the transcutaneous codelivery of other drugs in-vivo [167]. The treatment of open wounds with AUNPs enhanced the deposition of collagen and granulation tissue formation, reepithelialisation, accelerating wound closure in Wistar Albino rat [168]. Gold nanoparticles ceased the activity of *P. aeruginosa* and *S. aureus* and suppressed both their energy metabolism and the function of adenosine triphosphate (ATP) synthase—an enzyme that creates ATP, the principal molecule for storing and transferring energy in cells [22, 59].

Crosslinking with collagen, gelatin, and chitosan offers AuNPs biocompatibility and biodegradability and increases free radical scavenging capacity [169, 170]. Chitosan-AuNPs composite improved haemostasis as well as epithelial tissue formation in injured rats, compared with chitosan only. The topical application of AuNPs-cryopreserved human fibroblasts reduced inflammation and increased both collagen deposition as well as the rate of overall healing of burn wounds (Table 3) [171, 172].

#### (c) *Zinc oxide nanoparticles (ZnONPs)*

Zinc oxide nanoparticles (ZnONPs) are popular inorganic nanomaterials in burns and delayed wound heal-



**Fig. 2** The antibacterial activity of AgNPs and the promotion of wound healing through reepithelialisation

ing, because they facilitate collagen synthesis and due to their bacteriostatic and bactericidal effects *via* disrupting the cell membrane and ROS [59, 139, 173–176]. Zinc is one of the most important trace elements that regulate burns and slow-healing wounds *via* the regulation of DNA and RNA polymerases, ribonuclease, and thymidine kinase [173]. Zinc is a stable element of > 2000 transcription factors and > 300 metalloenzymes that are essential for the metabolism of nucleic acids, proteins, and lipids as well as gene transcription in living cells [174]. Zinc oxide nanoparticles with constant valency of zinc ions had high aggregate stability and lower toxicity with the same high permeability *via* the skin and lipid membranes, compared with AuNPs and AgNPs [175, 177]. The chitosan-ZnONPs hydrogel wound dressing displays proper antibacterial activity with minimal toxicity [178]. The wound dressings of ZnONPs-collagen with 1% orange essential oil had excellent biocompatibility, inhibited the growth of bacteria, and improved wound closure in-vitro and in-vivo [179, 180]. Unfortunately, the intrinsic toxicity of ZnONPs hampers their use in wound healing, which requires further assessments (Table 3).

(d) **Copper nanoparticles (CuNPs)**

Copper-based nanomaterials are potential candidates to accelerate wound healing after thorough toxicity assessment. Copper nanoparticles (CuNPs) accelerated wound closure by stimulating the proliferation of keratinocytes and fibroblasts, epithelialisation, collagen synthesis, extracellular matrix remodelling, and angiogenesis in rats [181, 182]. Copper oxide-based dressings improved wound healing by producing important signal proteins (e.g., transforming growth factor-beta [TGF- $\beta$ ], hypoxia-inducible factor-1 alpha [HIF-1 $\alpha$ ], matrix metalloproteinase-2 [MMP-2], and VEGF), that are involved in wound healing in diabetic mice [182]. Copper nanoparticles-based nanocomposites organise the healing process by regulating cytokines, cells, and growth factors that aid in wound healing [183]. Chitosan-based copper nanocomposites exhibited antifungal and antibacterial properties, increased interleukin-10 (IL-10), VEGF, and TGF- $\beta$ 1, and decreased tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), enhancing wound healing in mice (Table 3) [183].

(e) **Silica nanoparticles (SiNPs)**

Silica-based wound dressings and scaffold preparations have gained significant attention in wound healing. Silica nanoparticles (SiNPs) helped the skin fibroblast cells proliferate and spread over the wounded area, releasing silicic acid and improving topical wound

repair in-vitro [184]. The size, condensation degree, and surface charge of soluble silicic acid control the behaviour of colloidal species—that coexist with silicic acid in SiNPs solution—and cellular effects [184]. Silica nanoparticle-collagen hydrogel nanocomposites in wound dressings reduced fibroblast toxicity, increased the coordinated effect of both SiNPs and collagen, and improved the mechanical strengths and stability against the degradation of the hydrogel (Table 3) [185].

Collagen scaffold dressing containing an antibacterial (i.e., mupirocin) and silica microspheres had synergistic efficacy in wound healing in Wistar Albino rats [186]. Silica microspheres maintained drug release (e.g., antibiotics) and enhanced the proliferation of fibroblast, whereas collagen adsorbed the exudates and rehydrated the necrotic tissues [185]. Likewise, silicon dioxide nanoparticles and polyvinylpyrrolidone (PVP) as a vehicle accelerated the migration and reepithelialisation, supporting the wound healing role of silica-based nanomaterials (Table 3) [187].

(f) **Titanium dioxide nanoparticles (TiO<sub>2</sub>NPs)**

Titanium dioxide nanoparticles (TiO<sub>2</sub>NPs) are suitable wound healing materials due to their antibacterial and antiinflammatory actions, high swelling and WVTR, hydrophilicity, and biocompatibility. Titanium dioxide nanoparticles accelerated wound healing *via* the production and secretion of monocyte chemoattractant protein-1 (MCP-1), PDGF, macrophage inflammatory protein- $\alpha$  (MIP-1- $\alpha$ ), MIP-1- $\beta$ , IL-8, and VEGF, in conjunction to contact system (FXII) activation [188]. Bacterial cellulose-TiO<sub>2</sub> nanoconjugates are promising wound dressings due to their biocompatibility and antibacterial activities. The staining of mice burn wound tissues illustrated that bacterial cellulose-TiO<sub>2</sub> facilitated reepithelialisation, the migration of fibroblast, and angiogenesis, enhancing wound closure [189, 190]. The wound dressings of TiO<sub>2</sub>NPs enclosed with pectin and chitosan pose antibacterial and interesting wound healing properties [191]. Nano-TiO<sub>2</sub>-chitosan with collagen artificial skin nanocomposite sustained a moderate level of TNF- $\alpha$ , denoting its antiinflammatory action (Table 3) [190].

(g) **Super paramagnetic iron oxide nanoparticles (SPIONs)**

Super paramagnetic iron oxide nanoparticles (SPIONs) have appealing applications in wound healing and drug delivery vehicles, because they own unique antibacterial and physicochemical properties (i.e., nano size, ease-of-amalgamation, minor toxicity, and biodegradability) [192].

Super paramagnetic iron oxide nanoparticles are small types of magnetic nanoparticles that consist of iron oxide cores or mixtures of iron oxides with cobalt, copper, manganese, or nickel [193]. Gold-coated SPIONs strongly penetrate bacterial biofilms and show higher toxicity. The intensified bactericidal effect of SPIONs is attributed to the cores of SPIONs and the intermediary gold shell that induce heat upon the application of laser and magnetic fields [194]. Iron oxide nanoparticle-decorated carbon nanotubes successfully healed wounds with a broad-spectrum antibacterial activity in animals [195]. Super paramagnetic iron oxide nanoparticles are coated with specific biocompatible polymers (e.g., polyethylene glycol [PEG] or dextran) that facilitate the conjugation of therapeutic compounds and improve their blood distribution. Super paramagnetic iron oxide nanoparticle-thrombin conjugates ameliorated skin tensile strength and enhanced the wound healing ability of thrombin by increasing its half-life in human plasma versus the free thrombin in rat incisional wounds (Table 3) [196, 197].

### Ceramic nanoparticles

Ceramic nanoparticles are widely considered in imaging applications, catalysis and photocatalysis, drug delivery, and the photodegradation of dyes [198, 199]. Ceramic nanoparticles are inorganic nonmetallic solids (e.g., silica/alumina titania, zirconia, silicon nitride/carbide) that are synthesised *via* successive cooling and heating, and are available in dense, polycrystalline, amorphous, hollow or porous forms [200–203]. The encapsulation of dense bioactive glass into gelatin-chitosan polymer activated alkaline phosphatase with the highest rate (i.e., 80%) of bone formation [204]. The multifunctional poly-citrate-siloxane elastomer-based bioactive glass was effective in bone tissue regeneration [205]. Bioactive glass slowly releases silicon and calcium ions at wound sites, promoting angiogenesis by stimulating cell proliferation and the release of cytokines, such as HIF-1 and VEGF [206, 207]. The silicon ions generated by bioactive glass protect endothelial cells from hypoxia and stimulate the expression of connexin 43 between endothelial cells and fibroblasts, encouraging angiogenesis (Table 3) [208].

### Organic and hybrid nanoparticles in wound healing

#### (a) *Lipid-based nanoparticles*

Lipid-based nanoparticles such as liposomes are the foundation of lipid nanotechnology as a drug delivery vehicle due to ease-of-delivery, size modulation, and charge and surface properties [210, 211]. Loss of growth factor coreceptors leads to growth factor (i.e.,

glypican-1) resistance that may prevent the induction of angiogenesis in wound healing in diabetic mouse. The delivery of growth factor cell surface receptors in a proteoliposome overcame this resistance and improved both wound healing and ischaemic revascularisation [212]. Other lipid-based nanoparticles hold promise for treating critical limb ischaemia and peripheral vascular diseases (PVDs) (Table 4) [213].

Solid lipid nanoparticles (mean size of ~180 nm) stabilise drugs and sustain their release when compared to liposomes, and they are safer than polymeric carriers, because they do not employ organic solvents during their production [214, 215]. They are a modern pharmaceutical delivery system with reshaped characteristics of liposomes, microemulsions, suspensions, and polymeric nanoparticles. Solid lipid nanoparticles are highly stable, biodegradable, nontoxic, and achieve chemically stable drug delivery systems with fewer limitations, overcoming the common issues faced with other nanoparticles. With higher efficiency and minimal toxicity, solid lipid nanoparticles deliver the following to the target site: proteins and peptides, temperature-sensitive drugs and those with physicochemical incompatibilities and lower pharmacokinetic profiles. They also deliver bioactive compounds, including morphine, resveratrol, and silver sulfadiazine in wound healing. Topical morphine-loaded solid lipid nanoparticles sustained the release of morphine, enhanced reepithelialisation, allowed keratinocytes to spread over the dermis, and accelerated the wound closure of a human-based three-dimensional wound healing model with lower toxicity and irritation [216]. Nonetheless, the production of solid lipid nanoparticles may degrade or eject the used drugs because of the evolved heat and stress. The tendency of solid lipid nanoparticles towards gel formation, particle size, and various shapes should be considered as well (Table 4) [217].

#### (b) *Polymer nanoparticles*

Biomedicine and bioengineering have underlined the importance of biocompatible polymeric nanoparticles [218]. Poly lactic-co-glycolic acid (PLGA), chitosan, gelatine, alginate, and other polymer combinations are commonly used to prepare the majority of polymeric nanoparticles [219, 220]. Conjugation with polymeric nanoparticles stabilises drugs against proteases, facilitates controlled drug release, and therefore reduces dosing frequency. Polymeric nanoparticles are effective biomolecules for the delivery of genes, growth factors, and antibiotics [221, 222]. The availability of growth factors (e.g., fibroblast growth factor-2 [FGF-2] and EGF) ensures proper wound healing; however,

**Table 4** The properties/actions and applications of organic and hybrid nanoparticles in wound healing

Nanoparticles	Distinctive Properties/Actions	Application(s)	References
<i>Lipid-based nanoparticles</i>	<ul style="list-style-type: none"> <li>– Size modulation</li> <li>– Ease-of-delivery</li> <li>– Charge and surface properties</li> <li>– Overcome growth factor resistance</li> <li>– ↑ revascularisation and wound healing</li> </ul>	<ul style="list-style-type: none"> <li>– Drug delivery vehicle</li> <li>– Wound healing</li> </ul>	[210–212]
<i>Solid Lipid nanoparticles</i>	<ul style="list-style-type: none"> <li>– High stability, biodegradability, and efficiency</li> <li>– Nontoxic</li> <li>– Achieve chemically stable drug delivery systems with fewer limitations</li> <li>– Overcome the common issues faced with other nanoparticles</li> <li>– Deliver the following to the target site: proteins and peptides, temperature-sensitive drugs, drugs with physicochemical incompatibility, and others with lower pharmacokinetic profile</li> <li>– Deliver bioactive compounds, including morphine, resveratrol, and silver sulfadiazine in wound healing</li> </ul> <p><b>Disadvantages:</b></p> <ul style="list-style-type: none"> <li>– May degrade or eject the used drugs because of the evolved heat and stress</li> <li>– Gel formation</li> <li>– Particle size and various shapes should be considered</li> </ul>	<ul style="list-style-type: none"> <li>– Wound healing</li> <li>– Pharmaceutical delivery system</li> </ul>	[216, 217, 259–261]
<i>Polymer nanoparticles</i>	<ul style="list-style-type: none"> <li>– Antibacterial</li> <li>– Help drugs avoid degradation by the proteases</li> <li>– ↑ granulation tissue formation</li> <li>– ↑ collagen deposition</li> <li>– ↑ reepithelialisation and neovascularisation</li> <li>– ↑ IL-6 and VEGF</li> <li>– Control inflammation</li> <li>– ↑ controlled drug release and skin permeation</li> <li>– ↓ dosing frequency</li> <li>– ↑ delivery and stability of genes, EGF and FGF-2, and antibiotics upon encapsulation</li> </ul>	<ul style="list-style-type: none"> <li>– Wound and ulcer healing</li> <li>– Burn-induced infections</li> <li>– Therapeutic angiogenesis</li> <li>– Gene therapy</li> <li>– Tissue engineering</li> <li>– Drug delivery</li> </ul>	[218–227]
<i>Antibiotic-loaded nanoparticles (nanobiotics)</i>	<ul style="list-style-type: none"> <li>– Broad spectrum antibacterial activity</li> <li>– ↑ actions of antibiotics against MDR microorganisms</li> <li>– ↑ tissue regeneration</li> <li>– ↓ toxicity</li> </ul>	<ul style="list-style-type: none"> <li>– Wound healing</li> </ul>	[231–234]
<i>Nitric oxide-releasing nanoparticles</i>	<ul style="list-style-type: none"> <li>– ↑ skin homeostasis and collagen deposition</li> <li>– ↑ wound closure and strength</li> <li>– ↑ keratinocyte proliferation and angiogenesis</li> <li>– Broad spectrum antibacterial</li> <li>– ↑ reactive nitrogen intermediates</li> <li>– ↓ suppurative inflammation</li> <li>– ↓ degradation of collagen</li> </ul>	<ul style="list-style-type: none"> <li>– Wound healing and repair</li> </ul>	[236–242]



**Table 4** (continued)

Nanoparticles	Distinctive Properties/Actions	Application(s)	References
<i>Green synthesised nanoparticles</i>	<p><i>AgNPs</i></p> <ul style="list-style-type: none"> <li>– ↑ activity against MDR bacteria</li> <li>– ↑ wound healing and contraction rate</li> <li>– ↑ dermis reepithelialisation</li> <li>– ↓ scars, TNF-<math>\alpha</math>, IL-1<math>\beta</math>, and IL-6</li> </ul> <p><i>TiO<sub>2</sub>NPs, AuNPs, and CuONPs</i></p> <ul style="list-style-type: none"> <li>– ↑ activity against MDR bacteria</li> <li>– ↑ wound healing</li> <li>– ↑ connective tissue</li> <li>– ↑ dermis reepithelialisation</li> <li>– ↑ proliferation and migration of epidermal cells</li> <li>– ↑ wound contraction rate</li> <li>– ↑ fibroblasts, macrophages, and collagen fibers</li> <li>– ↓ prevent infections and treatment-related side effects</li> </ul>	– Wound healing	[252–258]

the wound microenvironment has various proteolytic enzymes (e.g., matrix metalloproteinases [MMPs]) that significantly reduce their half-life [223]. Fortunately, the encapsulation of these growth factors within polymer nanoparticles increases their stability and sustains their bioactivity and release (Table 4).

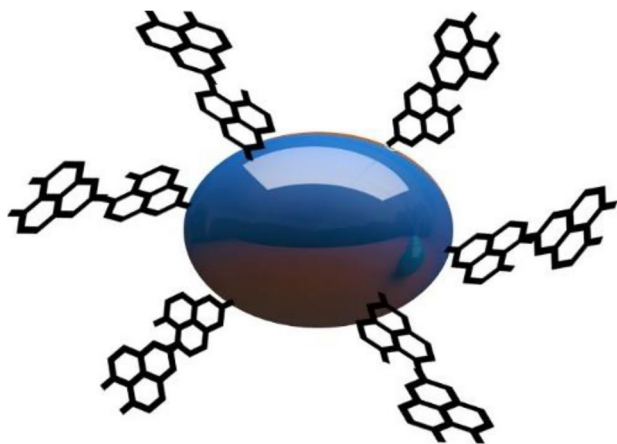
Reports have focused on the encapsulation of antimicrobials into polymeric nanoparticles [224, 225]. For instance, LL37-loaded PLGA nanoparticles accelerated wound healing, exhibited antibacterial activity against *E. coli*, and induced cell migration without affecting the proliferation and metabolism of keratinocytes in HaCaT cells. The treatment of full thickness excisional wound mouse model with PLGA-LL37 nanoparticles displayed higher deposition of collagen and granulation tissue formation, reepithelialisation, and neovascularisation. It also increased IL-6 and VEGF with the improvement of angiogenesis and control of the inflammatory response [224]. Topical norfloxacin-loaded PLGA nanoparticles were safe and sustained drug release to 24 h with better skin penetration and low number of in-vitro applications. Norfloxacin-loaded nanoparticles also had better performance against *S. aureus* and *P. aeruginosa.*, bringing hope to the treatment of burn-induced infections [225]. The gelatin microencapsulation of FGF-2 preserved its biological activity, promoting its application in therapeutic angiogenesis, gene therapy, tissue engineering, and drug delivery (Table 4) [226].

Poly-L-lactic (PLLA) acid-based wound dressings loaded with EGF enhanced the healing of gastric ulcers [227]. The Food and Drug Administration (FDA) has only approved the platelet-derived growth factor (PDGF-BB) for diabetic foot ulcers. Hyalu-

ronic acid-based porous nanoparticles supplied with PDGF-BB demonstrated higher efficacy to treat rat ulcers [228]. Poly-L-lactic acid are interesting nanocarriers to deliver extremely hydrophobic and poorly soluble medicines and proteins at the correct rate. Using PLLA nanoparticles reduced the toxic effects of curcumin-bortezomib compared to the unencapsulated form [229]. The use of PLA-PEG nanoparticles also increased the encapsulation efficiency of adapalene (a topical retinoid used for wound healing) (Table 4) [230].

#### (c) *Antibiotic-loaded nanoparticles (nanobiotics)*

Nanobiotics are the modern revolution that improves the functions of conventional antibiotics in wounds against MDR microorganisms. Vancomycin-modified nanoparticles exhibited a broad-spectrum activity in-vitro [231]. Polyacrylate nanoparticle-antibiotics and poly(butyl acrylate-styrene) nanoparticle-N-thiolated  $\beta$ -lactam conjugates had significant activity with lower toxicity against MRSA that cause severe infections in different parts of the body [232, 233]. The dressing of gelatin/chitosan/epigallocatechin gallate nanoparticles incorporated in a poly( $\gamma$ -glutamic acid)/gelatin hydrogel with activated carbon fibers and gentamicin, was easy to remove from the site of injury, inhibited bacterial growth, and improved reepithelialisation in-vitro and in-vivo. The PLGA nanoparticles having gentamicin were synthesised by the double emulsion evaporation method (Fig. 3) [234]. Gentamicin-loaded PLGA nanoparticles warrant the design of drug delivery systems using smart wound dressings with significant antibacterial properties (Table 4) [235].



**Fig. 3** The conjugation of nanoparticles with antibiotics. Nanoparticles are represented in **blue** colour, whereas antibiotics are depicted in **black**

#### (d) *Nitric oxide-releasing nanoparticles*

Nitric oxide controls skin homeostasis and the proliferation of keratinocytes and facilitates angiogenesis as well as the deposition of the extracellular matrix (ECM) proteins in wound healing. Nitric oxide is involved in systemic lupus erythematosus (SLE) and psoriasis that have deregulated inducible nitric oxide synthase levels [236, 237]. Inducible nitric oxide-knockout mice have a delayed reepithelialisation with a reduced number of keratinocytes in excisional wounds [238]. L-arginine—nitric oxide synthase substrate—enhanced the deposition of collagen, implicating nitric oxide as an essential element in wound closure (Table 4) [238].

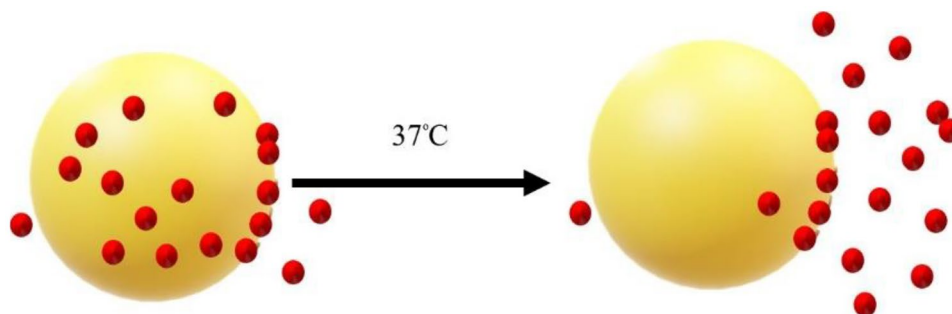
There is ample evidence for the broad-spectrum antibacterial role of nitric oxide. The transcription of inducible nitric oxide synthase is upregulated, and the production of high-output nitric oxide ensues upon the stimulation of microbial pattern recognition receptors in phagocytic cells. Nitric oxide disrupts DNA replication and cell respiration by deactivating zinc metalloproteins and interacting with ROS to create reactive nitrogen intermediates [239, 240]. Finally, the anti-

microbial effector molecules act within the microbial cells [237]. Nitric oxide-releasing coatings on biomaterials decrease the rate of biomaterial-related infections. Monofilament polypropylene mesh supported by nitric oxide-releasing carbon-based coatings eradicated *S. aureus* and other pathogen biofilms in vitro [241]. Coating medical grade silicone elastomer implants with a nitric oxide-releasing sol–gel-derived film decreased the percentage (82%) of infected subcutaneous implants inoculated with *S. aureus* in a murine model [242]. Figure 4 illustrates the fusion of the diazeniumdiolate [ $-\text{N}(\text{O})\text{N}=\text{O}^-$ ] functional group with nitric oxide-releasing polyurethane in aqueous environments [243]. Aminosilane-based sol–gel chemistry fabricates organic–inorganic polymer matrices where the properties are controlled by the nature and quantity of diamine-containing organosilane precursors and sol–gel processing conditions [242, 244, 245]. Nitric oxide-releasing SiNPs completely inhibited *Candida albicans*, *E. coli*, *P. aeruginosa*, *S. epidermidis*, and *S. aureus* in-vitro [246–248]. However, another study showed that bacteria display nitric oxide-mediated antibiotic resistance by the chemical refinement of harmful compounds and accumulating ROS [249]. Treatment with nitric oxide nanoparticles altered the local cytokine milieu, reduced the suppurative pattern of inflammation, and decreased both the pathological burden and the degeneration of collagen in mouse models infected with *A. baumannii* (Table 4) [250].

#### (e) *Green synthesised nanoparticles*

Green-synthesised  $\text{TiO}_2$ NPs, AgNPs, AuNPs, and CuONPs enhance wound healing and decrease or prevent infections and treatment-related side effects [168, 251, 252]. Green synthesised nanoparticles such as AgNPs coupled with phytoextracts are eco-friendly and cost-effective, possess antibacterial and antifungal properties, and promote wound healing [251, 252]. For example, the preparation of green-synthesised AgNPs using the extracts of *Catharanthus*

**Fig. 4** The release of nitric oxide (**red** spheres) upon the attachment of the diazeniumdiolate group to nitric oxide-releasing polymer (**yellow** spheres) by covalent or noncovalent bonding



*roseus* and *Azadirachta indica* was effective against MDR bacteria and ameliorated excision wound healing in mice [253]. The biosynthesis of stable AgNPs using the fungus of *Orchidantha chinensis* successfully treated the Sprague Dawley rats with multi-strain-infected wounds [254]. The produced AgNPs minimised the scars, reepithelialised the epidermis, accelerated wound healing as well as the wound contraction rate, and downregulated the level of IL-6, IL-1 $\beta$ , and TNF- $\alpha$  (Table 4) [254]. Genipin (a compound prepared from geniposide, which is extracted from *Penicillium nigricans*, a slow-growing fungus) when crosslinked with chitosan, PEG, and AgNPs enhanced wound healing with higher antibacterial activity (Table 4) [255]. In Wistar Albino male rats, AgNPs with *Coleus forskohlii* root extract was effective in healing full thickness excision wounds [168]. A mixture of AgNPs in octadecylamine-modified montmorillonite clay (ODA-MMT), *Homalomena aromatica* leaves extracts, and hyperbranched epoxy, also was an effective wound healing scaffold with inborn antimicrobial characteristics (Fig. 5) [256].

The gold nanoparticles synthesised by the extract of *Coleus forskohlii* root significantly accelerated the reepithelialisation of excision wounds and increased the rate of proliferation, formation of connective tissue, and the migration of epidermal cells in Wistar Albino rats [168]. In the presence of *Moringa oleifera* leaf extract, the synthesis of TiO<sub>2</sub>NPs reduced the excision wound area and enhanced wound contraction in Wistar Albino rats [257]. The biosynthesis of CuONPs using the extract of *Ficus religiosa* leaf facilitated wound healing, inhibited the human pathogenic bacteria, and increased the growth of fibroblasts, collagen fibers, and macrophages in Wistar Albino rats (Table 4) [258].

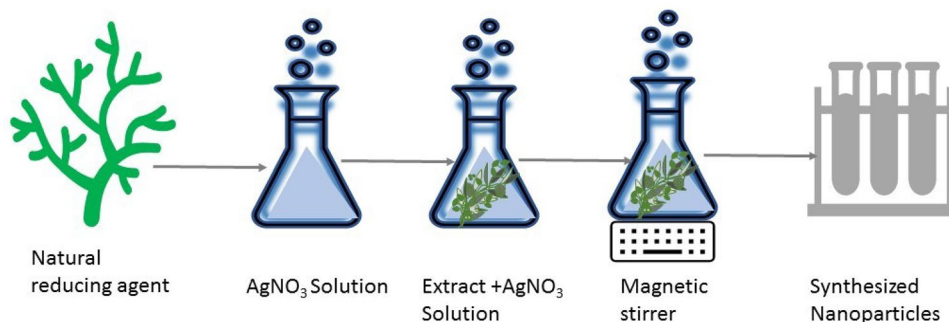
## Nanofibers in wound healing

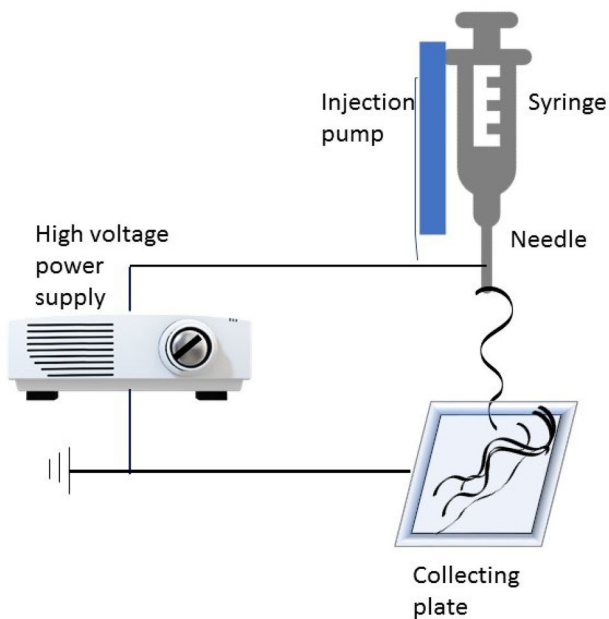
Nanofibers stand out in wound healing and drug delivery because of their small size, physical and mechanical qualities, high loading capacity, and controlled drug release

[262]. Electrospun nanofibers modulate cell proliferation, migration, differentiation, and the deposition of ECM, allowing their manufacturing into engineered skin tissues, dermal substitutes, wound dressings, and sutures for wound healing [263]. The careful choice of nanofiber components helps electrospun nanofibers mimic the biomechanical properties of the human skin [264, 265]. Electrospun nanofibers are highly porous with a large surface area-to-volume ratio to develop novel scaffolds of natural polymers that carry bioactive substances [263, 266]. Electrospinning builds up polymer nanofibers in a connected three-dimensional network to fabricate nanomaterials (Fig. 6) [267]. Natural polymers (e.g., silk fibroin, chitosan, collagen, gelatin, and synthetic biodegradable polymers) facilitate cell proliferation and attachment, whereas synthetic polymers offer scaffold mechanical stability [218]. These characteristics make them available for use in biosensors, intelligent textiles and clothing, tissue engineering scaffolds, and drug delivery systems [268]. Creative electrospinning develops specialised mats with porous, aligned, hollow, and core-shell nanofibers, which act as skin repair substitutes and enhance the removal of wound exudate, promote oxygen diffusion, and control water loss [269]. The electrospun nanofibrous matrix of type I collagen allowed half of the proliferating normal human epidermal keratinocytes to spread and to adhere, accelerating wound healing in early-stage wounds [270]. The in-vitro proliferation of primary human dermal fibroblast as well as the healing of ex-vivo full-thickness human skin wound model have improved with silk fibroin electrospun fibers with diameters of 250–300 nm compared with 1- $\mu$ m fibers (Table 5) [271].

The spatially arranged collagen containing nanofibrous matrices helped the human dermal fibroblasts elongate with focal adhesion clustering and display faster cell migration and a higher rate of differentiation to myoblasts in-vitro [272]. Such architecture stimulated the integrin  $\beta$ 1 signaling which is the key pathway for these cellular responses. Human dermal fibroblasts on fibrinogen containing nanofiber matrices had faster migration and higher expression of the differentiated phenotype  $\alpha$ -smooth muscle actin with the aid of exogenous TGF- $\beta$ 1. The electrospun PLA

**Fig. 5** The green synthesis of silver nanoparticles (AgNPs)





**Fig. 6** The production of nanofibers *via* electrospinning

nanofibers coated with fibrin significantly increased the type I collagen expression and synthesis, spreading, population density, and mitochondrial activity of human dermal fibroblasts (Table 5) [273].

#### (a) *Synthetic polymer-based electrospun nanofibers*

Polycaprolactone is a biocompatible and a biodegradable polyester polymer that reduces inflammatory infiltrate and increases wound healing and tissue regeneration [274, 275]. Polycaprolactone is a good matrix for carrying natural substances due to its encouraging mechanical properties, hydrophobicity, excellent spinning, and delayed degradation. Polyvinyl alcohol is a semicrystalline biocompatible polymer that is used in the biomaterials of orthopaedic and dermal tissue engineering. It is a copolymer that enhances the mechanical properties and the electrospinnability of chitosan, where higher ratio of chitosan in PVA-chitosan blends leads to higher bacterial activity (Table 5) [276–279].

Polycaprolactone-based electrospun nanofibrous membrane is an effective wound dressing that facilitates the adhesion and the proliferation of human dermal fibroblast *in-vitro*; it may be a possible alternative to treat burn-induced wounds and skin defects [280]. The electrospun PCL-collagen nanofibers maintain the active delivery of TGF- $\beta$ 1 to promote the differentiation of myofibroblasts [281]. The three-dimensional cultures of human hair-follicle-derived melanocytes and normal human epidermal melanocytes have reinforced the melanotic features

upon seeding on the mesh of electrospun PCL fibers *via* the expression of terminal melanotic differentiation genes [282]. The mesh of electrospun PCL nanofibrous scaffold also helped cultivated rat hair-follicle stem cells rapidly proliferate, migrate, and differentiate [283]. The electrospun poly(L-lactide-co- $\epsilon$ -caprolactone) (PLCL) and polyurethane random nanofiber scaffolds mitigated the hypertrophic scar (HSc) contraction *in-vitro* and *in-vivo* [284, 285]. The electrospun PLCL and polyurethane nanofiber scaffolds seeded with human dermal fibroblasts showed less contraction with fewer  $\alpha$ -SMA positive myofibroblasts. The scaffolds of collagen-coated polyurethane or PLCL nanofibers cultivated underneath skin grafts significantly reduced the HSc contraction and scar stiffness compared with the standard-of-care Integra (silicone membrane removed) in a murine model (Table 5).

#### (b) *Natural polymer-based electrospun nanofibers*

##### Polymers of protein origin

Electrospun nanofibers developed from healthy skin collagen allow the ECM to give extra support to keratinocytes and fibroblasts to strongly attach to the fibres, migrate through the wound bed, and regenerate and repair the injured tissue (Fig. 7) [286]. Collagen is the most predominant protein in the body and is the principal fibrous protein in the ECM that supports tissues' and organs' structures and regulates cell functions [287]. Collagen is malleable, bioresorbable, nontoxic, antimitogenic, highly biocompatible, could be combined with other copolymers, and is a suitable biomaterial for nanofibrous mats [288]. However, collagen has some drawbacks, including the difficult work involved, high purification cost, and the risk of disease transmission [289]. Silk fibroin, an ideal candidate for biomedical applications, has unique biocompatibility and biodegradability, causes low inflammatory reactions, and provides adequate oxygen and WVTR [290]. Various insects (e.g., silkworm) produce the typical fibrous protein—silk. Fibroin (silk filaments protein) can be regenerated in powders, membranes, fibers, or gels [291]. The adaptability and the simple production of fibroin make it easier to obtain materials with appropriate properties (Table 5) [286].

##### Algae polysaccharides

Alginate polysaccharide-based biomaterials are cost-effective, versatile, abundant, and play an essential role in wound healing [292, 293]. Sodium alginate is tissue-compatible, nontoxic, hydrophilic, biodegradable, and

**Table 5** The properties/actions and applications of nanofibers in wound healing

Nanofibers	Distinctive Properties/Actions	Application(s)	Reference(s)
<b>Synthetic Polymer-Based Electrospun Nanofibers</b>			
	<ul style="list-style-type: none"> <li>– ↑ mechanical properties and electrospinnability of biopolymers (e.g., chitosan)</li> <li>– ↑ wound closure</li> <li>– ↓ inflammatory infiltrate</li> <li>– Hydrophobic</li> <li>– Excellent spinning</li> <li>– Delayed degradation</li> </ul>	<ul style="list-style-type: none"> <li>– Wound healing</li> <li>– Tissue regeneration (e.g., dermatology)</li> <li>– Orthopaedics</li> </ul>	[274–279]
<b>Natural Polymer-Based Electrospun Nanofibers</b>			
<b>Polymers of protein origin</b>	<p><b>Collagen</b></p> <ul style="list-style-type: none"> <li>– Nontoxic</li> <li>– Not mitogenic</li> <li>– Better cellular response</li> <li>– Malleable</li> <li>– Bioresorbable</li> <li>– Highly compatible</li> <li>– Could be combined with other copolymers</li> </ul> <p><b>Disadvantages</b></p> <ul style="list-style-type: none"> <li>– ↑ purification cost</li> <li>– Difficult work involved</li> <li>– Risk of disease transmission</li> </ul> <p><b>Silk Fibroin</b></p> <ul style="list-style-type: none"> <li>– Biocompatible and biodegradable</li> <li>– Low inflammatory reactions</li> <li>– Adequate oxygen WVTR</li> </ul>	<ul style="list-style-type: none"> <li>– Suitable for nanofibrous mats</li> <li>– Biomedical applications</li> </ul>	[286, 288]
<b>Algae polysaccharides</b>	<ul style="list-style-type: none"> <li>– Biodegradable and affordable</li> <li>– Versatile and abundant</li> <li>– Tissue-compatible</li> <li>– Immunomodulatory</li> <li>– Antioxidant</li> <li>– Anticoagulant and antitumour</li> <li>– ↑ wound closure</li> </ul> <p><b>Disadvantages</b></p> <ul style="list-style-type: none"> <li>– Limited electrospinnability</li> </ul>	<ul style="list-style-type: none"> <li>– Wound dressings</li> <li>– Skin regeneration</li> </ul>	[292–296]
<b>Plant polysaccharides</b>	<p><b>Starch</b></p> <ul style="list-style-type: none"> <li>– Abundant</li> <li>– Physically or chemically amended to be utilised in wound dressings</li> <li>– <b>Electrospun starch-hyaluronic acid/ (polyurethane-based electrospun nanofibers patch:</b></li> <li>✓ biocompatible</li> <li>✓ biodegradable</li> <li>✓ confers surface hydrophilicity</li> <li>✓ improves the mechanical durability</li> </ul> <p><b>α-cellulose nanofibers</b></p> <ul style="list-style-type: none"> <li>– Antibiotic-loaded α-cellulose nanofibers diminish the wound size</li> </ul> <p><b>Pectins</b></p> <ul style="list-style-type: none"> <li>– Rapid exudate absorption</li> <li>– Moderate hydrophilicity</li> <li>– Antibacterial</li> </ul>	<ul style="list-style-type: none"> <li>– Wound healing</li> <li>– Drug delivery</li> <li>– Wound healing</li> <li>– Wound healing</li> </ul>	[299, 301]
			[304]
			[307, 308]

Table 5 (continued)

Nanofibers	Distinctive Properties/Actions	Application(s)	Reference(s)
<i>Animal polysaccharides</i>	<b>Chitosan</b> – Antioxidant and antiinflammatory – Antibacterial – Biocompatible – <b>Electrospun nanofiber mats with chitosan-graft-PCL:</b> ✓ excellent cell attachment and proliferation <b>Disadvantages</b> – Chitosan pristine fibers have limited biomedical applications because of its poor mechanical properties	– Wound healing – Drug development – Tissue engineering	[268, 279, 316–319]
	<b>Hyaluronic acid</b> – Nonimmunogenic – Biodegradable – Biocompatible – High wettability – High ability to be chemically modified	– Wound healing – Drug delivery – Tissue engineering – Viscosupplementation	[161]
<i>Fungal polysaccharides</i>	<b>Pullulan</b> – Nontoxic – Nonmutagenic – Tasteless – Odourless <b>Disadvantages</b> – The high hydrophilicity of pullulan hinders its tissue engineering applications, limiting cellular attachment and proliferation and preventing protein adsorption	– Pharmacy – Biomedicine	[326–330]
	<b>Sonifilan (SPG)</b> – Embrace molecular components, functional polymers, and nanoparticles to form water-soluble one-dimensional nanocomposites	– Drug delivery	[333]
<i>Bacterial polysaccharides</i>	<b>Dextran Gum</b> – Dextran crosslinking tailors its biodegradation stability and retains its mechanical features in moist conditions – <b>Electrospun dextran-boric acid:</b> – prepare a steady network of dextran-boric acid electrospun nanofibers with controlled degradation time	– Wound healing	[338–341]
	<b>Xanthan Gum</b> – Thermostable – Generates self-assembled micro or nanoscale structures	– Regenerative medicine – Tissue engineering – Controlled drug delivery	[342, 343]

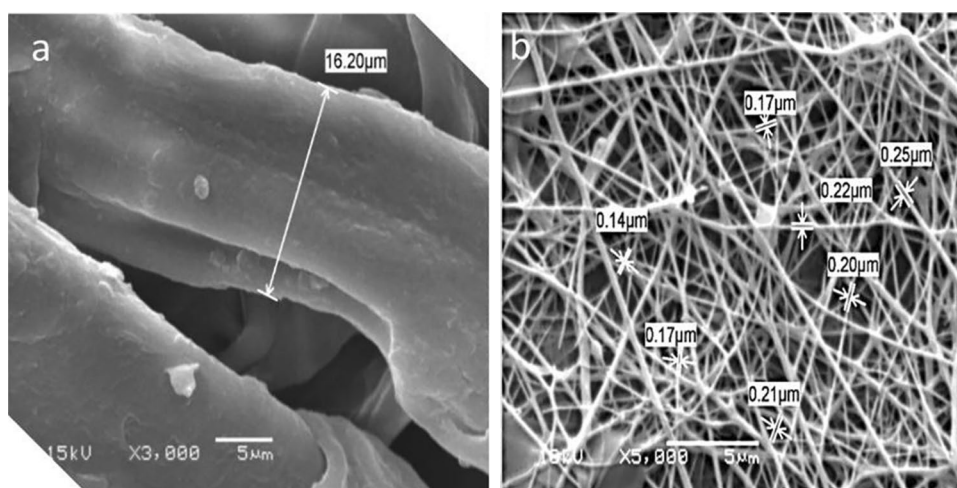
affordable, making it suitable in skin regeneration and curing exuding wounds [294]. Marine algae polysaccharides exhibit immunomodulatory, antioxidant, anticoagulant, and antitumour actions. *Pseudomonas* spp. and *Azotobacter vinelandii* and algae produce alginates, biodegradable polysaccharides, and negatively charged polymers. Alginates absorb the surplus exudate and provide moist conditions for rapid wound healing [295]. Yet, alginates have limited electrospinnability to be linked with compatible polymers [296]. Blending alginates with synthetic polymers (e.g., polyethylene oxide [PEO] or

PVA) enhances their electrospinnability and mechanical potency (Table 5) [297].

### Plant polysaccharides

Plant polysaccharides are biodegradable polymers with steady structures, diverse biological, physicochemical, and strong hydrophilicity/viscosity characteristics that regulate the rheological properties of the fluid system [298]. Starch is an abundant polysaccharide biopolymer with interesting applications in drug delivery and wound dressings. The main components of

**Fig. 7** The scanning electron microscope (SEM) images of collagen fibers (a) before and (b) after spinning



starch (i.e., amylopectin and amylose) can be physically/chemically amended to be utilised in wound dressings [299]. Wet electrospinning is a green method that develops pure starch-based nanofibers with high stability in water at room temperature using sodium palmitate [300]. Research currently focuses on manufacturing crosslinked electrospun nanofibers, such as PVA/starch/chitosan nanofibrous mats in wound dressings [299]. The modified coaxial electrospinning forms a core-shell starch-hyaluronic acid/polyurethane-based electrospun nanofibers patch that is biocompatible, biodegradable, confers surface hydrophilicity, and improves the mechanical durability (Table 5) [301].

Nanoscale cellulose fibers are attractive due to large surface area compared with their microscale forms [302]. Many cellulose derivatives such as carboxymethyl cellulose (CMC), cellulose acetate,  $\alpha$ -cellulose, and ethyl cellulose develop different electrospun nanofibers in wound dressings [303–305]. In contrast to drug-free  $\alpha$ -cellulose nanofibers, antibiotic-loaded  $\alpha$ -cellulose nanofibers diminish the wound size with desirable bioactivity (Table 5) [304]. Pectin-based electrospun nanofiber scaffolds might function as better wound dressings with significant antibacterial activity. They absorb more exudate in a shorter time versus alginate- and chitosan-based electrospun nanofiber patches. Pectin polysaccharides are complex molecules with irregular carbohydrate chains [306, 307]. Pectins act as an exudate-absorbing component in hydrocolloidal wound dressings due to their moderate hydrophilicity [307, 308]. Gums—a large group of polysaccharides—are a novel source of electrospun nanofiber biopolymers with different pharmaceutical applications [309]. For example, electrospun nanofiber scaffolds comprising gum Arabic, gum karaya, gum guar, Azivash gum, and gum tragacanth, are used in wound dressings (Table 5) [310–315].

### Animal polysaccharides

Animal polysaccharides—chitosan and hyaluronic acid—possess antioxidant, antibacterial, and antiinflammatory

properties, and can be used in wound healing and drug development [316]. Chitosan is a biocompatible biopolymer with interesting antiinflammatory and antimicrobial properties in wound healing [317]. Chitosan pristine fibers have limited biomedical applications because of their poor mechanical properties; although, chitosan composite fibers/synthetic polymer combinations gave better results [279, 317–319]. Electrospun nanofiber mats with chitosan-graft-PCL are promising substitutes for tissue engineering and show excellent cell attachment and proliferation (Table 5) [268, 319].

Hyaluronan/hyaluronic acid is a naturally occurring glycosaminoglycan that constitutes the major components of the ECM, connective tissue, and cartilage [320]. Hyaluronic acid has important applications in wound healing, drug delivery, tissue engineering, and viscosupplementation. It is nonimmunogenic, biodegradable, biocompatible, and has high wettability and the ability to be chemically modified [161]. Electroblowing, electrospinning, and heating synthesise nanofibers from pure hyaluronic acid aqueous solutions [321]. Linking hyaluronic acid with natural polymers forms regular nanofibers that increase its biological performance, whereas conjugating synthetic polymers with hyaluronic acid enhances its electrospinnability and mechanical properties [322, 323]. The bilayered electrospun nanofiber scaffolds of chitosan and hyaluronic acid merged with natural or synthetic polymers are used in wound healing (Table 5) [324, 325].

### Fungal polysaccharides

Fungi synthesise pullulan (an extracellular polysaccharide) and schizophyllan (Sonifilan, SPG) to create electrospun nanofibers. Pullulan is used for the preparation of ultrathin electrospun nanofibers and has massive applications in pharmaceuticals and biomedicine because it is nontoxic, nonmutagenic, tasteless, and odourless [326–329]. Nonetheless, the high hydrophilicity of pullulan hinders its application in tissue engineering, limiting cellular attachment and proliferation and preventing protein

adsorption. Fortunately, composite scaffolds comprising tissue-specific growth factors, inorganic materials, and ECM proteins, overcome such limitation [330]. Protein-pullulan blends also are reciprocally compatible in electrospun nanofibers [331, 332]. Schizophyllan forms a one-dimensional hydrophobic hollow within its helical superstructure during renaturation; thus, embraces molecular components, functional polymers, and nanoparticles to form water-soluble nanocomposites [333]. Diverse nanocomposites have examined SPG in various biomedical applications: SPG nanoparticles, nanogels, and SPG double network antibacterial hydrogel (Table 5) [334–336].

### Bacterial origin polysaccharides

Bacteria produce polysaccharides for their own aims without interactions with human tissues. Bacterial polymer-based electrospun nanofibers have gained much appreciation in wound healing as they are nonantigenic, histocompatible, and readily washed from the wound area [337]. Dextran (a neutral polymer produced by *Lactobacillus* spp.) and xanthan gum (an anionic polymer synthesised by *Xanthomonas campestris*) are common bacterial polysaccharides in wound dressings [338–340]. Due to its hydrophilic nature, the crosslinking of dextran is imperative to tailor its stability against biodegradation and retain its mechanical features in moist conditions. For example, the electrospinning of dextran-boric acid in aqueous solutions prepares a steady network of dextran-boric acid electrospun nanofibers with controlled degradation time. Such network hinders the duration of drug release about 500% versus pure dextran electrospun nanofibers [341]. Xanthan gum is thermostable and generates self-assembled micro/nanoscale structures in controlled drug delivery, tissue engineering, and regenerative medicine [342]. The internalisation of curcumin into xanthan gum-chitosan electrospun nanofibers improves their stability. The incubation of electrospun nanofibers with Caco-2 cells monolayers led to almost 80% of cell viability and enhanced the curcumin transepithelial permeability without menacing the cellular viability in-vitro (Table 5) [343].

### Conclusion and future perspectives

The present review has extensively discussed the current wound healing dressings and demonstrated the advantages and limitations of inorganic nanomaterials, organic and hybrid nanomaterials, and nanofibers in wound healing. Customised wound bandages with nanomaterials offer a vast potential for individualised wound healthcare. Polymeric nanomaterials of natural origin combined with biomolecules, growth factors, and antibiotics could overcome the constraints of the current wound healing materials, producing scaffolds with better mechanical resistance. A hybrid inorganic/natural polymer/antibiotic-based nanocomposite as a combination of antimicrobial and biodegradable nanomaterials could improve wound healing.

One should recognise the major challenges of nanomaterial wound dressings and the mechanism of interaction with the wound to achieve low resistivity and accelerated wound healing. The synthesis of nanomaterials affects their physical stability, mechanical durability, toxicity, and cost. Therefore, structural defects that arise during the production of nanomaterials should be considered. Moreover, the overall manufacturing costs should be reduced to comply with the international health protocols.

**Authors' contributions** MA: conceptualisation, preparation of the major parts of the manuscript and artwork; MMA: reviewing, writing, editing, and proofreading the manuscript; HS: writing parts of the manuscript, support, and advice during manuscript preparation.

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### Declarations

**Competing interests** The authors declared that they have no conflicts of interest.

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