Review

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Nanoparticles-assisted Wound Healing: A Review

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Abstract

Poor wound treatment impacts millions of humans worldwide, increasing deaths and costs. Wounds have three key complications: (a) a lack of an adequate environment for cell migration, proliferation, and angiogenesis; (b) microbial infection; and (c) unstable and prolonged inflammation.Regrettably, contemporary therapeutic treatments have not entirely tackled these basic difficulties and thus have insufficient medical accomplishment. The incorporation of the extraordinary capabilities of nanomaterials in wound healing has achieved major successes over the years. Nanomaterials can promote a variety of cellular and molecular processes that assist in the wound microenvironment through antibacterial, anti-inflammatory, and angiogenic activities, potentially shifting the surroundings from nonhealing to healing. The current review focuses on novel techniques, with a particular focus on recent revolutionary wound healing and infection control tactics based on nanomaterials, such as nanoparticles, nanocomposites, and scaffolds, which are discussed in depth. Furthermore, the effectiveness of nanoparticles as carriers for therapeutic compounds in wound-healing applications has been investigated which provide researchers an up-to-date sources on the use of nanomaterials and their creative ways that can improve wound-healing uses.

Keywords: wounds caring; zinc oxide nanoparticles (ZnO NPs); gold nanoparticles (Au NPs); sliver nanoparticle (Ag NPs)

Introduction

The largest organ in the human body is the skin. Adult skin covers about 2 m^2 of the body's surface. The skin serves as a protective layer, separating the human body from the outside environment [1]. It serves to moisturize, enhance sensory awareness, regulate body temperature, maintain humoral homeostasis, and protect against foreign infections [2]. The skin can withstand the effects of several external stimuli over time. Ailments were brought on by injuries or brought on by the breakdown of the skin's integrity [3]. Burns, surgical incisions, contusions, scrapes, and scratches brought on by trauma are the most commonly occurring wounds. Depending on the severity of the harm, an organism's self-healing ability causes wounds to recover in three months. But an unchecked infection turns a short-lived ailment into a long-lasting one [4]. Chronic diseases, including vascular dysfunction, obesity, and diabetes, have been rising significantly, leading to an increase in individuals with chronic wounds. Diabetes-related chronic abscesses are 15%–25% more likely to occur in diabetic patients [5]. Additionally, several

contagious skin conditions, such as dermatomyositis, sporotrichosis, autoimmune skin disorders, malignant skin tumours, and physical skin illnesses, might make patients more susceptible to chronic wounds [6]. For a prolonged period of time, the hypodermic tissue of chronic and nonhealing wounds is exposed to the outside environment, putting patients at risk for osteomyelitis and bleeding, as well as for dying if their conditions are severe [7]. Chronic infection lowers patients' quality of life, increases their financial burden, and creates serious mental and psychological difficulties [8].

In medicine, wound healing is always becoming more complicated, making fresh materials and methods extremely appealing [9]. The pharmaceutical and biotechnology industries have undergone a revolution thanks to significant advancements in nanotechnology, particularly in nano-chemistry and nanomanufacturing [10]. Due to their unique structure, nanoparticles (with at least one dimension below 100 nm) exhibit distinctive physicochemical characteristics, resulting in small size, surface, and macroscopic quantum tunnelling effects. Recently, because of their superior adsorption capacity, antibacterial characteristics, and medication loading, nanostructures also been have widely used in wound care [11].

The dressings for wounds serve as temporary skin substitutes and are crucial for hemostasis, infection prevention, and wound closure. For many years, several dressing materials have been investigated. In the past, skin abnormalities were treated with wound dressings like gauze and bandages [12]. The model dressing must mimic the extracellular matrix (ECM) in a moist environment. It must have antibacterial capabilities and promote cell proliferation and angiogenesis; as a result, it requires special components with exceptional qualities [13]. The market's high need for such resources has fueled the expansion of nanomaterial coatings [14]. At the moment, innovative nanomaterial-based bandages such as hydrogels, nanofibers, and films are widely used [15–18].

Despite the fact that a rising number of new nanomaterials have been identified for use in wound healing, the mechanisms have not been adequately summarized. In this review, new nanomaterials usage, putative processes, and potential toxicity for use in wound healing from a variety of perspectives were investigated. It was prominently highlight the limitations of current nanomaterial applications in medical and mechanistic investigations of wound healing, as well as remedies and creative research ideas that might develop into future avenues of investigation.

The physiological phases of wound Healing

A complex physiological process called skin regeneration entails the complex chronological organization of many different cell types, chemokines, and growth hormones. The four standard phases of the wound-healing process are as follows: Hemostasis, inflammation, proliferation, and maturation/remodeling.

Phase 1: Hemostasis

Healing begins with hemostasis, or the process of stopping bleeding as soon as possible after an injury. Collision between platelets and collagen results in activation and aggregation. In the first steps of thrombin's formation, a fibrin mesh forms around the platelets so they are strengthened and will clot for a long time [19].

Phase 2: Defensive/inflammatory

A wound bed must be cleared of debris and germs are killed as part of the process. Defensive/inflammatory phases begin after this. The second phase involves white blood cells removing germs and debris from the wound using neutrophils, for example. Cells in the wound heal by releasing growth hormones and proteins, which attract immune system cells and speed up the process of healing tissue. The edema, erythema, heat, and pain of this phase typically last between four and six days [20, 21].

Phase 3: Proliferative

The wound is cleaned in Phase 2, then it moves on to Phase 3, which is the proliferation phase, where the wound is filled and covered [22]. The proliferative phase consists of three distinct phases:

1. Recovering from injury;

2. Margin of wounds contracted;

3. The wound needs to be epithelialized (taken care of).

New blood vessels and shiny connective tissue are present in the wound bed at the beginning. In wounds that are compressed, the wound core becomes pushed

toward the wound margins. Epithelium then emerges from the wound bed, migration occurs in a leapfrog pattern across the wound bed, and the wound bed is covered in three stages. There are differences in the length of each proliferation phase, but most have a period of 4–24 days [23].

Phase 4: Maturation/remodeling

Regenerated tissue becomes stronger and more flexible during the maturation period. Injured tissue recovers, collagen fibers restructure, the tensile strength of the tissue increases (though to a limit of 80 percent of the pre-injury strength). It can take anything between 21 days and 2 years for the maturation phase to complete [24]. All four phases appear in Fig.1. The healing can be slowed by both locally occurring factors, such as humidity, infections, and maceration (local factors), as well as by systemic factors such as age, nutrition, and body type. If the proper healing environment is provided, the body heals devitalized tissues in a special way [25].

The natural treatment of wounds

Today, there are a wide range of options available for wound care, both traditional and contemporary. Debriding and dressing the wound traditionally take place. Different types of dressings are available for wounds. Dressings are classified into three categories according to standard definitions: traditional dressings, biomaterial-based dressings, and artificial dressings. In addition to traditional dressings, gauzes or gauze cotton composites are common no adhesive or adhesive dressings. A cellulose fiber dressing comes in three forms: allografts, tissue derivatives, and xenografts. As allografts, body parts such as scalp tissues and amniotic membranes are commonly obtained from relatives or cadavers. Clothing made with collagen or pigskin is an example of xenografts and tissue derivatives [26]. Dressings made from artificial materials can come from films, membranes, foam, gel, composites, or sprays. Natural-source goods include collagen, cellulose, polyurethanes, fibrin, alginate-replacement products, chitosan, hyaluronic acid, carboxymethylcellulose, and gelatin. *In vitro* and *in vivo* studies have shown that biocompatible and biodegradable synthetic polymers can improve wound closure by promoting epithelialization and cell proliferation, migration, and differentiation.

The use of commercially produced skin substitutes for the treatment of skin wounds and accidents has been reported [27]. An extensive review described a variety of wound-healing dressings. Wound dressings that can be infused with systemic antibiotics to help combat bacterial infections [28]. Several advanced therapies include stem cell/growth factor or gene therapy, combined with tissue engineering (decellularized tissues, hydrogels, bi-layered skin substitutes, and fibroblast/keratinocyte derived scaffolds). Hyperbaric oxygen therapy, vacuum

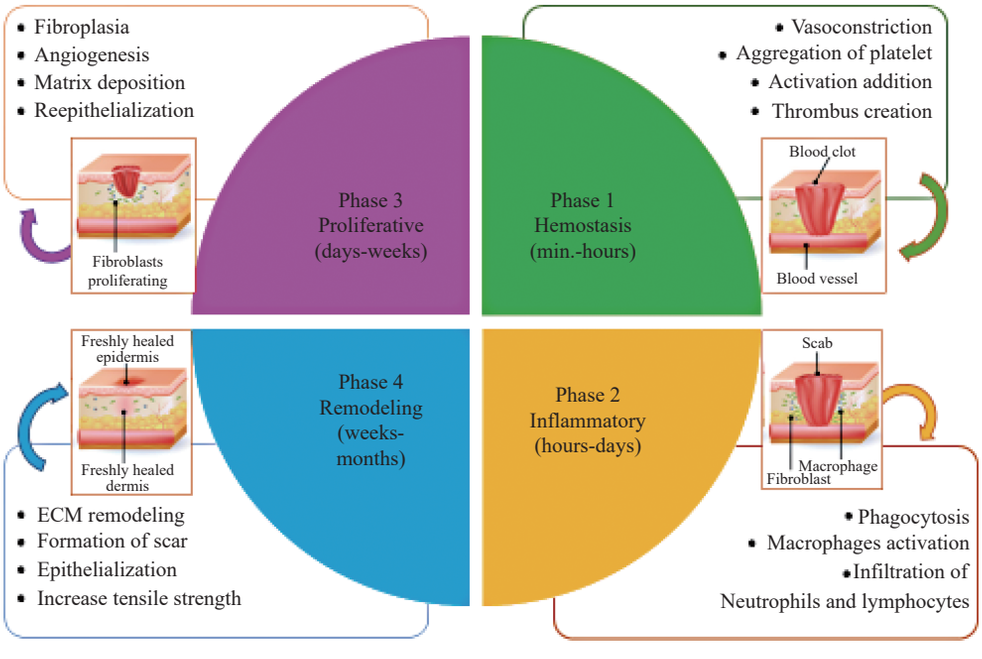

Fig. 1 Depicts the four stages of normal wound healing.

compression, negative pressure wound therapy, ultrasound wound healing devices, electromagnetic therapy, hydrotherapy, lasers, and light-emitting diodes are other types of wound care [29].

Unfortunately, some fundamental issues have not been resolved by current therapeutic approaches. As a result, their level of medical success is insufficient. Significant outcomes have been achieved throughout history by incorporating the amazing capabilities of nanomaterials into wound healing. Through antibacterial, anti-inflammatory, and angiogenic activities, nanomaterials can activate a variety of cellular and molecular processes that support the wound microenvironment and may even shift the environment from nonhealing to healing [30]. Figure 2 shows the depicts the stages of used nano scales on wound healing process.

Treatment improves with nanotechnology

The discovery of nanotechnology has led to the development of a number of innovative applications, such as smart materials, the agnostic nanoparticles, and cutting-edge materials. Nanotechnology-based wound healing therapies have shown promise in recent years for treating chronic wounds [31]. The wound-healing therapy can be divided into two categories by NMs type. The healing powers of nanoscale materials or using nanoscale materials as delivery mechanisms for therapeutic agents have attracted considerable attention with the aim of designing effective therapeutic approaches [32] (Fig. 3). Analysis of the percentage of several NMs used in treating wounds on the cutaneous surface in the publications.

Wound healing is highly influenced by the NMs physicochemical properties. Different NMs and their potency can have different effects. Biomaterial properties, size, colloidal stability, surface functionalization, and surface charge are a few of the aspects of NMs that can influence wound healing outcomes [33]. Nanotechnology can be classified into main kinds depend on the biochemical composition of the particles: polymers, carbon-based, lipid-containing, ceramics, metal or metal oxide nanoparticles (M/M-oxide NPs), and scaffolds embedded with nanomaterials (Fig. 3). Table 1 Shows several NMs were used in treatment of wounds and appears their role in the process.

Treatment improves with metallic and metallic oxide nanoparticles

Sliver nanoparticle (Ag NPs)

Since silver compounds and ions have powerful antibacterial characteristics and a broad spectrum of activity, they have long been used for hygiene and medicine [25]. Many medicinal formulations containing silver have been used for treating chronic wounds due to their antibacterial properties.

Burns were first treated with silver nitrate in 1960, and sores were first healed with it in the 17th and 18th century. In recent years, there has been a resurgence of interest in silver due to bacterial antibiotic resistance and advances in polymer technology, following a decline in its use after the introduction of antibiotics in 1940 [26]. As a result, silver-containing dressings can be purchased from a wide variety of sources. Despite being less effective than silver sulfadiazine, silver is still considered necessary as a treatment for burns, such as

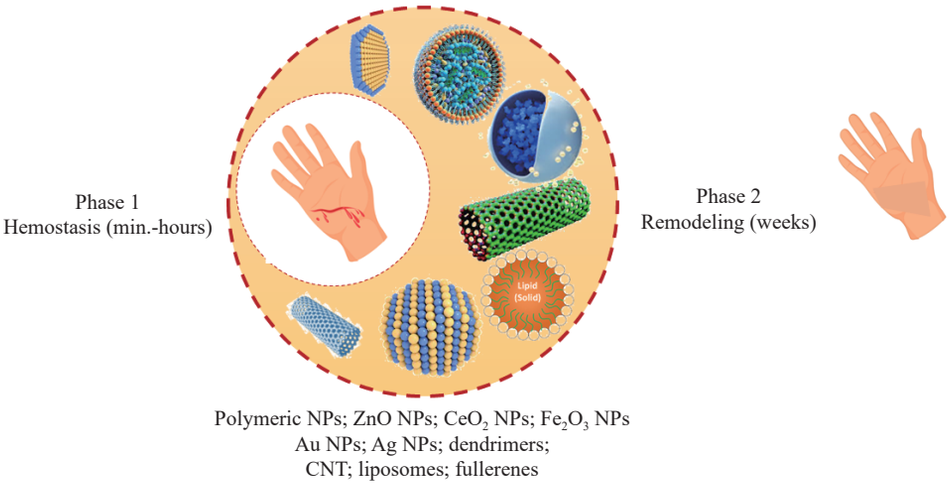

Fig. 2 Depicts the stages of used nano scales on wound healing process.

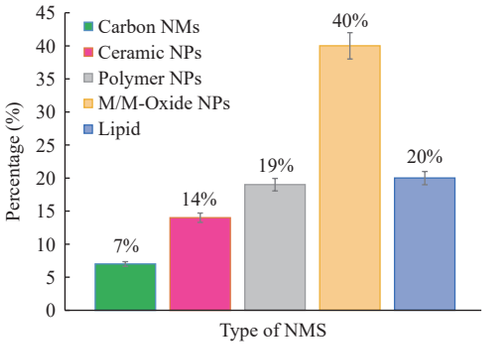

Fig. 3 The percentage of several NMs used in treating wounds on the cutaneous surface in the publications.

impregnated bandages or a cream. The end of the 1990s saw a number of manufacturers introduce Ag-containing dressings to the market. A variety of fibers and polymer scaffolds are able to be coated or impregnated with silver by adding silver salts or nanoparticles [27]. The majority of them contain antibacterial activity that can effectively fight both Gram-positive and Gram-negative bacteria. Recently several studies have examined the mechanism of action of silver, proving that it has multilayer antibacterial properties. Anti-microbial properties of silver have been demonstrated despite minimal systemic side effects (Table 2). There are no cytotoxic effects reported on fibroblasts or keratinocytes; these qualities have been confirmed in several clinical studies [28–31].

Gold nanoparticles (Au NPs)

The gold nanoparticle is a good candidate for wound therapy because of its chemical stability and ability to absorb near infrared light. In addition, synthesis of Au NPs is relatively straightforward [36]. Au NPs target bacterial cell walls and block DNA from unraveling to carry out their bactericidal and bacteriostatic functions [37]. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are good examples of pathogens that are resistant to the drug. Additionally, Au NPs act as antioxidants and facilitate the healing process by inhibiting the formation of reactive oxygen species [39, 38]. Au NPs showed excellent ability to help wound healing (Table 3).

Zinc oxide nanoparticles (ZnO NPs)

ZnO NPs are antibacterial agents, since they perforate a bacterial cell's membrane [40]. The added contact time means there is more time for keratinocytes to migrate when included in hydrogel wound dressings [41]. In recent studies, microporous chitosan hydrogel/ZnO NPs dressings were also shown significant ability to absorb wound exudates, inhibit clot formation and possess antibacterial properties without excessive cytotoxicity (Table 3) [42].

These materials, however, are not suitable for treating wounds due to their inherent toxicity. The release of lactate dehydrogenase is linked to higher concentrations of ZnO NPs, such as research in ref [43]. In addition, ZnO NPs cause oxidative stress in keratinocytes by generating reactive oxygen species and suppressing glutathione peroxidase and

Table 1 Nanomaterial's role in wound treatment

Nanomaterials	Role in Wound Healing	Ref.
Ag NPs	Essential antibacterial agent; polymer conjugated in scaffold for synergistic antibacterial activity; synergistic effects in nanostructure for gene nano treatment	[25–35]
Au NPs	Intrinsic antibacterial agent; nanocarriers for antibiotics to reach target site; synergistic activity in nanocomposite for hyperthermia treatment; effectively used siRNA delivery for gene; nano therapy	[36–39]
BP	Mostly used as photo thermal agent for hyperthermia treatment; embedded in hydrogel or as a moldable platform for wound healing	[40]
Chitosan	As wound-dressing material; conjugated with metal, metal oxide for synergistic antibacterial and wound-healing properties; conjugated with other nanomaterials in scaffold formation and antibacterial activity	[42, 41]
ZnO NPs	Intrinsic antibacterial agent for wound dressing; conjugated with polymer in scaffold for synergic antibacterial activity	[43]
CNTs	Intrinsic antibacterial agent; photo thermal agent for hyperthermia treatment	[44]
Fullerene	Intrinsic antibacterial agent	[45]
Graphene	Conjugated with metal, metal oxide for synergistic antibacterial and wound-healing properties; photo thermal agent for hyperthermia treatment; synergistic activity in nanocomposite for gene nano therapy	[46]
Iron oxide NPs	Synergistic antibacterial activity in scaffold AMF-mediated hyperthermia treatment	[47]
Liposomes	Primarily used as nano carriers for antibiotics to reach target site	[48]
PLGA NPs	Nanocarriers for antibiotics to reach target site; nanocarriers for NO release at target site hybrid scaffold material	[49]
Silica NPs	Nanocarriers for NO release at target site	[50]

Notes: BP, black phosphorus; CNTs, carbon nanotubes; NO, nitric oxide; NPs, nanoparticles; PLGA, poly(lactic-*co*-glycolic acid).

Table 2 Silver nanoparticles-based membrane composites for wound management

Polymer used	Method of preparation of nanoparticle	Size (nm)	Result
Bacterial cellulose	Using the thermal reduction method (80 °C)	10–30	Staphylococcus aureus reduction of 99%. Cytotoxicity was not observed during cell growth. [29]
Chitin	Irradiation method	3–13	Efficacious against bacterial infections [30]
Bacterial cellulose	Green method (cellulose from acetobacterxylinum)	50–150	The product has antibacterial effect against *Escherichia Coli* and *Streptococci* spp. [31]
Chitosan, polyvinyl alcohol, curcumine	Green method (chitosan)	16	The antioxidant activity is impressive against *E. colona*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans* [32]
Chitosan and chitin	Green method (*Camelia sinensis*)	60–150	Good healing activity[33]
Chitosan	Chemical method ($NaBH_4$)	15	Bacterial infections are reduced and cell growth is facilitated [35, 34]

Table 3 Wound healing with metal nanoparticles preclinical studies

Nanoparticles	Preclinical model	Procedures	Wound	Outcome
Au NPs	Rat	Burns	Wound healing with Au NPs with micro current	Improved mitochondrial function improves tissue repair
Ag NPs	Rat	Excision wound	As a result of microwave irradiation, Ag NPs are formed from Naringicrenulata leaf extract	Wound healing that is very efficient, with the possibility of healing tropical wounds
Ag NPs coated with bacterial cellulose (BC) nanofibers	Rat	Partial thickness wound	Researchers are investigating Ag NPs-BC's antibacterial activities and cytocompatibility	A method for reducing inflammation and promoting healing of scald wounds
Copper and zinc NPs	Rat	Soft tissue full layer excision wound	Wounds were either Aseptic or Infected	Regeneration is attributed to antibacterial properties
Ag NPs in alginate fibers	Rat	Excision wound (2 cm)	Studies have been conducted to evaluate the wound healing effects of Ag NPs alone and in combination with alginate fibers	Alginate fibers containing Ag NPs increased fibroblast migration to the wound and increased epidermal thickness
Ag NPs as a dressing	Dog	Severe burns (50% of total body surface area (TBSA))	Ag NPs and vacuum-assisted closure (VAC) dressings were used to facilitate wound healing	VAC and Ag NPs were effective in treating the dog

superoxide dismutase genes. ZnO NPs are also known to cause carcinogenic effects [51].

Treatment improves with nanoparticles non-metallic

As wound healing continues, NO levels decline as the healing process progresses. In recent years, it has emerged as an important component of wound healing. A new technology known as NO-releasing nanoparticles was evaluated to see if it influenced wound healing. Nanoparticles of NO (NO NPs) helped wounds heal faster.A process known as wound healing is stimulated by NO NPs, which stimulates the growth of new blood vessels in the wound site by stimulating leukocytes and tumor growth factors. Human dermal fibroblasts migrated and formed collagen in response to NO NPs treatment. NO-releasing nanoparticles are clearly capable of regulating wound healing pleiotropically as well as speeding it up [52].

As the concentration of NO in the wound area is so critical, NO-based therapy for long-term wounds has a number of challenges because it can either exasperate the lesion or not exasperate it. [53]. By decreasing collagen formation and wound strength, down-regulating NO production can delay wound healing. The inflammatory phase of wound healing can be unnecessarily prolonged in the presence of sustained high NO levels, leading to the development of keloid scars. Creating a stable, reliable, and cheap system has solved this issue. Using hydrogel-based nanoparticles (NO NPs), an easily deployable and topically applicable NO-releasing platform. NO release rates in physiological concentrations can be controlled by changing the way nanoparticles are manufactured, allowing for continuous release of NO throughout the day for many hours, per dose [54]. As for application to experimental skin diseases and abscesses, a study of NO NPs demonstrated that it was antibacterial against drug-resistant *S. aureus* and *Acinetobacter baumannii* [55].

Treatment improves with nanostructures made of polymers

Current approaches have been developed to encapsulate nanomaterials, both organic and inorganic, in polymers, such as biopolymers that are

abundant in nature, or embed them in carriers, commonly nanostructures [56]. Researches recently examined several strategies for synthesizing inorganic nanoparticles as well as organic nanoparticles. Alternately, the synthesis is carried out through a variety of hazardous processes that use laser ablation, pyrolysis, lithography, vapor deposition, sol-gel techniques, and electro-deposition. Scientists have been experimenting with microbial systems and plants as a way to create low-cost, energy-efficient, and ecological approaches [57]. The effectiveness of innovative nanotechnology can be greatly enhanced if simple preparation procedures are followed. Three steps are essential in developing formulations for wound healing: assessing *in vitro* biological compatibility, assessing antimicrobial activity *in vitro*, and confirming efficacy *in vivo* [58].

In order to deliver, encapsulate, dissolve, or entrap a medicine, polymer nanoparticles need to be used. These goods are manufactured by using natural, synthetic, and semi-synthetic materials that include gelatin, albumin, alginate, chitosan, poly(glycolic acid) and its copolymers, and polyalkylcyanoacrylate. Among the many advantages of these formulations are controlled release, sustained release, high encapsulation levels, and increased bioavailability [59]. Numerous approaches have been studied to use polymeric nanoparticles in wound healing. For instance, angiogenesis was stimulated (by increased production) and granulation tissues were produced (activating epidermal cells and fibroblasts). Excision models proved this to be true. Tumour necrosis factor (TNF) levels and wound healing were affected by the reduction in TNF expression in macrophages [60, 61].

Treatment improves with nano-scaffold

Cutaneous leishmaniasis is one of the deadliest parasite illnesses, while it is curable rapidly and leaves no scarring or self-consciousness with the help of nano-scaffolds. Nano-scaffolds that mimic tissue characteristics are quickly being adopted in tissue engineering and regenerative medicine [62]. A bioactive polymer named chitosan (CS) is well-known in biomedicine for its antimicrobial properties and wound healing properties [63, 64]. Studies also confirmed the effectiveness of fibers made of polyethylene oxide (PEO), berberine (BBR), and CS in treating experimental Leishmania major ulcers in BALB/c mice [65].

Treatment improves with lipid nanoparticles

To improve wound healing, eucalyptus and rosemary essential oils were combined with nanoparticles of lipid (solid lipid nanoparticles and nanostructured lipid carriers (NLC)) [66]. Lipid nanoparticles that consist of solid lipids like cocoa butter or liquid lipids like olive oil or sesame oil are created by using natural lipids. The use of lecithin as a surfactant stabilized and prevented the aggregation of nanoparticles. For preparation, the systems were homogenized at high speed and ultrasonic application was followed. Bio adhesion, cytocompatibility, proliferation augmentation, and wound healing abilities of nanoparticles were studied in human normal dermal fibroblasts. *S. aureus* and *S. pyogenic* were used as reference microbiological strains [44–47, 67, 68]. In a rat burn model, nanoparticles were tested for their effectiveness,and found: proliferation, wound healing, and wound healing capability were observed in NLCs derived from olive oil and eucalyptus oil. Its antibacterial properties are a result of all of these characteristics. NLC have been demonstrated to enhance healing processes *in vivo* [48–50, 69–72]. In addition to improving wound healing and antimicrobial properties, olive oil and eucalyptus oil contain high levels of oleic acid.

The challenges of nanoparticles in healing wounds

The potential for NPs to promote wound healing is commendable, and there are many opportunities for their development in the future. However, it should be emphasized that undamaged skin does not cover the wound site. Because NPs used in wound care come into direct contact with wound tissue, it is essential to determine their biological safety before usage. Skin irritability and allergy are the most frequently mentioned transdermal toxicities of NPs. For instance, it has been noted that the surface coatings and ions produced by carbon nanotubes and nickel nanotubes might result in skin hypersensitivity. According to research, transdermal skin contact with NPs can aggravate psoriasis, skin irritation, and inflammation. In several investigations, fibroblasts and keratinocytes exposed to NPs displayed oxidative stress, autophagy, and programmed cell death. The form, size, surface charge, stability, and concentration of NPs determine their toxicity. Therefore, it is essential to modify the physicochemical features of new NPs to treat wounds in order to lessen their

toxicity against skin cells. Dermatitis brought on by NPs is decreased by an increase in NP stability. Surfactants, metal shells, polymers, and other stabilizers can all be utilized [73–76].

In order to lessen skin irritation, low-sensitization materials must be utilized when coating NPs surfaces. The idea of cell cancellation has also been suggested by the claims that NPs cause DNA damage and decrease gene methylation. However, there is no conclusive evidence to show that NPs can cause heritable gene mutations and malignant changes in skin cells. Furthermore, it is necessary to prove through future extended exposure studies that the prolonged exposure of NPs to percutaneous and epidermal deposition will have dramatic impacts. However, there is no solid data to support this claim .

Once NPs enter the body, they directly contact blood cells via damaged blood vessels in lesions and enter the blood circulation, leading to hemolysis. A few metal NPs, such as AgNPs and ZnO NPs, have been shown to cause hemolysis. To overcome the aforementioned complication, the material's physicochemical properties can be adjusted, or the surface of NPs can be wrapped with biologically active substances, for example, polysaccharides and phospholipids.

View for the future

Future development of electronic skin monitoring of inflammatory variables, pH, humidity, and signaling pathway proteins is possible with the use of this technology. This will assist the medical professional in carefully regulating wound care and choosing the best NPs according to the current condition. Following the filling of flaws, wound therapy requires full functional and visual recovery. Researchers have successfully used NPs to speed up wound healing and prevent the formation of scars. Additionally, nanotechnology holds significant promise for improving aberrant pigmentation, paresthesia management, and hair follicle regeneration. Recently, new ideas for paresthesia recovery after wound invention and a clever concept for wound healing have been made possible by the growth of electronic skin and the coupling of computer technology and nanotechnology.

Conclusion

The main purpose of this review was to highlight the advantages of using nanomaterials for the wound-healing process. It is noteworthy that the unique physiochemical properties of nanomaterials render them ideal candidates for wound-healing applications. The nanomaterial-based wound-healing process also proved to be more effective than conventional wound therapy, which is primarily based on dressing. Nanomaterials can alter one or more wound-healing phases of the wound-healing process since they possess antibacterial, anti-inflammatory, and anti-proliferative properties.

The development of effective NP-based wound dressings for the detection and treatment of bacteria has been greatly increased, but there are still many insurmountable obstacles, such as reproducibility, stability, toxicity, and histocompatibility, that significantly impede the transition of NPs from a laboratory experiment to a clinical setting. Animal studies are typically used to learn how NP-based wound dressings behave in vivo. As a result of the numerous differences between human and animal models, it is crucial to discover an alternative method for preclinical studies.

CRediT Author Statement

Sarah Habeeb Hamed: Data curation, visualization, and writing–original draft. **Ebaa Adnan Azooz**: Conceptualization, investigation, project administration, supervision, and writing–review & editing. **Emad Abbas Jaffar Al-Mulla**: Data curation, formal analysis, methodology, and investigation.

Conflicts of Interest

The authors declare that no competing interest exists.

References

[1] M.H. Kim. Nanoparticle-based therapies for wound biofilm infection: Opportunities and challenges. *IEEE Transactions on NanoBioscience*, 2016, 15(3): 294−304. https://doi.org/10.1109/TNB.2016.2527600

[2] Y. Peng, Y. Liu, X.L. Lu, et al. Ag-Hybridized plasmonic Au-triangular nanoplates: Highly sensitive photoacoustic/Raman evaluation and improved antibacterial/photothermal combination therapy. *Journal of Materials Chemistry B*, 2018, 6(18): 2813−2820. https://doi.org/10.1039/c8tb00617b

[3] T. Brunella, T. Giovanni, B. Barbara, et al. Use of polylactide-Co-glycolide-nanoparticles for lysosomal delivery of a therapeutic enzyme in glycogenosis type II fibroblasts. *Journal of Nanoscience and Nanotechnology*, 2015, 15(4): 2657−2666. https://doi.org/10.1166/jnn.2015.9251

[4] A. Kushwaha, L. Goswami, B.S. Kim. Nanomaterial-based therapy for wound healing. *Nanomaterials*, 2022, 12(4): 618. https://doi.org/10.3390/nano12040618

[5] D.M. dos Santos, D.S. Correa, E.S. Medeiros, et al. Advances in functional polymer nanofibers: From spinning fabrication techniques to recent biomedical applications. *ACS Applied Materials & Interfaces*, 2020, 12(41): 45673−45701. https://doi.org/10.1021/acsami.0c12410

[6] X.L. Lu, R.H. Chen, J. Lv, et al. High-resolution bimodal imaging and potent antibiotic/photodynamic synergistic therapy for osteomyelitis with a bacterial inflammation-specific versatile agent. *Acta Biomaterialia*, 2019, 99: 363−372. https://doi.org/10.1016/j.actbio.2019.08.043

[7] E.A. Azooz, E.A. Azooz, R.K. Kadhum. Rapid palladium preconcentration and spectrophotometric determination in water and soil samples. *Analytical and Bioanalytical Chemical Research*, 2022, 9(3): 251−258.

[8] N. Siebert, W.G. Xu, E. Grambow, et al. Erythropoietin improves skin wound healing and activates the TGF-β signaling pathway. *Laboratory Investigation*, 2011, 91(12): 1753−1765. https://doi.org/10.1038/labinvest.2011.125

[9] A.K.M. Al-Toriahi, E.A. Azooz, E.A.J. Al-Mulla. Metal nanoparticles and nano-filters for the disposal of hospital waste: A review. *Nano Biomedicine and Engineering*, 2023, 15(2): 179−190. https://doi.org/10.26599/NBE.2023.9290017

[10] C.A. Cobbold, J.A. Sherratt. Mathematical modelling of nitric oxide activity in wound healing can explain keloid and hypertrophic scarring. *Journal of Theoretical Biology*, 2000, 204(2): 257−288. https://doi.org/10.1006/jtbi.2000.2012

[11] M.K. Swamy, U.R. Sinniah. Patchouli (*Pogostemon cablin* Benth.): Botany, agrotechnology and biotechnological aspects. *Industrial Crops and Products*, 2016, 87: 161−176. https://doi.org/10.1016/j.indcrop.2016.04.032

[12] S.K. Mohanty, M.K. Swamy, U.R. Sinniah, et al. *Leptadenia reticulata* (Retz.) Wight & Arn. (Jivanti): Botanical, agronomical, phytochemical, pharmacological, and biotechnological aspects. *Molecules*, 2017, 22(6): 1019. https://doi.org/10.3390/molecules22061019

[13] A.R. Hussein, M.S. Gburi, N.M. Muslim, et al. A greenness evaluation and environmental aspects of solidified floating organic drop microextraction for metals: A review. *Trends in Environmental Analytical Chemistry*, 2023, 37: e00194. https://doi.org/10.1016/j.teac.2022.e00194

[14] V. Vijayakumar, S.K. Samal, S. Mohanty, et al. Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management. *International Journal of Biological Macromolecules*, 2019, 122: 137−148. https://doi.org/10.1016/j.ijbiomac.2018.10.120

[15] S. Hamdan, I. Pastar, S. Drakulich, et al. Nanotechnology-driven therapeutic interventions in wound healing: Potential uses and applications. *ACS Central Science*, 2017, 3(3): 163−175. https://doi.org/10.1021/acscentsci.6b00371

[16] M.A.M. Hassan, A.H. Mohammed, , Hameed, E. M. Application of *Aloe vera* gel blended polymer-collagen scaffolds for bone tissue engineering. *Nano Biomedicine and Engineering*, 2023, 15(2): 118–125. https://doi.org/10.26599/nbe.2023.9290016

[17] T.J. Shaw, P. Martin. Wound repair at a glance. *Journal of Cell Science*, 2009, 122(18): 3209−3213. https://doi.org/10.1242/jcs.031187

[18] E.A. Azooz, H.S.A. Al-Wani, M.S. Gburi, et al. Recent modified air-assisted liquid–liquid microextraction applications for medicines and organic compounds in various samples: A review. *Open Chemistry*, 2022, 20(1): 525−540. https://doi.org/10.1515/chem-2022-0174

[19] K.P. Hoversten, L.J. Kiemele, A.M. Stolp, et al. Prevention, diagnosis, and management of chronic wounds in older adults. *Mayo Clinic Proceedings*, 2020, 95(9): 2021−2034. https://doi.org/10.1016/j.mayocp.2019.10.014

[20] M.L. Wang, X.W. Huang, H.X. Zheng, et al. Nanomaterials applied in wound healing: Mechanisms, limitations and perspectives. *Journal of Controlled Release*, 2021, 337: 236−247. https://doi.org/10.1016/j.jconrel.2021.07.017

[21] G. Han, R. Ceilley. Chronic wound healing: A review of current management and treatments. *Advances in Therapy*, 2017, 34: 599−610. https://doi.org/10.1007/s12325-017-0478-y

[22] M.M. Mihai, M.B. Dima, B. Dima, et al. Nanomaterials for wound healing and infection control. *Materials*, 2019, 12(13): 2176. https://doi.org/10.3390/ma12132176

[23] C.Y. Mao, Y.M. Xiang, X.M. Liu, et al. Repeatable photodynamic therapy with triggered signaling pathways of fibroblast cell proliferation and differentiation to promote bacteria-accompanied wound healing. *ACS Nano*, 2018, 12(2): 1747−1759. https://doi.org/10.1021/acsnano.7b08500

[24] R. Ahmadi, E.A. Azooz, Y. Yamini, et al. Liquid-liquid microextraction techniques based on *in situ* formation/decomposition of deep eutectic solvents. *TrAC Trends in Analytical Chemistry*, 2023, 161: 117019. https://doi.org/10.1016/j.trac.2023.117019

[25] S.S.D. Kumar, N.K. Rajendran, N.N. Houreld, et al. Recent advances on silver nanoparticle and biopolymer-based biomaterials for wound healing applications. *International Journal of Biological Macromolecules*, 2018, 115: 165−175. https://doi.org/10.1016/j.ijbiomac.2018.04.003

[26] T.G. MPharm, T. Nigusse, M.D.D. MPharm. Silver nanoparticles as real topical bullets for wound healing. *Journal of the American College of Clinical Wound Specialists*, 2011, 3(4): 82−96. https://doi.org/10.1016/j.jcws.2012.05.001

[27] W. Sim, R. Barnard, M.A.T. Blaskovich, et al. Antimicrobial silver in medicinal and consumer applications: A patent review of the past decade (2007–2017). *Antibiotics*, 2018, 7(4): 93. https://doi.org/10.3390/antibiotics7040093

[28] J.S. Möhler, W. Sim, M.A.T. Blaskovich, et al. Silver bullets: A new lustre on an old antimicrobial agent. *Biotechnology Advances*, 2018, 36(5): 1391−1411. https://doi.org/10.1016/j.biotechadv.2018.05.004

[29] R. Szmyd, A.G. Goralczyk, L. Skalniak, et al. Effect of silver nanoparticles on human primary keratinocytes. *Biological Chemistry*, 2013, 394(1): 113−123. https://doi.org/10.1515/hsz-2012-0202

[30] M. Ahmadi, M. Adibhesami. The effect of silver nanoparticles on wounds contaminated with *Pseudomonas aeruginosa* in mice: An experimental study. *Iranian Journal of Pharmaceutical Research*, 2017, 16(2): 661−669.

[31] S. Pal, R. Nisi, M. Stoppa, et al. Silver-functionalized bacterial cellulose as antibacterial membrane for wound-healing applications. *ACS Omega*, 2017, 2(7): 3632−3639. https://doi.org/10.1021/acsomega.7b00442

[32] J. Wu, Y.D. Zheng, W.H. Song, et al. *In situ* synthesis of

silver-nanoparticles/bacterial cellulose composites for slow-released antimicrobial wound dressing. *Carbohydrate Polymers*, 2014, 102: 762–771. https://doi.org/10.1016/j.carbpol.2013.10.093

[33] E.A. Azooz, G.J. Shabaa, E.A.J. Al-Mulla. Methodology for preconcentration and determination of silver in aqueous samples using cloud point extraction. *Brazilian Journal of Analytical Chemistry*, 2021, 9(35): 39−48. https://doi.org/10.30744/brjac.2179-3425.ar-61-2021

[34] R. Singh, D. Singh. Chitin membranes containing silver nanoparticles for wound dressing application. *International Wound Journal*, 2014, 11(3): 264−268. https://doi.org/10.1111/j.1742-481x.2012.01084.x

[35] W. Hu, S. Chen, X. Li, et al.. *In situ* synthesis of silver chloride nanoparticles into bacterial cellulose membranes. *Materials Science and Engineering*: *C*, 2009, 29(4): 1216–1219. https://doi.org/10.1016/j.msec.2008.09.017

[36] K. Niska, E. Zielinska, M.K. Radomski, et al. Metal nanoparticles in dermatology and cosmetology: Interactions with human skin cells. *Chemico-Biological Interactions*, 2018, 295: 38−51. https://doi.org/10.1016/j.cbi.2017.06.018

[37] M.G. Arafa, R.F. El-Kased, M.M. Elmazar. Thermoresponsive gels containing gold nanoparticles as smart antibacterial and wound healing agents. *Scientific Reports*, 2018, 8: 13674. https://doi.org/10.1038/s41598-018-31895-4

[38] M.A. Sherwani, S. Tufail, A.A. Khan, et al. Gold nanoparticle-photosensitizer conjugate based photodynamic inactivation of biofilm producing cells: Potential for treatment of C. albicans infection in BALB/c mice. *PLoS One*, 2015, 10(7): e0131684. https://doi.org/10.1371/journal.pone.0131684

[39] O. Akturk, K. Kismet, A.C. Yasti, et al. Collagen/gold nanoparticle nanocomposites: A potential skin wound healing biomaterial. *Journal of Biomaterials Applications*, 2016, 31(2): 283−301. https://doi.org/10.1177/0885328216644536

[40] L. Shahzadi, A.A. Chaudhry, A.R. Aleem, et al. Development of K-doped ZnO nanoparticles encapsulated crosslinked chitosan based new membranes to stimulate angiogenesis in tissue engineered skin grafts. *International Journal of Biological Macromolecules*, 2018, 120: 721−728. https://doi.org/10.1016/j.ijbiomac.2018.08.103

[41] P.C. Balaure, A.M. Holban, A.M. Grumezescu, et al. *In vitro* and *in vivo* studies of novel fabricated bioactive dressings based on collagen and zinc oxide 3D scaffolds. *International Journal of Pharmaceutics*, 2019, 557: 199–207. https://doi.org/10.1016/j.ijpharm.2018.12.063

[42] F.A. Wannas, E.A. Azooz, R.K. Ridha, et al. Separation and micro determination of zinc(II) and cadmium(II) in food samples using cloud point extraction method. *Iraqi Journal of Science*, 2023, 64(3): 1046−1061. https://doi.org/10.24996/ijs.2023.64.3.2

[43] R. Rakhshaei, H. Namazi. A potential bioactive wound dressing based on carboxymethyl cellulose/ZnO impregnated MCM-41 nanocomposite hydrogel. *Materials Science and Engineering*: *C*, 2017, 73: 456−464. https://doi.org/10.1016/j.msec.2016.12.097

[44] E.A.J. Al-Mulla, K. Al-Janabi. Extraction of cobalt(II) from aqueous solution by *N, N*'-carbonyl difatty amides. *Chinese Chemical Letters*, 2011, 22(4): 469−472. https://doi.org/10.1016/j.cclet.2010.10.037

[45] J.U. Choi, S.W. Lee, R. Pangeni, et al. Preparation and *in vivo* evaluation of cationic elastic liposomes comprising highly skin-permeable growth factors combined with hyaluronic acid for enhanced diabetic wound-healing therapy. *Acta Biomaterialia*, 2017, 57: 197−215. https://doi.org/10.1016/j.actbio.2017.04.034

[46] E.A.J. Al-Mulla. Preparation of polylactic acid/epoxidized palm oil/fatty nitrogen compounds modified clay nanocomposites by melt blending. *Polymer Science Series A*, 2011, 53(2): 149−157. https://doi.org/10.1134/s0965545x11020015

[47] A. Naskar, H. Khan, R. Sarkar et al. Anti-biofilm activity and food packaging application of room temperature solution process based polyethylene glycol capped Ag-ZnO-graphene nanocomposite. *Materials Science and Engineering*: *C*, 2018, 91: 743−753. https://doi.org/10.1016/j.msec.2018.06.009

[48] Y.Z. Zhou, R. Chen, T.T. He, et al. Biomedical potential of ultrafine Ag/AgCl nanoparticles coated on graphene with special reference to antimicrobial performances and burn wound healing. *ACS Applied Materials & Interfaces*, 2016, 8(24): 15067−15075. https://doi.org/10.1021/acsami.6b03021

[49] E.A.J. Al-Mulla, W.M.Z.W. Yunus, N.A.B. Ibrahim, et al. Epoxidized palm oil plasticized polylactic acid/fatty nitrogen compound modified clay nanocomposites: Preparation and characterization. *Polymers and Polymer Composites*, 2010, 18(8): 451−460. https://doi.org/10.1177/096739111001800806

[50] R.H. Dong, Y.X. Jia, C.C. Qin, et al. *In situ* deposition of a personalized nanofibrous dressing via a handy electrospinning device for skin wound care. *Nanoscale*, 2016, 8(6): 3482−3488. https://doi.org/10.1039/c5nr08367b

[51] G.J. Shabaa, F.A. Semysim, R.K. Ridha, et al. Air-assisted dual-cloud point extraction coupled with flame atomic absorption spectroscopy for the separation and quantification of zinc in pregnant women's serum. *Journal of the Iranian Chemical Society*, 2023, 20(9): 2277−2284. https://doi.org/10.1007/s13738-023-02834-6

[52] G. Han, L.R. Martinez, M.R. Mihu, et al. Nitric oxide releasing nanoparticles are therapeutic for staphylococcus aureus abscesses in a murine model of infection. *PLoS One*, 2009, 4(11): e7804. https://doi.org/10.1371/journal.pone.0007804

[53] L.R. Martinez, G. Han, M. Chacko, et al. Antimicrobial and healing efficacy of sustained release nitric oxide nanoparticles against *Staphylococcus aureus* skin infection. *Journal of Investigative Dermatology*, 2009, 129(10): 2463−2469. https://doi.org/10.1038/jid.2009.95

[54] M.R. Mihu, U. Sandkovsky, G. Han, et al. The use of nitric oxide releasing nanoparticles as a treatment against*Acinetobacter baumannii*in wound infections. *Virulence*, 2010, 1(2): 62−67. https://doi.org/10.4161/viru.1.2.10038

[55] E.A. Azooz, J.R. Moslim, S.M. Hameed, et al. Aspirin in Food Samples for Separation and Micro Determination of Copper(II) using Cloud Point Extraction/Solvation Method. *Nano Biomedcine and Eng*ineering, 2021,13(1): 62–71. https://doi.org/10.5101/nbe.v13i1.p62-71

[56] B.D. Ulery, L.S. Nair, C.T. Laurencin. Biomedical applications of biodegradable polymers. *Journal of Polymer Science Part B*: *Polymer Physics*, 2011, 49(12): 832−864. https://doi.org/10.1002/polb.22259

[57] H.K. Makadia, S.J. Siegel. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers*, 2011, 3(3): 1377−1397. https://doi.org/10.3390/polym3031377

[58] V.P. Torchilin. Drug targeting. *European Journal of Pharmaceutical Sciences*, 2000, 11: S81−S91. https://doi.org/10.1016/S0928-0987(00)00166-4

[59] E.A. Azooz, R.K. Ridha, H.A. Abdulridha. The Fundamentals and Recent Applications of Micellar System Extraction for Nanoparticles and Bioactive Molecules: A Review. *Nano Biomedicine and Eng*ineering, 2021, 13(3): 264–278. https://doi.org/10.

5101/nbe.v13i3.p264-278
[60] F. Norouzinezhad, F. Ghaffari, A. Norouzinejad, et al. Cutaneous leishmaniasis in Iran: Results from an epidemiological study in urban and rural provinces. *Asian Pacific Journal of Tropical Biomedicine*, 2016, 6(7): 614−619. https://doi.org/10.1016/j.apjtb.2016.05.005
[61] A. Stejskalová, B.D. Almquist. Using biomaterials to rewire the process of wound repair. *Biomaterials Science*, 2017, 5(8): 1421−1434. https://doi.org/10.1039/c7bm00295e
[62] M.I.N. Ahamed, S. Sankar, P.M. Kashif, et al. Evaluation of biomaterial containing regenerated cellulose and chitosan incorporated with silver nanoparticles. *International Journal of Biological Macromolecules*, 2015, 72: 680−686. https://doi.org/10.1016/j.ijbiomac.2014.08.055
[63] N. Levi-Polyachenko, R. Jacob, C. Day, et al. Chitosan wound dressing with hexagonal silver nanoparticles for hyperthermia and enhanced delivery of small molecules. *Colloids and Surfaces B*: *Biointerfaces*, 2016, 142: 315−324. https://doi.org/10.1016/j.colsurfb.2016.02.038
[64] R. Jayakumar, M. Prabaharan, P.T. Sudheesh Kumar, et al. Biomaterials based on chitin and chitosan in wound dressing applications. *Biotechnology Advances*, 2011, 29(3): 322−337. https://doi.org/10.1016/j.biotechadv.2011.01.005
[65] S.H. Hsu, Y.B. Chang, C.L. Tsai, et al. Characterization and biocompatibility of chitosan nanocomposites. *Colloids and Surfaces B*: *Biointerfaces*, 2011, 85(2): 198−206. https://doi.org/10.1016/j.colsurfb.2011.02.029
[66] R.A.B. Sanad, H.M. Abdel-Bar. Chitosan-hyaluronic acid composite sponge scaffold enriched with Andrographolide-loaded lipid nanoparticles for enhanced wound healing. *Carbohydrate Polymers*, 2017, 173: 441−450. https://doi.org/10.1016/j.carbpol.2017.05.098
[67] P.S. Rabbani, A. Zhou, Z.M. Borab, et al. Novel lipoproteoplex delivers *Keap1* siRNA based gene therapy to accelerate diabetic wound healing. *Biomaterials*, 2017, 132: 1−15. https://doi.org/10.1016/j.biomaterials.2017.04.001
[68] F.H.J. Al-Shemmari, E.A.J. Al-Mulla, A.A. Rabah. A comparative study of different surfactants for natural rubber clay nanocomposite preparation. *Rendiconti Lincei*, 2014, 25(3): 409−413. https://doi.org/10.1007/s12210-014-0307-z
[69] W.H. Hoidy, M.B. Ahmad, E.A.J. Al-Mulla. Chemical synthesis and characterization of palm oil-based difatty Acyl thiourea. *Journal of Oleo Science*, 2010, 9(5): 229−233. https://doi.org/10.5650/jos.59.229
[70] K.H. Gathwan, I.H.T. Al-Karkhi, E.A.J. Al-Mulla. Hepatic toxicity of nickel chloride in mice. *Research on Chemical Intermediates*, 2013, 39: 2537−2542. https://doi.org/10.1007/s11164-012-0780-x
[71] N. Volkova, M. Yukhta, O. Pavlovich, et al. Application of cryopreserved fibroblast culture with Au nanoparticles to treat burns. *Nanoscale Research Letters*, 2016, 11: 22. https://doi.org/10.1186/s11671-016-1242-y
[72] M. Mirzahosseinipour, K. Khorsandi, R. Hosseinzadeh, et al. Antimicrobial photodynamic and wound healing activity of curcumin encapsulated in silica nanoparticles. *Photodiagnosis and Photodynamic Ther*apy, 2020, 29: 101639. https://doi.org/10.1016/j.pdpdt.2019.101639
[73] I.A. Mohammed, E.A.J. Al-Mulla, N.K.A. Kadar, et al. Structure-property studies of thermoplastic and thermosetting polyurethanes using palm and soya oils-based polyols. *Journal of Oleo Science*, 2013, 62(12): 1059−1072. https://doi.org/10.5650/jos.62.1059
[74] M.M. Radhi, E.A. Jaffar Al-Mulla, W.T. Tan. Electrochemical characterization of the redox couple of Fe(III)/Fe(II) mediated by grafted polymer electrode. *Research on Chemical Intermediates*, 2014, 40(1): 179−192. https://doi.org/10.1007/s11164-012-0954-6
[75] N.M. Muslim, B.K. Hussain, N.M. Abdulhussein, et al. Determination of selenium in black tea leaves using the air-assisted cloud point extraction method: evaluation the method's environmental performance. *Analytical Bioanalytical Chemistry Research*, 2024, 11(1): 10−21.
[76] C.Y. Tong, W. Zou, W.M. Ning, et al. Synthesis of DNA-guided silver nanoparticles on a graphene oxide surface: Enhancing the antibacterial effect and the wound healing activity. *RSC Advances*, 2018, 8(49): 28238−28248. https://doi.org/10.1039/c8ra04933e