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Review

Nanoparticles impregnated wound dressing material and its mechanistic insight for chronic wound healing: Recent progress

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Abstract: Wounds are structural and functional disruptions of the skin that occur because of trauma, surgery, acute illness, or chronic disease conditions. Chronic wounds are caused by a breakdown in the finely coordinated cascade of events that occurs during wound healing. Wound healing is a long process that split into at least three continuous and overlapping processes: an inflammatory response, a proliferative phase that leads to tissue repair, and third one is tissue remodeling. Therefore, wound healing studies are extensively studied to develop techniques that can achieve maximum recovery with minimum scar. Several growth hormones and cytokines secreted at the wound site tightly regulate wound healing processes. The traditional approach for wound management has been represented by topical treatments. Metal nanoparticles (e.g., silver, gold, zinc) are increasingly being employed in dermatology due to their favorable effects on wound healing, as well as in treating and preventing bacterial infections. The development of wound dressings materials has now been used to overcome the issues of external environments. The impregnated nanomaterials have provided moist environment that removes the exudates and avoid maceration. This review highlights the mechanism and focus on the current advancement of various nanoparticles impregnation material for wound healing process that can protect wound from infection and maintain the optimum exchange of gases.

Keywords: Wound; Impregnated materials; Nanoparticles; Dermatology

1. Introduction

A wound is described as any disruption in the anatomic structures, function, or any break in the continuity of the skin [1,2]. The term "wound" refers to the destruction of biological tissues such as the skin, mucosal membranes, and organ tissues. Cuts, scares, and scratches are common, and the skin loses morphological traits and functions in the damaged region. There are two methods for measuring and analyzing the wound's range: invasive and non-invasive. There are non-invasive techniques available for assessing the maximum length, tissue viability, surface area, wound perimeter, volume, width parameters, volume, and amount of weakening. Invasive techniques evaluate the wound range in terms of tissue levels from the wound's surface to the wound's depth [1]. Additional aspects that may offer evidence of the wound's genesis, etiology, and condition include inflammation, edema, repetitive trauma, blood flow, oxygen, infection, innervations, prior injury management, systematic factors, wound metabolism, nutrition, and prior injury management [3]. Wounds are sometimes called as "silent epidemics" because if they are not treated, they can result in the loss of limbs, legs, or even death [4]. Postoperative surgical wounds account for 13% of all wounds in the community, according to a recent study of five acute hospital and community NHS (National Health Service) trusts [5]. In the United Kingdom, the National Health Service (NHS) treated 2.2 million people with wounds in 2012/2013, accounting for 4.5 percent of the adult population [6]. The NHS expects wound care and accompanying co-morbidities to cost £53 billion per year. In 2013, this amounted to 4% of total public health expenditure in the United Kingdom (£125

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billion). The wounds may remain open for months as in case of diabetic foot, giving patient's agony, concern, and discomfort, as well as financial hardship [6]. The Centers for Disease Control and Prevention (CDC) advice people to examine their wounds every 24 hours. This includes taking off the bandages and checking the wounds for signs of infection. After disinfecting and drying the wound, a clean adhesive bandage or Band-Aid should be placed. Chronic wounds are defined as those that do not heal on time and in a systematic way to re-establish anatomical and functional stability [7,8]. Many scientists predict that a wound takes 6-8 weeks to heal, even though chronic wounds need more than 8 weeks to heal. Under wound infection, the presence of a foreign pathogen, prolonged irritation, trauma, and ischemia are some of the causes of chronic wound healing [9,10]. Chronic wounds do not heal in a progressive fashion. Hypoxia, pH shift, and bacterial colonization are only a few of the pathophysiologic variables that have slowed wound healing. As chronic wounds and significant burns demand surgical intervention, they are both costly and time-consuming to cure. The healthcare system is put under a lot of burden because of poor wound healing. Over $ 25 billion is spent yearly in the United States on wound care, and 4.5 million individuals are infected with chronic wounds [11], which are on the rise owing to obesity and diabetes [12,13]. Because of the severity of the damage, treating the burn wound is challenging, as over 40,000 burn patients are hospitalized each year, with 4000 of them dying because of this injury [14]. Chronic wound affects around 1% of the European population and have a detrimental influence on the affected individual's quality of life, and chronic wound care consumes nearly 2% of the health budget. The various factors directly or indirectly responsible for chronic wound development are shown in Fig.1 [15].

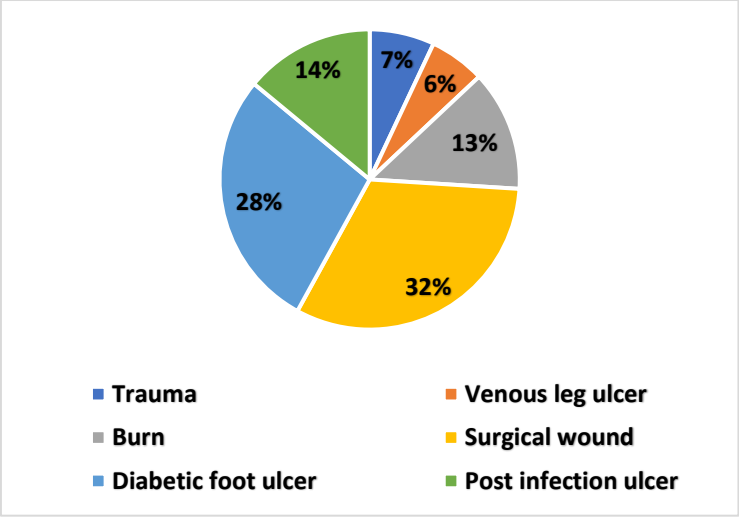

Fig.1. Pie chart representation on percentage of wound resources.

There are many bacteria that operate as microbiota and perform a positive role in limiting the growth of other germs. However, once they reach the infection site, they disrupt the healing process and create biofilms [16]. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. aureus* are the most prevalent bacteria that impair wound healing in the early stages, whereas *Escherichia coli* and *Pseudomonas aeruginosa* infect the deeper layers of the skin [17]. Chronic wounds include a variety of microorganisms due to their synergistic bacterial growth [18]. The resources are being shared consequently among the microbes that support each other's proliferation, due to which *S. aureus and P. aeruginosa* grows on multiple wounds at the same time [16]. Wound healing is a complicated, carefully controlled process that involves the regeneration, reformation, and repair of injured tissues [19], all of which are necessary for the skin's barrier function to be maintained. Homeostasis, inflammation, proliferation, and remodeling are the four phages required for wound healing. Homeostasis is the initial step, which begins with damage. The healing

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cascade begins when torn collagen meets platelets, leading in the deposition of platelets and coagulating chemicals that form fibrin clots and eventually arrest bleeding at the wound sites. The inflammatory phase, starts by ensuring that thrombosis form inflammatory cells called platelets, which produce signals called cytokines or growth factors, which also reach damage sites and serve two major functions- first, cytokines detect and remove pathogens from injury, and second, cytokines segregate the cell that is in the proliferation phase [20]. The proliferation phase, which can last up to two weeks, is the third stage. When granulation tissues start to cover the wound, this phase begins. Stem cells and fibroblasts are important components in this phase, since they release inflammatory mediators, collagen, preserves inflammatory deposits, and move to the damaged region [21,22]. Remodeling will be the third step, which might take at least two years. This phase oversees repairing the structure and function of the tissue [20]. Necrotic tissue, microbial contamination, foreign particle entrapment, and co-morbidities are all external and internal factors that contribute towards wound healing (e.g. in the case of diabetes mellitus).

2. Wound infection development and its progression

All skin injuries or illnesses induced by trauma or therapeutic treatments are referred to as wounds. Open wounds and closed wounds are the two types of wounds created by cutting, hitting, or burning [23]. Open wounds are commonly associated with bleeding and the rupturing of skin layers [24-27]. Closed wounds are produced by bruises, dead blood, or impacts. Based on their clinical features, wound is classified into acute or chronic. Burns, cuts, and surgical incisions generate acute wounds, which need 8–12 weeks to heal [26]. Tumors, bed wounds, and diabetic wounds cause chronic wounds by causing prolonged inflammation and a lengthier healing period. There are four types of wound based on their cleanliness-: class 1, class 2, class 3, and class 4 [8]. While bacteria are naturally present in the skin and wounds, 10^5 bacteria have been identified as the essential threshold between colonization and clinically significant illness [28]. Bacteria can enter the underlying tissues of injured skin, triggering inflammation and the production of proteases and reactive oxygen species by inflammatory cells [16,29]. Bacterial endotoxins raise cytokine levels while lowering growth factor production and collagen synthesis [30]. The infection can then advance from contamination to colonization, which is inhibited by biofilm formation [31]. Biofilms were found in 60% of chronic wound biopsy samples and 6% of acute wound biopsy samples [29]. In infected wounds, Bessa et al. [32] detected bacterial infections as well as treatment resistance profiles. The researchers gathered 312 wound swab samples from 213 persons suffering from various sorts of wounds and 28 species were isolated. *S. aureus, P. aeruginosa, P. mirabilis, E. coli and Corynebacterium spp*. were the most often found in bacterial species [32]. *P. aeruginosa* possesses a variety of resistance mechanisms that reduce permeability, synthesizes antibiotic-inactivating enzymes and change target proteins [33]. The most common cause of drug resistance is the use of unsuitable antibiotics and irrational antibiotic treatment [34]. Some common type of wounds infections and their preventive measures has been discussed in the Table 1.

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Table 1. The description of some common wounds and its traditional treatments

Causative bacteria	Wound types	Diseases/Infections associated	Preventive measures	Drugs	References
Staphylococcus aureus	Acute wound	Abscesses (boil), Furuncles, Cellulitis	Maintaining good hygienic and regular and frequent hand washing	Penicillin	[35]
Escherichia coli	Clinical wound	Cholecystitis, bacteremia, Cholangitis, Urinary tract infection (UTI)	Wash hands before handling, serving, or eating food, and especially after touching animals, working in animal environments	Erythromycin, Amoxicillin, Vancomycin and Tetracycline.	[36]
Pseudomonas aeruginosa	Open wound	Pneumonia, Urinary tract infections (UTIs)	1% acetic acid is a simple, safe, and effective topical antiseptic that can be used in the elimination of *P. aeruginosa* from chronic infected wounds	Ciprofloxacin and Tobramycin	[37]
Klebsiellia pneumonia	Chronic wound	Urinary tract infection	Strict adherence to hand hygiene and wearing gowns and gloves	Meropenem and Cefroperazone.	[38]
Streptococcus pyogens	Acute wound	Strep throat, pharyngitis, scarlet fever (rash), impetigo, cellulitis, or erysipelas.	Wash hands before handling, serving, or eating food	Benzathine and Penicillin	[39]
Proteus species	Surgical acute	Urinary tract infections	Minimizing the incidence of infection using urinary catheterization and using high spectrum antibiotics	Ofloxacin and Ciprofloxacin	[40]
Enterococcus faecalis	Surgical wound	Bacteremia, UTI, catheter-related infections, pelvic infections.	Practicing good hygiene and intense antibiotics	Ampicillin	[41]

3. Traditional wound healing approach

Wound healing is the process of a wound on the skin healing. The healing wound is the outer manifestation of a complex series of cellular and metabolic processes aimed to restoring tissue integrity and functional capabilities following injury [42]. Homeostasis, inflammation, proliferation and remodeling are the four phases of traditional wound healing. Homeostasis is the body's first response to an injury, occurring near the injury site to prevent bleeding and minimize damage. Platelets, which are also known as inflammatory cells, are the first cells to arrive at a lesion site. They are activated by the breakdown of collagens and the production of thrombin, which initiates the coagulation cascade, which results in the formation of a fibrin clot at the damage site. Platelets also activate the complement system, which leads to the synthesis of platelet-derived growth factors (PDGF), transforming growth factors (TGF), interleukin, and insulin growth factors. Platelets also form a cluster in the event of an injury, which prevents blood flow. By interacting with fibroblasts, connective tissue cells that deposit collagen and prevent bleeding and platelet-derived growth factors (PDGF) increase vascularization [43]. The inflammatory phase lasts six days and begins immediately after the damage is caused [44]. After 24-48 hours, the wound site produces numerous vasoactive mediators and chemotactic factors and mast

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cells release enzyme, histamine, and other active amines, resulting in an inflammatory response. Neutrophils are the first cells to arrive at the injury site, attaching to endothelial cells within 24 hours and becoming active. Pathogens, foreign substances, and dead cells are all phagocytized by neutrophils. Endothelial cells adhere to the injury and release cell adhesion molecules (CAMs) which function as hooks, and more neutrophils attach onto the endothelial cell surface and push against permeable cell connections via mast cell mediators [45,46] and triggering the inflammatory cell response. In roughly two days, monocytes and lymphocytes migrate to the site of the injury and transform into macrophages, removing necrotic tissue and pathogens and starting the formation of granulation tissue [47]. Macrophages produce a protease inhibitor, which helps them to release neutrophils [48] as well as growth factors including TGF, PDGF, Tumor necrosis factor, TNF, and cytokines, which are required for fibroblast, smooth muscle cell, and endothelial cell proliferation and ECM (extracellular macromolecules and minerals), deposition [49]. The proliferative phase begins with the repair of injured tissues and the initiation of angiogenesis through ECM synthesis. This stage lasts for around 2-3 days following the injury and continues until the wound heals. Fibroblasts and endothelial cells are the primary cells at this stage. Angiogenesis, which is required for the production of granulation tissue, is stimulated by vascular endothelial growth factors A (VEGF-A), FGF-2, PDGF, and TGF. Inflammatory cytokines like IL-1 and TNF-a cause fibroblasts to release growth factors like EGF, KGF, and HGF, which attract keratinocytes to the wound bed and cause granulation tissue to develop [50]. From wound borders and skin appendages, basal keratinocytes move to the injured area, proliferate, differentiate, and eventually form a covering over the wound. Wound contraction occurs when the wound edges are pulled together by fibroblasts in the wound bed to seal the wound [51]. The final stage is maturation and reconstruction, which begin three days after the damage and can extend up to two years. Endothelial cells, myofibroblasts, and macrophages are all killed or removed from the wound [50]. Small capillaries combine to generate bigger blood vessels and wound-healing metabolic activity decreases. The bulk of the ECM in a damaged area is made up of collagen and other ECM proteins. Fibroblasts generate the lysyl oxidases which realigns collagen into an organized network, increasing tensile strength about 80% of normal tissue. Matrix metalloproteinase (MMPs) which are secreted by fibroblasts and other cells, control the collagen formation [52-54]. MMPs help wound healing by rebuilding and degrading the ECM (Fig.2).

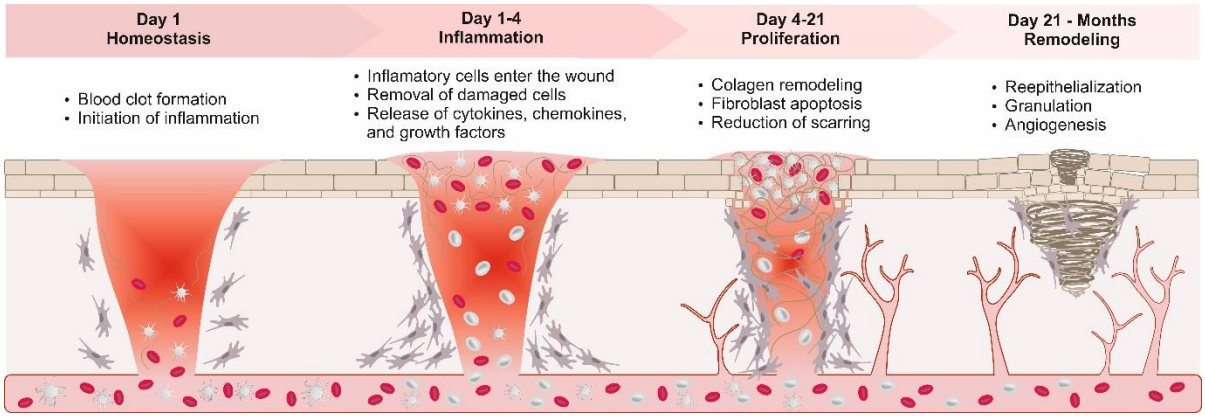

Fig.2. A practical approach for chronic wound healing and outcomes.

4. Nanotechnology and wound healing

Nanotechnology is a rapidly expanding discipline that combines material science and engineering. It deals with the understanding and control of matter at dimensions between 1-100nm. Nanoparticles have distinct qualities like as physicochemical, optical, and biological properties that may be employed for a variety of applications. They can be differentiated or classified according to the size, morphology, physical and chemical properties.

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Metals, polymers, polysaccharides, and plant-derived bioactive compounds can be chemically formed into nanoparticles that can be combined with active drugs and used against human pathogens such as bacteria and viruses, as well as used to treat various anatomical and physiological conditions such as cancer, hemophilia, stroke, blood disorder, and so on [55,56]. The utilization of nanotechnology materials is one of the most promising approaches for the invention of antibacterial agents and development of wound dressings [57]. Nanoparticles include things like nano capsules, solid lipid nanoparticles (SLNs), and nanospheres. Nanospheres are made up of various biodegradable polymers such as poly lactic-co-glycolic acid (PLGA), poly(lactide) (PLA) and natural polymers like alginate, chitosan and gelatin-based colloidal systems used for the delivery of protein and peptides important in wound healing. Some of the nanosphere have low loading ability due to high poly-dispersity and variable size [58]. Biopolymers containing lipidic/lipophilic components are used to make nano capsules. They have the potential to penetrate deeper into the skin. The topical delivery of protein into cells is accomplished using Nanostructure Lipid Carriers (NLCs). NLCs such as liposome, solid lipid nanoparticles and ethosomes are ideal drug delivery systems with advantages of biodegradation and nanotoxicity [59]. They have precise target identification, which increases their efficacy while decreasing adverse effects. Since ancient times, elements such as silver, gold, copper, zinc, and titanium have shown to be more beneficial than others in the treatment of many human conditions. Metal nanoparticles are antibacterial and have a low skin invasion force and are transparent after application. Furthermore, physicochemical, and biological applications should be enhanced. As a result, metals, and metal oxides such as zinc and gold nanoparticles are utilized. They have toxicity that is proportional to their size; therefore, their synthesis may be managed [60,61]. Many scientists have raised awareness regarding nanoparticles and how they might be employed in medication delivery, diagnostics and imaging, biosensors, and cosmetics [62]. Only a few examples of specific molecular nanomaterials include fullerene, quantum dots, liposome, carbon nanotubes, dendrimers, graphenes, titanium oxide, iron, gold, and silver nanoparticles. The dressing material offers a moist environment that promotes healthy healing. Nowadays, wound dressing materials such as bioactive dressings including sponges, foams, wafers, hydrogels, films, membranes, and nanofibers are used which are designed from the natural and synthetic polymers such as chitosan, cellulose, pectin and elastin.. The most frequent antibiotics used in dressing are tetracycline, quinolones, aminoglycosides, and cephalosporin [16,63]. Nano-composite materials are formed when nanoparticles are encapsulated in biomaterial and scaffold, which can improve wound healing through antimicrobial activity, pro-angiogenic properties, and acting as gene delivery vectors that change intracellular gene expression and protein synthesis that is used in healing. Furthermore, they can have an impact on healing by influencing collagen deposition and realignment. The combination of bioactive chemicals and antibacterial wound dressing has shown to be effective treatment for wound therapy in recent years. This bioactive chemical is utilized in the dressing material for the treatment of chronic wounds or non-healing wounds. The enzymes associated with wound such as hydrolysates are generally found in exudates and wound fluid, releases bioactive substances, but it's less efficient since the material is quickly absorbed by the wound exudates [64]. With recent research in nanotechnology, electrospinning functions as a flexible approach for creating nano-fibres for usage in biomedical applications. Because of its huge surface area, porosity, strong cell adhesion, and multi drug encapsulating capabilities, electrospum nano fibres are used in wound healing and drug delivery systems [65].

Nanofiber scaffolds are artificial extracellular metrices which provide natural environment for tissue formation. They offer several wound cares uses, including excellent absorption of wound exudates, bacterial infection prevention, and gas permeability. It changes the cell's behavior by stimulating cell adhesion, migration, and secretion of

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related biomolecules from the matrix as well as providing mechanical and biological stimuli [66,67]. Tissue reformation requires a deep understanding of cell activity to develop nanofibrous scaffolds. Cell adhesion, orientation, and cytoskeletal condensation may all be affected by changes in the nanoscale topography of the scaffolds, as well as modulation of the signaling system, which can activate transcriptional activity and gene expression. Polymers are utilized in the production of wound healing scaffolds and because for their unique physiochemical and biological properties, can be utilized as nanoparticles carriers for the regulated and sustained administration of wound care treatments. The type of polymer utilized is decided by the severity of the wound, type of wound, depth of infection, and stage of healing. Hydrophilic polymers, which create the porous, swell able dressing and inhibit excess fluid flow, are typically utilized for severely exuding wounds [68]. The mechanical strength and bio-functionality of the scaffold are improved when polymeric nanofibers are combined with nanoparticles [69]. Carbon nanotube (CNTs) are cylindrical large molecules consisting of a hexagonal arrangement of hybridized carbon atoms. Their impregnation with nanoparticles improves the mechanical strength and electrical conductivity of the scaffolds [70,71]. Furthermore, proteolytic enzymes embedded in a synthetic scaffold work well as a wound debridement dressing [72]. The proper distribution of hormones from entrapped nanofibers accelerates wound healing and seals the lesion via skin cell migration and proliferation [73]. The utilization of nanofibrous scaffolds in tissue regeneration has been established through biocompatibility experiments with various cell types. These electrospun scaffolds' reported nano topographical features promote cell adhesion, proliferation, migration, and differentiation, suggesting the scaffolds' tunability. Because traditional dressing materials lack appropriate physicochemical properties and have a specific biological reaction, nanotechnology improves wound dressing material, which is required for wound treatment [74]. Nanoparticles are modified materials utilized in medicine, engineering, and electronics at the nanoscale level [75].

It is possible to plan to use them during the healing period to improve wound healing [74]. Today, silver (Ag)-based dressing products such as Ag-alginates, Ag-collagen preparation, Ag-hydrogel, Ag-hydrocolloids, Ag-fabrics, Ag cream and powder are employed [76]. When compared to standard dressing materials such as paraffin gauze dressing, Acticoat uses a nanocrystalline Ag that shows a considerable reduction in the timing of wound healing for severe partial thick burns in humans [77]. However, as compared to typical Ag dressings such as sulfadiazine cream, Silver nanoparticle (AgNPs) -based dressing material produces better outcomes [78]. AgNPs combined with hydrogel form a nanocomposite with antibacterial and cytocompatibility characteristics that is frequently employed in wound dressing materials. In addition to AgNPs, many nanoparticles such as copper, graphene oxides, titanium oxides, fibrin, polycatonic NPs, and zinc oxide, among others and have an antibacterial characteristics and are employed in the wound healing process when combined with biocompatible scaffolds [79-85]. Antimicrobial properties of graphene-based nanoparticles promote wound healing [86-88]. Furthermore, these nanoparticles can be employed in the distribution of growth factors as well as to boost the bioactivity of the material and increase angiogenesis [89,90].

5. Role of nanoparticles in wound healing

The treatment of wounds necessitates wound care. Wound dressing materials can be made from any biomaterial that has been combined with nanoparticles. Nanotechnology has the potential to bring up a wide variety medical reform approach. By altering active substance transport, penetrability, and cellular responses, nanoparticles size and shape impact biological efficiency [91-93]. Nanomaterials are now becoming very often used in modern health and nanotechnology. Nanoparticles, nanocarriers, nanoemulsion, nanosphere, nanocapsules, and nanocolloids are some of the nanomaterials used for tissue regeneration[81]. Nanoparticles (NPs) are commonly utilized in wound therapy and come in two varieties: (1) Nanoparticles have wound-healing properties by their very nature. (2)

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Metallic nanomaterials and nonmetallic nanoparticles are used to deliver medicinal medications. Because of their unique antimicrobial properties and high penetration into the skin, silver, gold, and zinc compounds are the most researched metallic nanoparticles [94]. The mechanism of effectivity comprises the disrupting of cell membrane, interactions with proteins, inactivation of respiratory enzyme and DNA modifications (Fig. 3) [76].

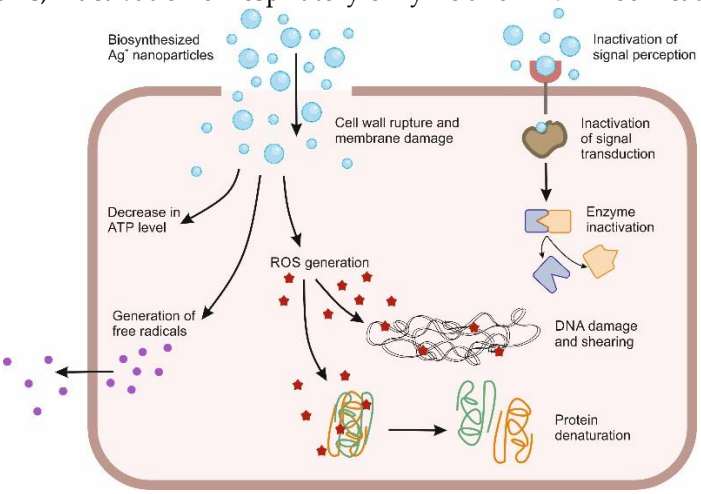

Fig.3. Biofunctionalized nanoparticles as topical bullet for enhanced delivery and promising technology for wound healing.

5.1. Silver nanoparticles (AgNPs)

Silver has a bactericidal component that is commonly used to treat wound infection, burns, and different ulcers. Chronic non-healing lesions are treated with silver nitrate. Silver-coated wound dressings, which aid in the healing process, are now available in a variety of styles. AgNPs are more hazardous at lower concentrations because their surface-to-volume ratio is higher. Pure silver nanoparticles can control the release of anti-inflammatory cytokines, allowing for faster wound healing without scarring [95]. By stimulating myofibroblast differentiation from normal fibroblasts, AgNPs aid to reduce the size of the wound and speed up the healing process. AgNPs also enhance epidermal re-epithelialization by stimulating keratinocyte proliferation and migration [96]. Szmyd et al. discovered that larger concentrations of AgNPs affect keratinocyte metabolism, migration, survival, and differentiation by activating caspases 3 and 7 (proteases implicated in programmed cell death) and causing dose-dependent DNA damage. AgNPs with tetracycline decreased bacterial load in the superficial and deep tissue layers of a mouse model, resulting in quicker wound healing [97]. AgNPs may now be used with antibacterial medicines or dressings to treat infected wounds more effectively. For example, biocellulose coupled with AgNPs worked as an antibacterial covering for open wounds, with strong keratinocyte adhesion and proliferation around the wound margins. This nanomaterial has a high bacterial killing efficacy against Gram negative pathogens and has been shown to accelerate wound healing [98]. When AgNPs and collagen are combined, they have a powerful antibacterial action and may be used as a wound dressing component [99,100]. AgNPs are used to prevent infection in medical equipment, burn ointments, and pressure ulcer wound dressings [101]. AgNPs are utilized to destroy bacteria, fungus, viruses, and protozoa due to their antibacterial properties [102]. AgNPs disrupt quorum sensing, reducing biofilm development and bacterial clearance of hazardous substances [103,104]. AgNPs were reported to lower oxidative stress, inhibit inflammatory cytokines, and improve healing in a recent in vitro study using dermal fibroblasts and human keratinocytes [105]. AgNPs were shown to lower neutrophil and interleukin (IL)-6 levels in mice burn wounds, which were linked to high levels of TGF, IL-10, interferon gamma, and vascular endothelial growth factor.

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AgNPs, according to the findings, aid in the removal of bacteria from the wound site and speed up the healing process. In another study, AgNPs coupled with poly(Dopamine Methacrylamide-co-methyl methaacrylate) (MADO) nanofiber wound dressing therapy resulting in full wound healing with the synthesis of epidermis on the wound area within two weeks, compared to AgNPs individually, which result in partial wound healing or required a long time to heal the wound [106-108] . Zhou et al. created silver-silver chloride nanoparticles integrated in reduced graphene oxide (Ag/AgCl/rGO nanomaterial) that produced silver ions when exposed to acceptable environmental conditions [90]. More oxygen radicals, also known as oxidative free radicals, are produced by Ag/AgCl/rGO nanoparticles, which are efficient against both gram-positive and gram-negative bacteria. Y.C. Yeh and colleagues discovered that the Ag/AgCl/rGO nanomaterial improved wound healing with fast wound closure in mice burn wounds by improving reepithelialization and boosting collagen fiber deposition [108]. Lu et al. [109] observed that inorganic particles like silica are persistently bound to open wounds in animals. The novel chemical generated exhibits outstanding antibacterial characteristics while being less damaging to cells due to the disulphide connection between AgNPs and mesoporous silica nanoparticles.
AgNPs have a huge surface area, which helps them to fight against germs. AgNPs adhere to the bacterial cell membrane before penetrating the cells, where they bind with proteins containing sulphur and phosphorous groups, as well as DNA [110]. AgNPs observed penetrating bacterial cells would transform into a low molecular region in the bacteria's centre, hiding and shielding the cellular DNA from silver ions. The nanoparticles initially released silver ions in the centers of the bacterial cells, displaying and expanding their bactericidal effect. The nanoparticles are designed to disrupt the respiratory chain, leading the cell to die [111].

5.2. Gold nanoparticles (AuNPs)

Biocompatible AuNPs help in tissue remodeling, therapeutic delivery systems, and wound healing. Growth factors, peptides, polysaccharides, and cell adhesion molecules may all be combined with AuNPs, which are attached to the gold surface. These AuNPs modifications have two properties that help in wound healing: biocompatibility and biodegradability. Chitosan and gelatin, in addition to AuNPs, have been utilized to assist wound healing [112-114]. Antibacterial drugs and other types of nanoparticles are combined with gold to boost their ability to kill microbes. When vancomycin is coupled with gold nanoparticles, for example, the action of vancomycin is enhanced against *E. coli* [36].Gold nanoparticles are coupled with pathogen-specific antibodies [111] and photosensitizing chemicals [115] to induce antibacterial activity in photothermal and photodynamic treatment. AuNPs adhere to bacterial DNA or target the bacterial cell wall directly by inhibiting the double helix from twisting during replication and transcription and demonstrating bacteriostatic and bactericidal actions. As a result, multidrug-resistant bacteria like *S. aureus* and *P. aeruginosa* can be controlled. According to Lu et al. [115] low dosage of gold nanoparticle can stimulate keratinocyte proliferation and differentiation, while higher amounts are linked to cytotoxicity. Marza et al. [116] studied the effects of AuNPs mixed with vaseline on basic fibroblast growth factor (BFGF) for period of 14 days at different vaseline concentrations. This chemical, according to his studies, stimulates angiogenesis and fibroblast proliferation, as well as improves wound healing in 18% of cases without causing cell toxicity [116]. According to a recent ex vivo research, AuNPs are transdermally active and useful in the treatment of burns by speeding healing and inhibiting microbial development [117]. The wound healing mechanism of AuNPs is improved when they are combined with polymers or stem cells [118,119]. Chitosan-AuNPs significantly increased the capacity of AuNPs to scavenge free radicals while also increasing their biocompatibility. In addition, polycationic chitosan is required for the production of AuNPs. In a rat surgical wound model study, chitosan-AuNPs significantly improved homeostasis, enhanced epithelial tissue formation, and quicker wound healing and closure when compared to regular tegaderm

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dressings or chitosan dressing individually. AuNPs were combined with freeze-dried human fibroblasts (HFC-AuNP) and given topically to burn wounds in rats in a separate in vitro investigation. Wounds treated with HFC-AuNP healed more quickly and had a shorter inflammatory period. Antibacterial activity of AuNPs has been demonstrated in two methods. To begin with, when AuNPs invade bacterial cells, they impair the enzyme ATP synthase, causing ATP levels to drop and cell death to occur. Second, when AuNPs cause cell death in drug-resistant bacteria by processes that is not dependent on ROS [120].

5.3. Zinc oxide (ZnO) **nanoparticles**

Inorganic antibacterial agents like ZnO are more stable than organic antibacterial agents. Zinc is a chemical substance that may be found in living tissue for such a long time and therefore is essential during wound and burn treatment. Zinc topical use was developed to decrease pain, enhance re-epithelialization or inhibit bacterial growth in chronic wounds. Zinc is a necessary cofactor for metalloproteinase and for extracellular matrix and minerals (ECM). ZnO nanoparticles are commonly utilized in cosmetics, skin creams, and ointments because of their antibacterial, anti-inflammatory, and antiseptic qualities [121-123].The structure or amount of ZnO nanoparticles have an impact on wound healing. Because of its small size and high surface-to-volume ratio, ZnO has improved antibacterial activity. Whenever ZnO is combined with chitosan hydrogel, it possesses powerful antibacterial characteristics, making it an excellent component for wound dressings [124]. ZnO nanoparticles may be synthesized as a biocompatible polymer that is effective at low concentrations. Zinc is also involved in wound healing by regulating keratinocyte migration and autophagocytosis. ZnO uses a biphasic technique to release Zn ions from nanomaterials. Zn ions quickly hydrate and generate hydrated ZnO, which kills bacteria when they come into contact with biological fluids [125].

6. Impregnated dressing nanomaterial

Various materials have been used to stop bleeding, absorb exudates, and promote healing since ancient times. Honey, cobwebs, dirt, leaves, animal grease, fat, and animal feces were among the various materials [126]. When selecting the ideal dressing, there are four crucial elements to consider. The wound must be hydrated first and foremost if it is dry or dried. If a wound's exudates are overly generated, it has to be absorbed. The wound must be debrided if it contains necrotic tissue or visible debris. Antibiotics must also be taken if a wound becomes infected. A large variety of wound healing products are currently regulated by the US Food and Drug Administration to be used in the US. There are three sorts of dressings: passive, medicated, and active interactive [127]. Wound dressings including drugs are categorized as pharmaceutical formulations and assigned to an FDA Centre under the PMOA, which has primary regulatory authority and control over the product [128]. The Integra® Omnigraft™ Dermal Regeneration Matrix is one such dressing (PMA). As AuNPs have high biocompatibility so it can reduce inflammation and promote granulation tissue growth while also not being rejected by skin tissues [129]. By inhibiting the respiratory routes that maintain keratocytes and fibroblasts active, AgNPs can promote their development. It can also suppress the innate immune system, which has been associated to quicker wound healing and scar formation [130]. Acticoat® would be the first silver nanoparticles wound therapy that comes to market. The use of silver nanoparticles in skin regeneration was demonstrated in a case of toxic epidermal necrolysis caused by carbamazepine medication, which caused vesiculobullous lesions and degradations on 70% of the patient's body surface. Instead of using typical antibiotics, a nanosilver dressing (based on silver nanocrystals) were injected and secured to a skin lesion using microfiber cloths and crepe gauze. Re-epithilization occurred after five days, and healing occurred after nine days [131]. Nanoceria (35nm spherical cerium oxide nanoparticles) is another example, which promotes cell survival, migration, and proliferation while minimizing the risks of Ultraviolet light exposure mostly on epidermis at low dosages [132]. Metallic nanoparticles

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(20, 40, and 80 nm in size, each circular) promote endothelial cell migration in a size and dosage dependent manner, whereas keratinocyte and fibroblast cell proliferation happen at specific locations and ratios. In cultivated fibroblast cells, larger Copper nanoparticles (CuNPs) (80nm) activate collagens more efficiently than smaller CuNPs (40nm). Copper nanoparticles have also been found to enhance complete epidermis healing process and enhance the neovascularization in rat models with no negative effects. At present there are various dressing materials with low toxicity and improved antimicrobial property which makes them a perfect candidate for integration with various nanoparticles (Fig.4) [16].

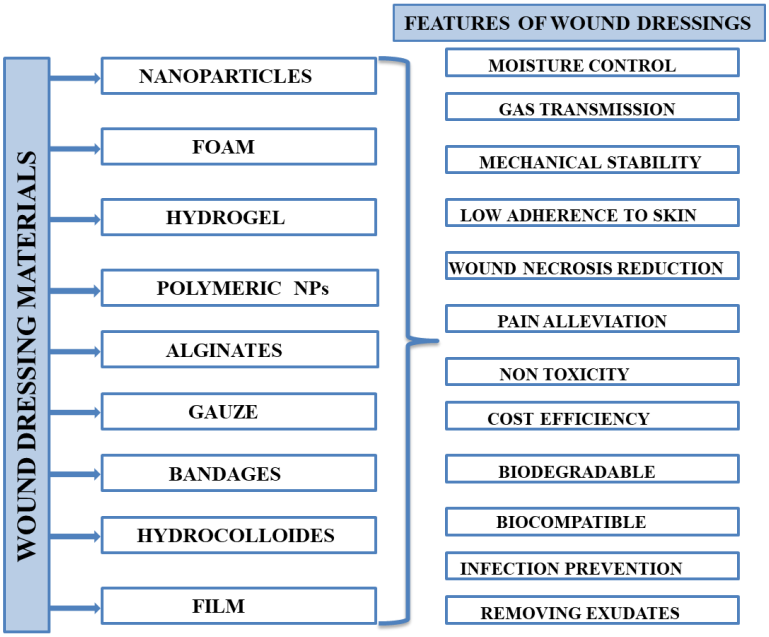

Fig.4. Ideal wound dressing materials with improved characteristic properties.

This review also focused on summarizing and discussing the role on nano-based dressing materials as a potential impregnation for wound healing and skin regeneration, with a special reference on advanced hydrogel, thin film dressing, alginate, hydrocollides, foam and multilayered dressings (Fig.5) [133].

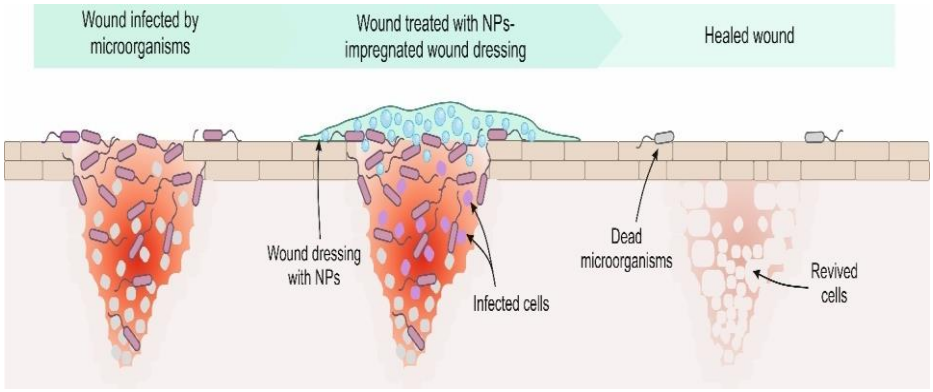

Fig.5. Nano functionalized wound dressing bed for skin regeneration

6.1. Advanced hydrogel for wound dressings

Hydrogels are among the most interesting wound management material since they can be manipulated precisely and can resemble the extracellular matrix and produce a suitable atmosphere for tissue regeneration, facilitating epithelial cell migration and re-epithelialization. They are comprised of a three-dimensional chemically bonded polymer structure that can endure high water pressure while maintaining its structure. This gives it flexibility

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similar to surrounding tissues, as well as oxygen permeability, which inhibits anaerobic bacteria from growing. Hydrogels also speed up the healing process by promoting homeostasis, cell migration, and proliferation [134]. Antimicrobial components have been incorporated into a hydrogel dressing. Kumar et al., [81] investigated chitosan hydrogel and ZnO nanoparticles-based composite wound treatments. Chitosan and ZnO particles antibacterial activity, together with zinc ion release, increased keratinocyte motility in the wound, promoting epithelialization and healing. Another issue with using hydrogels is that they dehydrate quickly if not covered properly. Incorporating hygroscopic materials, on the other hand, might help to prevent dehydration. Depending on the moisture level of the wound, hydrogels should be replaced every 1–3 days. Nunes et al., [135] created an efficient approach for the development of wound dressing materials with better properties, using biodegradable chitosan mixed poly (vinyl alcohol) hydrogels containing incorporated silver nanoparticles as an effective antibacterial action. In the presence of *E. coli and S. aureus*, the hydrogel dressings showed to be non-cytotoxic and antibacterial. Pressure ulcers offer a unique problem in the care of chronic wounds since the major objective of therapy is to keep the wound clean while allowing it to heal [135].

6.2. Transparent thin film dressing

A polyurethane-based synthetic wound dressing that is translucent and stretchy. Such polymeric materials are flexible, permitting the wounded body part to move freely. Polyurethane films were semi-permeable, enabling oxygen, vapour or carbon dioxide to flow through while simultaneously functioning as a germ barrier. Furthermore, the wound bed may be examined to measure wound healing due to the transparency of the thin film covering. Applying a thin coating of polyurethane to a wound with a high exudates level, on the other hand, may result in the buildup of bodily fluids and maceration. As a result, dressings like Opsite™, Tegaderm™, and Biooclusive should be used on epithelializing wounds, superficial wounds, and shallow wounds with minor exudates. Film dressings, on the other hand, should be removed with caution because of the risk of causing damage to the epidermal skin layer. As a result, when film dressings are used to treat sensitive skin, inappropriate removal may result in skin damage. Depending on the size and kind of wound, as well as its placement, films could be kept in place until up to 7 days [136]. Hubner et al., report innovative gelatin-based wound dressings using glycerol as a plasticizer and various quantities of silver-impregnated clinoptilolitezeolite [137]. Silver-based compounds were employed as antiseptics because dressings used within acute and chronic wound management should have antibacterial characteristics. For this aim, casting was employed to generate films. *S. aureus* and human skin infections were resistant to all concentrations of gelatin/clinoptilolite-Ag films. Electrospinning can also be used to make semipermeable nanofiber-based film dressings [138-142]. Rivero et al. developed nanofibrous membranes that operate as smart dressings, delivering drugs whenever an infection develops [138]. Electrospun film dressing's releases nitrofurazone when the pH of the environment changes was successfully generated using polymers with selective solubility at pH values greater than 7. This study proved the importance of nanotechnology in the medical field. Mazloom-Jalali et al. examined such issues and create biodegradable nanocomposites using Cephalexin antimicrobial medication and zeolitic imidazolate framework-8 (ZIF-8) nanoparticles made of chitosan and polyethylene glycol [143]. Such compounds antibacterial characteristics were proven in tests against a range of bacteria

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(especially *B. cereus*), and when tested against L929 fibroblast cells, all films exhibited good cell viability. Semipermeable film wound dressings are a notable advancement in wound treatment among current wound dressings [144].

6.3. Alginate as dressing material

Alginate is a polysaccharide made up of mannose or guluronic acid molecules found in nature [145]. Alginate has such a special ability to absorb a lot more water. As results, whenever applied on injuries, the dressing absorbed fluid and creates a hydrogel, dramatically reducing bacterial activity. Alginate dressings are very beneficial for wounds that produce a lot of fluid. The calcium ions inside the dressing also showed bioactivity during wound healing cellular mechanisms, in addition to chemically bonding alginate to generate stable physical gel [146]. One research compared Kaltostat, a commercially available nanofibrous dressing, to two alginate-based dressings crosslinked with poly-ethylenimines and ethylene diamine [147]. The bigger pore diameters of alginate dressings (100-250m) aided with air permeability. They also enhanced wound moisture control, allowing animals to heal wounds quicker. For very exudative wounds, alginate dressings are the best option [148]. The dressings help in homeostasis by producing Ca^{2+}, which raises coagulation factors in the coagulation cascade [149]. Alginates require a secondary dressing, which should be changed every one to two weeks or until gel lost all fluidity [150]. Alginate dressings generally soluble and can be removed with salt washing, making them painless to change. Alginates' yellow-brown color and foul odor might be misconstrued as infection. Kaygusuz et al. combined chitosan with cerium ion antibacterial capabilities. Cerium cross-linked alginate-chitosan films were the first to be reported. The samples had antibacterial activity towards *E. coli* and *S. aureus* [151]. Munhoz et al. [152] studied the antimicrobial capabilities of silver sulfadiazine with the regenerating, biodegradable, and non-toxic qualities of alginate. Their findings suggested a method for developing novel active wound dressings that may also serve as effective drug delivery systems [153]. Liang et al., [154] revealed another approach for manufacturing antibacterial molecules sodium alginate as a dressing material. Polydopamine silver composite nanospheres were used to functionalize an oxidized sodium alginate sponge. They demonstrated minimal cytotoxicity in cells, high inhibitory efficiency, excellent blood compatibility and excellent homeostatic performance against *S. aureus*, *P. aeruginosa*, and *E. coli*.

6.4. Hydrocollides dressing

Hydrocolloides are moisture-retentive biopolymer dressings, which contain gel-forming agents like gelatin, pectin, or carboxymethylcellulose [155,156]. When colloidal materials are applied topically to wounds, they accumulate excess fluid and form a gel that binds to the wounds while remaining permeable to oxygen and water. Hydrocolloid dressings can provide heat insulation as well as a moist environment under working conditions due to their lack of mechanical stiffness, so they are easy to remove. As a result, hydrocolloid dressings usually include a thick, impermeable film backing that isolates wounds from germs and minimizes the risk of infection. Hydrocolloids were hydrophobic and absorbent and therefore do not require any further treatment [157]. According to current wound healing theories hydrocolloid dressing appears to have been studied for its possible utility in neurosurgical wounds [158]. Clinical investigations for wound healing, wound infection and cost-effectiveness were carried out, with outstanding outcomes in wound healing and cosmetics.

6.5. Foam dressing

Polyesters and other synthetic polymer foams have more mechanical flexibility than thin film dressings, allowing the injured body part to move. They also soak more exudates

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[159]. Foams can also help in maintaining a moist wound environment around the wound bed as well as gas exchange, and both are important for wound healing. Moreover, foams porous qualities provide cushioning for wounded tissue as well as improved heat isolation. Foams, in general, are a low-cost, efficient wound dressing that may be used on a variety of wound. Their high-water consumption, on the other hand, limits their use as medication delivery devices. Semi permeable dressing foams based on polyurethane have been widely employed due to their high-water absorption capacity, cost effectiveness and remarkable mechanical qualities. Polyurethane's limited bioactivity and poor healing properties, however, limit its use in polyurethane foam dressings in severe wound healing situations [160,161]. To accomplish so, scientists studied a variety of nanomaterials in depth. Namviriyachote et al., [160] discovered that changing the quantity of ZnO nano filler in a foam dressing might boost its antibacterial activity in a recent study published in 2019. Bio-based thermoplastic polyurethane/ZnO nano composite foams were created using an induced phase separation approach. Their findings demonstrated that the foam dressings they received had the necessary morphology to keep the wound/dressing contact in the right environment. In addition, the dressings had a minimal cytotoxic potential despite being very efficient against both gram-positive and gram-negative germs.

6.6. Multilayer dressing

Multilayered dressings are often made up of a combination of the dressings mentioned above. Lacerations, burns, abrasions, and surgical wounds are commonly treated with a mixture of a semi- or non-adherent layer and a waterproof layer made of rayon fabric, cotton, or other absorbent fibers [162,163]. A mixture of hydrocolloids and alginates was also used to treat burns, superficial pressure wound and leg ulcers. The foam, hydrogel, and polyurethane layers were fused together to produce a multilayered dressing for the treatment of chronic wounds [164,165]. To meet the demands of wound healing, multilayered hydrogels with more than two layers are generated by altering the chemical and physical features of the component biomaterials. The advantages of each constituent are combined in layered hydrogel wound dressings. By restricting the mass transfer of drug molecules across the polymeric matrix, multilayer hydrogels with a drug-loaded layer allow controlled drug release over a lengthy period [166,167]. LBL was utilized by Weller and Sussman [168] studied binding of lysozyme with gold nanoparticles on nanofibers, yielding antibacterial multilayer films. In the microbial inhibition test, the mixed nanofibrous sheets demonstrate high antibacterial activity against *S. aureus* and *E. coli*, indicating that they might be used in wound dressing applications. As they promote quicker healing, multilayer wound dressings have become good options than single-layer wound dressings [169]. In a recent work, Tamahkar et al., developed a novel multilayer hydrogel wound dressing constructed of natural polymers for antibiotic release and employed a water-based technique for optimal wound healing. Multilayer hydrogels were generated by electrostatic interactions between four polymeric layers using gelatin, hyaluronic acid, carboxylated polyvinyl alcohol and LBL self-assembly. During a seven-day period, antibiotics were released from ampicillin-treated multilayer hydrogels. The dressings also showed antibacterial activity towards oxacillin-sensitive *S. aureus* but had no harmful effects upon developed fibroblasts, indicating that they might be used to treat specific pathogenic bacteria [167]. In 2020, Shokrollahi et al., [170] developed a new nontoxic multilayered nanofibrous dressing by electrospinning PCL nanofibers as its first layer, hybridized nanofibers of chamomile/carboxyethyl chitosan (CECS)/PVA and PCL as the second layer and chamomile loaded CECS/PVA as the third layer. Nanofibers created from wound dressings outperformed commercial wound dressing Ag coatings in terms of antibacterial efficacy. A 20-wt. chamomile-loaded mat with antioxidant, antibacterial, biocompatibility, and mechanical qualities should be appropriate for wound healing applications, according to the findings of this study [170].

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7. Outstanding of molecular science in wound healing

In general, skin has a high potential for restoration, which is governed by the efficient and well-ordered cellular and molecular processes. Furthermore, a disruption in the normal healing process can cause chronic wounds like artery ulcers, non-healing surgical wounds, foot ulcers, and pressure sores [171]. Wound infection, persistence of foreign particles or microbial proteins, prolonged irritation and shock, and ischemia can all contribute to a delayed recovery. The overexpression and continuous production of interleukins (ILs) and inflammatory cytokines causes an imbalance in important proteases, growth factors, and cytokines, resulting in excessive degradation, proteolysis, and insufficient accessibility of crucial receptors, growth factors, and ECM. Many local factors, including cytokines, chemokines, proteases, growth factors, and immune cell activity, have been shown to be influenced by host defense peptides (HDPs). The function of immune cell in the inflammatory phase is to eradicate intracellular pathogens by generating host defense peptides, which increase the recruitment of immune cells such neutrophils, monocytes/macrophages, dendritic cells, and T cells [172]. The LL-37 peptide not only stimulates growth factors like EGF and VEGF, but it also binds to their receptors[173,174]. Furthermore, high levels of hBD-2 and hBD-3 found at wound sites enhance keratinocyte migration and proliferation, showing that they play a role in the re-epithelialization of the healing epithelium [175,176]. Recent research showed that applying topical insulin to a wound increased the levels of extracellular-signal regulated kinase (ERK) and protein kinase B (Akt) [177]. Increased Akt enhanced angiogenesis through activation of VEGF signalling [178,179]. ERK is a component of a phosphorylation pathway that increases gene transcription and leads to cell [180,181]. Many variables influence macrophage polarization into appropriate phenotypes during different stages of wound healing, and different HDPs (such as LL-37) promote polarization to M1 macrophages [182]. In RAW264.7 cells, Cathelicidin-WA(CWA) can reduce increased levels of interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor (TNF), and chemokine CCL3 [183]. TLR-4 expression and phosphorylation of STAT1 and NF- B are suppressed by CWA peptide, which reduces the activity of pro-inflammatory macrophages while boosting STAT6 phosphorylation and activating *E. coli* K88-induced anti-inflammatory macrophages [181]. LL-37 is one of the most extensively utilized peptides for wounds with poor healing and infections [182-187]. To overcome previously observed limited cellular penetration, new 3D nanofiber scaffolds might be used to improve transdermal peptide delivery [182]. In vitro and in vivo, nanoparticles lipid carriers (NLCs) encapsulating LL-37 and applied topically accelerated wound healing, re-epithelization, and reduced inflammation[183]. Furthermore, topical application of LL-37 coated with PLGA nanoparticles accelerated wound closure, re-epithelialization, and wound bed granulation tissue formation [186]. Additionally, increased IL-6 and VEGF expression controlled the inflammatory wound response, resulting in improved neovascularization [186]. In comparison to LL-37 alone, LL-37-conjugated gold nanoparticles improved cell migration mediated by phosphorylation of EGFR and ERK1/2 in vivo wound healing activities [188]. IL-6 and VEGF levels were higher in wounds treated with LL-37-conjugated gold nanoparticles [188]. Chronic diabetic wounds treated with antimicrobial peptide (LL-37) and coupled with ultra-small gold nanoparticles (AuNPs) as a gene delivery method facilitated wound closure by covering the wounds with newly created blood vessels and reducing the bacterial load [187].

8. Conclusion

Almost everyone must deal with an injury which may lead to wound. Most wounds are cured easily, but some wounds lead to cause major damage to tissue and muscle, for treatment of this kind of wound we need treatment. Such development of lesions leads tom chronic wound which remains a major challenge as therapies mostly failed to provide favorable outcome. Nowadays biological and synthetic nanocomposite are used to treat

various types of inflammatory and infectious infection, also this kind of material are used for wound healing process. In this study we summarized the current scenario about wound care and active molecules or medications. The purpose of this review study is to show the many applications of nanocomposite in wound healing as well as their mechanisms. Nanoparticles- coated dressing material shown outstanding antibacterial activity and anti-inflammatory activity which help in speedy healing of wound. The optimal wound dressing should be flexible, strong, porous, and non-adherent to the wound surface. More studies are needed to develop dressings for the treatment of chronic wounds using large mammalian models. As current commercial dressings don't meet the needs of patients with chronic wounds, therefore cost-effective alternative designs containing various dressing materials should be developed. In addition to these, novel nanomaterials capable of controlling all phases of wound healing, as well as self-healing, superior mechanical qualities, and adhesive capabilities into wound dressings to increase their efficacy.

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References

1. Lazarus, G.S.; Cooper, D.M.; Knighton, D.R.; Percoraro, R.E.; Rodeheaver, G.; Robson, M.C. Definitions and guidelines for assessment of wounds and evaluation of healing. *Wound Repair Regen* **1994**, *2*, 165-170.
2. Robson, M.C.; Steed, D.L.; Franz, M.G. Wound healing: biologic features and approaches to maximize healing trajectories. *Curr Probl Surg* **2001**, *38*, 72-140.
3. Guo, S.; Dipietro, L.A. Factors affecting wound healing. *J Dent Res* **2010**, *89*, 219-229.
4. Ward, J.; Holden, J.; Grob, M.; Soldin, M. Management of wounds in the community: five principles. *Br J Community Nurs* **2019**, *24*, S20-S23.
5. Ousey, K.; Stephenson, J.; Barrett, S.; King, B.; Morton, N.; Fenwick, K.; Carr, C. Wound care in five English NHS Trusts: Results of a survey. *Wounds UK* **2013**, *9*, 20-28.
6. Guest, J.F.; Ayoub, N.; McIlwraith, T.; Uchegbu, I.; Gerrish, A.; Weidlich, D.; Vowden, K.; Vowden, P. Health economic burden that wounds impose on the National Health Service in the UK. *BMJ Open* **2015**, *5*, e009283.
7. Bischoff, M.; Kinzl, L.; Schmelz, A. [The complicated wound]. *Unfallchirurg* **1999**, *102*, 797-804.
8. Peterson, A.S.; Aument, W.L. In *The "Golden period" for wound repair*, 2010.
9. Attinger, C.E.; Janis, J.E.; Steinberg, J.; Schwartz, J.; Al-Attar, A.; Couch, K. Clinical approach to wounds: debridement and wound bed preparation including the use of dressings and wound-healing adjuvants. *Plast Reconstr Surg* **2006**, *117*, 72S-109S.
10. Degreef, H.J. How to heal a wound fast. *Dermatol Clin* **1998**, *16*, 365-375.
11. Frykberg, R.G.; Banks, J. Challenges in the Treatment of Chronic Wounds. *Adv Wound Care (New Rochelle)* **2015**, *4*, 560-582.
12. Fife, C.E.; Carter, M.J. Wound Care Outcomes and Associated Cost Among Patients Treated in US Outpatient Wound Centers: Data From the US Wound Registry. *Wounds* **2012**, *24*, 10-17.
13. Sen, C.K.; Gordillo, G.M.; Roy, S.; Kirsner, R.; Lambert, L.; Hunt, T.K.; Gottrup, F.; Gurtner, G.C.; Longaker, M.T. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen* **2009**, *17*, 763-771.

14. Richmond, N.A.; Lamel, S.A.; Davidson, J.M.; Martins-Green, M.; Sen, C.K.; Tomic-Canic, M.; Vivas, A.C.; Braun, L.R.; Kirsner, R.S. US-National Institutes of Health-funded research for cutaneous wounds in 2012. *Wound Repair Regen* **2013**, *21*, 789-792.
15. van Doesburg, P.G.; El Saddy, S.; Alta, T.D.; van Noort, A.; van Bergen, C.J.A. Treatment of coracoid process fractures: a systematic review. *Arch Orthop Trauma Surg* **2021**, *141*, 1091-1100.
16. Negut, I.; Grumezescu, V.; Grumezescu, A.M. Treatment Strategies for Infected Wounds. *Molecules* **2018**, *23*.
17. Mihai, M.M.; Holban, A.M.; Giurcaneanu, C.; Popa, L.G.; Buzea, M.; Filipov, M.; Lazar, V.; Chifiriuc, M.C.; Popa, M.I. Identification and phenotypic characterization of the most frequent bacterial etiologies in chronic skin ulcers. *Rom J Morphol Embryol* **2014**, *55*, 1401-1408.
18. Mihai, M.M.; Holban, A.M.; Giurcaneanu, C.; Popa, L.G.; Oanea, R.M.; Lazar, V.; Chifiriuc, M.C.; Popa, M.; Popa, M.I. Microbial biofilms: impact on the pathogenesis of periodontitis, cystic fibrosis, chronic wounds and medical device-related infections. *Curr Top Med Chem* **2015**, *15*, 1552-1576.
19. Flanagan, M.; Fletcher, J. Wound care: the healing process. *Nurs Stand* **1997**, *11*, 5-17; quiz 21-15.
20. Li, J.; Chen, J.; Kirsner, R. Pathophysiology of acute wound healing. *Clin Dermatol* **2007**, *25*, 9-18.
21. Addis, R.; Cruciani, S.; Santaniello, S.; Bellu, E.; Sarais, G.; Ventura, C.; Maioli, M.; Pintore, G. Fibroblast Proliferation and Migration in Wound Healing by Phytochemicals: Evidence for a Novel Synergic Outcome. *Int J Med Sci* **2020**, *17*, 1030-1042.
22. Oda, Y.; Bikle, D.D. Vitamin D and calcium signaling in epidermal stem cells and their regeneration. *World J Stem Cells* **2020**, *12*, 604-611.
23. MacNeil, S. Progress and opportunities for tissue-engineered skin. *Nature* **2007**, *445*, 874-880.
24. Kapoor, M.; Appleton, I. Wound healing: Abnormalities and future therapeutic targets. *Current Anaesthesia & Critical Care* **2005**, *16*, 88-93.
25. Bhardwaj, N.; Chouhan, D.; Mandal, B.B. Tissue Engineered Skin and Wound Healing: Current Strategies and Future Directions. *Curr Pharm Des* **2017**, *23*, 3455-3482.
26. Cañedo-Dorantes, L.; Cañedo-Ayala, M. Skin Acute Wound Healing: A Comprehensive Review. *Int J Inflam* **2019**, *2019*, 3706315-3706315.
27. Moura, L.I.; Dias, A.M.; Carvalho, E.; de Sousa, H.C. Recent advances on the development of wound dressings for diabetic foot ulcer treatment--a review. *Acta Biomater* **2013**, *9*, 7093-7114.
28. Han, G.; Ceilley, R. Chronic Wound Healing: A Review of Current Management and Treatments. *Adv Ther* **2017**, *34*, 599-610.
29. Morton, L.M.; Phillips, T.J. Wound healing and treating wounds: Differential diagnosis and evaluation of chronic wounds. *J Am Acad Dermatol* **2016**, *74*, 589-605; quiz 605-586.
30. Lin, Y.H.; Hsu, W.S.; Chung, W.Y.; Ko, T.H.; Lin, J.H. Silver-based wound dressings reduce bacterial burden and promote wound healing. *Int Wound J* **2016**, *13*, 505-511.
31. Leaper, D.; Assadian, O.; Edmiston, C.E. Approach to chronic wound infections. *Br J Dermatol* **2015**, *173*, 351-358.
32. Bessa, L.J.; Fazii, P.; Di Giulio, M.; Cellini, L. Bacterial isolates from infected wounds and their antibiotic susceptibility pattern: some remarks about wound infection. *Int Wound J* **2015**, *12*, 47-52.
33. Bassetti, M.; Vena, A.; Croxatto, A.; Righi, E.; Guery, B. How to manage *Pseudomonas aeruginosa* infections. *Drugs Context* **2018**, *7*, 212527.
34. Khan, H.A.; Ahmad, A.; Mehboob, R. Nosocomial infections and their control strategies. *Asian Pacific Journal of Tropical Biomedicine* **2015**, *5*, 509-514.
35. Tong, S.Y.; Davis, J.S.; Eichenberger, E.; Holland, T.L.; Fowler, V.G., Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev* **2015**, *28*, 603-661.

36. Welch, R.A. Uropathogenic *Escherichia coli*-Associated Exotoxins. *Microbiol Spectr* **2016**, *4*, 10.1128/microbiolspec.UTI-0011-2012.
37. Ahmadi, M.; Adibhesami, M. The Effect of Silver Nanoparticles on Wounds Contaminated with *Pseudomonas aeruginosa* in Mice: An Experimental Study. *Iran J Pharm Res* **2017**, *16*, 661-669.
38. Liu, S.; Long, Q.; Xu, Y.; Wang, J.; Xu, Z.; Wang, L.; Zhou, M.; Wu, Y.; Chen, T.; Shaw, C. Assessment of antimicrobial and wound healing effects of Brevinin-2Ta against the bacterium *Klebsiella pneumoniae* in dermally-wounded rats. *Oncotarget* **2017**, *8*, 111369-111385.
39. Webber, B.J.; Kieffer, J.W.; White, B.K.; Hawksworth, A.W.; Graf, P.C.F.; Yun, H.C. Chemoprophylaxis against group A streptococcus during military training. *Prev Med* **2019**, *118*, 142-149.
40. Kim, H.J.; Na, S.W.; Alodaini, H.A.; Al-Dosary, M.A.; Nandhakumari, P.; Dyona, L. Prevalence of multidrug-resistant bacteria associated with polymicrobial infections. *J Infect Public Health* **2021**, *14*, 1864-1869.
41. Li, M.; Yang, F.; Lu, Y.; Huang, W. Identification of *Enterococcus faecalis* in a patient with urinary-tract infection based on metagenomic next-generation sequencing: a case report. *BMC Infect Dis* **2020**, *20*, 467.
42. Chard, R. Wound classifications. *AORN Journal* 2008/07//, 2008, p 108+.
43. Bielefeld, K.A.; Amini-Nik, S.; Alman, B.A. Cutaneous wound healing: recruiting developmental pathways for regeneration. *Cell Mol Life Sci* **2013**, *70*, 2059-2081.
44. Simpson, D.M.; Ross, R. The neutrophilic leukocyte in wound repair a study with antineutrophil serum. *J Clin Invest* **1972**, *51*, 2009-2023.
45. Albelda, S.M.; Buck, C.A. Integrins and other cell adhesion molecules. *FASEB J* **1990**, *4*, 2868-2880.
46. Velnar, T.; Bailey, T.; Smrkolj, V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Int Med Res* **2009**, *37*, 1528-1542.
47. Schaffer, M.; Barbul, A. Lymphocyte function in wound healing and following injury. *Br J Surg* **1998**, *85*, 444-460.
48. Braund, R.; Hook, S.; Medlicott, N.J. The role of topical growth factors in chronic wounds. *Curr Drug Deliv* **2007**, *4*, 195-204.
49. Gainza, G.; Villullas, S.; Pedraz, J.L.; Hernandez, R.M.; Igartua, M. Advances in drug delivery systems (DDSs) to release growth factors for wound healing and skin regeneration. *Nanomedicine* **2015**, *11*, 1551-1573.
50. Kiwanuka, E.; Junker, J.; Eriksson, E. Harnessing growth factors to influence wound healing. *Clin Plast Surg* **2012**, *39*, 239-248.
51. Singer, A.J.; Clark, R.A. Cutaneous wound healing. *N Engl J Med* **1999**, *341*, 738-746.
52. Caley, M.P.; Martins, V.L.; O'Toole, E.A. Metalloproteinases and Wound Healing. *Adv Wound Care (New Rochelle)* **2015**, *4*, 225-234.
53. Hunt, T.K.; Hopf, H.; Hussain, Z. Physiology of wound healing. *Adv Skin Wound Care* **2000**, *13*, 6-11.
54. Martins, V.L.; Caley, M.; O'Toole, E.A. Matrix metalloproteinases and epidermal wound repair. *Cell Tissue Res* **2013**, *351*, 255-268.
55. Eckhardt, S.; Brunetto, P.S.; Gagnon, J.; Priebe, M.; Giese, B.; Fromm, K.M. Nanobio silver: its interactions with peptides and bacteria, and its uses in medicine. *Chem Rev* **2013**, *113*, 4708-4754.
56. Shankar, P.D.; Shobana, S.; Karuppusamy, I.; Pugazhendhi, A.; Ramkumar, V.S.; Arvindnarayan, S.; Kumar, G. A review on the biosynthesis of metallic nanoparticles (gold and silver) using bio-components of microalgae: Formation mechanism and applications. *Enzyme Microb Technol* **2016**, *95*, 28-44.
57. Rozhin, A.; Batasheva, S.; Kruychkova, M.; Cherednichenko, Y.; Rozhina, E.; Fakhrullin, R. Biogenic Silver Nanoparticles: Synthesis and Application as Antibacterial and Antifungal Agents. *Micromachines (Basel)* **2021**, *12*.
58. Shen, S.; Wu, Y.; Liu, Y.; Wu, D. High drug-loading nanomedicines: progress, current status, and prospects. *Int J Nanomedicine* **2017**, *12*, 4085-4109.

59. Duan, Y.; Dhar, A.; Patel, C.; Khimani, M.; Neogi, S.; Sharma, P.; Siva Kumar, N.; Vekariya, R.L. A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems. *RSC Advances* **2020**, *10*, 26777-26791.
60. Ouyang, S.; Hu, X.; Zhou, Q.; Li, X.; Miao, X.; Zhou, R. Nanocolloids in Natural Water: Isolation, Characterization, and Toxicity. *Environ Sci Technol* **2018**, *52*, 4850-4860.
61. Najimu Nisha, S.; Aysha, O.S.; Syed Nasar Rahaman, J.; Vinoth Kumar, P.; Valli, S.; Nirmala, P.; Reena, A. Lemon peels mediated synthesis of silver nanoparticles and its antidermatophytic activity. *Spectrochim Acta A Mol Biomol Spectrosc* **2014**, *124*, 194-198.
62. Syed, A.; Ahmad, A. Extracellular biosynthesis of platinum nanoparticles using the fungus *Fusarium oxysporum*. *Colloids Surf B Biointerfaces* **2012**, *97*, 27-31.
63. Simoes, D.; Miguel, S.P.; Ribeiro, M.P.; Coutinho, P.; Mendonca, A.G.; Correia, I.J. Recent advances on antimicrobial wound dressing: A review. *Eur J Pharm Biopharm* **2018**, *127*, 130-141.
64. Azuma, K.; Izumi, R.; Osaki, T.; Ifuku, S.; Morimoto, M.; Saimoto, H.; Minami, S.; Okamoto, Y. Chitin, chitosan, and its derivatives for wound healing: old and new materials. *J Funct Biomater* **2015**, *6*, 104-142.
65. Zahedi, P.; Rezaeian, I.; Ranaei-Siadat, S.-O.; Jafari, S.-H.; Supaphol, P. A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. *Polymers for Advanced Technologies* **2010**, *21*, 77-95.
66. Jayarama Reddy, V.; Radhakrishnan, S.; Ravichandran, R.; Mukherjee, S.; Balamurugan, R.; Sundarrajan, S.; Ramakrishna, S. Nanofibrous structured biomimetic strategies for skin tissue regeneration. *Wound Repair Regen* **2013**, *21*, 1-16.
67. Chen, Z.; Wei, B.; Mo, X.; Lim, C.T.; Ramakrishna, S.; Cui, F. Mechanical properties of electrospun collagen–chitosan complex single fibers and membrane. *Materials Science and Engineering: C* **2009**, *29*, 2428-2435.
68. Sezer, A.D.; Cevher, E. Biopolymers as Wound Healing Materials: Challenges and New Strategies. 2011.
69. Hoogesteijn von Reitzenstein, N.; Bi, X.; Yang, Y.; Hristovski, K.; Westerhoff, P. Morphology, structure, and properties of metal oxide/polymer nanocomposite electrospun mats. *Journal of Applied Polymer Science* **2016**, *133*.
70. Rajesh, R.; Ravichandran, Y.D. Development of a new carbon nanotube-alginate-hydroxyapatite tricomponent composite scaffold for application in bone tissue engineering. *Int J Nanomedicine* **2015**, *10 Suppl 1*, 7-15.
71. Veetil, J.V.; Ye, K. Tailored carbon nanotubes for tissue engineering applications. *Biotechnol Prog* **2009**, *25*, 709-721.
72. Shoba, E.; Lakra, R.; Kiran, M.S.; Korrapati, P.S. Design and development of papain–urea loaded PVA nanofibers for wound debridement. *RSC Advances* **2014**, *4*, 60209-60215.
73. Satish, A.; Korrapati, P.S. Fabrication of a triiodothyronine incorporated nanofibrous biomaterial: its implications on wound healing. *RSC Advances* **2015**, *5*, 83773-83780.
74. Rajendran, N.K.; Kumar, S.S.D.; Houreld, N.N.; Abrahamse, H. A review on nanoparticle based treatment for wound healing. *Journal of Drug Delivery Science and Technology* **2018**, *44*, 421-430.
75. Chou, S.-F.; Gunaseelan, S.; Kiellani, M.H.H.; Thottempudi, V.V.K.; Neuenschwander, P.; Nie, H. A Review of Injectable and Implantable Biomaterials for Treatment and Repair of Soft Tissues in Wound Healing. *Journal of Nanotechnology* **2017**, *2017*, 6341710.
76. Krishnan, P.D.; Banas, D.; Durai, R.D.; Kabanov, D.; Hosnedlova, B.; Kepinska, M.; Fernandez, C.; Ruttkay-Nedecky, B.; Nguyen, H.V.; Farid, A., *et al.* Silver Nanomaterials for Wound Dressing Applications. *Pharmaceutics* **2020**, *12*.
77. Gravante, G.; Montone, A. A retrospective analysis of ambulatory burn patients: focus on wound dressings and healing times. *Ann R Coll Surg Engl* **2010**, *92*, 118-123.
78. Bahramsoltani, R.; Farzaei, M.H.; Rahimi, R. Medicinal plants and their natural components as future drugs for the treatment of burn wounds: an integrative review. *Arch Dermatol Res* **2014**, *306*, 601-617.
79. Gopal, A.; Kant, V.; Gopalakrishnan, A.; Tandan, S.K.; Kumar, D. Chitosan-based copper nanocomposite accelerates healing in excision wound model in rats. *Eur J Pharmacol* **2014**, *731*, 8-19.

80. Peng, C.C.; Yang, M.H.; Chiu, W.T.; Chiu, C.H.; Yang, C.S.; Chen, Y.W.; Chen, K.C.; Peng, R.Y. Composite nano-titanium oxide-chitosan artificial skin exhibits strong wound-healing effect-an approach with anti-inflammatory and bactericidal kinetics. *Macromol Biosci* **2008**, *8*, 316-327.
81. Kumar, P.T.; Lakshmanan, V.K.; Anilkumar, T.V.; Ramya, C.; Reshmi, P.; Unnikrishnan, A.G.; Nair, S.V.; Jayakumar, R. Flexible and microporous chitosan hydrogel/nano ZnO composite bandages for wound dressing: in vitro and in vivo evaluation. *ACS Appl Mater Interfaces* **2012**, *4*, 2618-2629.
82. P, T.S.; Lakshmanan, V.K.; Raj, M.; Biswas, R.; Hiroshi, T.; Nair, S.V.; Jayakumar, R. Evaluation of wound healing potential of beta-chitin hydrogel/nano zinc oxide composite bandage. *Pharm Res* **2013**, *30*, 523-537.
83. Atar-Froyman, L.; Sharon, A.; Weiss, E.I.; Houri-Haddad, Y.; Kesler-Shvero, D.; Domb, A.J.; Pilo, R.; Beyth, N. Anti-biofilm properties of wound dressing incorporating nonrelease polycationic antimicrobials. *Biomaterials* **2015**, *46*, 141-148.
84. Tiwari, M.; Narayanan, K.; Thakar, M.B.; Jagani, H.V.; Venkata Rao, J. Biosynthesis and wound healing activity of copper nanoparticles. *IET Nanobiotechnol* **2014**, *8*, 230-237.
85. Vedakumari, W.S.; Prabu, P.; Sastry, T.P. Chitosan-Fibrin Nanocomposites as Drug Delivering and Wound Healing Materials. *J Biomed Nanotechnol* **2015**, *11*, 657-667.
86. Palmieri, V.; Papi, M.; Conti, C.; Ciasca, G.; Maulucci, G.; De Spirito, M. The future development of bacteria fighting medical devices: the role of graphene oxide. *Expert Rev Med Devices* **2016**, *13*, 1013-1019.
87. Shahnawaz Khan, M.; Abdelhamid, H.N.; Wu, H.F. Near infrared (NIR) laser mediated surface activation of graphene oxide nanoflakes for efficient antibacterial, antifungal and wound healing treatment. *Colloids Surf B Biointerfaces* **2015**, *127*, 281-291.
88. Shams, E.; Yeganeh, H.; Naderi-Manesh, H.; Gharibi, R.; Mohammad Hassan, Z. Polyurethane/siloxane membranes containing graphene oxide nanoplatelets as antimicrobial wound dressings: in vitro and in vivo evaluations. *J Mater Sci Mater Med* **2017**, *28*, 75.
89. Li, Z.; Wang, H.; Yang, B.; Sun, Y.; Huo, R. Three-dimensional graphene foams loaded with bone marrow derived mesenchymal stem cells promote skin wound healing with reduced scarring. *Mater Sci Eng C Mater Biol Appl* **2015**, *57*, 181-188.
90. Zhou, Y.; Chen, R.; He, T.; Xu, K.; Du, D.; Zhao, N.; Cheng, X.; Yang, J.; Shi, H.; Lin, Y. Biomedical Potential of Ultrafine Ag/AgCl Nanoparticles Coated on Graphene with Special Reference to Antimicrobial Performances and Burn Wound Healing. *ACS Appl Mater Interfaces* **2016**, *8*, 15067-15075.
91. Ferrari, M. Nanogeometry: beyond drug delivery. *Nat Nanotechnol* **2008**, *3*, 131-132.
92. George, S.; Lin, S.; Ji, Z.; Thomas, C.R.; Li, L.; Mecklenburg, M.; Meng, H.; Wang, X.; Zhang, H.; Xia, T., *et al.* Surface defects on plate-shaped silver nanoparticles contribute to its hazard potential in a fish gill cell line and zebrafish embryos. *ACS Nano* **2012**, *6*, 3745-3759.
93. Lin, P.C.; Lin, S.; Wang, P.C.; Sridhar, R. Techniques for physicochemical characterization of nanomaterials. *Biotechnol Adv* **2014**, *32*, 711-726.
94. Gautam, R.; Yang, S.; Maharjan, A.; Jo, J.; Acharya, M.; Heo, Y.; Kim, C. Prediction of Skin Sensitization Potential of Silver and Zinc Oxide Nanoparticles Through the Human Cell Line Activation Test. *Frontiers in Toxicology* **2021**, *3*.
95. Hamdan, S.; Pastar, I.; Drakulich, S.; Dikici, E.; Tomic-Canic, M.; Deo, S.; Daunert, S. Nanotechnology-Driven Therapeutic Interventions in Wound Healing: Potential Uses and Applications. *ACS Cent Sci* **2017**, *3*, 163-175.
96. Vijayakumar, V.; Samal, S.K.; Mohanty, S.; Nayak, S.K. Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management. *Int J Biol Macromol* **2019**, *122*, 137-148.
97. Szmyd, R.; Goralczyk, A.G.; Skalniak, L.; Cierniak, A.; Lipert, B.; Filon, F.L.; Crosera, M.; Borowczyk, J.; Laczna, E.; Drukala, J., *et al.* Effect of silver nanoparticles on human primary keratinocytes. *Biol Chem* **2013**, *394*, 113-123.

98. Pal, S.; Nisi, R.; Stoppa, M.; Licciulli, A. Silver-Functionalized Bacterial Cellulose as Antibacterial Membrane for Wound-Healing Applications. *ACS Omega* **2017**, *2*, 3632-3639.
99. Yildirimer, L.; Thanh, N.T.; Loizidou, M.; Seifalian, A.M. Toxicology and clinical potential of nanoparticles. *Nano Today* **2011**, *6*, 585-607.
100. Sarhan, W.A.; Azzazy, H.M.; El-Sherbiny, I.M. Honey/Chitosan Nanofiber Wound Dressing Enriched with Allium sativum and Cleome droserifolia: Enhanced Antimicrobial and Wound Healing Activity. *ACS Appl Mater Interfaces* **2016**, *8*, 6379-6390.
101. Kaba, S.I.; Egorova, E.M. In vitro studies of the toxic effects of silver nanoparticles on HeLa and U937 cells. *Nanotechnol Sci Appl* **2015**, *8*, 19-29.
102. Cameron, P.; Gaiser, B.K.; Bhandari, B.; Bartley, P.M.; Katzer, F.; Bridle, H. Silver Nanoparticles Decrease the Viability of *Cryptosporidium parvum* Oocysts. *Appl Environ Microbiol* **2016**, *82*, 431-437.
103. Lambadi, P.R.; Sharma, T.K.; Kumar, P.; Vasnani, P.; Thalluri, S.M.; Bisht, N.; Pathania, R.; Navani, N.K. Facile biofunctionalization of silver nanoparticles for enhanced antibacterial properties, endotoxin removal, and biofilm control. *Int J Nanomedicine* **2015**, *10*, 2155-2171.
104. Singh, B.R.; Singh, B.N.; Singh, A.; Khan, W.; Naqvi, A.H.; Singh, H.B. Mycofabricated biosilver nanoparticles interrupt *Pseudomonas aeruginosa* quorum sensing systems. *Sci Rep* **2015**, *5*, 13719.
105. Frankova, J.; Pivodova, V.; Vagnerova, H.; Juranova, J.; Ulrichova, J. Effects of silver nanoparticles on primary cell cultures of fibroblasts and keratinocytes in a wound-healing model. *J Appl Biomater Funct Mater* **2016**, *14*, e137-142.
106. Liu, J.; Sonshine, D.A.; Shervani, S.; Hurt, R.H. Controlled release of biologically active silver from nanosilver surfaces. *ACS Nano* **2010**, *4*, 6903-6913.
107. Tian, J.; Wong, K.K.; Ho, C.M.; Lok, C.N.; Yu, W.Y.; Che, C.M.; Chiu, J.F.; Tam, P.K. Topical delivery of silver nanoparticles promotes wound healing. *ChemMedChem* **2007**, *2*, 129-136.
108. Yeh, Y.C.; Creran, B.; Rotello, V.M. Gold nanoparticles: preparation, properties, and applications in bionanotechnology. *Nanoscale* **2012**, *4*, 1871-1880.
109. Lu, M.M.; Bai, J.; Shao, D.; Qiu, J.; Li, M.; Zheng, X.; Xiao, Y.; Wang, Z.; Chang, Z.M.; Chen, L., *et al.* Antibacterial and biodegradable tissue nano-adhesives for rapid wound closure. *Int J Nanomedicine* **2018**, *13*, 5849-5863.
110. Norman, R.S.; Stone, J.W.; Gole, A.; Murphy, C.J.; Sabo-Attwood, T.L. Targeted photothermal lysis of the pathogenic bacteria, Pseudomonas aeruginosa, with gold nanorods. *Nano Lett* **2008**, *8*, 302-306.
111. Marambio-Jones, C.; Hoek, E.M.V. A review of the antibacterial effects of silver nanomaterials and potential implications for human health and the environment. *Journal of Nanoparticle Research* **2010**, *12*, 1531-1551.
112. Akturk, O.; Kismet, K.; Yasti, A.C.; Kuru, S.; Duymus, M.E.; Kaya, F.; Caydere, M.; Hucumenoglu, S.; Keskin, D. Collagen/gold nanoparticle nanocomposites: A potential skin wound healing biomaterial. *J Biomater Appl* **2016**, *31*, 283-301.
113. Jayakumar, R.; Prabaharan, M.; Sudheesh Kumar, P.T.; Nair, S.V.; Tamura, H. Biomaterials based on chitin and chitosan in wound dressing applications. *Biotechnol Adv* **2011**, *29*, 322-337.
114. Gil-Tomás, J.; Tubby, S.; Parkin, I.P.; Narband, N.; Dekker, L.; Nair, S.P.; Wilson, M.; Street, C. Lethal photosensitisation of Staphylococcus aureus using a toluidine blue O–tiopronin–gold nanoparticle conjugate. *Journal of Materials Chemistry* **2007**, *17*, 3739-3746.
115. Lu, S.; Xia, D.; Huang, G.; Jing, H.; Wang, Y.; Gu, H. Concentration effect of gold nanoparticles on proliferation of keratinocytes. *Colloids Surf B Biointerfaces* **2010**, *81*, 406-411.
116. Marza, S.M.; Magyari, K.; Bogdan, S.; Moldovan, M.; Pestean, C.; Nagy, A.; Tabaran, F.; Licarete, E.; Suarasan, S.; Dreanca, A., *et al.* Skin wound regeneration with bioactive glass-gold nanoparticles ointment. *Biomed Mater* **2019**, *14*, 025011.

117. Arafa, M.G.; El-Kased, R.F.; Elmazar, M.M. Thermoresponsive gels containing gold nanoparticles as smart antibacterial and wound healing agents. *Sci Rep* **2018**, *8*, 13674.
118. Hsu, S.H.; Chang, Y.B.; Tsai, C.L.; Fu, K.Y.; Wang, S.H.; Tseng, H.J. Characterization and biocompatibility of chitosan nanocomposites. *Colloids Surf B Biointerfaces* **2011**, *85*, 198-206.
119. Volkova, N.; Yukhta, M.; Pavlovich, O.; Goltsev, A. Application of Cryopreserved Fibroblast Culture with Au Nanoparticles to Treat Burns. *Nanoscale Res Lett* **2016**, *11*, 22.
120. Gobin, A.M.; O'Neal, D.P.; Watkins, D.M.; Halas, N.J.; Drezek, R.A.; West, J.L. Near infrared laser-tissue welding using nanoshells as an exogenous absorber. *Lasers Surg Med* **2005**, *37*, 123-129.
121. Garg, T.; Rath, G.; Goyal, A.K. Comprehensive review on additives of topical dosage forms for drug delivery. *Drug Deliv* **2015**, *22*, 969-987.
122. Pati, R.; Mehta, R.K.; Mohanty, S.; Padhi, A.; Sengupta, M.; Vaseeharan, B.; Goswami, C.; Sonawane, A. Topical application of zinc oxide nanoparticles reduces bacterial skin infection in mice and exhibits antibacterial activity by inducing oxidative stress response and cell membrane disintegration in macrophages. *Nanomedicine* **2014**, *10*, 1195-1208.
123. Ms, B.; Sg, G. In *Recent nanotechnological aspects in cosmetics and dermatological preparations*, 2012.
124. Păunica-Panea, G.; Ficai, A.; Marin, M.M.; Marin, Ș.; Albu, M.G.; Constantin, V.D.; Dinu-Pîrvu, C.; Vuluga, Z.; Corobea, M.C.; Ghica, M.V. New Collagen-Dextran-Zinc Oxide Composites for Wound Dressing. *Journal of Nanomaterials* **2016**, *2016*, 5805034.
125. Sirelkhatim, A.; Mahmud, S.; Seeni, A.; Kaus, N.H.M.; Ann, L.C.; Bakhori, S.K.M.; Hasan, H.; Mohamad, D. Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism. *Nanomicro Lett* **2015**, *7*, 219-242.
126. Ferris, C.J.; Gilmore, K.J.; Beirne, S.; McCallum, D.; Wallace, G.G.; In Het Panhuis, M. Bio-ink for on-demand printing of living cells. *Biomater Sci* **2013**, *1*, 224-230.
127. Dhivya, S.; Padma, V.V.; Santhini, E. Wound dressings - a review. *Biomedicine (Taipei)* **2015**, *5*, 22.
128. Hankin, C.S.; Knispel, J.; Lopes, M.; Bronstone, A.; Maus, E. Clinical and cost efficacy of advanced wound care matrices for venous ulcers. *J Manag Care Pharm* **2012**, *18*, 375-384.
129. Lo, S.; Fauzi, M.B. Current Update of Collagen Nanomaterials-Fabrication, Characterisation and Its Applications: A Review. *Pharmaceutics* **2021**, *13*.
130. Ovais, M.; Ahmad, I.; Khalil, A.T.; Mukherjee, S.; Javed, R.; Ayaz, M.; Raza, A.; Shinwari, Z.K. Wound healing applications of biogenic colloidal silver and gold nanoparticles: recent trends and future prospects. *Appl Microbiol Biotechnol* **2018**, *102*, 4305-4318.
131. Neema, S.; Chatterjee, M. Nano-silver dressing in toxic epidermal necrolysis. *Indian J Dermatol Venereol Leprol* **2017**, *83*, 121-124.
132. Ribeiro, F.M.; de Oliveira, M.M.; Singh, S.; Sakthivel, T.S.; Neal, C.J.; Seal, S.; Ueda-Nakamura, T.; Lautenschlager, S.O.S.; Nakamura, C.V. Ceria Nanoparticles Decrease UVA-Induced Fibroblast Death Through Cell Redox Regulation Leading to Cell Survival, Migration and Proliferation. *Front Bioeng Biotechnol* **2020**, *8*, 577557.
133. Weller, C.D.; Team, V.; Sussman, G. First-Line Interactive Wound Dressing Update: A Comprehensive Review of the Evidence. *Front Pharmacol* **2020**, *11*.
134. Ahmed, E.M. Hydrogel: Preparation, characterization, and applications: A review. *J Adv Res* **2015**, *6*, 105-121.
135. Nunes, P.S.; Albuquerque, R.L.C., Jr.; Cavalcante, D.R.R.; Dantas, M.D.M.; Cardoso, J.C.; Bezerra, M.S.; Souza, J.C.C.; Serafini, M.R.; Quitans, L.J., Jr.; Bonjardim, L.R., *et al.* Collagen-based films containing liposome-loaded usnic acid as dressing for dermal burn healing. *J Biomed Biotechnol* **2011**, *2011*, 761593-761593.
136. McCord, S.S.; Levy, M.L. Practical Guide to Pediatric Wound Care. *Semin Plast Surg* **2006**, *20*, 192-199.
137. Hubner, P.; Donati, N.; Quines, L.K.M.; Tessaro, I.C.; Marcilio, N.R. Gelatin-based films containing clinoptilolite-Ag for application as wound dressing. *Mater Sci Eng C Mater Biol Appl* **2020**, *107*, 110215.

138. Naseri-Nosar, M.; Farzamfar, S.; Sahrapeyma, H.; Ghorbani, S.; Bastami, F.; Vaez, A.; Salehi, M. Cerium oxide nanoparticle-containing poly (epsilon-caprolactone)/gelatin electrospun film as a potential wound dressing material: In vitro and in vivo evaluation. *Mater Sci Eng C Mater Biol Appl* **2017**, *81*, 366-372.
139. Tang, Y.; Lan, X.; Liang, C.; Zhong, Z.; Xie, R.; Zhou, Y.; Miao, X.; Wang, H.; Wang, W. Honey loaded alginate/PVA nanofibrous membrane as potential bioactive wound dressing. *Carbohydr Polym* **2019**, *219*, 113-120.
140. Zhou, Y.; Yang, H.; Liu, X.; Mao, J.; Gu, S.; Xu, W. Electrospinning of carboxyethyl chitosan/poly(vinyl alcohol)/silk fibroin nanoparticles for wound dressings. *Int J Biol Macromol* **2013**, *53*, 88-92.
141. Zou, P.; Lee, W.H.; Gao, Z.; Qin, D.; Wang, Y.; Liu, J.; Sun, T.; Gao, Y. Wound dressing from polyvinyl alcohol/chitosan electrospun fiber membrane loaded with OH-CATH30 nanoparticles. *Carbohydr Polym* **2020**, *232*, 115786.
142. Balakrishnan, S.B.; Thambusamy, S. Preparation of silver nanoparticles and riboflavin embedded electrospun polymer nanofibrous scaffolds for in vivo wound dressing application. *Process Biochemistry* **2020**, *88*, 148-158.
143. Buzarovska, A.; Dinescu, S.; Lazar, A.D.; Serban, M.; Pircalabioru, G.G.; Costache, M.; Gualandi, C.; Averous, L. Nanocomposite foams based on flexible biobased thermoplastic polyurethane and ZnO nanoparticles as potential wound dressing materials. *Mater Sci Eng C Mater Biol Appl* **2019**, *104*, 109893.
144. Erring, M.; Gaba, S.; Mohsina, S.; Tripathy, S.; Sharma, R.K. Comparison of efficacy of silver-nanoparticle gel, nano-silver-foam and collagen dressings in treatment of partial thickness burn wounds. *Burns* **2019**, *45*, 1888-1894.
145. Thomas, S. Alginate dressings in surgery and wound management--Part 1. *J Wound Care* **2000**, *9*, 56-60.
146. Sayag, J.; Lieaume, S.; Bohbot, S. Healing properties of calcium alginate dressings. *J Wound Care* **1996**, *5*, 357-362.
147. Chiu, C.T.; Lee, J.S.; Chu, C.S.; Chang, Y.P.; Wang, Y.J. Development of two alginate-based wound dressings. *J Mater Sci Mater Med* **2008**, *19*, 2503-2513.
148. Zare-Gachi, M.; Daemi, H.; Mohammadi, J.; Baei, P.; Bazgir, F.; Hosseini-Salekdeh, S.; Baharvand, H. Improving anti-hemolytic, antibacterial and wound healing properties of alginate fibrous wound dressings by exchanging counter-cation for infected full-thickness skin wounds. *Mater Sci Eng C Mater Biol Appl* **2020**, *107*, 110321.
149. Rahmani, S.; Mooney, D.J. In *Tissue-Engineered Wound Dressings for Diabetic Foot Ulcers*, 2018.
150. Ziegler, U.E.; Schmidt, K.; Keller, H.P.; Thiede, A. [Treatment of chronic wounds with an alginate dressing containing calcium zinc and manganese]. *Fortschr Med Orig* **2003**, *121*, 19-26.
151. Asghari, S.; Logsetty, S.; Liu, S. Imparting commercial antimicrobial dressings with low-adherence to burn wounds. *Burns* **2016**, *42*, 877-883.
152. Munhoz, D.R.; Bernardo, M.P.; Malafatti, J.O.D.; Moreira, F.K.V.; Mattoso, L.H.C. Alginate films functionalized with silver sulfadiazine-loaded [Mg-Al] layered double hydroxide as antimicrobial wound dressing. *Int J Biol Macromol* **2019**, *141*, 504-510.
153. Resmi, R.; Unnikrishnan, S.; Krishnan, L.K.; Kalliyana Krishnan, V. Synthesis and characterization of silver nanoparticle incorporated gelatin-hydroxypropyl methacrylate hydrogels for wound dressing applications. *Journal of Applied Polymer Science* **2017**, *134*.
154. Liang, L.; Hou, T.; Ouyang, Q.; Xie, L.; Zhong, S.; Li, P.; Li, S.; Li, C. Antimicrobial sodium alginate dressing immobilized with polydopamine-silver composite nanospheres. *Composites Part B: Engineering* **2020**, *188*, 107877.
155. Dealey, C. Role of hydrocolloids in wound management. *Br J Nurs* **1993**, *2*, 358, 360, 362 passim.
156. Fletcher, J. Understanding wound dressings: hydrocolloids. *Nurs Times* **2005**, *101*, 51.
157. Janowska, A.; Macchia, M.; Paggi, B. Advanced Dressings in Pressure Ulcers. In *Science and Practice of Pressure Ulcer Management*, Romanelli, M.; Clark, M.; Gefen, A.; Ciprandi, G., Eds. Springer London: London, 2018; pp 159-173.
158. Clark, M. Alginates in Dressings and Wound Management. In *Alginates and Their Biomedical Applications*, Rehm, B.H.A.; Moradali, M.F., Eds. Springer Singapore: Singapore, 2018; pp 213-222.

159. Vermeulen, H.; Ubbink, D.T.; Goossens, A.; de Vos, R.; Legemate, D.A. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. *Br J Surg* **2005**, *92*, 665-672.
160. Namviriyachote, N.; Lipipun, V.; Akkhawattanangkul, Y.; Charoonrut, P.; Ritthidej, G.C. Development of polyurethane foam dressing containing silver and asiaticoside for healing of dermal wound. *Asian J Pharm Sci* **2019**, *14*, 63-77.
161. Namviriyachote, N.; Muangman, P.; Chinaroonchai, K.; Chuntrasakul, C.; Ritthidej, G.C. Polyurethane-biomacromolecule combined foam dressing containing asiaticoside: fabrication, characterization and clinical efficacy for traumatic dermal wound treatment. *Int J Biol Macromol* **2020**, *143*, 510-520.
162. Zhou, B.; Li, Y.; Deng, H.; Hu, Y.; Li, B. Antibacterial multilayer films fabricated by layer-by-layer immobilizing lysozyme and gold nanoparticles on nanofibers. *Colloids Surf B Biointerfaces* **2014**, *116*, 432-438.
163. Choi, J.; Konno, T.; Takai, M.; Ishihara, K. Smart controlled preparation of multilayered hydrogel for releasing bioactive molecules. *Current Applied Physics* **2009**, *9*, e259-e262.
164. Aruan, N.M.; Sriyanti, I.; Edikresnha, D.; Suciati, T.; Munir, M.M.; Khairurrijal. Polyvinyl Alcohol/Soursop Leaves Extract Composite Nanofibers Synthesized Using Electrospinning Technique and their Potential as Antibacterial Wound Dressing. *Procedia Engineering* **2017**, *170*, 31-35.
165. Sampathkumar, S.K. Design and Characterization of Secondary and Tertiary Layers of a Multilayer Wound Dressing System. *Journal of Testing and Evaluation* **2018**, *48*.
166. Groves, A.R.; Lawrence, J.C. Alginate dressing as a donor site haemostat. *Ann R Coll Surg Engl* **1986**, *68*, 27-28.
167. Tamahkar, E.; Özkahraman, B.; Süloğlu, A.K.; İdil, N.; Perçin, I. A novel multilayer hydrogel wound dressing for antibiotic release. *Journal of Drug Delivery Science and Technology* **2020**, *58*, 101536.
168. Weller, C.D.; Team, V.; Sussman, G. First-Line Interactive Wound Dressing Update: A Comprehensive Review of the Evidence. *Front Pharmacol* **2020**, *11*, 155-155.
169. Matthew, I.R.; Browne, R.M.; Frame, J.W.; Millar, B.G. Subperiosteal behaviour of alginate and cellulose wound dressing materials. *Biomaterials* **1995**, *16*, 275-278.
170. Shokrollahi, M.; Bahrami, S.H.; Nazarpak, M.H.; Solouk, A. Multilayer nanofibrous patch comprising chamomile loaded carboxyethyl chitosan/poly(vinyl alcohol) and polycaprolactone as a potential wound dressing. *Int J Biol Macromol* **2020**, *147*, 547-559.
171. Sharifi, S.; Hajipour, M.J.; Gould, L.; Mahmoudi, M. Nanomedicine in Healing Chronic Wounds: Opportunities and Challenges. *Mol Pharm* **2021**, *18*, 550-575.
172. Hancock, R.E.; Haney, E.F.; Gill, E.E. The immunology of host defence peptides: beyond antimicrobial activity. *Nat Rev Immunol* **2016**, *16*, 321-334.
173. Mookherjee, N.; Hancock, R.E. Cationic host defence peptides: innate immune regulatory peptides as a novel approach for treating infections. *Cell Mol Life Sci* **2007**, *64*, 922-933.
174. Tokumaru, S.; Sayama, K.; Shirakata, Y.; Komatsuzawa, H.; Ouhara, K.; Hanakawa, Y.; Yahata, Y.; Dai, X.; Tohyama, M.; Nagai, H., *et al.* Induction of keratinocyte migration via transactivation of the epidermal growth factor receptor by the antimicrobial peptide LL-37. *J Immunol* **2005**, *175*, 4662-4668.
175. Raziyeva, K.; Kim, Y.; Zharkinbekov, Z.; Kassymbek, K.; Jimi, S.; Saparov, A. Immunology of Acute and Chronic Wound Healing. *Biomolecules* **2021**, *11*.
176. MacLeod, A.S.; Mansbridge, J.N. The Innate Immune System in Acute and Chronic Wounds. *Adv Wound Care (New Rochelle)* **2016**, *5*, 65-78.
177. Lima, M.H.M.; Caricilli, A.M.; de Abreu, L.L.; Araújo, E.P.; Pelegrinelli, F.F.; Thirone, A.C.P.; Tsukumo, D.M.; Pessoa, A.F.M.; dos Santos, M.F.; de Moraes, M.A., *et al.* Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. *PLoS One* **2012**, *7*, e36974-e36974.

178. Mouritzen, M.V.; Abourayale, S.; Ejaz, R.; Ardon, C.B.; Carvalho, E.; Dalgaard, L.T.; Roursgaard, M.; Jenssen, H. Neurotensin, substance P, and insulin enhance cell migration. *J Pept Sci* **2018**, *24*, e3093.

179. Lima, M.H.; Caricilli, A.M.; de Abreu, L.L.; Araujo, E.P.; Pelegrinelli, F.F.; Thirone, A.C.; Tsukumo, D.M.; Pessoa, A.F.; dos Santos, M.F.; de Moraes, M.A., *et al*. Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. *PLoS One* **2012**, *7*, e36974.

180. Scheenstra, M.R.; van Harten, R.M.; Veldhuizen, E.J.A.; Haagsman, H.P.; Coorens, M. Cathelicidins Modulate TLR-Activation and Inflammation. *Front Immunol* **2020**, *11*, 1137.

181. Chen, S.; Lu, Z.; Wang, F.; Wang, Y. Cathelicidin-WA polarizes E. coli K88-induced M1 macrophage to M2-like macrophage in RAW264.7 cells. *Int Immunopharmacol* **2018**, *54*, 52-59.

182. Jiang, J.; Chen, S.; Wang, H.; Carlson, M.A.; Gombart, A.F.; Xie, J. CO2-expanded nanofiber scaffolds maintain activity of encapsulated bioactive materials and promote cellular infiltration and positive host response. *Acta Biomater* **2018**, *68*, 237-248.

183. Garcia-Orue, I.; Gainza, G.; Girbau, C.; Alonso, R.; Aguirre, J.J.; Pedraz, J.L.; Igartua, M.; Hernandez, R.M. LL37 loaded nanostructured lipid carriers (NLC): A new strategy for the topical treatment of chronic wounds. *Eur J Pharm Biopharm* **2016**, *108*, 310-316.

184. Luo, G.; Sun, Y.; Zhang, J.; Xu, Z.; Lu, W.; Wang, H.; Zhang, Y.; Li, H.; Mao, Z.; Ye, S., *et al.* Nanodefensin-encased hydrogel with dual bactericidal and pro-regenerative functions for advanced wound therapy. *Theranostics* **2021**, *11*, 3642-3660.

185. Tsikourkitoudi, V.; Karlsson, J.; Merkl, P.; Loh, E.; Henriques-Normark, B.; Sotiriou, G.A. Flame-Made Calcium Phosphate Nanoparticles with High Drug Loading for Delivery of Biologics. *Molecules* **2020**, *25*.

186. Chereddy, K.K.; Her, C.H.; Comune, M.; Moia, C.; Lopes, A.; Porporato, P.E.; Vanacker, J.; Lam, M.C.; Steinstraesser, L.; Sonveaux, P., *et al.* PLGA nanoparticles loaded with host defense peptide LL37 promote wound healing. *J Control Release* **2014**, *194*, 138-147.

187. Wang, S.; Yan, C.; Zhang, X.; Shi, D.; Chi, L.; Luo, G.; Deng, J. Antimicrobial peptide modification enhances the gene delivery and bactericidal efficiency of gold nanoparticles for accelerating diabetic wound healing. *Biomaterials Science* **2018**, *6*, 2757-2772.

188. Comune, M.; Rai, A.; Chereddy, K.K.; Pinto, S.; Aday, S.; Ferreira, A.F.; Zonari, A.; Blersch, J.; Cunha, R.; Rodrigues, R., *et al.* Antimicrobial peptide-gold nanoscale therapeutic formulation with high skin regenerative potential. *Journal of Controlled Release* **2017**, *262*, 58-71.