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Artificial intelligence for regular monitoring of diabetogenic wounds and exploring nanotherapeutics to combat the multifaceted pathophysiology

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Abstract:

The multifaceted pathophysiology of diabetic wounds coupled with impaired diabetic wound healing remains a significant challenge for the medical community in the 21st century. Possibility of bacterial infections, insufficient vascular supply, increment in levels of oxidative stress, and abnormalities in defenses mechanism of antioxidant causes diabetic foot ulcers (DFU) that leads to significant morbidity. An effective treatment for diabetic wounds is still lacking. Chronic wounds are taking epidemic proportions, leading to an increased interest in exploring novel therapies to meet the challenges. Evaluating the progression in diabetic ulcers poses a major threat for the patients and clinician owing to logistics as irregular visits to the clinics. Unique properties of nanoparticles contain ultra-small size, increased surface-to-volume ratio, low cytotoxicity, enhanced cellular uptake, improved antibacterial activity, biocompatibility and biodegradability making their applications attractive against DFUs. Their potential for healing can be due to their superior antioxidant and anti-inflammatory activities. Further, nanoparticles are effective delivery vehicles for various small molecules, exosomes, metallic molecules, or conjugated with numerous biomaterials- chitosan (CS), hyaluronic acid (HA) and smart hydrogels (HG) to enhance their healing efficacy against diabetic wounds. This review focuses on the futuristic and potential viewpoints of nanoparticles for the therapeutics of diabetic wounds/DFUs. Artificial intelligence (AI) tools and optical sensors can further contribute effectively for the monitoring procedures. Software based on AI technology plays crucial role in assessment and provide continuous care throughout the treatment. AI also helps to connect healthcare experts with larger number of patients at the same time. Nanotherapeutics represents a promising innovative strategy for targeted treatment that can change the landscape of wound healing, by providing a physiologically stable micro-environment for the thorough wound-healing process.

Keywords: DFUs; Diabetic/chronic wound; Nanoparticles; Optical sensors; Wound healing

1. Introduction

Diabetic foot ulcers (DFUs) have multifactorial etiologic and key complexity in uncontrolled *Diabetes mellitus* (DM) cases that are associated with morbidity and mortality [1]. Globally, over 400 million people are suffering from DM, a multifaceted metabolic disorder that has a major burden on health care systems [2]. The complications occur largely due to the inadequate glycaemic control, poor foot care, peripheral vascular disease, or chronicity caused by delayed or non-curated diabetic wounds, primarily the minor extremities referred to as diabetic foot ulcer (DFU), that gets worsened and cause $15-25\%$ of the diabetic patients to

opt for amputation and subsequent disability during their lifetimes [3, 4]. The risk of developing DFU in diabetic patients is 15% in their lifetime and approximately 85% of limb amputation maybe due to non-healing ulcers. External infections that enter the body due to the comprised integrity of the skin may lead to structural deformities, wherever skin acts as a protective shell that avoids the invasion often causes unhealed and gangrenous wounds [5].

To understand the complexity of healing process, the normal physiological phenomenon that encompasses a cascade of intricate cellular and biomolecular cross-talks is necessary. Repairing of wound is a natural, yet complex biological process and involves four classical phases: haemostasis, inflammation, proliferation, and remodelling with a vibrant interplay of various cells, cytokines, and the extracellular matrix (ECM). The key requirement for wound management is the swift and complete healing without any infection or spread of infection leading to sepsis followed by the sequential processes that help in the closure of wound [6]. In healthy individuals the entire process occurs at an ideal rate. Even acute wounds normally heal without any problem. The foremost and most relatable worry includes stage of development related variations in usual physiological functions such as obesity, slowed blood circulation, environmental stress, and diseases like diabetes [3, 6].

Delayed wound healing mechanism is multifactorial in nature, which involves prolonged inflammatory stage and postponed proliferation followed by remodelling steps. DeClue and Shornic reported the release of pro-inflammatory cytokines (*e.g.*, TNF-α, IL-6, and IL-1β) that involves diabetic wound healing [7]. Qiu et al. [8] suggested that diabetic patients having high blood glucose levels causes restricted cell proliferation and indicate a decline in growth factors and collagen during the healing process [8]. Another important parameter for delayed wound healing maybe reduced angiogenesis having low transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) growth factors [9]. This can be very challenging to heal due to impaired regeneration of the tissue and compromised immune responses as shown in (Fig. 1) [7, 9].

The advent of nanotechnology has revolutionized the medical applications that promise efficacy, safety, and prolonged circulation and targeted delivery. Nanomaterials such as Gold, Silver, Zinc exhibit strong antimicrobial properties that can be incorporated into wound dressing materials to accelerate wound healing, or applied to medical devices to enhance their biocompatibility and antimicrobial activity [10].

Generally, AI technology implementation has improved over the years which ameliorate healthcare facilities. In 1970, AI contributed towards the medical sector primarily in health related issues indicating improved and promising results [11]. Diabetic wound cases and their assessment has also been made easier by AI based solutions, as it may help in early-stage detection and reducing morbidity and amputation in various cases thereby giving satisfactory results. Deep learning about AI helps to reduce known and unknown risk factors associated with wounds. More focus and attention in this research area with collaboration of clinical practitioners and researchers will bridge the gap giving faster healing strategies [12].

This review aims to focus on the fundamentals of acute and

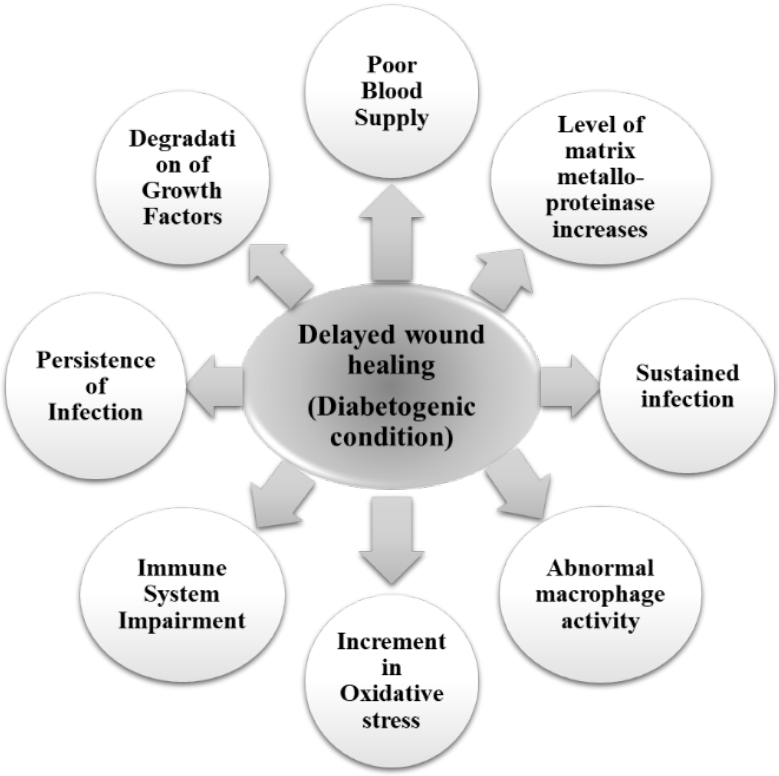

Figure 1. Factors affecting Diabetic wound healing.

chronic healing of wound, with a nanotherapeutic approach which will make it feasible for patients to get the better and cost-effective treatments. For remote monitoring, the patients are required to send the photographs of the ulcers/wounds electronically to the professionals' in-charge of diabetic care. This helps to avoid patient transport to clinics that further helps to reduce the pressures on the clinics. Over the past years it has been observed that an avalanche of artificial intelligence-based technologies being developed for improvement in the remote observation of DFU with the help of mobile apps. It is predicted to make a vast influence on care of diabetogenic wounds. It is important to discuss and further understand the wounds to be able to compile evidences.

2. Acute and chronic wound healing

Wound healing is an extremely complicated process that includes an interplay of various growth factors (GF), cytokines and extracellular matrix (ECM) in different types of cells. Wound healing includes sequential processes like homeostasis, inflammation, cell movement and proliferation followed by wound compression and remodelling [13]. Trauma in the superficial layer of skin further results in bleeding, which is considered as he 'wound' [14]. Homeostasis is the initial process in wound healing that involves blood coagulation resulting in stopping of bleeding at the injury site. The first line of defence at the wound site are platelets and neutrophils; various growth factors like platelets derived growth factor (PDGF), endothelial growth factor (EGF), TGF-β and fibroblast growth factor (FGF) are released leading to the onset of inflammation [15, 16]. The secreted pro-inflammatory molecules and inflammatory mediators including histamine, prostaglandins, and migration of immune cells will permeate at the injury site [17]. Macrophages secrete TGF-β, VEGF, and FGF to promote angiogenesis. They also produce tumour necrosis factor alpha (TNF-α) that breaks down the necrotic tissue and promotes the development of fibroblasts to accumulate collagen which helps in granulation of tissue. Neutrophils help fight the microbial infections [18]. Shrinking of wound or closure begins within two weeks after a deep dermal wound. Alpha smooth muscle actin (αSMA) is a component of cytoskeleton that plays a very important part in closing of the wound *i.e.* when the fibroblasts differentiate into myofibroblasts. Tissue granulation, keratinocyte migration further helps to recover by initiation of new layers of tissue that helps in the formation of epidermis at the injury site [19]. The last phase of the healing is the remodelling phase where the granulation of tissue is accompanied by the replacement of ECM with type 1 collagen via mediators like PDGF and TGF-β [20]. In diabetic wounds, inflammatory macrophages occupy the wound site in large numbers when compared to the numbers at a regular wound healing site. These macrophages generate more TNF-α and IL-6, and pro-inflammatory cytokines increase the ROS levels, resulting in prolonged inflammation. It also stimulates proliferative factors for effective wound healing. However, the ineffective efferocytosis (apoptosis of phagocytic cells) of macrophages maybe associated with the load of apoptotic cells as it disrupts the common cytokine cascade. The unusual death of fibroblasts and keratinocytes may be accompanied by reduction in angiogenesis, if the ratio of matrix metalloproteinase-9 (MMP-9), pro-inflammatory cytokines (IL-1 and TNF-α) gets enhanced, while the ratio of anti-inflammatory signals (CD206, TGF-β, IGF-1, and IL-10 may be reduced as depicted in (Fig. 2) [21–24]. Fig. 2 schematically represents the difference in the healing process between normal wound vs diabetic wound.

Diabetic wound healing is impaired as the differentiation of fibroblast into myofibroblast is not sequential. There is reduced mechanical tension in ECM due to the absence of alpha-SMA that further hinders the proper healing of the wound. Protease increment not only helps the tissue to reconstruct rapidly, allows degradation of the ECM, collagen and growth factor that are essential for efficient wound healing [25, 26].

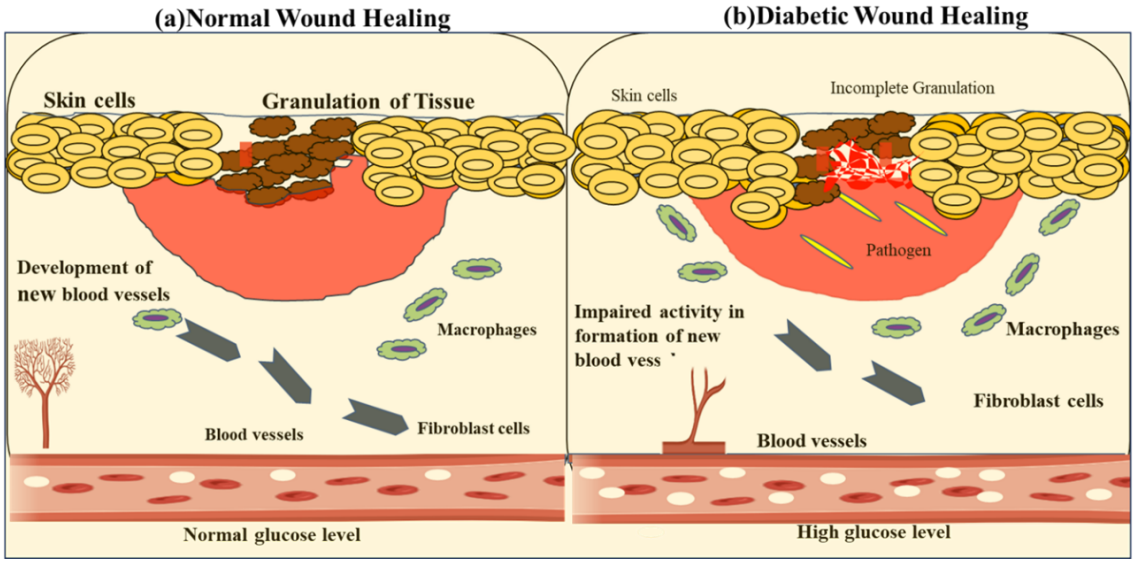

Figure 2. Structural representation of (a) normal (b) diabetic wound healing.

3. Clinical pathology of diabetogenic wounds

DFUs are open wounds having a circular outline, mainly formed at the bottom of the foot surface and often proceed by a haemorrhagic sub-epidermal blister. The nearby tissue area appears dark, and often becomes gangrenous. Since foot ulcers are painless, they are mostly neglected causing sufficient delays in visiting health professionals [27].

4. Conventional wound dressings and their limitations

Conventional wound dressings are fabricated from natural materials that are often used to treat the wounds. The choice of suitable dressings for healing of wound is highly individualised based on the wound size, its type, the quantity of exudation, the infection risk, and other considerations [28]. Many wound dressings work to create a moist and suitable environment that impedes the process of healing. Currently, a variety of materials for bandages are available, including, foam or film, ointments, hydrogels, antibacterial creams, and polymers combined with antibacterial compound that are still in use. The addition of bioactive compounds with an antiseptic wound dressing has recently gained attention for efficient therapies. For chronic wounds, using bioactive chemicals in dressings used as wound material has been successful. The integrated bioactive chemicals released at the wound site may interact with the enzymes released by the hydrolysate activity in the exudates or from the wound fluid [28, 29]. The bioactive components in the dressings can also be released by several additional techniques, including diffusion, swelling, and hydration. If the absorption by the wound exudates is fast, the bioactive chemicals in the dressings will have minimal effects. Despite the variety of wound dressings available commercially, none can be categorised as most suitable for DFUs [30].

5. Advancement in therapies of chronic wound healing

Acute and mild medical case studies can be treated using conventional treatment strategies whereas chronic wounds and those appearing as consequent metabolic disorder complications need rigorous pharmaceutical attention and pharmacotherapy [31]. The ulcerations and complications of chronic wounds led to the let-down of former conventional treatments and this steered the advent of nanotechnology related therapeutic interventions to manage the complex diabetic wounds [32]. Nanotherapeutics enables prolonged bio-availability of the desired molecule at the site of wound, may accelerate the healing process, and helps to circumvent secondary complications thereby improving patient compliance [31, 32]. Further, wound healing approaches based on nanotechnology presents distinct advantages that include suitability for topical drug delivery, sustained/ controlled release of encapsulated drugs, cell specificity, and prolonged circulation till the wound heals. Nanotherapeutics is ideal for wound healing especially for topical delivery that facilitates improved connections with the biological target with enhanced infiltration at the site of wound [33]. Nanoparticles have emerged as a scientific and technological revolution in the management of DFUs, making major contributions to pharmaceutical applications offering improved strategies for the treatment of DFUs [20, 34]. Outstanding features like minimal *in-vivo* toxicity, bacteriostatic, and bactericidal activity have been demonstrated by metallic nanoparticles including silver, gold, and zinc etc [32]. This review discusses the potential of nanoparticles such as peptide, polymeric, metallic, non-metallic, lipid, inorganic, siRNA-based and nanofibrous structures currently in use for the management of DFUs [33] (Fig. 3).

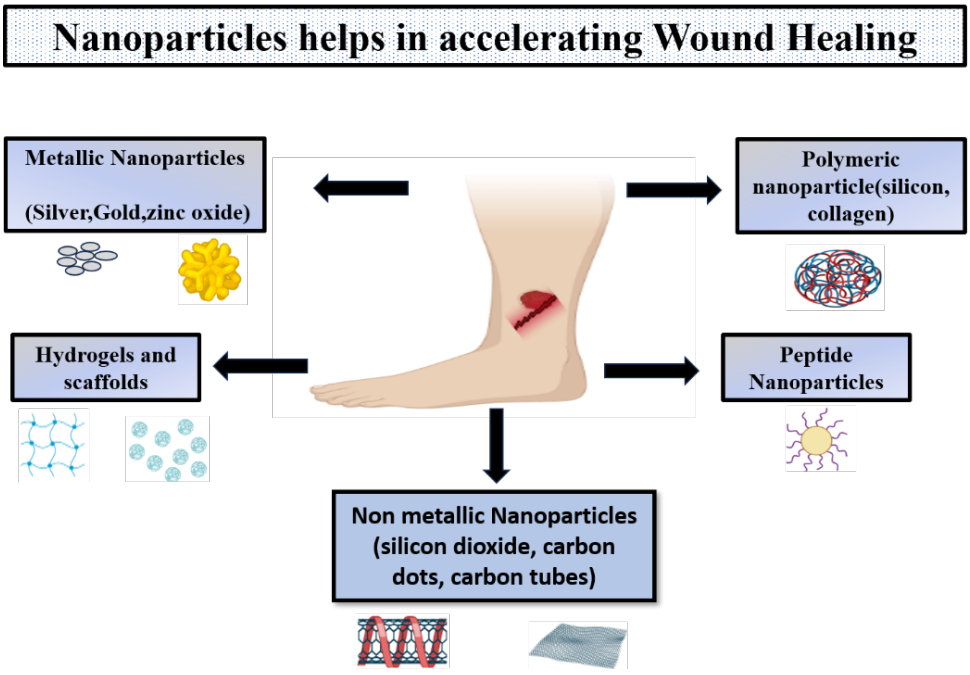

Figure 3. Different nanoparticles used for therapeutics of chronic wound healing.

5.1 Peptide nanoparticles

Peptide-based nanoparticles are emerging as self-assembled scaffolds are functionally adjusted to improve their interaction with different tissues and cells, possesses similar properties as natural ECM. Peptide nanostructures are useful to study cell signalling that has been used for biological therapies [35]. Peptide hydrogels are smart materials that are biocompatible and cyto-compatible in mammalian cells [36]. Synthesized peptides also fold into fibrils turning them into hydrogels that can be activated in cell culture conditions [37]. Literature suggests that peptide hydrogels trigger the division of liver progenitor cells into hepatocytes causing improved cell attachment, leading to significant regeneration of liver tissues along with improved cellular micro-environment that facilitates prolonged survival of the endothelial cells [37, 38]. Peptide Amphiphile (PA) systems specifically improve the scaffolds. For instance, the Arg-Gly-Asp-Ser (RGDS) cell adhesion epitope was synthesized and associated with PA. The RGDS bound PA stimulates growth of enamel-containing epithelial cells and the bone marrow mononuclear cells. Alternatively, absence of RGDS motif in the control group results in reduction of single-nuclear cells in the bone marrow [39]. Reports on PA inserted into a cell adhesion epitope displayed a progressive cell-responsive matrix formation for enhanced proliferation of dental stem cell [40]. Several hyaluronic acids were reportedly combined to produce a sealed pouch encapsulating the human mesenchymal stem cells (MSCs) that could be utilised to transport the MSCs to specific areas for regeneration of tissues [41]. A self-assembled conjugated peptide has shown support for regeneration of chondrocyte and significant recovery in cases of bone injury [42]. The reported peptide nanoparticles were non-immunogenic and did not cause the graft rejection when implanted for wound healing [43, 44].

5.2 Polymeric nanoparticles

Mostly polymers are biomaterials that are frequently used for making vascular grafts, implanted devices, coatings for healthcare devices, and surgical instruments [45]. Unlike hyaluronic acid, DNA, collagen, and gelatin are natural polymers. Synthetic polymers include), polysiloxanes, polyvinyl chloride (PVC), polytetrafluoroethylene (PTFE), polyethylene (PE), polymethyl methacrylate (PMMA), polystyrene (PS), polypropylene (PP) and polyamides (nylon) that have been applied for wound healing applications [46, 47]. Natural polymers are preferred as they provide flexibility to produce a wide variety of dressing materials. For vascular grafts, scaffold making, biological transporters, and surgical sutures, synthetic polymeric nanostructures are in use [48]. Natural polymers have low cost and a longer life span in comparison to biological scaffolds. Several scientific reports on rat models suggest that natural polymers indirectly increase the cellular proliferation by efficiently stimulating re-epithelization and angiogenesis at wound site [49]. Gelatin, derived from collagen has been used significantly to make biodegradable and biocompatible materials for dressing of wound. Powel and Boyce showed that the permeability and inter-fibre layout of a gelatin scaffold played main role in regeneration of skin cells [50].

5.3 Metallic nanoparticles

Metallic nanoparticles are attractive as they remain stable for long periods, can be easily modified for specific targeting, and hence can be best applied for chronic wound management.

5.3.1 Zinc oxide (ZnO)

ZnO is one of the most stable inorganic antibacterial agents with a long-lifespan and is crucial for healing of wound, particularly impaired wounds and burns. ZnO nanoparticles are commonly used in cosmetics, skin creams, and ointments because they have anti-inflammatory, antibacterial and antiseptic properties [51, 52]. The antibacterial activity was increased when ZnO was embedded in chitosan-based hydrogel, making it a superior dressing for wounds [53]. ZnO nanoformulations are effective at lower doses as they may have a biocompatible polymer coating as release of Zn ions from ZnO is in a biphasic manner having dual effects. When the Zn ions encounter the biological fluid, it quickly hydrates to make hydrated that ZnO that possesses bactericidal activities [54]. Additionally, Zn being a cofactor often used for metalloproteinases and subsequent generation of ECM can be easily absorbed. Further, Zn controls the migration of keratinocyte and auto-phagocytosis that is an essential component for wound healing [53, 54].

5.3.2 Silver (Ag)

Ag can also be used to treat wound ulcers and infections owing to its bactericidal nature. Silver nitrate ($AgNO_3$) is commonly used for treatments of non-healing wounds along with several new variants of silver that are commercially available as wound dressings [62, 63]. Minimal adverse effects have been reported regarding dressings and bandages coated with silver nanoparticles (AgNPs) [64]. When collagen combines with AgNPs, it makes an ideal material for wound dressings possessing antibacterial properties [65]. AgNPs are generally used as constituents in preparation of burn ointments, wound bandages for ulcer, and few healthcare products as they can effectively eliminate bacteria, fungus, protozoa, and even viruses [58, 59, 66]. AgNPs efficiently disrupt the quorum sensing and inhibit the production of biofilms and helps in detoxification of bacterial toxins [56, 67]. *In-vivo* studies indicate that AgNPs are oxidised into silver ions due to acidic environment that can damage the cell wall, prevent adenosine triphosphate (ATP) production that results in ROS production causing DNA damage [57, 68]. AgNPs therapy drastically decreases the levels of oxidative stress and inhibits the release of inflammatory cytokines. Further, *in-vitro* investigation using cutaneous fibroblasts and human keratinocytes to facilitate wound healing have also been reported [69]. While various studies on mice model with burn wounds indicated that a topical treatment of AgNPs reduced the neutrophil counts and levels of interleukin (IL)-6, and simultaneous rise in levels of TGF-β, IFN-γ, VEGF and IL-10 levels. AgNPs initially adhere on the cell membrane of bacteria and are internalized by the cells, hence they interact with proteins and DNA that contain phosphorus and sulphur groups

[70]. When AgNPs penetrate the bacterial cells, Ag ions are released inside the bacterial cell displaying improved bactericidal activity by targeting the respiratory chain that may disrupt the cellular processes leading to cell death [71]. In *in-vivo* models, AgNPs have been reported to increase re-epithelization, decrease lymphocyte infiltration, and reduce the inflammation in normal wounds by regulating the release of pro-inflammatory cytokines [72].

5.3.3 Gold (Au)

AuNPs have been used for drug delivery and tissue regeneration and wound healing process. It AuNPs are preferred as safe indicating effective results for study on wound healing in comparison to the usage of collagen, gelatin, and chitosan [73, 74]. Unlike silver, AuNPs per se do not possess any antibacterial properties. Without altering the structure of collagen, AuNPs can target biomolecules such polysaccharides, peptides, cell adhesion molecules and growth factors. To enhance the antibacterial activities, AuNPs may be coupled with antibodies that are pathogen specific for photosensitizing molecules using photo dermal therapy (PDT) [75, 76]. The free radical scavenging capacity of AuNPs can be improved by making chitosan-AuNPs nanoformulations, which further increases its biocompatibility. In comparison to conventional chitosan dressing or Tegaderm chitosan-AuNPs significantly improves haemostasis, increases epithelial tissue development which accelerates the healing rate as reported in a surgical wound model of rat [77]. When AuNPs penetrate the bacterial cells, they alter the membrane potential, and in the process inhibits ATP synthase enzyme which depletes the ATP, ultimately triggering the collapse of metabolic activities leading to cell death. These are mechanisms that are independent of ROS, and can be helpful in attacking resistant bacteria [78]. Further, regulating the anti-inflammatory cytokines may trigger angiogenesis and improve the wound healing process [33].

5.4 Non-Metallic Nanoparticles

5.4.1 Silicon dioxide (SiO_2NPs)

SiO_2NPs are biocompatible and non-immunogenic [79]. Silica is a readily available raw material, the processing and preparation techniques are also well established. Non-porous nanoparticles, silica gel, mesoporous nanoparticles, and various structures of silica can be created from the raw silica [80]. The strong physic- chemical adsorption capability of silica makes them excellent carriers for various drugs and proteins [81].

5.4.2 Carbon Nanoparticles

Carbon nanoparticles can be broadly classified into carbon nanotubes, graphene/GO, carbon dots. The structure of carbon nanoparticles supports the development of cells and tissues. Carbon nanotubes resemble collagen fibres and can impact cell adhesion, proliferation and differentiation [82]. Surface functionalization of pharmaceuticals, proteins, and other nanomaterials can be facilitated by the distinctive base plane structure and shape of graphene [83]. Graphene nanosheets are advantageous for adhesion and cell growth as they increase the adsorption capacity having high surface area [55]. Additionally, carbon nanoparticles, carbon dots, graphene, and carbon nanotubes exhibit enhanced antibacterial activity in several ways that include altering the charge on surface of the bacteria, penetrating the cell wall of bacteria causing release of cellular contents [84]. Aslan et al. reported the development of antibacterial biofilm by layering together the carbon nanotubes with polypeptides to kill bacteria rapidly [85]. Table 1 represents the various nanoparticles and their biological applications.
Table 2 describes the various nanoparticles formulation used to treat chronic wound healing.

6. Role of Artificial Intelligence (AI) in monitoring the diabetogenic wounds

Literature survey indicates that development of algorithms for machine learning should initially involve the detection of DFUs by photographs of foot taken from different angles. The additional refinement of machine learning needs to be developed via incorporating the DFUs classification system like the real-world. Professionals like Wagner (University of Texas) used a different kind of classification system of DFUs for the monitoring and management and SINBAD

Table 1. Tabular representation of various nanoparticles and their biological applications.

Nanoparticles	Biological applications	References
Gold	Wound healing effectively, antibacterial and antioxidant properties, regeneration of tissue	[55]
Silver	Antibacterial, accelerates wound healing	[56, 57]
Zinc oxide	Antibacterial, Re-epithelialization, healing of wound, anti-inflammatory, and antiseptic properties	[58, 59]
Silicon dioxide	Biocompatible , healing of wound , anti-oxidant properties	[60]
Carbon	Cell adhesion, proliferation, and differentiation antibacterial activity, good biocompatibility	[61]
Polymeric	Cellular proliferation, re-epithelization, angiogenesis	[50]
Peptide	Biological therapies, regeneration of cells, biocompatible, wound healing	[38]

Table 2. Tabular representation of various nanoparticles formulation used to treat chronic wound healing.

Nanoparticles	**Mode of study**	**Findings**	**Mechanism of action**	**Ref.**
(NO-NP) Diazeniumdiolate	*In-vivo* study	Accelerated wound closure in diabetic mice	Increased blood vessels formation, fibroblasts proliferation, reduced inflammatory cells, and enhanced collagen production	[86]
PLGA nanoparticles-incorporated with rhEGF	*In-vivo* study	Accelerates closure of wound, boosted epithelization	Enhanced fibroblast proliferation in diabetic rats	[86]
Silver nanoparticles and bacterial cellulose nanofiber	*In-vitro* study	These nanoparticles possess potent antibacterial potential against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*	Encouraged keratinocyte development and proliferation	[87]
AuNPs	*In-vitro* study	AuNPs have therapeutic applications that improves the healing when applies topically at the wound site. Topical usage of AuNPs to dermal wounds in rats improved healing	Higher collagen fibre content, increased re-epithelialization, granulation of tissue formed, and ECM increment	[60]
AuNPs coupled with (CrHFC-AuNP) photosensitizer with Candida albicans,	*In-vitro* study	Topically applied to burn wounds. Wounds treated with CrHFC-AuNP shows improved overall healing stages, and downmodulation in inflammatory phase	Due to more collagen have been deposited	[60]
Reduced graphene with Ag-AgCl nanoparticles (Ag/AgCl/rGO nanomaterial)	*In-vitro* study	Ag/AgCl/rGO shows applications for burn wounds in mice marked with improved wound healing by increment in closure of wound,	More deposition of collagen fibre, improves re-epithelialization	[61]
Gelatine-based scaffolds with epidermal growth factor	*In-vitro* study	Scaffold for topical administration on rat wounds which shows the early closure of wound and improves healing of wound	Increased re-epithelialization, granulation of tissue formed	[88]

(Site, Ischaemia, Neuropathy, Bacterial infection, Area, and Depth) of DFUs. The listed methodologies are labour intensive and subject to human errors and can surely take advantage of the automated processes of AI [89].
The complexity in AI-technology requires its incorporation in daily clinical practice to improve diagnostics and prognostics can be very interesting. The challenges consist of: (1) significant burden of time involved in data collection in terms of images of DFUs and to label them appropriately (2) differences in the intra and inter class differences based on DFUs classification (3) optimisation is further needed for the datasets of DFUS (angle of camera at a suitable distance from foot, image condition and orientation of light) (4) the alterations in ethnicity, age, foot size of the patients and sex [90].

6.1 Harnessing the visible spectrum

Visible spectroscopy (VIS) ranges from wavelengths of $\lambda = 780\,nm$ and $\lambda = 380\,nm$. Since the effects are visible under the light, it helps to identify the wound area or the contours of the wound to help measure the surface wound size accurately. Further, van Netten et al [90]. studied that these optical sensors enable identification among various deformities in the skin [91, 92]. The digital images can be acquired and utilized for regular monitoring of the characteristics of the wounds. Wound assessment and monitoring can be done regularly by digital-coloured images that can be photographed even using mobile phones and assessing them by computer applications, hand-held devices to identify the wound condition [93].

6.2 Remote monitoring of DFU

It is quintessential to understand the non-invasive sensor technologies especially a) to encourage patients in self-care, b) to regularly observe the risk related with DFUs, c) for effective delivery, prevention and monitoring the at high-risk patients, d) to address the issues related to health care for the people residing in remote areas [94]. To manage the diabetic foot remotely, sensor technologies are now being been used vastly. Photography has become a necessity since the 1980s; post the invention of digital technology in 1975. Usage of digital cameras for photography has become extremely popular with every single villager possessing a smart phone. An easy solution is to collect digital photos from mobile camera phones. Further, archiving of the digital photographs of DFUs in computer databases will ensure a giant rise in monitoring of the patients of DFUs via various expertises [95]. Till today, DFU photograph prints are not in use for remote monitoring in the villages, where the internet and computers are still not available causing inconvenience in follow-up in clinical practice. Poor quality prints together with colour print outs fades over time and

worsens the situation grimmer as far as monitoring of DFUs is considered. A series of digital photographs placed chronically in the computer database can help the professionals review the work conveniently and lot easier [94, 95]. An added advantage of digital archiving of DFU images is that no degradation of quality of images takes place over time, when compared to the printed photographs.

Mobile phones had become popular for telephonic communications globally in the early 2000s and updated versions of these devices with advanced cameras and video recording facilities have flooded the market in the recent years [92]. Twenty first century has witnessed a rapid technological progression in smartphone devices, use of high-resolution cameras and ease of availability that has made smart phones an integral part of modern life. Professionals involved in care of diabetic patients have initiated the use of cameras of smart phone and video facilities for regular monitoring and supervision of DFUs [92, 96]. Fig. 4 indicates how the patients themselves were using their mobile phones to obtain images of their DFUs prior to their visits to foot clinics. These images can be subjected to analysis using various softwares to get near accurate data on the size, shape, depth, and the overall biochemical condition of the wound. Although the initial studies on use of mobile phones for monitoring DFUs were not very promising, subsequent studies have shown encouraging results [97, 98].

Validation has to be done across the globe by numerous professionals from several institutions that will help to refine the consequences in machine learning algorithms for management of DFUs [99]. Development of AI algorithms is far more labour-intensive as larger datasets are required for demarcation exercises to improve deep learning models, along with clinical and biochemical parameters of individual patients to be incorporated within the neural network. Availability of competent staff is a major limitation as training of personnel requires using large datasets of DFUs for ease of classification and diagnosis. Deep learning AI algorithms need to be developed, for which big datasets for automated DFU analysis need to be generated to get reproducible and comparable results. Globally, scientists are working in isolation and may not accomplish reproducible research outputs. Various challenges have been faced by the researchers and clinicians because the datasets are available publically, but are difficult to access. Nonetheless, appropriate use of computer technology integrated with digital applications may help to ease the physical burden on researchers in developing such models [100].

7. Conclusion and Future perspectives

Inflammation, proliferation, and remodelling are all key components of the complex stages in wound healing process. In most DFU cases, both internal and external factors including changed cytokine response and poor vascularization, cellular and microbial contamination interfere with the pathophysiology of the healing process. Nanotherapeutics has emerged as a promising strategy to address all stages of wound healing. Primarily this review focuses on how nanoparticles interact with wounds to promote the healing process by inhibition of inflammatory process. Wound dressings with metal nanoparticles coatings shows excellent antibacterial activities that are crucial for the wound healing. In chronic and diabetic wounds, polymeric nanostructures and peptide combined with wound dressing materials (gelatin, Chitosan, hydrogel, etc.) have shown im-

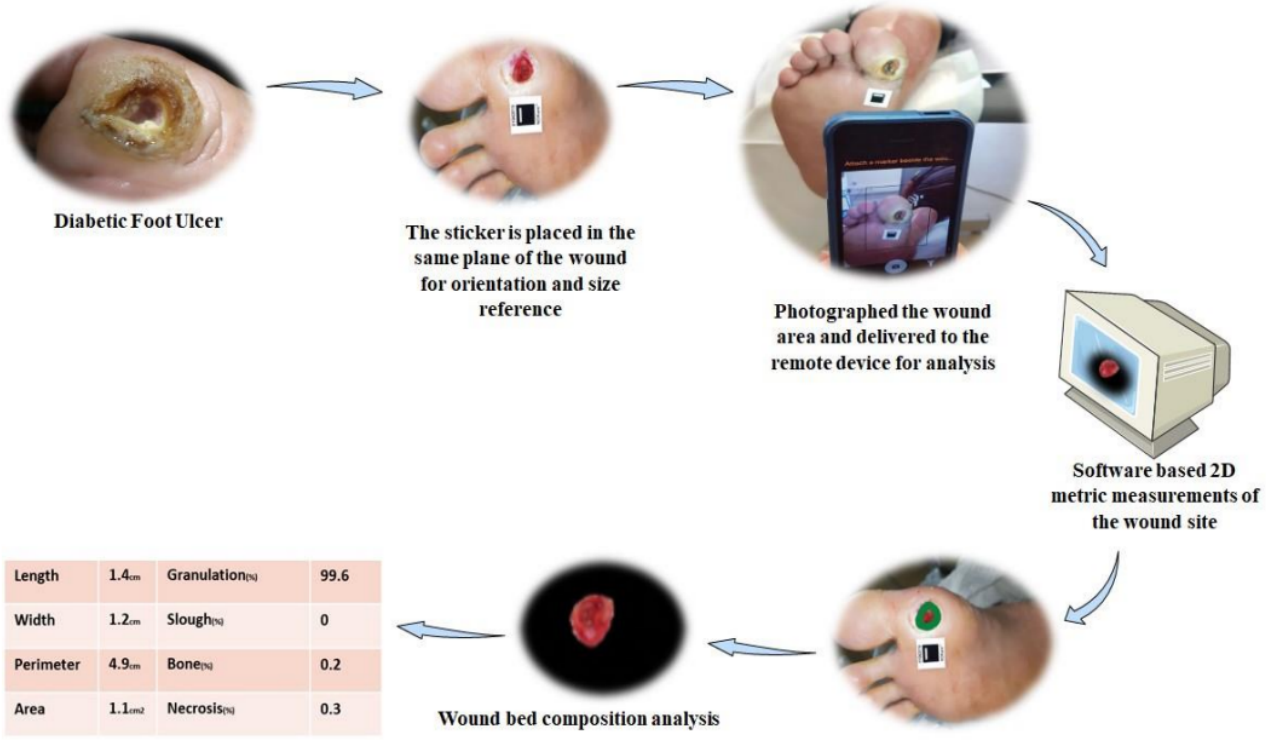

Figure 4. Schematic representation of Diabetic foot ulcers assessment *via* AI [Adapted from *van Netten, et al.* [91]; 2017].

proved outcomes in manipulating the growth of cells, re-epithelialization, collagen fibre deposition, tissue regeneration, and eventually closing of the wound. Nanomaterials in wound dressings offer tremendous possibilities for treatment of wounds. Present wound healing materials have many limitations that could be solved by using naturally originated polymeric nanoparticles in combination with antibiotics, growth hormones and biomolecules to create scaffolds with improved mechanical resistance. The past few years have witnessed a mass increase in digital application cases, and day to day management of DFUs have also evolved swiftly to a basic stage of remote diagnosis and wound monitoring in field and community settings. Mobile apps have been developed to integrate the new technological advancements and in near future, these apps are going to change the scenario of DFU care globally. Further Globally, AI experts are establishing AI-based algorithms rapidly by collaborative efforts in tandem with patients and clinical teams. Remote diagnosis applications have enhanced as regular follow-up and monitoring of DFUs is based on the newer digital technologies in mobile camera. AI experts are developing prediction models for wound healing, by use of links of ulceritic characteristics and DFU images for the laboratory parameters and clinical practices of the patients. The collective efforts of clinicians, patients, and computer scientists across the globe is expected to revolutionise wound care management as it will empower the monitoring and management by DFUs patients themselves to a great extent.

Abbreviations:

DFU	Diabetic foot ulcers
DM	Diabetes mellitus
ECM	Extracellular matrix
NADP	Niacinamide adenine dinucleotide phosphate
ROS	Reactive oxygen species
PAD	Peripheral arterial Disease
TGF	Tumour growth factor
SMA	Smooth muscle actin
MMP	Matrix metalloproteinase
miRNA	microRNA
GF	Growth factors
FGF	Fibroblast growth factor
EGF	Epidermal growth factor
PA	Peptides amphiphile
MSCs	Mesenchymal stem cells
PE	Polyethylene
PP	Polypropylene
PS	Polystyrene
PVC	Polyvinyl chloride
PMMA	Polymethyl methacrylate
PTFE	Polytetrafluoroethylene
AgNPs	Silver nanoparticles
IL	Interleukin
IFN	Interferon gamma
AuNPs	Gold nanoparticles
SiO_2	Silicon dioxide
PDT	Photo dermal therapy
ATP	Adenosine triphosphate
AI	Artificial intelligence
SINBAD	Site, Ischaemia, Neuropathy, Bacterial infection, Area, and Depth
VIS	Visible spectroscopy

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Authors Contributions
All authors have contributed equally to prepare the paper.

Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.A. Ansari, K. Ali, Z. Farooqui, H.A. Al-Dossary, M. Zubair, and J. Musarrat. *Nanotechnology and Diabetic Foot Ulcer: Prospects.* 2021. DOI: https://doi.org/10.1007/978-981-15-7639-3_20.

[2] J.M. Clements, B.T. West, Z. Yaker, B. Lauinger, D. McCullers, J. Haubert, and G.J. Everett. Disparities in diabetes-related multiple chronic conditions and mortality: The influence of race. *Diabetes Res. Clin. Pr*, **159**:107984, 2020. DOI: https://doi.org/10.1016/j.diabres.2019.107984.

[3] A. Al Wahbi. Cutting-edge terahertz technology. *Operative versus non-operative treatment in diabetic dry toe gangrene.*, **13**:959–963, 2019. DOI: https://doi.org/10.1016/j.dsx.2018.12.021.

[4] C.T. Tan, K. Liang, Z.H. Ngo, C.T. Dube, and C.Y. Lim. Application of 3d bioprinting technologies to the management and treatment of diabetic foot ulcers. *Biomedicines*, **8**:441, 2020. DOI: https://doi.org/10.3390/biomedicines8100441.

[5] S. Mascharak, H.E. desJardins Park, M.F. Davitt, N.J. Guardino, G.C. Gurtner, D.C. Wan, and M.T. Longaker. Modulating cellular responses to mechanical forces to promote wound regeneration. *Adv. Wound CarefAD*, **11**:479–495, 2022. DOI: https://doi.org/10.1089/wound.2021.0040.

[6] R.J. Litany and P.K. Praseetha. Tiny tots for a big-league in wound repair: Tools for tissue regeneration by nano techniques of today. *J Control Release*, **349**:443–459, 2022. DOI: https://doi.org/10.1016/j.jconrel.2022.07.005.

[7] C.E. Declue and L.P. Shornick. The cytokine milieu of diabetic wounds. *Diabetes Management*, **5**:525–37, 2015. DOI: https://doi.org/10.2217/dmt.15.44.

[8] Z. Qiu, A.H. Kwon, and Y. Kamiyama. Effects of plasma fibronectin on the healing of full-thickness skin wounds in streptozotocin-induced diabetic rats. *J. Surg. Res*, **138**:64–70, 2007. DOI: https://doi.org/10.1016/j.jss.2006.06.034.

[9] D. Abou El-ezz, L.H. Abdel-Rahman, B.S. Al-Farhan, D.A. Mostafa, E.G. Ayad, M.T. Basha, M. Abdelaziz, and E.M. Abdalla. Enhanced in vivo wound healing efficacy of a novel hydrogel loaded with copper (ii) schiff base quinoline complex (cusq) solid lipid nanoparticles. *Pharmaceuticals*, **15**:978, 2022. DOI: https://doi.org/10.3390/ph15080978.

[10] A. Kwiatkowska, M. Drabik, A. Lipko, A. Grzeczkowicz, R. Stachowiak, A. Marszalik, and L.H. Granicka. Composite membrane dressings system with metallic nanoparticles as an antibacterial factor in wound healing. *Membranes*, **12**:215, 2022. DOI: https://doi.org/10.3390/membranes12020215.

[11] D.M. Anisuzzaman, C. Wang, B. Rostami, S. Gopalakrishnan, J. Niezgoda, and Z. Yu. Image-based artificial intelligence in wound assessment: A systematic review. *Adv. Wound CarefADV*, pages 687–709, 2022. DOI: https://doi.org/10.1089/wound.2021.0091.

[12] A.C.D.O. Gonzalez, T.F. Costa, Z.D.A. Andrade, and A.R.A.P. Medrado. Wound healing-a literature review. *An. Bras. Dermat. B*, **91**:614–620, 2016. DOI: https://doi.org/10.1590/abd1806-4841.20164741.

[13] D.Y. Matar, B. Ng, O. Darwish, m. Wu, D.P. Orgill, and A.C. Panayi. Skin inflammation with a focus on wound healing. *Adv. Wound CarefADV*, **12**:269–287, 2023. DOI: https://doi.org/10.1089/wound.2021.0126.

[14] A. Iqbal, A. Jan, M.A. Wajid, and S. Tariq. Management of chronic non-healing wounds by hirudotherapy. . *World J. Plast. Surg*, **6**:9, 2017. DOI: https://doi.org/PMCID: PMC5339604.

[15] L. Cañedo-Dorantes and M. Cañedo-Ayala. Skin acute wound healing: a comprehensive review. *Int. J. Infla*, page 3706315, 2019. DOI: https://doi.org/10.1155/2019/3706315.

[16] F. Yang, X. Bai, X. Dai, and Y. Li. The biological processes during wound healing. *Regen. Med*, **16**: 373–390, 2021. DOI: https://doi.org/10.2217/rme-2020-0066.

[17] M.J. Pickup. Pathophysiology of wound healing. *J. Forensic Leg. Med*, **18**:103–107, 2022. DOI: https://doi.org/https://doi.org/10.4324/9780429318764.

[18] J.P. Yadav. Based on clinical research matrix metalloprotease (mmp) inhibitors to promote diabetic wound healing. *Horm. Metab. Res.HO*, **55**:752–757, 2023. DOI: https://doi.org/10.1055/a-2171-5879.

[19] S. Knoedler, L. Knoedler, M. Kauke-Navarro, Y. Rinkevich, G. Hundeshagen, L. Harhaus, and A.C. Panayi. Regulatory t cells in skin regeneration and wound healing. *Mil Med Res*, **10**:49, 2023. DOI: https://doi.org/10.1186/s40779-023-00484-6.

[20] C.D. Marshall, M.S. Hu, T. Leavitt, L.A. Barnes, H.P. Lorenz, and M.T. Longaker. Cutaneous scarring: basic science, current treatments, and future directions. *Adv. Wound Care*, **7**:29–45, 2018. DOI: https://doi.org/10.1089/wound.2016.0696.

[21] N. Joshi, L. Pohlmeier, M. Ben-Yehuda Greenwald, E. Haertel, P. Hiebert, M. Kopf, and S. Werner. Comprehensive characterization of myeloid cells during wound healing in healthy and healing-impaired diabetic mice. *Eur. J. Immunol*, **50**:1335–1349, 2020. DOI: https://doi.org/10.1002/eji.201948438.

[22] H. Cho, M.R. Blatchley, E. J. Duh, and S. Gerecht. Acellular and cellular approaches

to improve diabetic wound healing. *Adv. Drug Deliv. Rev*, **146**:67–288, 2019. DOI: https://doi.org/10.1016/j.addr.2018.07.019.

[23] N. Maimon, Z.Z. Zamir, P. Kalkar, O. Zeytuni-Timor, S. Schif-Zuck, S. Larisch, and A. Ariel. The pro-apoptotic arts protein induces neutrophil apoptosis, efferocytosis, and macrophage reprogramming to promote resolution of inflammation. *Apoptosis*, **25**:558–573, 2020. DOI: https://doi.org/10.1007/s10495-020-01615-3.

[24] T.T. Nguyen, S. Mobashery, and M. Chang. *Roles of matrix metalloproteinases in cutaneous wound healing.* 2016. DOI: https://doi.org/http.//dx.doi.org/10.5772/64611.

[25] P. Monika, P.V. Waiker, M.N. Chandraprabha, A. Rangarajan, and K.N.C. Murthy. Myofibroblast progeny in wound biology and wound healing studies. *Wound Repair Regen*, **29**:531–547, 2021. DOI: https://doi.org/10.1111/wrr.12937.

[26] V.A. Solarte David, V.R. Güiza-Argüello, M.L. Arango-Rodríguez, C.L. Sossa, and S.M. Becerra-Bayona. Decellularized tissues for wound healing: towards closing the gap between scaffold design and effective extracellular matrix remodeling. *Front. Bioeng. Biotechnol*, **10**:821852, 2022. DOI: https://doi.org/10.3389/fbioe.2022.821852.

[27] S. Maharajan, R. Dua, L.K. Saini, N. Kumar, and R. Gupta. Prevalence and predictors of restless legs syndrome among patients having stable chronic obstructive pulmonary disease. *Sleep Med*, **118**:32–38, 2024. DOI: https://doi.org/https://doi.org/10.1016/j.sleep.2024.03.041.

[28] M. Shao, Z. Hussain, H.E. Thu, S. Khan, M. de Matas, V. Silkstone, ..., and S.N. A. Bukhari. Emerging trends in therapeutic algorithm of chronic wound healers: recent advances in drug delivery systems, concepts-to-clinical application and future prospects. *s. CRIT Rev. Ther. Drug*, **34**:387–452, 2017. DOI: https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2017016957.

[29] K. Naik, P. Singh, M. Yadav, S.K. Srivastava, S. Tripathi, R. Ranjan, ..., A.K. Verma, and A.S. Parmar. 3d printable, injectable amyloid-based composite hydrogel of bovine serum albumin and aloe vera for rapid diabetic wound healing. *J. Mater. Chem. B*, **11**:8142–8158, 2023. DOI: https://doi.org/10.1039/d3tb01151h.

[30] A. Gaspar-Pintiliescu, A.M. Stanciuc, and O. Craciunescu. Natural composite dressings based on collagen, gelatin and plant bioactive compounds for wound healing: A review. *Int. J. Biol*, **138**:854–865, 2019. DOI: https://doi.org/10.1016/j.ijbiomac.2019.07.155.

[31] S.K. Nethi, S. Das, C.R. Patra, and S. Mukherjee. Recent advances in inorganic nanomaterials for wound-healing applications. *Biomater Sci*, **7**:2652–2674, 2019. DOI: https://doi.org/10.1039/c9bm00423h.

[32] Q. Bai, K. Han, K. Dong, C. Zheng, Y. Zhang, Q. Long, and T. Lu. Potential applications of nanomaterials and technology for diabetic wound healing. *Int. J. Nanomedicine*, **15**:9717–9743, 2020. DOI: https://doi.org/10.2147/IJN.S276001.

[33] H. Ezhilarasu, D. Vishalli, S.T. Dheen, B.H. Bay, and D.K. Srinivasan. Nanoparticle-based therapeutic approach for diabetic wound healing. *Phys Rev B Condens Matter Mater Phys*, **87**:075416, 2020. DOI: https://doi.org/10.3390/nano10061234.

[34] K. Niveria, M. Yadav, K. Dangi, and A.K. Verma. Overcoming challenges to enable targeting of metastatic breast cancer tumour microenvironment with nanotherapeutics: current status and future perspectives. *Opennano*, page 100083, 2022. DOI: https://doi.org/https://doi.org/10.1016/j.onano.2022.100083.

[35] A.K. Das and P.K. Gavel. Low molecular weight self-assembling peptide-based materials for cell culture, antimicrobial, anti-inflammatory, wound healing, anticancer, drug delivery, bioimaging and 3d bioprinting applications. *Soft MatterSOFT MA*, **16**:10065–10095, 2020. DOI: https://doi.org/10.1039/d0sm01136c.

[36] M.K. Yazdi, V. Vatanpour, A. Taghizadeh, M. Taghizadeh, M.R. Ganjali, M.T. Munir, ..., and M. Ghaedi. Hydrogel membranes: A review. *Mater. Sci. Eng. C*, **114**:111023, 2020. DOI: https://doi.org/10.1039/d0sm01136c.

[37] D. Bairagi, P. Biswas, K. Basu, S. Hazra, D. Hermida-Merino, D.K. Sinha, ..., and A. Banerjee. Self-assembling peptide-based hydrogel: regulation of mechanical stiffness and thermal stability and 3d cell culture of fibroblasts. *ACS Appl. Bio Mater.*, **2**:5235–5244, 2019. DOI: https://doi.org/10.1021/acsabm.9b00424.

[38] G. Agarwal, S. Agiwal, and A. Srivastava. Hyaluronic acid containing scaffolds ameliorate stem cell function for tissue repair and regeneration. *Int J Biol Macromol*, **165**:388–401, 2020. DOI: https://doi.org/10.1016/j.ijbiomac.2020.09.107.

[39] E. Garbayo, S. Pascual-Gil, C. Rodríguez-Nogales, L. Saludas, A. Estella-Hermoso de Mendoza, and M.J. Blanco-Prieto. Nanomedicine and drug delivery systems in cancer and regenerative medicine. *Wiley Interdisciplinary Reviews: WIRES NANOMED NANOBI*, **12**:e1637, 2020. DOI: https://doi.org/10.1002/wnan.1637.

[40] S. Yang and L. Jiang. Biomimetic self-assembly of subcellular structures. *Chem. Comm*, **56**:8342–8354, 2020. DOI: https://doi.org/10.1039/d0cc01395a.

[41] K. Liang, K.H. Bae, and M. Kurisawa. Recent advances in the design of injectable hydrogels for stem cell-based therapy. *J Mater Chem BJ MA*, **7**:3775–3791, 2019. DOI: https://doi.org/https://doi.org/10.1039/C9TB00485H.

[42] X. Ding, H. Zhao, Y. Li, A.L. Lee, Z. Li, M. Fu, ..., and P. Yuan. Synthetic peptide hydrogels as 3d scaffolds for tissue engineering. *Adv. Drug Deliv. Rev*, **160**:78–104, 2020. DOI: https://doi.org/10.1016/j.addr.2020.10.005.

[43] L. Cui, J. Liang, H. Liu, K. Zhang, and J. Li. Nanomaterials for angiogenesis in skin tissue engineering. *Tissue Eng Part B Rev*, **26**:203–216, 2020. DOI: https://doi.org/10.1089/ten.TEB.2019.0337.

[44] M.S. Taha, S. Padmakumar, A. Singh, and M.M. Amiji. Critical quality attributes in the development of therapeutic nanomedicines toward clinical translation. *Drug Deliv. Transl. Res*, **10**:766–790, 2020. DOI: https://doi.org/10.1007/s13346-020-00744-1.

[45] N. Ashammakhi, M.A. Darabi, N.S. Kehr, A. Erdem, S.K. Hu, M.R. Dokmeci, ..., and A. Khademhosseini. Advances in controlled oxygen generating biomaterials for tissue engineering and regenerative therapy. **21**:56–72, 2019. DOI: https://doi.org/10.1021/acs.biomac.9b00546.

[46] M. Badv, F. Bayat, J.I. Weitz, and T.F. Didar. Single and multi-functional coating strategies for enhancing the biocompatibility and tissue integration of blood-contacting medical implants. *Biomaterials*, **258**:120291, 2020. DOI: https://doi.org/10.1016/j.biomaterials.2020.120291.

[47] J.A.D. Olmo, L. Ruiz-Rubio, L. Pérez-Alvarez, V. Sáez-Martínez, and J.L. Vilas-Vilela. Antibacterial coatings for improving the performance of biomaterials. *Coatings*, **10**:139, 2020. DOI: https://doi.org/https://doi.org/10.3390/coatings10020139.

[48] S. Guhathakurta and S. Galla. Progress in cardiovascular biomaterials. *Asian Cardiovasc Thorac Ann*, **27**:744–750, 2019. DOI: https://doi.org/10.1177/0218492319880424.

[49] K.M. Agarwal, P. Singh, U. Mohan, S. Mandal, and D. Bhatia. Comprehensive study related to advancement in biomaterials for medical applications. *Sens. Int*, **1**:100055, 2020. DOI: https://doi.org/https://doi.org/10.1016/j.sintl.2020.100055.

[50] M.R. Crabbe-Mann. *Electrospinning of Cellulose Based Wound Dressing*. 2019. DOI: https://doi.org/https://discovery.ucl.ac.uk/id/eprint/10082026.

[51] J. Nandhini, E. Karthikeyan, and S. Rajeshkumar. Nanomaterials for wound healing: Current status and futuristic frontier. *Biomed tech*, **6**:26–45, 2024. DOI: https://doi.org/https://doi.org/10.1016/j.bmt.2023.10.001.

[52] F.S. Youssef, S.H. Ismail, O.A. Fouad, and G.G. Mohamed. Green synthesis and biomedical applications of zinc oxide nanoparticles. *Review. Egyp. j. vet. sci*, **55**:287–311, 2024. DOI: https://doi.org/10.21608/ejvs.2023.225862.1576.

[53] V. Hmingthansanga, N. Singh, S. Banerjee, S. Manickam, R. Velayutham, and S. Natesan. Improved topical drug delivery: role of permeation enhancers and advanced approaches. *Pharmaceutics*, **14**:2818, 2022. DOI: https://doi.org/10.3390/pharmaceutics14122818.

[54] P. Pino, F. Bosco, C. Mollea, and B. Onida. Antimicrobial nano-zinc oxide biocomposites for wound healing applications: A review. *Pharmaceutics*, **15**:970, 2023. DOI: https://doi.org/10.3390/pharmaceutics15030970.

[55] M. Aggarwal, S. Husain, and B. Kumar. Role of functionalized carbon nanotubes in antimicrobial activity: a review. *Functionalized carbon nanotubes (CNTs)*, pages 377–411, 2023. DOI: https://doi.org/10.1002/9781119905080.ch15.

[56] B.R. Singh, B.N. Singh, A. Singh, W. Khan, A.H. Naqvi, and H.B. Singh. Mycofabricatedbiosilver nanoparticles interrupt pseudomonas aeruginosa quorum sensing systems. *Sci. Rep*, **5**:13719, 2015. DOI: https://doi.org/10.1038/srep13719.

[57] D. Acharya, P. Pandey, and B. Mohanta. A comparative study on the antibacterial activity of different shaped silver nanoparticles. *Chem. Zvesti*, **75**:4907–4915, 2021. DOI: https://doi.org/https://doi.org/10.1007/s11696-021-01722-8.

[58] S.I. Kaba and E.M. Egorova. In vitro studies of the toxic effects of silver nanoparticles on hela and u937 cells. *Nanotechnol Sci Appl*, **8**:19–29, 2015. DOI: https://doi.org/10.2147/NSA.S78134.

[59] M.A. Rahman, H. Abul Barkat, R.K. Harwansh, and R. Deshmukh. Carbon-based nanomaterials: carbon nanotubes, graphene, and fullerenes for the control of burn infections and wound healing. *Curr. Pharm. Biotechnol*, **23**:1483–1496, 2022. DOI: https://doi.org/10.2174/1389201023666220309152340.

[60] F. Lavaee, M. Yousefi, and P. Haddadi. Comparison of the fungicidal efficacy of photodynamic therapy with methylene blue, silver nanoparticle, and their conjugation on oral candida isolates using cell viability assay. *Curr. Med. Mycol*, **6**:35, 2020. DOI: https://doi.org/10.18502/cmm.6.4.5332.

[61] M. Puccetti, A. Donnadio, M. Ricci, L. Latterini, G. Quaglia, D. Pietrella, ..., and V. Ambrogi. Alginate ag/agcl nanoparticles composite films for wound dressings with antibiofilm and antimicrobial activities. *J. Funct. Biomater*, **12**:84, 2023. DOI: https://doi.org/10.3390/jfb14020084.

[62] B. Lallo da Silva, M.P. Abuçafy, E. Berbel Manaia, J.A. Oshiro Junior, B.G. Chiari-Andréo, R.C.R. Pietro, and L.A. Chiavacci. Relationship between structure and antimicrobial activity of zinc oxide nanoparticles: An overview. *Int. J. NanomedicineI*, pages 9395–9410, 2019. DOI: https://doi.org/10.2147/IJN.S216204.

[63] K. Shimizu, S. Kashiwada, and M. Horie. Cellular effects of silver nanoparticle suspensions on lung epithelial cells and macrophages. *Appl. Sci*, **12**:3554, 2022. DOI: https://doi.org/https://doi.org/10.3390/app12073554.

[64] W. Yang, L. Wang, E.M. Mettenbrink, P.L. DeAngelis, and S. Wilhelm. Nanoparticle toxicology. *Anne Joutel*, **61**:269–289, 2021. DOI: https://doi.org/10.1146/annurev-pharmtox-032320-110338.

[65] S. Al-Musawi, S. Albukhaty, H. Al-Karagoly, G.M. Sulaiman, M.S. Alwahibi, Y.H. Dewir, ..., and H. Rizwana. Antibacterial activity of honey/chitosan nanofibers loaded with capsaicin and gold nanoparticles for wound dressing. *Molecules*, **25**:4770, 2020. DOI: https://doi.org/10.3390/molecules25204770.

[66] D. Hassan, M. Farghali, H. Eldeek, M. Gaber, N. Elossily, and T. Ismail. Antiprotozoal activity of silver nanoparticles against cryptosporidium parvum oocysts: New insights on their feasibility as a water disinfectant. *J. Microbiol. Methods.*, **165**:105698, 2019. DOI: https://doi.org/10.1016/j.mimet.2019.105698.

[67] P. Muenraya, S. Sawatdee, T. Srichana, and A. Atipairin. Silver nanoparticles conjugated with colistin enhanced the antimicrobial activity against gram-negative bacteria. *Molecules*, **27**:5780, 2022. DOI: https://doi.org/10.3390/molecules27185780.

[68] A. Rodriguez-Garraus, A. Azqueta, A. Vettorazzi, and A. Lopez de Cerain. Genotoxicity of silver nanoparticles. *Nanomaterials*, **10**:251, 2020. DOI: https://doi.org/10.3390/nano10020251.

[69] N.K. Rajendran, S.S.D. Kumar, N.N. Houreld, and H. Abrahamse. A review on nanoparticle-based treatment for wound healing. *J. Drug Deliv. Sci. Techn*, **44**:421–430, 2018. DOI: https://doi.org/https://doi.org/10.1016/j.jddst.2018.01.009.

[70] H. Dahm. Silver nanoparticles in wound infections: present status and future prospects. *Nanotech. (SSBI)*, pages 151–168, 2020. DOI: https://doi.org/https://doi.org/10.1007/978-3-030-35147-2_9.

[71] D. Mittal, K. Narang, A. Leekha Kapinder, K. Kumar, and A.K. Verma. Elucidation of biological activity of silver based nanoparticles using plant constituents of syzygium cumini. *Int. J. Nano. Nanotech*, **15**: 189–198, 2019.

[72] M. Yusuf. Silver nanoparticles: Synthesis and applications. *Handbook of Ecomaterials*, page 2343, 2019. DOI: https://doi.org/10.1007/978-3-319-68255-6_16.

[73] E. Rezvani, A. Rafferty, C. McGuinness, and J. Kennedy. Adverse effects of nanosilver on human health and the environment. *Acta biomaterialia*, **94**:145–159, 2019. DOI: https://doi.org/10.1016/j.actbio.2019.05.042.

[74] V. Vijayakumar, S.K. Samal, S. Mohanty, and S.K. Nayak. Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management. *Int. J. Biol. Macromol*, **122**:137–148, 2019. DOI: https://doi.org/10.1016/j.ijbiomac.2018.10.120.

[75] T. Yang, D. Wang, and X. Liu. Assembled gold nanorods for the photothermal killing of bacteria. *Colloids Surf. B*, **173**:833–841, 2019. DOI: https://doi.org/10.1016/j.colsurfb.2018.10.060.

[76] M.M. Hossain, S.A. Polash, T. Saha, and S.R. Sarker. Chapter book: Gold nanoparticles: a lethal nanoweapon against multidrug-resistant bacteria. *Nano-strategies for addressing antimicrobial resistance: nano-diagnostics, nano-carriers, and nano-antimicrobials. Cham: Springer International Publishing.*, pages 311–351, 2022. DOI: https://doi.org/https://doi.org/10.1007/978-3-031-10220-2_9.

[77] X Chen, A. Laurent, Z. Liao, S. Jaccoud, P. Abdel-Sayed, M. Flahaut, ..., and N. Hirt-Burri. Cutaneous cell therapy manufacturing timeframe rationalization: allogeneic off-the-freezer fibroblasts for dermo-epidermal combined preparations (de-fe002-sk2) in burn care. *Pharmaceutics*, **15**:2334, 2023. DOI: https://doi.org/10.3390/pharmaceutics15092334.

[78] T.A.J. de Souza, L.R.R. Souza, and L.P. Franchi. Silver nanoparticles: an integrated view of green synthesis methods, transformation in the environment, and toxicity. *Ecotoxicol. Environ. Saf. E*, **171**:691–700, 2019. DOI: https://doi.org/10.1016/j.ecoenv.2018.12.095.

[79] F. Arriagada, S. Nonell, and J. Morales. Silica-based nanosystems for therapeutic applications in the skin. *Nanomed*, **14**:2243–2267, 2019. DOI: https://doi.org/10.2217/nnm-2019-0052.

[80] S. Jafari, H. Derakhshankhah, L. Alaei, A. Fattahi, B.S. Varnamkhasti, and A.A. Saboury. Mesoporous silica nanoparticles for therapeutic/diagnostic applications. *Biomed. pharmacother*, **109**:1100–1111, 2019. DOI: https://doi.org/10.1016/j.biopha.2018.10.167.

[81] L. Chen, X. Zhou, and C. He. Mesoporous silica nanoparticles for tissue-engineering applications. *Nanomed. Nanobiotechnol*, **11**:e1573, 2019. DOI: https://doi.org/10.1002/wnan.1573.

[82] P. Bellet, M. Gasparotto, S. Pressi, A. Fortunato, G. Scapin, M. Mba, ..., and F. Filippini. Graphene-based scaffolds for regenerative medicine. *Nanomaterials*, **11**:404, 2021. DOI: https://doi.org/10.3390/nano11020404.

[83] D. Mallaiah. Antibacterial activity by functionalized carbon nanotubes. *Nanostructures for Antimicrobial and Antibiofilm Applications*, pages 63–77, 2020. DOI: https://doi.org/https://doi.org/10.1007/978-3-030-40337-9_3.

[84] F. Cui, J. Sun, J. Ji, X. Yang, K. Wei, H. Xu, ..., and X. Sun. Carbon dots-releasing hydrogels with antibacterial activity, high biocompatibility, and fluorescence performance as candidate materials for wound healing. *J. Hazard. Mater*, **406**:124330, 2021. DOI: https://doi.org/10.1016/j.jhazmat.2020.124330.

[85] M.A. Saleemi, Y.L. Kong, P.V.C. Yong, and E.H. Wong. An overview of antimicrobial properties of carbon nanotubes-based nanocomposites. *Adv Pharm Bull*, **12**:449, 2022. DOI: https://doi.org/10.34172/apb.2022.049.

[86] M. Karyel and N. Akcelik. Carbon dots-releasing hydrogels with antibacterial activity, high biocompatibility, and fluorescence performance as candidate materials for wound healing. *proceedings of IV of international agricultural, biological & life science conference AGBIOL 2022*, page 421, 2022.

[87] M.J. Saadh. Green synthesis of silver nanoparticles using piper betle exhibit high antimicrobial activity against salmonella enteritidis and e. coli. *Iraqi J. Vet. Sci*, **37**:759–763, 2023. DOI: https://doi.org/10.33899/ijvs.2023.136475.2585.

[88] H. Afjoul, A. Shamloo, and A. Kamali. Freeze-gelled alginate/gelatin scaffolds for wound healing applications: An in vitro, in vivo study. *Mater. Sci. Eng. CMAT SCI*, **113**:110957, 2020. DOI: https://doi.org/10.1016/j.msec.2020.110957.

[89] J.M. Pappachan, B. Cassidy, C.J. Fernandez, V. Chandrabalan, and M.H. Yap. The role of artificial intelligence technology in the care of diabetic foot ulcers: The past, the present, and the future. *World J. Diabetes*, **13**:1131, 2022. DOI: https://doi.org/10.4239/wjd.v13.i12.1131.

[90] B. Ploderer, R. Brown, L.S.D. Seng, P.A. Lazzarini, and J.J. van Netten. Promoting self-care of diabetic foot ulcers through a mobile phone app: user-centered design and evaluation. *JMIR diabetes*, **3**: e10105, 2018. DOI: https://doi.org/10.2196/10105.

[91] J.J. van Netten, D. Clark, P.A. Lazzarini, M. Janda, and L.F. Reed. The validity and reliability of remote diabetic foot ulcer assessment using mobile phone images. *Sci. Rep*, **7**:9480, 2017. DOI: https://doi.org/10.1038/s41598-017-09828-4.

[92] Y.W. Jeong, H.J. Chang, and J.A. Kim. Development and feasibility of a safety plan mobile application for adolescent suicide attempt survivors. *Comput Inform Nurs*, **38**:382–392, 2020. DOI: https://doi.org/10.1097/CIN.0000000000000592.

[93] J. Golledge, M. Fernando, P. Lazzarini, B. Najafi, and G.D. Armstrong. The potential role of sensors, wearables and telehealth in the remote management of diabetes-related foot disease. *Sensors*, **20**:4527, 2022. DOI: https://doi.org/10.3390/s20164527.

[94] B. Najafi and R. Mishra. Harnessing digital health technologies to remotely manage diabetic foot syndrome: A narrative review. *Medicina (Kaunas)ME.*, **57**:377, 2021. DOI: https://doi.org/10.3390/medicina57040377.

[95] C.A. Cabal Mirabal, J. Berlanga Acosta, J. Fernández Montequín, L. Oramas Díaz, E. González Dalmau, L Herrera Martínez, ..., and D.G. Armstrong. Quantitative studies of diabetic foot ulcer evolution under treatment by digital stereotactic photography. *J. diabetes Sci. Techno.*, **13**:821–826, 2019. DOI: https://doi.org/10.1177/1932296819853843.

[96] C. Pak, J. In Jeon, H. Kim, J. Kim, S. Park, K.H. Ahn, ..., and C.Y. Heo. A smartphone-based teleconsultation system for the management of chronic pressure injuries. *Wound Repair Regen. W*, **26**:S19–S26, 2018. DOI: https://doi.org/10.1111/wrr.2.

[97] R.B. Kim, J. Gryak, A. Mishra, C. Cui, S.R. Soroushmehr, K. Najarian, and J.S. Wrobel. Utilization of smartphone and tablet camera photographs to predict healing of diabetes-related foot ulcers. *Comput. Biol. Med.CO*, **126**:104042, 2020. DOI: https://doi.org/10.1016/j.compbiomed.2020.104042.

[98] L. Wang, P.C. Pedersen, D.M. Strong, B. Tulu, E. Agu, and R. Ignotz. Smartphone-based wound assessment system for patients with diabetes. *IEEE. Trans. Biomed. Eng*, **62**:477–488, 2014. DOI: https://doi.org/10.1109/TBME.2014.2358632.

[99] M.H. Yap, C. Kendrick, N.D. Reeves, M. Goyal, J.M. Pappachan, and B. Cassidy. *Development of diabetic foot ulcer datasets: An overview.* 2021. DOI: https://doi.org/https://doi.org/10.1007/978-3-030-94907-5_1.

[100] B. Cassidy, C. Kendrick, N.D. Reeves, J.M. Pappachan, C. O'Shea, D.G. Armstrong, and M.H. Yap. Diabetic foot ulcer grand challenge 2021: evaluation and summary. *Diabetic Foot Ulcers Grand Challenge. Springer. 90-105. Wound area measurement Arti.f Organs*, **38**:346–352, 2021. DOI: https://doi.org/https://doi.org/10.1007/978-3-030-94907-5_7.