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REVIEW ARTICLE

The current and advanced therapeutic modalities for wound healing management

Nadia Fallah[1] · **Milad Rasouli**[2,3] · **Mohammad Reza Amini**[2,4]

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Abstract

Ever-increasing demands on improving efficiencies of wound healing procedures are a strong driving force for the development of replacement approaches. This review focuses on wound healing management from the point of formation to the point of healing procedures. The most important usual healing modality with key characteristic is explained and their limitations are discussed. Novel interesting approaches are presented with a concentration of the unique features and action mechanisms. Special attention is paid to gas plasma and nanotechnology impact on wound healing management from fundamental processes to beneficial outcomes. Challenges and opportunities for the future trend that combined common protocols and emerging technologies are discussed.

Keywords Wound healing · Wound process · Advanced approach · Common treatment · Gas plasma · Nanomedicine

Introduction

Wound healing is a very complex process that is basically divided into 3 stages of inflammation, proliferation, and tissue regeneration. to get optimal results in the wound healing process all of these stages should be done at the right moment and correct order. Many factors can impress wound healing and intervene in one or more stages of the process [1–4].

Despite significant efforts to develop therapeutic strategies, owing to the lack of knowledge about wound repair in different stages such as immunological, biological and mechanical procedures clinical experiments fail [2, 5]. Impaired mobility, amputation, or even death are the main consequences of lack of management in wound healing, which led to a huge burden on patients and the healthcare system [6]. The inefficiency of ongoing approaches such as treatment of infection, debridement of wounds, and wound dressing causes health-related challenges [1–3, 7].

Hence, wound repair management requires the progress of new ideas through close collaboration between researchers in many disciplines. In this regard, many innovative strategies have been implemented to heal wounds due to easy access to the target tissue. Although designing more innovative and practical strategies for transferring technologies to clinical therapies remains a challenge, we have seen significant progress in recent years [8, 9]. New technologies such as nanotechnology and gas plasma with promising results in extracorporeal, in vivo, and clinical phases, have given rise to the emergence of researchers and the health system [10–15]. On the other hand, we are witnessing some progress in the wound healing process through the application of new approaches such as hyperbaric oxygen therapy, electrical materials, photonics, negative pressure, and new methods used for dressing and debridement [15–17].

Nadia Fallah and Milad Rasouli equally contributed as first authors

✉ Nadia Fallah
nadiafallah44@yahoo.com

✉ Mohammad Reza Amini
mramini@tums.ac.ir

1 Department of Cell and Molecular Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran

2 Plasma Medicine Group, Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

3 Institute for Plasma Research and Department of Physics, Kharazmi University, Tehran, Iran

4 Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Here we first focus on the structure of the wound and wound healing process. Next, along with reviewing common methods, we introduce the current state-of-the-art of novel trends in wound healing management, including numerous emerging modalities where nanotechnology, gas plasma, photonic, and negative pressure that their benefits have documented (Fig. 1).

Wound healing

Wounds based on the length of their treatment divided into two types of acute and chronic. In a healthy person, the duration of acute wound treatment lasts about 2 weeks While chronic wounds have lagging or stagnant healing and it takes occasionally up to 3–4 weeks. Some conditions can be the reason for chronic ulcers such as diabetes, chemical agents, autoimmune diseases, infections, peripheral vascular diseases, and radiotherapy agents [18–21].

Chronic ulcers have always been a major challenge for wound care professionals and consume many health resources around the world [22]. The inefficiency of existing methods to achieve recovery in such patients with chronic wounds cause an urgent requirement to introduce alternative methods. Although by managing and focussing on new methods besides the current methods we can reach successful recovery for this disease [23, 24]. The outcome of chronic wound therapy can be outstanding by prevailing the factors which cause to delay the healing [25].

However, choosing the right treatment needs re-evaluated conditions. Assessment of patients, the wounds and healthcare facilities are the important aspect of choosing the type of treatment. The underlying pathologies that do not heal these wounds vary between different types of chronic wounds. therefore, acquiring knowledge about various kind of ulcers at both levels of cellular and molecular help to reach new therapy and accelerate the rate of healing. [19, 26–28].

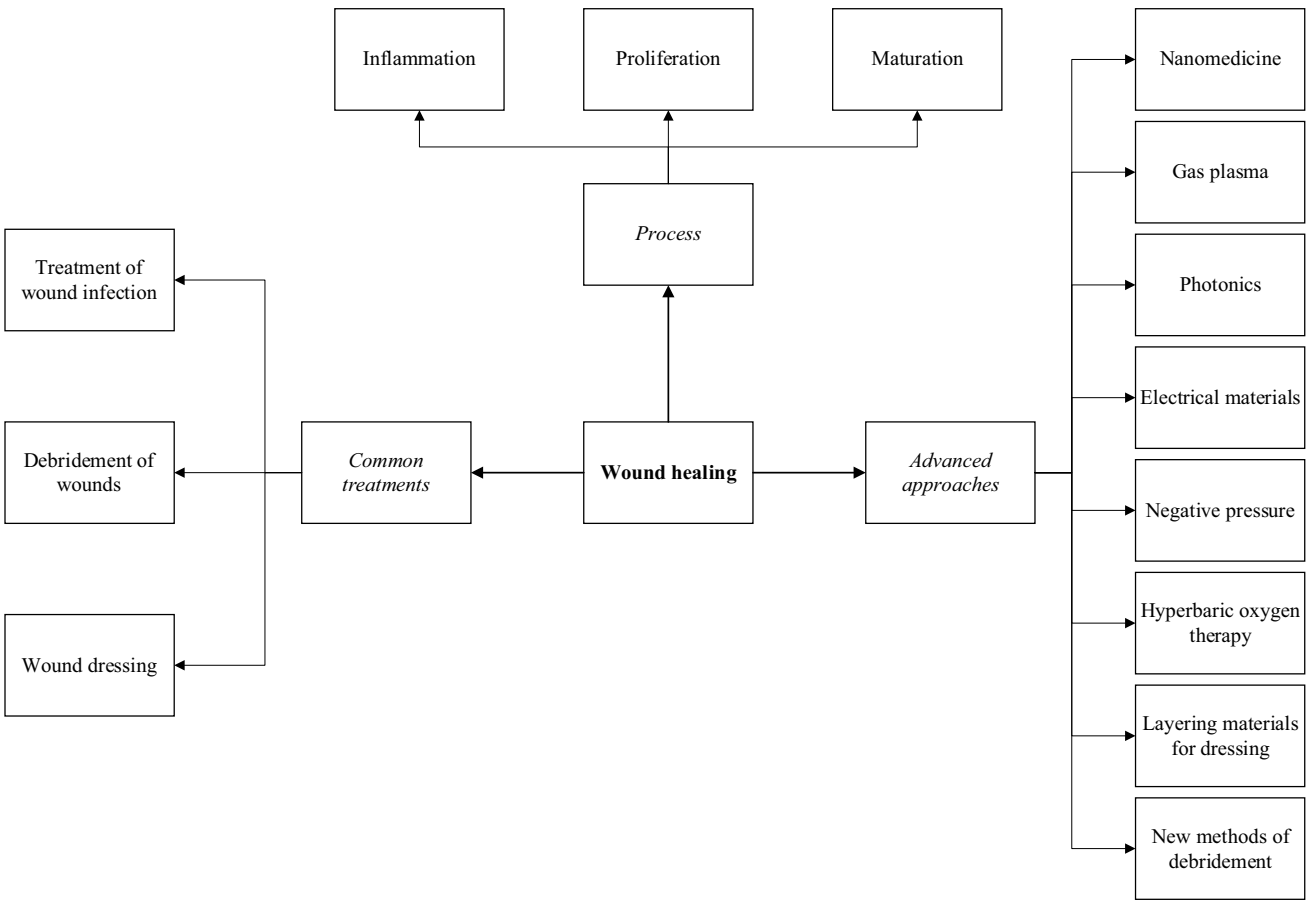

Fig. 1 Flow chart of this study from wound healing process to common and advanced therapeutic agents

Wound healing process

Understanding wound healing today goes beyond expressing the three stages of inflammation, proliferation, and maturation. Wound treatment is an intricate set of cell-mediated reactions and interactions. Because wound healing is a set of complex cellular interactions, discovering the new technology in recent years, lead to an increase in our understanding of this cell-mediated process. The physician's performance relies on many external and internal factors to deal with barriers to wound healing and to prescribe the appropriate medication [29].

Inflammation

The inflammatory phase indeed comprising two stages: homeostasis and inflammation. In most sources, the homeostasis stage is not divided into a separate stage due to its shortness. Both external and internal signaling pathways of the clotting cascade can be operated by collagen throughout wound formation especially at the onset of inflammation. After the injury, secretion prostaglandin-2 and thromboxane A2 are enhanced by the cell membrane. secretion of cytokines and growth factors have a crucial role at the beginning of inflammation and during this phase, the clot is formed of thrombin, collagen, fibronectin, and platelets. Furthermore, this clot helps in entering some cells like endothelial cells, fibroblasts, neutrophils and monocytes. This initial stage of wound healing usually takes 3–5 days [26, 27, 30].

Immediately after clot formation, neutrophils are the first responders to the cellular signal. Adjacent blood vessels are vasodilated to allow increased cell traffic simultaneously with the aggregation of prostaglandins and inflammatory mediators because neutrophils are affected by platelet factor-4 (PF4), growth factor (TGF), interleukin-1 (IL), tumor necrosis factor (TNF), and local bacterial infections are spread to the affected area [31]. Once neutrophils reach the wound, it takes up to clear it of invading bacteria and cell debris. Proteolytic enzymes released by neutrophils digest bacteria and non-living tissue. Monocytes are usually absorbed into the adjoining tissue via the blood and convert to macrophages. Macrophage activation is essential for the transfer to proliferation and wound healing. Activated macrophages synthesize fibroplasia, nitric oxide, and angiogenesis. macrophages (monocytes) and Leukocytes are other cells in the wound. Macrophages secrete an array of enzymes and cytokines, including TNF and interleukins that incite fibroblasts to generate collagen and cause angiogenesis; collagenases that kill wounds; and TGF, which motivates keratinocyte cells [32, 33].

Proliferation

After the phases of inflammation and homeostasis, the next event is the proliferation of different cells and extracellular matrix. Growth factors and cytokines secreted in the wound affect several cell types to increase their migration, proliferation, and synthesis. The proliferative part is the stage at which the wound closes. Proliferation is made up of collagen deposition, granulation tissue formation, epithelialization and angiogenesis [34, 35]. Repair of epithelial flaws is important for wound healing. Otherwise, important skin functions such as protein discharge, thermoregulation, sustaining water equilibrium, and acting as a barrier against bacterial invasion may not occur properly at another stage in wound healing in epithelialization. In areas where the basement membrane is not damaged, epithelial cells can migrate up, and after 2–3 days epidermis begins to regenerate. On contrary, in areas where basement membranes are annihilated, epithelial cells begin to send a message for multiply and restablish. [34, 36].

Another thing that happens at this stage and creates enough oxygen and nutrients to repair the tissue is angiogenesis especially the migration of capillaries. Endothelial cells in healthy venules begin to form new capillaries by VEGF (which is mainly secreted by keratinocytes at the edge of the wound but capable of producing fibroblasts, macrophages, platelets, and other endothelial cells). Endothelial cells can generate NO which causes hypoxia, and then motivating them to produce more VEGF [19, 23, 34]. New tissue by incrementing the NO concentration prevents the harmful effect of ischemia. unhealed ulcers require granulation and tissue deposition for regeneration which rely on nutrition from capillaries [37]. For the creation protective barrier, epithelial cells should send messages and proliferate, and then bacterial attack stimulates epidermal growth factor (EGF), TGF-α and epithelial proliferation, generated by active platelets and macrophages [38]. Inflammatory cytokines arouse epithelialization. IL-1 and TNF-α regulate keratinocyte growth factor (KGF) gene expression in fibroblasts. Fibroblasts synthesize and secrete KGF-1, KGF-2, and IL-6, which mimic neighboring keratinocytes for migration, proliferation, and differentiation in the epidermis. KGF-2 has been shown to be very important for humans to guide this process [39, 40].

Granulation can be mentioned in the last part of the proliferation process. Fibroblasts transfer from the neighboring tissue to the wound site, become active, and begin collagen synthesis and proliferation. Platelet-derived growth factor (PDGF) and EGF as two main signals of fibroblasts that come from platelets and macrophages [41]. Collagenation is initiated by fibroblasts that have already been placed at the wound site (so-called wound fibroblasts), which become myofibroblasts for wound contraction. They are

less proliferative than fibroblasts that enter the wound environment. Fibroblasts take up to make a temporary matrix consisting of glycosaminoglycans, collagen type III, and fibronectin, in response to PDGF. The transient matrix of proteases, consist of neutrophil-derived elastase, solves into a constant matrix composed primarily of collagen happen in the initial stage of wound care. [42]. The migration of fibroblasts to the wound area is related to the agglomeration and synthesis of collagen. Growth factors involved in collagen synthesis, TGF-β is one of the most important factors [43].

Maturation

The final step of wound care that prolongs more than other stages is maturation. The vital processes of maturation are collagen reconstruction and the formation of a mature scar. Likely, maturation is a long period process, it usually happens 3 weeks after a harm, and in some cases prolongs up to 20 years. If patients have difficulty (diet or disease), wound healing power is severely compromised [19, 44]. This starts with the production of collagen by fibroblasts and may keep going for months to years. Producing excess collagen results in a hypertrophic scar or colloid. On the whole, unfortunately, improved and restored tissue can never represent the structure created by the intact natural dermis. Not only is the synthesis of collagen associated with incrementing of fibroblast, but it is also related to the rate of collagen production in the cell. The collagen that is initially placed is thinner and its orientation is parallel to the skin [44, 45].

Progressively, the initial collagen fibers are thickened, organized along stress lines. These changes are also associated with an increase in tensile strength of a wound, the increase in fibril collagen diameter is directly proportional to the increase in the wound tensile strength. With the progress of maturity, cross-linking among molecules becomes intricate which causes enhancement in stability and resistance. In granulation tissue, the collagen is various from the collagen in undamaged skin. The amount of hydroxylation and N-glycosylation of collagen in granulation tissue is more, and this is associated with the production of thinner fibers [39, 41, 44].

Wound healing management

Common treatments

Treatment of wound infection

Chiefly, bacteria can found around the chronic wound and do not interfere in the treatment. However, by incrementing the load of bacteria wound repair is disrupted and leads to infection. infection via the extension to adjacent tissues can be getting worse and convert to systemic infection. Infection may conduct lag in therapy, augmentation smelly discharge, pain enhancement, increased amount of wound, and instable tissue. Treating a local wound infection with topical cleansers and antimicrobials can accelerate healing. [1, 2].

Water and normal saline solution are suitable options for cleaning wounds. Detergents should be avoided due to their tissue damage and toxicity [46]. On the other hand, wound cleansing with dilute vinegar or acetic acid (0.5%) has considerable antimicrobial effects. In one study, it was shown that soaking a wound in acetic acid 0.5% for 10 min for disinfectants the gram-positive and negative bacteria of the wound [47].

Topical antimicrobials are preferred for superficial wounds due to their direct targeting of bacterial loads to systemic therapies that are resistant to systemic microbes after a while. However, it has been seen in some cases topical agents lead to bacteria resistance, therefore it should be stopped after treatment. Also, it should be noted that repeated use of some kinds of these antibiotics, for instance, gentamicin and neomycin in chronic wounds can cause contact dermatitis and should be avoided [48].

Debridement of wounds

First, wound management requires a perfect analysis of the wound and the patient. This process begins with the diagnosis of the etiology of the wound and continues with the optimization of the patient's medical condition. In wound repair, the removal of damaged tissue has an essential role. The necrotic tissue in ulcers can interrupt therapy and prevent keratinocytes from migrating to the wound bed. Surgical, mechanical, enzymatic, or biological are the methods for debridement. Vascular evaluation is necessary for debridement, mainly for wounds in the lower part of the leg. Surgery can be done with its special instruments, under local anesthesia or general anesthesia except for patients with peripheral neuropathy. However, one of the disadvantages of surgery is the damage to both defective and intact tissue [49–51].

Wound dressing

Moisture balance requires choosing the right dressing to absorb the discharge. Wound dressing is divided into different types from simple ones like over-the-counter bandages to complex such as engineered dressing with stem cells. Moisture-retentive dressings (MRD) are widely utilized in clinical trials especially for chronic wounds, and their benefits have been proven. To be economical in caring is one of the benefit of these dressing for chronic wounds (for instance; nursing, cost of materials, and travel time). There are 5 types

of MRD include hydrocolloid, hydrogel, film, alginate and foam [52, 53].

Films are usually made from polyurethane in a clear and thin sheet and can attach to the skin by acrylic. The films are also applicable for acute surgical wounds. On the other hand, foams have two-layer, the outer layer is made of hydrophobic polyurethane and the inner layer for preventing bacterial contamination is made from a hydrophilic material. These kinds of bandages are appropriate for gentle to moderate wounds [52, 54].

Hydrocolloids are dressings consisting of polyurethane foam or film which adhere to a carboxymethylcellulose, gelatin, or pectin matrix. From the interaction of hydrocolloid and wound discharge, a yellow gel is produced. These dressings are useful for wounds that have a small amount of discharge. this dressing also can be used during bathing or swimming owing to waterproof ability, but it can cause sores on the edges. This dressing is generally changed every 2–4 days [55].

Alginates dressings are generated from cellulose polysaccharides such as algae-derived or kelp (a type of seaweed) and are much absorbent. Moisture absorbance in alginate dressings is because of exchanging calcium with sodium, and it also gives them a hemostatic feature. They are made from fluffy sheets that soak up with secretions of wounds. Alginates are not suitable for dry or less secretive wounds and they should be used for highly secretive lesions [56, 57].

Hydrogels are like liquid gels in a hydrophilic polymer network. They can be placed in the form of sheets on the wound surface. Unlike alginate, the most common use of hydrogels is for dry and necrotic wounds and especially alleviates painful wounds in patients [58].

Advanced approaches to wound healing management

Negative pressure wound healing

Negative pressure is another approach for wound treatment. Negative pressure by implementing a controlled and permanent vacuum improves wound repair. Elimination of extra discharge wound shrinkage and increased blood flow along with negative pressure are necessary for wound healing. In this procedure, a sponge is inserted into the wound, which is connected to a microprocessor-controlled pump through a tube [59]. Therefore, permanent and controlled pressure makes a condition for rapid wound healing. Various types of wounds including acute wounds, surgical wounds and chronic wounds can be treated by this method. This feature helps reduce patients' rehabilitation time [60].

Hyperbaric oxygen therapy

In hyperbaric oxygen therapy, 100% oxygen at higher pressures above sea level or in an atmosphere periodically is used for patients. Precise information on the benefits of this treatment has not yet been obtained except and cost-effectiveness. However, increased angiogenesis and improved fibroblast and leukocyte function have been demonstrated by increased oxygen. In using this method, the available facilities should also be considered, and since there are still shortcomings in the field, the use of this treatment method is very limited. This treatment as a supplement to standard wound care can be very effective for treating diabetic patients, especially those suffering from foot ulcers. In a study, hypertensive oxygen therapy was used versus standard treatment for foot wounds in diabetic patients. [61, 62].

Layering materials for dressing

Another new method of wound healing is the use of different properties of the material to make layered dressings. Clinically, absorbing dressings used to consist of a non-adhesive layer or semi-adhesive and a highly absorbent layer of fibers such as rayon fabrics, cotton, and other compounds. In this regard, Gunawati et al. created a three-layer dressing [63]. In this dressing, the layer in contact with the wound is made of non-woven polyester fibers, the absorbent layer is made of non-woven bamboo fibers, while the top layer is made of 6/PCL nylon [64]. Sussman et al. combined a layer of alginate with a layer of hydrofiber to form a sheet of fibers. These layers attach to a layer of activated carbon and combine with an additional viscous outer layer [65].

Another example of a multilayer dressing is a combination of hydrocolloids and alginates, which are especially suitable for the treatment of superficial foot wounds, burns, and pressure sores. Lopez et al. developed a multilayer dressing of a combination of hydrogel foam and polyurethane layers for the treatment of chronic wounds in which the physiological environment of the wound should be further preserved during the granulation and epithelialization stages [66]. Recently, a study has been conducted on how to combine the materials used in multilayer wound dressings with combination drugs to optimize the treatment of chronic wounds. The aim of this study was to prepare a multilayer wound dressing with a combination of drugs from two different pharmacodynamic groups. PTE (first layer) includes.

Lidocaine was effective for immediate release and rapid pain relief, and diclofenac in alginate (second layer) and viscose (third layer) was effective for long-term pain relief (Fig. 2) [67].

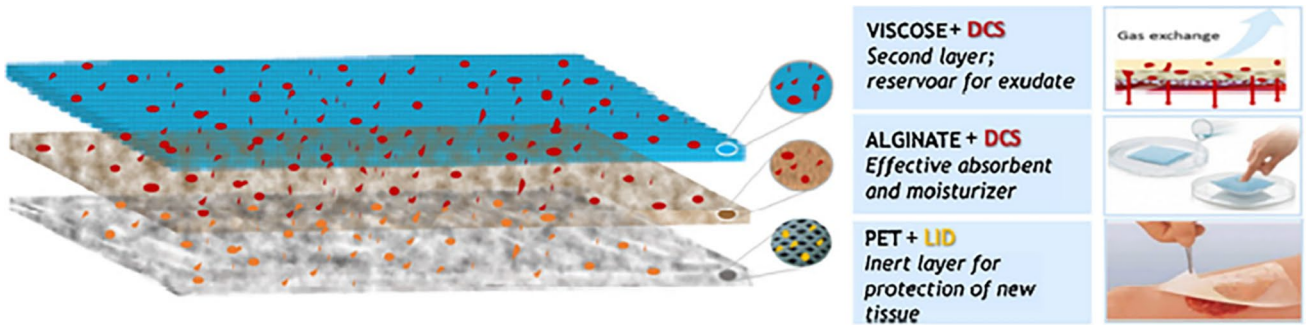

Fig. 2 Achievement optimal method for caring of painful wounds by Multi-layer dressing. This figure was obtained with permission from [67] under the terms of the creative commons CC BY license

New methods of debridement

A completely different method of wound care is the use of larvae. Larvae (Greenflies *Lucilia sericata*) have beneficial effects on a chronic incurable wound. These properties contain: removal of necrotic tissue (debridement), wound disinfection and active strengthening of granulation tissue formation. The interactions of the two have a significant effect on the formation of new tissue. Sterile larvae are placed in a cage in a wound dressing. The larvae usually remain in the dressing area for 24–60 h, then are washed with saline solution. If necessary, this is repeated by new sterile larvae [68].

Collagenase ointment (250 units per gram), derived from the bacterium *Clostridium histolyticum*, is very effective for dry wounds with fibrin debris and no granulation tissue, especially when surgical procedures are not possible. Collagenase increases endothelial cells and keratinocyte migration [69]. Enzymatic destroyers are an effective option for removing necrotic material from pressure ulcers, foot ulcers, and partial-thickness wounds. Biological debridement that used medical maggots is a rapid and efficient debridement method commonly used for fibrinous wounds. This method is often used less due to high pain and intolerance of the patient and the provider. A recent randomized controlled trial showed that people treated with larvae experienced more discomfort than those treated with hydrogel dressings [70].

Nanomedicine in wound healing

Nanomedicine has made advances in diagnosing and treating different types of diseases, including cancer, cardiovascular disease, tissue engineering, diabetes, regenerative medicine, inflammatory diseases, and wound healing [71]. Due to their unique physical, chemical, and biological properties, nanoparticles are used to suppress inflammation, control microbial infections and accelerate wound healing (Fig. 3) [10]. Dressings made of nanoparticles due to greater porosity, the ability to absorb wound secretions,

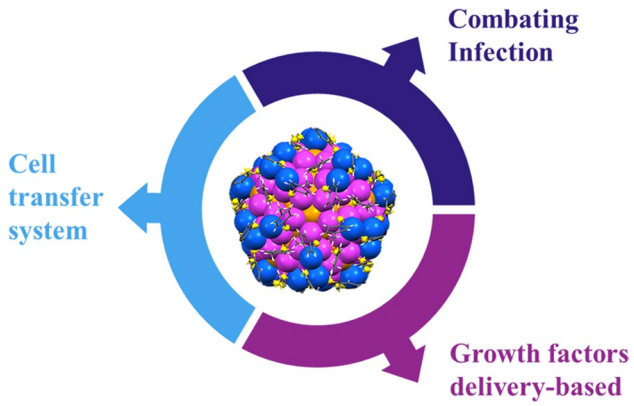

Fig. 3 Nanoparticle based modalities for wound healing

increase wound respiration, mimic the structure of the extracellular matrix (ECM) and produce reactive oxygen species (ROS) or release ions by affecting several cellular and molecular pathways accelerate wound healing [72].

Use of nanotechnology in reducing infection Infections are a significant concern in patients with incurable wounds. Although secretions are part of the body's natural defenses, secretions often prevent wound healing and are an efficient environment for bacteria to grow. Such wounds require special treatment because improper treatment can lead to serious infections or even death. To prevent and eliminate infections, antimicrobial creams, hydrogels, foams, polymer films, hydrocolloids, and textile medical dressings currently are used. Nevertheless, recently, dressings comprising nanocrystalline materials receiving considerable attention according to their unique properties [73, 74]. Nanoparticles with intrinsic antimicrobial properties as well as carriers of antibiotics or other antimicrobial agents play an important role in reducing the microbial load of the wound. Transfer of antibiotics by polymer vesicles can reduce these side effects [74].

One of the mechanisms by which nanoparticles exert toxicity against various bacteria could be due to the direct interaction of the bacterial cell wall with toxic ions or reactive oxygen species (ROS) released. The nanoparticles attach to the bacterial cell wall by bonding van der Waals, electrostatic forces, hydrophobic, or receptor-ligand interactions, affecting its permeability and integrity. They can also cross cell membranes and interact with various components within the cell, including proteins and DNA, and kill them by affecting gene expression and protein function. For example, iron ions released from iron oxide nanoparticles can interfere with the flow kinetics by directly attaching to pumps or interfering with flow kinetics, resulting in impaired homeostasis or destructive changes in membrane surface load, while Metal and ionic forms of copper and silver nanoparticles impair basic proteins and DNA by producing hydroxyl radicals [74–76].

In the following, we will review some examples of dressings in which silver nanoparticles have been used. It is worth noting that silver has been used for years in the wound healing process owing to its high antimicrobial properties. But recently, due to the toxic effects that may be caused by silver particles, its use has been little discussed. For example, because silver is best used in various forms in the nanoscale, various techniques have been enlarged in recent decades to produce it. Numerous studies have shown that the release of Ag + ions from the NPs used, especially above the toxic threshold concentration, can damage DNA and break DNA strands. Interference with DNA repair pathways or mitochondrial damage can also cause toxicity in cell lines exposed to silver nanoparticles [77–80].

The sol–gel process is one of the most interesting methods for combining silver nanoparticles on cellulose matrices (e.g., viscose) due to its simplicity and easy preparation conditions. Inorganic sol–gel matrices provide higher mechanical, thermal, chemical, and photochemical stability and are toxic and biologically ineffective [81] compared to organic matrices. The produced materials were observed to be effective against wound-infecting bacteria. Choosing a suitable sol–gel system can be considered a good starting point in preparing safe wound dressings with beneficial efficacy on the wound healing process due to the excellent antimicrobial properties of the viscous material used.

An environmentally friendly method for dressing is the use of regenerated cellulose fibers with silver nanoparticles, which are developed in three stages [82]. First, cellulose fibers in NaOH solution are treated. The alkaline treatment causes silver nanoparticles to adhere to the surface and all parts of the cellulose fibers. The alkaline solution also acts as a source to reduce the excess hydroxyl groups required for the synthesis of silver nanoparticles. The second step is to saturate the cellulose fibers in a silver nitrate solution. Finally, the treated materials are neutralized, washed, and dried. Cellulose fibers prepared by the method described have higher durability against washing and antimicrobial properties even after the washing cycle [83, 84].

As a controlled local heating, photothermal therapy causes kill the bacteria under NIR irradiation. But to eradicate all the bacteria in the wound requires a lot of radiation and local temperature, which may damage the adjacent area. Therefore, using multifunctional nanoparticles, improve this treatment method [85]. In one study, a multifunctional nanocomposite consisting of a silver core and a CuO_2 shell with photothermal capability was used to kill bacteria (E. coli and MRSA). In addition to the healing properties and the production of silver ions, which reduce the load, the released copper ions also improve the healing of diabetic wounds by inducing collagen deposition and resumption of epithelialization [86].

In addition, polydopamine (PDA) and silver-modified MoS2 nanoparticles, eradicate S. aureus bacteria and leading to acceleration of the healing of infected wounds. Therefore, heat treatment synergistically increases the antibacterial effects of silver ions [87].

As mentioned, copper nanoparticles (CuS NP) exhibit photothermal and photodynamic properties. Elevated temperatures, oxidative stress, and ROS (such as hydroxyl radicals) disrupt structural proteins and bacterial membranes (both S. aureus and E. coli). In addition, this combined hydrogel releases copper ions, which not only destroy DNA and bacterial proteins, but also promote cell proliferation, angiogenesis, and tissue regeneration at the wound site [88].

LL-37 is a cationic peptide that provides an important antimicrobial defense mechanism for damaged skin. Moreover, the peptide was attached to gold nanoparticles and used for gene delivery. This transmission system was used as a dual-purpose system to reduce infection and increase angiogenesis [89]. Other nanoparticles are lipid ones that are used for the simultaneous transport of LL37 and Serpin A1 as peptides involved in the immune system and reducing bacterial load. They accelerate wound healing by suppressing inflammation in fibroblasts and keratinocytes, collagen-1 deposition increased, as well as, enhancing antibacterial effects against both gram-positive (S. aureus) and gram-negative (E. coli) bacteria [90].

Transfer of growth factors by nanoparticles Wound healing in the skin is a complex, multi-step process that is regulated by an equally complex signaling network including growth factors, cytokines, and chemokines. Growth factors are secretory soluble proteins that are able to affect a variety of important cellular processes for tissue regeneration. Recently, biomaterial carriers and advanced delivery systems such as nanoparticles and nanofibers for the transfer of growth factors and peptides have received much attention [31, 91].

As a common growth factor for treat skin ulcers, EGF is utilized. Besides, to transfer and releasing of EGF, succinylated dextrin is used [92]. Using heparin-conjugated fibrin, the FGF2 stable delivery system is another new strategy for wound healing. The carrier system consisting of fibrin hydrogels loaded with bFGF-dual emulsion increases the proliferation of endothelial cells in comparison to the control group [93]. In another study, injured mice were treated with heparin-bound epidermal growth factor, which showed the results of increased keratinocyte migration while maintaining wound proliferation and regeneration after 7 days [94].

Recently, with several growth factors, it has been shown that biodegradable and biocompatible scaffolds can act as the most promising treatment for skin tissue regeneration. Dextran hydrogel filled with chitosan nanoparticles was employed to transfer EGF and VEGF, which showed accelerated wound healing. In addition, histological analysis revealed the absence of granulomatosis or a reactive inflammatory reaction in the skin lesions [95, 96].

Cell transfer system Migration, penetration, proliferation and differentiation of cells that affected the wound healing process reach their peak in the inflammatory response, the formation of new tissue and finally wound closure [1, 31]. Transfer of these cells and stem cells by biological carriers is another treatment for wound healing. However, this treatment strategy may be ineffective for chronic or deep wounds if there is insufficient blood supply [97].

The multifunctional poly (ethylene) glycol (PEG) hyaluronic acid (HA) hybrid hydrogel with several acrylate functional groups provides an efficient dressing system for human fat-derived stem cells (hADSCs). Although cell proliferation was inhibited in this study, VEGF and PDGF production, increased within 7 days [98].

In another study, the aim was to design a highly efficient system for epidermal stem cell (ESC) transfer and to evaluate transfected ESCs (TESCs) as a therapeutic agent. B-Cyclodextrin-binding polyethylenes (CYD-PEI) were used as a non-viral vector. Gelatin scaffold containing β-tricalcium phosphate (β-TCP) was used as a substrate for the culture and transfection of ESCs. Using the three-dimensional scaffold transmission system, long-term expression of VEGF with higher levels in ESCs than two-dimensional plates was obtained on the seventh day. Topical application of TESC also significantly accelerated skin re-epithelialization, skin collagen synthesis and hair follicle regeneration, and by regulating the distribution of different types of collagen, the potential for scarring was created [99].

Human mesenchymal stem cells (hMSCs) treated with iron and gold nanoparticles (AuFe NPs) were also designed to release iron ions intracellularly through endocytosis. Intracellular iron ions regulate hypoxia-induced factor 1α and vascular endothelial growth factor (VEGF). The results of the treatment group compared to the control group showed a significant increase in epithelialization, angiogenesis and tissue regeneration [100].

Gas plasma as an innovative technology for wound healing

Gas plasma: a general perspective Gas plasma (GP), also known as cold plasmas, on the grounds that it provides a suitable environment for diverse medical applications, especially in wound healing and oncology, has received great attention. [101]. The multimodality nature of gas plasma is distinguished it from traditional physical therapies and leads to a variety of interesting outcomes. Gas plasmas are comprising of ions, radicals, electrons, RONS, and electromagnetic radiation that brings about a unique chemically-physically environment for multiple applications [102]. While the temperature of heavy particles is at room temperature range, electrons have a much higher temperature leading to the production of reactive agents [103].

Treatment time, discharge voltage, discharge frequency, distance to effluent, treatment area, direct vs indirect, type of working gas, flow rate, and gas mixture, as the main factors, have been influencing each gas plasma-based therapy. Based on these multiple factors, RONS, EM radiation, and UV light as plasma doses are adjustable for the specific target as an alternative technology [104, 105].

Among the various biomedical applications of GP, wound healing and bacterial eradication have shown significant progress in clinical application. Indeed, several clinical trials have demonstrated the potential use of GP to bacterial load diminishing in patients with chronic wounds (Fig. 4) [106]. This success led to the commercialization of a number of plasma sources for skin-related diseases. Although four plasma sources have been received CE certification, research into GP sources continues to develop and characterize the extensive optimization of plasma systems and their biological effects. So that studies on new applications of GP biomedicine are currently being actively developed [107]. As a recognized application area of plasma medicine, the clinical consequences of GP on skin diseases (e.g., melanoma and psoriasis) and wound healing (e.g., diabetic foot) have been very promising [108, 109].

GP is used to enhance the regeneration process because it accelerates the tissue regeneration process by inducing cell division and increasing the content of adenosine triphosphate (ATP). Furthermore, GP is able to healing wound healing faster and reduce the side effects of the ongoing wound healing management approaches by affecting bacteria and fungi. When bacteria are constantly exposed to the plasma, bacterial resistance does not increase. These findings suggest that GP is a potential candidate for antibiotic therapy [110].

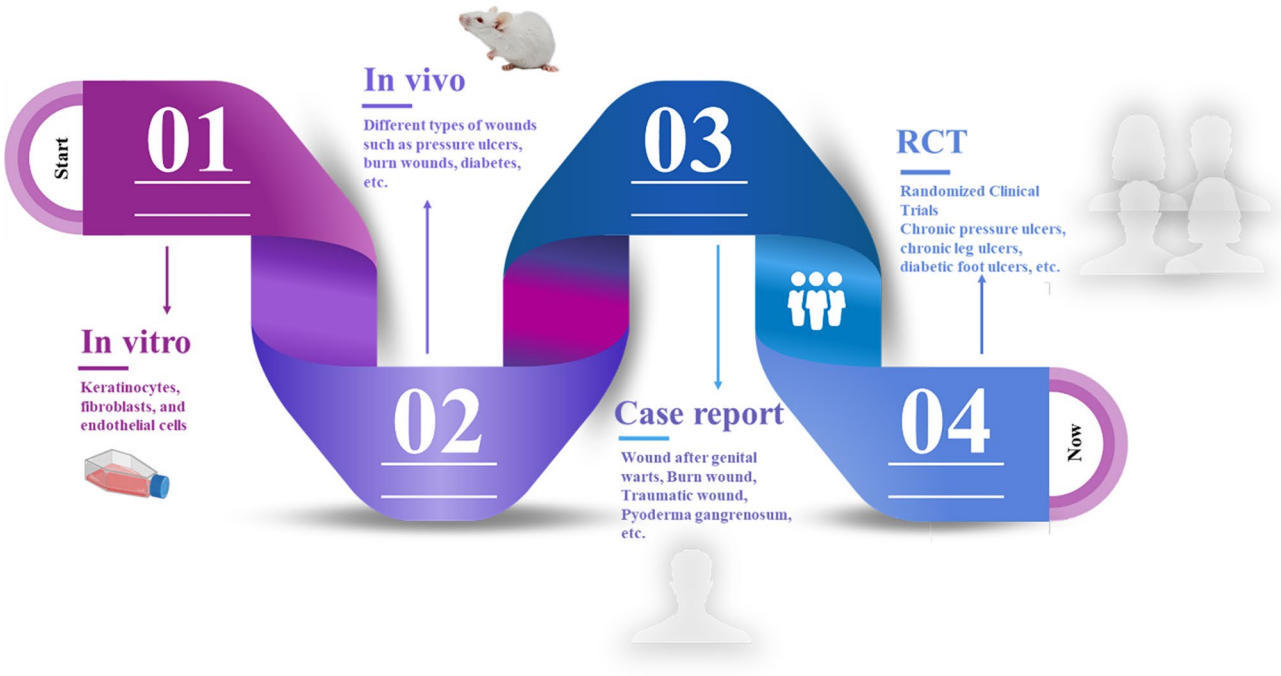

Fig. 4 Gas plasma irradiation from in vitro studies to randomized clinical trials (RCT)

Owing to the adjustable nature, gaseous state, combating multiple resistant pathogens, non-invasive, and painless of GP, it has great potential to revolutionized common wound healing management. Moreover, while GP has an antibacterial effect and did not show any side effects yet, is able to reduce pH and by releasing growth factors stimulating angiogenesis which are crucial for wound healing [111, 112].

Clinical impact of Gas plasma technology The antimicrobial efficacy of GP against individual pathogens, resistant microorganisms, and biofilms is obvious thanks to the numerous preclinical and clinical works. So that the beneficial impress of plasma has shown on a number of wounds including chronic pressure ulcers, chronic leg ulcers, chronic ulcers, chronic venous leg ulcers, diabetic foot ulcers, Wistar rats pressure ulcers, fractional CO_2 laser skin wound, wounds at the donor skin graft sites, CO_2 skin laser lesion, and burn wounds in animal models [113].

Actually, compared to standard therapy, multi-resistant germs elimination, painless and non-invasive along with reducing pH value and gaseous state introduce GP as an emerging multimodal therapeutic modality that is able to enhance blood flow and promote tissue generation in healing of wounds. During the consecutive steps of wound healing, different mechanisms of action that accelerates wound healing are influenced by GP. In summary, controlling the inflammatory response and Nrf2 signaling in skin cells, changes in Cx43 expression, mild pro-oxidant therapy are the highlights of beneficial effects of GP in wound healing [104, 106].

First studies focused on the performance of GP, especially in the bacterial load removal of chronic wounds and safety of used devices compared to ongoing modalities. In one study, MicroPlaSter α and MicroPlaSter β are employed to the investigated effects of GP on chronically infected wounds of different etiology. Besides modern wound healing, these patients received GP treatments. It is interesting that regardless of the device used and the duration of treatment, GP leads to a significantly higher bacterial reduction in plasma-irradiated wounds [114, 115].

Further, regardless of the treatment type, fewer fibrin layers, improving re-epithelialization, and blood crusts are positive findings of another study, in which GP or argon gas for 2 min are randomly used in the treatment of upper leg skin graft donor sites [116]. Moreover, for a group of patients with chronically infected wounds of various etiology, the positive impress of GP therapy has been revealed in a retrospective randomized controlled trial. The GP irradiation was adjusted to between 3 to 7 min for three divided groups. Although no significant difference in wound width or length was measured, in the two more homogeneous groups a remarkable decrement in wound width was explored at 5 min GP irradiation [117].

In two randomized clinical studies, 44 patients with diabetic foot ulcers were randomly double-blinded for three consecutive weeks, into two groups of standard care (n = 22) and standard care and GP treatment (n = 44),

were examined. The fraction of wound size in GP irradiation patients was effectively reduced in comparison to the control group. Albeit immediate antiseptic was observed after GP treatment, it seems that does not appear in the last long [118]. Moreover, the GP treatment impacts on 45 diabetic leg ulcer patients with 65 chronic wounds, in a prospective, randomized, placebo-controlled, blinded, multi-centered study, was investigated. Standard treatment was applied to all wounds. Whilst 33 wounds were treated via eight GP applications, 32 wounds were placebo (argon gas) irradiation. It is interesting that, while there are no significant differences in the microbial load and reduction of infection in control and GP-treated groups, wound size reduction and shortening the wound healing period were observed in the GP-treated group [106].

Our understanding about the molecular action mechanisms of gas plasma Generally, regulation of inflammation, migration, angiogenesis/reperfusion, re-epithelialization, and proliferation are some highlighted beneficial effects of GP therapy in wound healing management, which achieve by physical and chemical factors, especially RONS. By activating angiogenesis-related molecules in endothelial, keratinocytes, and fibroblasts cells, the capability of GP to inducing wound angiogenesis has been demonstrated [119].

Besides, with autocrine and paracrine mechanisms, GP can activate angiogenesis-related molecules in keratinocytes, fibroblasts, and endothelial cells, as cells involving in the wound healing process. Briefly, GP therapy leading to high expression of EG-VEGF (PK1), Artemin, FGF-2 (FGF basic), EGF, IL-8 (CXCL8), Endothelin-1 (ET-1), and uPA in keratinocytes, as well as, for HUVEC endothelial cells, Angiostatin (PLG), Endostatin, FGF-2, Amphiregulin (AR), Angiopoietin-2 (Ang-2), and expression of VEGF R1 and FGF R1 activated through GP therapy. Next, in fibroblasts, GP induces Endostatin (Col18A1), Angiogenin (ANG), TIMP-1, MCP-1 (CCL2), VEGF, uPA, and MMP-9 expression [119]. In another work, while GP promotes alpha-SMA and collagen type I production, induces TGF-ß1, TGF-ß2, MCP-1, IL-6, and IL-8 expression as essential wound healing relevant molecules [120].

As a key factor in cutaneous tissue repair, the cellular migration enhancement ability of GP has been investigated by applying it to in vitro models. It seems that a low dose of RONS producing by CAP increase cellular migration of dermal fibroblast and epidermal keratinocytes. Furthermore, GP therapy enhances extracellular matrix deposition and wound maturity and these effects were associated with the increase of Tgfbr1 mRNA level and collagen I protein [121]. Recently, based on the plasma-derived ROS, Schmidt et al. conclude that GP is able to introduce as a promising sensitive toll of skin barrier regulation [122].

An interesting study has shown that GP produces nitric oxide (NO) and increases cell migration and endothelial cell assembly into vessel-like structures. Moreover, endogenous NO levels in endothelial cells increase with phosphorylation and activation of eNOS, leading to stimulation of VEGFA/VEGFR2 pro-angiogenic signaling [123]. Besides, GP irradiation by modulation of focal adhesion, tissue oxygenation, and matrix remodeling, promotes the physical integrity of healed skin [15].

More recently, 44 patients were divided into two groups, while the first group of patients received standard care (SC) (n = 22), SC + GP treatment applied for the second group (n = 22). Considering accelerating the treatment period of diabetic foot ulcers and reduces bacterial load, the authors conclude that GP therapy represents an effective alternative modality for diabetic foot ulcers. Besides the mentioned results, for the first time, after GP exposure, the underlying molecular mechanism emphasizing the role of the inflammatory phase was recognized. By employing GP therapy, the levels of IL-1, IL-8, TNF-α, and IFN-γ as cytokines and growth factors are positively affected. Compared to the ongoing protocols, GP-based treatment acts as a very promising modality for accelerating diabetic foot ulcers and the molecular mechanism was related to the inflammatory phase [124].

Looking at the studies, it can be seen that its operation depends on various components such as electromagnetic fields, UV light, RONS, which often act synergistically and lead to specific results. In preclinical and clinical studies, RONS are often considered as the main factor influencing the process of GP treatment, and the role of physical factors rarely has been mentioned. The role of physical factors is expected to be emphasized in the coming years as explored in oncotherapy. In this regard, it has been reported [121] that the application of RONS (e.g., H_2O_2, NO_2^-, NO_3^-) at least at the level of this in vitro, is not effective compared to the use of plasma, and this highlights the synergistic importance of physical and chemical effects in GP therapy (Fig. 5).

Photonics in medicine

Despite the great progress of photonics in health-related areas, on account of penetration depth restriction, its application for clinical purposes faces many challenges. To overcome these obstacles, implantable light delivery vehicles, which can transmit light have been invented. These devices are absorbed by the tissue and have not toxicity thanks to their biodegradable and biocompatible nature [125]. This treatment method has been used as in vivo experiment to heal wounds on the surface of pig skin and good results have been obtained [126].

The potential for hydrogen (pH) evaluation is an important indicator in the wound healing phase. In a study in

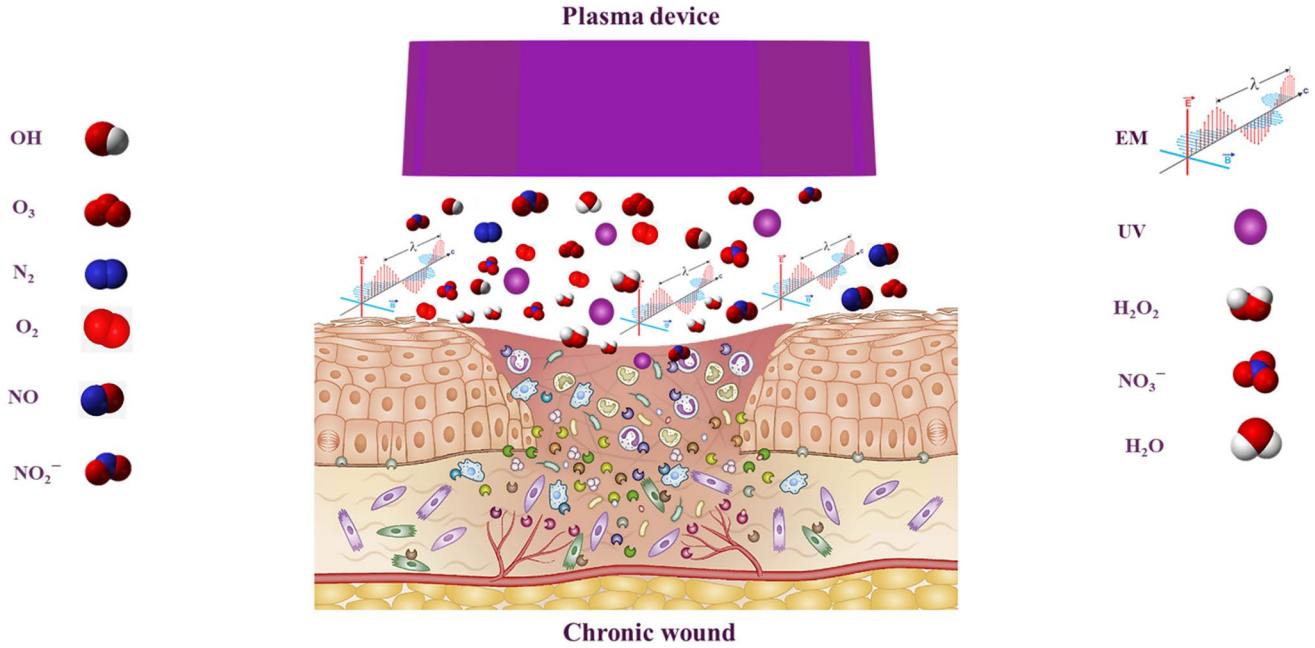

Fig. 5 Interaction of key components of gas plasma with chronic wounds

2021, for the first time, a smart wound dressing equipped with fiber optics was used to assess pH. In this study, pH-sensitive intrinsic fiber optics were labeled with rhodamine B dye using polymethylsiloxane (PDMS) precursor, the mentioned fiber was then placed in a hydrocolloid wound dressing [127].

Use of electrical materials for effective wound healing

Novel electrically active material was released recently by the US National Aeronautics and Space Administration (NASA) for wound healing contingent on polyvinylidene fluoride. By utilizing electrical activity that protecting the wound, this technology simultaneously promotes the wound healing process. The bandage is made of an electrical material (polyvinylidene fluoride, a thermoplastic fluoropolymer that is highly piezoelectric when polarized) stimulating cell growth by pressure and body heat, whereas no external energy source is required. The primary advantages of these materials are the improvement of the wound healing process and a multitude of active healing and wound protection concomitantly [128].

In one study, Zhao et al. examined an antibacterial electric injection hydrogel dressing that relied on its self-healing ability to extend the dressing life and acceleration of the wound healing process with its unique properties including antibacterial, antioxidant, adhesion, conductivity, and biocompatibility [129]. In another experiment, by mixing the mechanical traits of polycaprolactone (PCL), the wettability of polyethylene glycol (PEG) parts, and the electrification of aniline triple (AT), a set of elastomers Polyurethane-urea was electrically designed and synthesized as an antibacterial, antioxidant, and electrochemical coating to heal skin wounds. The electrochemical film with an appropriate concentration of AT increased the adhesion and proliferation of mouse fibroblasts. Also, by promoting granulation tissue, the wound healing process was significantly accelerated compared to the film without active electricity and normal dressing [130].

With aiming to produce appropriate environment for wound dressing, in a trial inspired by Mussel chemistry, reduced dopamine (PDA), graphene oxide (pGO), chitosan (CS) and silk fibrin (SF) (pGO-CS/SF) with high mechanical, electrical and antioxidant properties were used. First, enhancing mechanical traits of CS/SF scaffolding are done by nano-reinforcer pGO. Second, the uniform distribution of pGO in the scaffolding creates a fully interconnected electrical path, which is able to provide a channel for the transmission of electrical signals in the scaffold. pGO also acts as an antioxidant to kill reactive oxygen species (ROS), thus preventing excessive oxidation of ROS. In general, pGO-CS/SF electroactive scaffolds can respond to electrical signals and improve cytological behavior. This can effectively increase wound healing and regeneration (Fig. 6) [131].

In another test, multifunctional hydrogels based on regenerated bacterial cellulose (rBC) and MXene (Ti3C2Tx) were developed that could modulate cell behaviors to heal active skin wounds under external electrical stimulation. Optimal mechanical properties, good flexibility, good biodegradation and high water absorption capacity are the prominent

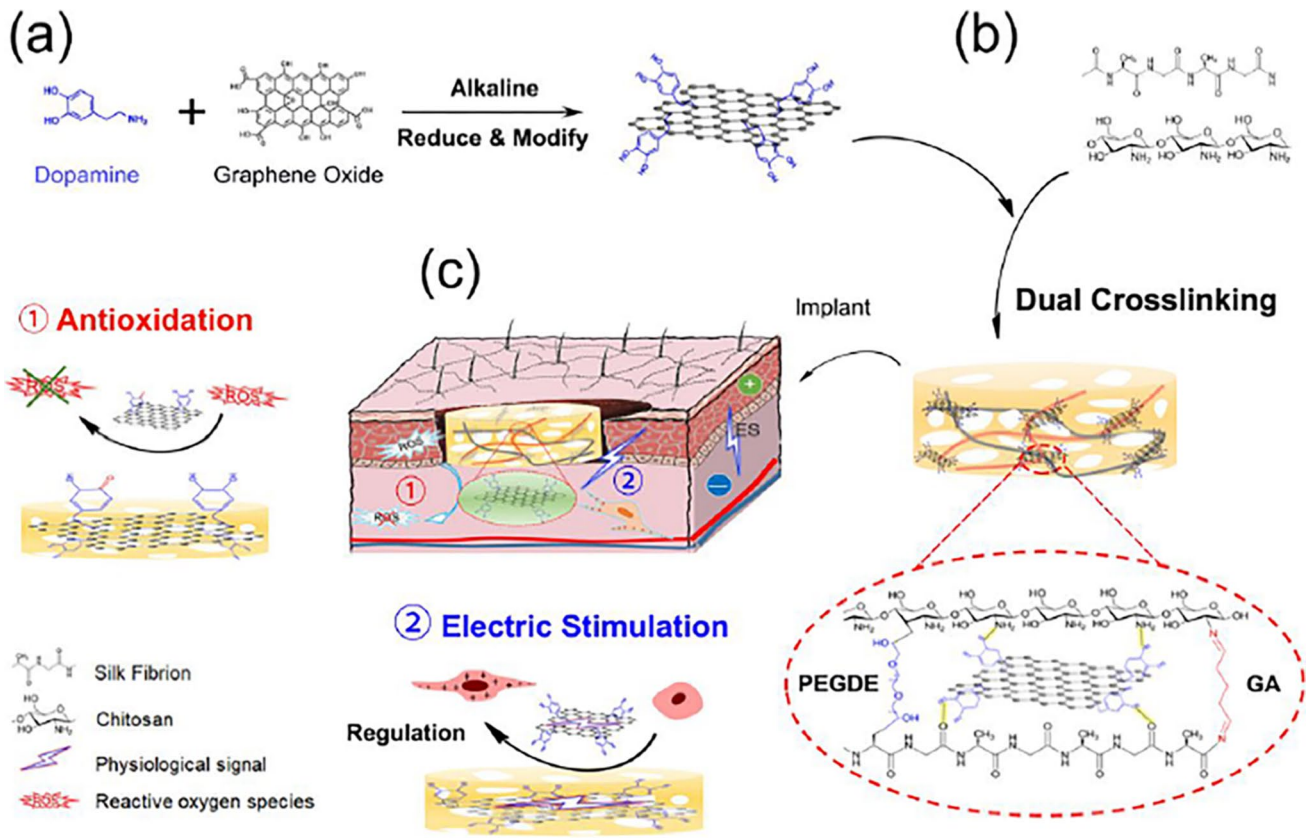

Fig. 6 This figure represents the arrangement of the electroactive and anti-oxidative pGO-CS/SF scaffold. **a** Graphene oxide (pGO) is functionalized by synthesis PDA. **b** Formation of the dual-cross-linked pGO-CS/SF scaffold. **c** Application of scaffold for healing skin wounds. The scaffold on the skin tissue demonstrates anti-oxidative properties and electric incitement during the wound regeneration process. This figure was obtained with permission from [131] under the terms of the creative commons CC BY license

features of this wound dressing that accelerates the wound healing process [132].

Concluding thoughts and future directions

Here, we discussed the current and advanced wound healing therapeutic modalities. It can be seen that ongoing wound healing therapies are several limited including inefficacy of antibiotics due to the biofilm formation, rapid degradation or deactivation of biological therapeutics such as growth factors in the chronic wound environment, poor bioavailability of drugs in medicated wound dressing, whereas nanotechnology and gas plasmas based strategies create an interesting platform to overcome wound healing challenges. However, the integration of gas plasma and nanotechnology may bring about a synergistic impact that cannot be solved by plasmas and nanotechnologies alone, or traditional methods. Despite significant progress in the application of nanotechnology and gas plasmas, there are still unknowns mechanisms and many challenges. Fortunately, with increasing collaboration between plasma, nanomedicine, and biology researcher, in a short time, we are able to cover most of the wound healing challenges via the concomitant modality of gas plasma and nanotechnology.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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